

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201699Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and Composition)
and/or Method of Use*

NDA NUMBER

201,699

NAME OF APPLICANT/NDA HOLDER

Optimer Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Dificid

ACTIVE INGREDIENT(S)

fidaxomicin

STRENGTH(S)

200 mg

DOSAGE FORM

Film-coated tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

7,378,508

b. Issue Date of Patent

May 27, 2008

c. Expiration Date of Patent

July 31, 2027

d. Name of Patent Owner

Optimer Pharmaceuticals Inc.

Address (of Patent Owner)

10110 Sorrento Valley Road

City/State

San Diego CA

ZIP Code

92121

FAX Number (if available)

858-909-0737

Telephone Number

858-909-0736

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Robert Smyth

Morgan, Lewis & Bockius LLP

Address (of agent or representative named in 1.e.)

1111 Pennsylvania Avenue

City/State

Washington DC

ZIP Code

20004

FAX Number (if available)

202-739-3001

Telephone Number

202-739-5139

E-Mail Address (if available)

rsmyth@morganlewis.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) 1-13 & 15-20	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
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4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
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5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> <p style="text-align: center;"></p>	<p>Date Signed</p> <p style="text-align: center;">10/01/2010</p>
---	--

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input checked="" type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name Robert Smyth c/o Morgan, Lewis & Bockius LLP</p>	
<p>Address 1111 Pennsylvania Avenue</p>	<p>City/State Washington DC</p>
<p>ZIP Code 20004</p>	<p>Telephone Number 202-739-5139</p>
<p>FAX Number (if available) 202-739-3001</p>	<p>E-Mail Address (if available) rsmyth@morganlewis.com</p>

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 201699

SUPPL #

HFD # 520

Trade Name Dificid

Generic Name Fidaxomicin 200 mg Tablet

Applicant Name Optimer

Approval Date, If Known May 27, 2011

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)(1)

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.

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:

d) Did the applicant request exclusivity?

YES NO

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

5 years

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?

No

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:

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: Fariba Izadi, PharmD
Title: Regulatory Project Manager, Division of Anti-Infective Products
Date: May 27, 2011

Name of Office/Division Director signing form: Edward Cox, MD, MPH
Title: Office Director, Office of Antimicrobial Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

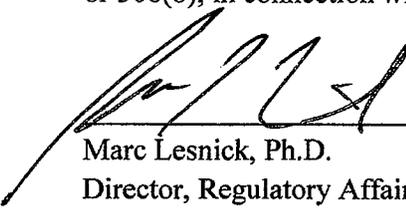
/s/

FARIBA IZADI
05/27/2011

EDWARD M COX
05/27/2011

1.3.3 DEBARMENT CERTIFICATION

Optimer Pharmaceuticals, Inc. hereby certifies under FD&C Act Section 306(k)(1) that it did not and will not use in any capacity the services of any person debarred under Section 306(a) or 306(b), in connection with this application.



Marc Lesnick, Ph.D.
Director, Regulatory Affairs

8/27/2010

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 201699 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Difucid Established/Proper Name: Fidaxomicin Dosage Form: 200 mg Tablets		Applicant: Optimer Agent for Applicant (if applicable):
RPM: Fariba Izadi		Division: Anti-Infective Products
<p>NDA: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>05-30-2011</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 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 _____		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority</p> <p>Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch</p> <p><input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch</p> <p><input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E</p> <p><input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41)</p> <p><input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H</p> <p><input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide</p> <p><input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan</p> <p><input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU</p> <p><input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
❖ 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 type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² 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.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
---	--

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	Enclosed 05-27-2011
Officer/Employee List	
❖ 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 type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 05-27-2011
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	05-26-2011
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	11-29-2010
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.

❖ 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"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
❖ Labels (full color 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"> • Most-recent draft labeling 	
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	Letter 03-09-2011 Review 03-08-2011
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 03-10-2011 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 04-21-2011 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	02-04-2011
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input type="checkbox"/> Not a (b)(2)
❖ 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	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<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 type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>04-20-2011</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Enclosed

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg July 1, 2010
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg July 7, 2007
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	04-05-2011
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 05-27-2011
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 05-25-2011
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 05-19-2011
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 05-26-2011 total 4
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	05-19-2011
• Clinical review(s) (<i>indicate date for each review</i>)	04-25-2011
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<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 type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Clinical Review Page 11
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• 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>)	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 03-25-2011

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04-13-2011
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04-13-2011
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04-15-2011 concurred
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04-15-2011, Amended 05-18-2011
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04-12-2011 concurred
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04-11-2011
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04-07-2011 concurred
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04-06-2011
❖ 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
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04-18-2011
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04-14-2011 concurred
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04-13-2011, Amended 05-09-2011
❖ Microbiology Reviews <input 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 (DMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ 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</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	CMC Review page 160
<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"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<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)

⁶ 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.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

FARIBA IZADI
05/27/2011

Izadi, Fariba

From: Izadi, Fariba
Sent: Wednesday, May 25, 2011 11:44 AM
To: 'Marc Lesnick'
Cc: 'Candice Durrence'
Subject: final-labeling-text.doc revised 05-24-11.doc

Importance: High

Attachments: final-labeling-text.doc revised 05-24-11.doc

Dr. Lesnick

Here is our proposed draft labeling for NDA 201699.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov



final-labeling-text.d
oc revise...

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

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

/s/

FARIBA IZADI
05/26/2011

Izadi, Fariba

From: Marc Lesnick [mlesnick@optimerpharma.com]
Sent: Wednesday, May 18, 2011 5:15 PM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201,699 Clarification requested

Thank you for the clarification. I'll pass along to our nonclinical folks.

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Wednesday, May 18, 2011 5:13 PM
To: Marc Lesnick
Cc: Candice Durrence
Subject: RE: NDA 201,699 Clarification requested

Dear Dr. Lesnick,

The data used for the dose multiples in the label are shown below. In consultation with our Clinical Pharmacology team, the AUC(0-t) value in healthy humans was 48.3 ± 18.4 ng.h/mL. The respective rat and rabbit AUC(0-t) values are 9300 ng.h/mL and 2600 ng.h/mL respectively. The exposure multiples for rat and rabbit calculate to 194 and 54 respectively.

Reproductive Toxicity with Fidaxomicin by the intravenous route			
Study	Species	Max. Dose/NOAEL	AUC _{0-t} of fidaxomicin at NOAEL (ng.hr/mL)
Fertility	Rat	6.3 mg/kg	4750/5080
Embryo-fetal development	Rat	12.6 mg/kg	9330
Embryo-fetal development	Rabbit Study # 1069-008	7.0 mg/kg	3233
Embryo-fetal development	Rabbit Study # 1069-018	7.0 mg/kg	3170

(/) = (AUC in males/AUC in females)

Best regards,

Fariba Izadi, Pharm.D.
 Regulatory Health Project Manager
 Division of Anti-Infective Products
 Phone: (301) 796-0563
 Fax: (301) 796-9881
 E-mail: Fariba.Izadi@fda.hhs.gov

Please confirm receipt of this e-mail.

From: Marc Lesnick [mailto:mlesnick@optimerpharma.com]
Sent: Tuesday, May 17, 2011 1:16 PM
To: Izadi, Fariba
Cc: Candice Durrence; LeSane, Frances V; Pam Sears
Subject: NDA 201,699 Clarification requested

Fariba-

Our nonclinical team has a short question regarding the data used in the proposed PI. See below:

[Redacted content] (b) (4)

[Redacted content] (b) (4)

Thank you.

Marc

Marc L. Lesnick, Ph.D.
Vice President, Regulatory Affairs
Optimer Pharmaceuticals
101 Hudson Street, Suite 3501
Jersey City, NJ 07302
Ph: 201-333-8819 x166
Fax: 858-909-0737
mlesnick@optimerpharma.com

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/s/

FARIBA IZADI
05/19/2011

Izadi, Fariba

From: Marc Lesnick [mlesnick@optimerpharma.com]
Sent: Monday, May 16, 2011 6:39 PM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201699-(Fidaxomicin) - Response to IR of Fidaxomicin

Thanks! I'll pass along to our biometrics group.

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Monday, May 16, 2011 5:13 PM
To: Marc Lesnick
Cc: Candice Durrence
Subject: NDA 201699-(Fidaxomicin) - Response to IR of Fidaxomicin

Dear Dr. Lesnick,

Below, please find responses to your information requests submitted on May 5th, 2011 for NDA 201699 (Fidaxomicin).

About Disagreements and Missing Sustained Cure

The attached csv file [SustainedCure_Day36CutOff_May2011.csv] shows the sustained response assessment of FDA at study day 36 **for those identified as globally cured by applicant**. The variables in the dataset mean the following

- FDAglobcure is the FDA assessment of sustained response at study day 36. The possible values are 'Y' for success in sustained response, 'N' for failure in sustained response, and 'NA' for missing sustained response.
- Deaths is an indicator variable of death before study day 36 [Values 'Y' for deaths, 'N' for survival]
- SuspectedRecurrence is an indicator variable of suspected recurrence. [Values of 'Y' : taking CDAD concomitant medication during follow up with evidence of diarrhea at follow up, and 'N' otherwise]
- ConcomitantMed is an indicator variable of subject's taking CDAD concomitant medication for any reason, during the treatment period or during follow up.[Values of 'Y' for taking CDAD concomitant medication, and 'N' otherwise]
- EarlyVisit is an indicator variable of recurrence assessment visit occurring before study day 36. [Values of 'Y' for early visit, and 'N' otherwise]

About multiple imputation algorithm

The information below provides some details on coding used for multiple imputation. Please refer to the AC briefing package for references on algorithm used, the R library used, the logistic model, and constructing confidence interval using imputed datasets.

The two lines of code used to generate 25 imputed datasets are the following:

```
library(mi)  
myimp3 = mi(SensAnalysis,n.imp = 25)
```

The derived dataset SensAnalysis (used in above command) has the following variables

```
"globcure" "arm" "studyid" "country" "sex" "race" "sgpatsta" "sgstratu" "sgbsev"  
"sgmetrfl" "ca.trt" "age" "sgubm" "weight" "bmi" "dmcdadsm" "trtdur" "albdays1bin"  
"FolCol"
```

Variable globcure is the FDA derived sustained cure response at study day 36 for all subjects (possible values are failures, successes and missing). Variables "arm" to "trtdur" are the same as in the applicant's datasets. Variables "albdays1bin" and "FolCol" are derived as follows:

- albdays1bin is an indicator variable of whether the albumin level at baseline is < 2.5 or not
- FolCol is a categorical variable derived from the three follow up visits assessing diarrhea after test of cure. There are three categories: (a) Diarrhea at least at one of the follow up visits (b) Diarrhea at none of the follow up and none of the follow up visits is missing (c) Some of the follow up visits are missing but there is no diarrhea in the available visits.

Best Regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov

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/s/

FARIBA IZADI
05/18/2011

Izadi, Fariba

From: Izadi, Fariba
Sent: Monday, May 16, 2011 5:16 PM
To: Izadi, Fariba
Subject: Difucid (NDA 201699) labels and labeling

Dear Dr. Lesnick,

Below, Please find additional comments from our review team on revised labeling submitted on April 29, 2011. General Comment

- The established name continues to lack sufficient prominence. Increase the thickness of the font used for the established name to ensure it has a prominence commensurate with the proprietary name as per 21 CFR 201.10(g)(2).

Container Labels (20 count, 60 count)

- The statement of strength is small in size and inadequately prominent. Increase the size and prominence of the statement of strength.

Blister Labels

- Increase the prominence of the statement of strength (e.g., use a bold font)

Carton Labeling (20 count, 60 count, 100 count blisters)

- The statement of strength is small in size and inadequately prominent. Increase the size and prominence of the statement of strength.
- Add the statement of strength to the top panel.
- Ensure the lot number is present on the carton labeling.

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/s/

FARIBA IZADI
05/18/2011

Izadi, Fariba

From: Izadi, Fariba
Sent: Friday, May 13, 2011 11:09 AM
To: 'Marc Lesnick'
Cc: Candice Durrence
Subject: NDA 201699 (Fidaxomicin)

Attachments: AE Response May 9.doc

Dear Dr. Lesnick,

Attached, please find additional comments from our clinical team regarding Fidaxomicin draft label.



AE Response May
9.doc (59 KB)

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov

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/s/

FARIBA IZADI
05/18/2011

Teleconference Date and Time: May 9, 2011
Application Number: NDA 201699
Product Name: Fidaxomicin Tablet
Indication: Treatment of C. difficile and prevention of recurrences.
Sponsor/Applicant Name: Optimer

Division of Anti-Infective Products (DAIP) Attendees:

John Farley, MD	Division Director
Katherine Laessig, MD	Deputy Director
Sumati Nambiar, MD, MPH	Deputy Director, Safety
John Alexander, MD, MPH.	Medical Team Leader
Dimitri Iarokov, MD.	Medical Officer
Thamban Valappil, PhD	Statistics Team Leader
Rima Izem, PhD	Statistics Reviewer
Scott Komo, PhD	Statistics Reviewer
Wendelyn Schmidt, PhD	Pharmacology/Toxicology Team Leader
Frederick Marsik, PhD	Clinical Microbiology Team Leader
Shanmugam, Balajee, PhD	Product Quality Reviewer
Aryun Kim, Pharm. D	Clinical Pharmacology Reviewer
Kimberly Bergman, Pharm.D	Clinical Pharmacology Reviewer
Fariba Izadi, Pharm.D.	Regulatory Health Project Manager

Optimer Attendees:

Sherwood Gorbach, MD	Chief Scientific Officer
Kasia Petchel, MD	Senior Vice President, Pharmacovigilance
Nancy Ruiz, MD	Senior Vice President, R&D
Pam Sears, PhD	Executive Director, Biology & Pre-clinical Science
Sylva Collins, PhD	VP Biometrics
Yin Kean	Manager, Biometrics
Marc Lesnick, PhD	Vice President, Regulatory Affairs
Candice Durrence	Manager, Regulatory Affairs
Michael Hui, PhD	VP Quality

Background:

After receiving labeling from the Division, Optimer submitted their counter proposal for the label and supporting documents for discussion at the teleconference.

Discussion:

The teleconference discussion consisted of Optimer's counter proposed label.

Action Items:

Optimer will submit revised label as discussed during the teleconference.

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/s/

FARIBA IZADI
05/24/2011

Izadi, Fariba

From: Izadi, Fariba
Sent: Friday, April 29, 2011 2:48 PM
To: 'Marc Lesnick'
Cc: Candice Durrence
Subject: NDA 201699 (Fidaxomicin Tablet) Proposed draft labeling

Attachments: Division Proposed Labeling April 2011.doc

Dear Dr. Lesnick,

Attached, please find the proposed draft labeling for NDA 201699 (Fidaxomicin Tablet). This is your submitted labeling from January 06, 2011 with our changes shown in red.

Please confirm receipt of this e-mail and inform us if you find this label acceptable.



Division Proposed
Labeling Apr...

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov

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

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/s/

FARIBA IZADI
05/02/2011

Izadi, Fariba

From: Marc Lesnick [mlesnick@optimerpharma.com]
Sent: Thursday, April 21, 2011 10:02 AM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201699-(Fidaxomicin) carton and container labeling- requests and recommendations.

Fariba-

We acknowledge receipt, but we have an immediate question. We were asked, and agreed in the letter from last week, to update the carton and container labeling by this Friday with the new established name, and are in the process of finalizing that submission. Should we complete that submission today and then send in new pieces with the changes suggested below, or delay that submission and update the pieces and submit late next week with all of the changes suggested below and the update to the established name?

Please let us know how you would like us to proceed.

Regards,

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Thursday, April 21, 2011 6:58 AM
To: Marc Lesnick
Cc: Candice Durrence
Subject: NDA 201699-(Fidaxomicin) carton and container labeling- requests and recommendations.

Dear Dr. Lesnick,

Below, please find requests and recommendations from our review team regarding the Carton and Container Labeling for NDA 201699 (Fidaxomicin).

A. General Comments for all Container Labels and Carton Labeling

1. [REDACTED] (b) (4) Place the statement of strength on the principal display panel immediately below the established name.
2. [REDACTED] (b) (4). Relocate the net quantity statement to a less prominent area on the principal display panel such as the top portion of the panel to the left or right of the NDC number.
3. On all the labels and labeling revise the established name to read “(fidaxomicin) tablets”.

B. Container Labels (20-count bottle and 60-count bottle)

1. The established name is difficult to see due to the font. Increase the thickness of the established name in order to improve visibility. Additionally, ensure the established name (which includes the active ingredient and dosage form statements) is printed in letters that are at least ½ as large as the letters comprising the proprietary name and that the established name has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features [21 CFR 201.10(g)(2)].

2. Add a usual dosage statement to the side panel (e.g., “See package insert for dosage information”) as per 21CFR 201.55.
3. The company logo is prominent on the container labels. Decrease its size and prominence.
4. Delete the statements (b) (4) and (b) (4) These statements are unnecessary and add clutter to the labels.

C. Blister Labels

1. See comment B(1), above.
2. The statement of strength is difficult to see. Increase the size and prominence of the statement of strength.

D. Carton Labeling

1. Delete the statement (b) (4) from the front and back panels. The statement is not required on oral products and it adds clutter to the carton labeling.
2. 20-count and 60-count bottles—Relocate the statement “Each tablet contains...” to the side panel and delete the statement (b) (4) statement creates clutter and is not necessary because the net quantity statement and “Each tablet contains...” statements are on the carton and provide the same information.
3. 100-count blister carton—The statement “Each tablet contains...” is located on the front, back, and one of the side panels and will add clutter to the front and back panels once the statement of strength is added. Therefore, delete the “Each tablet contains...” statements from the front and back panels.
4. 100-count blister carton—If the packaging is not child-resistant, state this on one of the side panels of the blister carton labeling.

Please confirm receipt of this e-mail.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov

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/s/

FARIBA IZADI
04/25/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 14, 2011

TIME: 11:30 AM EST

SUBJECT: T-CON for Change to the dosage form name on the carton and container label.

APPLICATION/DRUG: 201-699

ATTENDEES:

FDA

Rapti Madurawe, Ph.D., Branch Chief
Balajee Shanmugan, Ph.D., CMC Reviewer
Cathy Tran-Zwanetz, Regulatory Project Manager

APPLICANT- OPTIMER PHARMACEUTICALS

Marc L. Lesnick, Ph.D., Vice President, Regulatory Affairs
Candice Durrence, Manager, Regulatory Affairs
Rachel Wilson, Senior Manager, Regulatory Affairs
Jessica Warren, Senior Regulatory Associate

Applicant provided the call in phone number. FDA requested the t-con to discuss the placement of the dosage form name, tablet, in the proposed label name drug product name, (b) (4)
(b) (4) FDA explained that the current placement of the dosage form name within the parenthesis is acceptable, (b) (4)
(b) (4)

The applicant will send confirmation of their agreement by email on April 14, 2011 and will provide new label mock ups at a later date. The applicant will also formally submit this same letter to EDR on April 15, 2011.

Attached is the email from the applicant.

Tran-Zwanetz, Catherine

From: Marc Lesnick [mlesnick@optimerpharma.com]
Sent: Thursday, April 14, 2011 1:04 PM
To: Tran-Zwanetz, Catherine; Cuff, Althea
Cc: Izadi, Fariba; Candice Durrence
Subject: NDA 201,699 Established name for Difucid
Attachments: NDA 201699 cover-letter.docx

All,

Per the teleconference from earlier today, Optimer agrees to update the NDA to amend the established name from [REDACTED] ^{(b) (4)} to "(fidaxomicin) tablets". The attached letter will be submitted officially to the NDA tomorrow, and the updated draft labeling reflecting this change will be submitted the following week.

Regards,

Marc

Marc L. Lesnick, Ph.D.

Vice President, Regulatory Affairs
Optimer Pharmaceuticals
10110 Sorrento Valley Road, Suite C
San Diego, CA 92121
Ph: 858-458-5543
Fax: 858-909-0737
mlesnick@optimerpharma.com

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April 14, 2011

Wiley Chambers, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective & Ophthalmology Products, HFD-520
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attn: Fariba Izadi, Project Manager

RE: **NDA 201,699**
Dificid™ (fidaxomicin) tablets
Serial No. 0012
AMENDMENT TO A PENDING APPLICATION
(REVISED ESTABLISHED NAME)

Dear Dr. Chambers,

As discussed by teleconference on April 14, 2011, Optimer agrees to change the established name to: (fidaxomicin) tablets.

We plan to submit revised draft labeling and mock-ups by Friday, April 22.

If you have any questions regarding this submission, please do not hesitate to contact me.

Sincerely,

Marc Lesnick, Ph.D.
Vice President, Regulatory Affairs
Phone: (858) 909-0736 ext. 166
Fax: (858) 430-5966
Email: mlesnick@optimerpharma.com

cc: Althea Cuff and Fariba Izadi by email

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/s/

CATHERINE A TRAN-ZWANETZ
04/14/2011



NDA 201,699

INFORMATION REQUEST

Optimer Pharmaceuticals, INC.
Attention: Marc Lesnick, Ph.D.
Director, Regulatory Affairs
10110 Sorrento Valley Road, Suite C
San Diego, CA 92121

Dear Dr. Lesnick:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dificid (Fidaxomicin) Tablet, 200 mg

We have reviewed the referenced material and have the following comments and requests for information. We request a prompt written response by April 11, 2011.

1. In response to the Information Request of March 11, 2011, you indicate removing an (b) (4) [redacted] While information submitted in the response demonstrates producing (b) (4) [redacted] we recommend that you reinstate the (b) (4) [redacted] and the test included in the drug substance specification which you had agreed to include.
2. Please include a test for (b) (4) [redacted] in the drug substance specification and as post-marketing commitment, you should submit to the Agency the method validation used for testing (b) (4) [redacted]. This specification test may be implemented by submitting a supplement (CBE-0) within 6-months of post-approval of the application.

If you have any questions, call Althea Cuff, Regulatory Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Rapti Madurawe, Ph.D.
CMC Lead Reviewer
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURAWA
04/08/2011



NDA 201,699

INFORMATION REQUEST

Optimer Pharmaceuticals, INC.
Attention: Marc Lesnick, Ph.D.
Director, Regulatory Affairs
10110 Sorrento Valley Road, Suite C
San Diego, CA 92121

Dear Dr. Lesnick:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Difucid (Fidaxomicin) Tablet, 200 mg

We have reviewed the referenced material and have the following comments and requests for information. We request a prompt written response by March 25, 2011.

1. The proposed drug substance and drug product post-approval stability protocols do not include a test for (b) (4). We believe (b) (4) is a critical quality attribute and should be part of the post-approval stability testing protocol. In addition to (b) (4), (b) (4) (the later two tests can be performed at the time of initiating stability studies) should be included in the drug substance protocol. Please include these tests and submit the revised protocol.
2. While drug product stability studies have monitored (b) (4), the drug product specification does not include a test for this quality attribute. Please propose a test and acceptance limit for (b) (4) in the drug product specification.
3. Please clarify the purpose of using (b) (4) for storing the drug product specifically addressing reasons for using (b) (4) and the proposal to (b) (4). Furthermore, indicate how long you propose to store the (b) (4) and provide information on the compatibility of the (b) (4) to the drug product. We will also require a DMF reference and letter of authorization for the (b) (4). We also require stability data for the drug product stored in the (b) (4).

If you have any questions, call Althea Cuff, Regulatory Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Rapti Madurawe, Ph.D.
CMC Lead Reviewer
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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RAPTI D MADURAWA
03/22/2011



NDA 201,699

INFORMATION REQUEST

Optimer Pharmaceuticals, INC.
Attention: Marc Lesnick, Ph.D.
Director, Regulatory Affairs
10110 Sorrento Valley Road, Suite C
San Diego, CA 92121

Dear Dr. Lesnick:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for for Difucid (Fidaxomicin) Tablet, 200 mg.

We also refer to your November 29, 2010, submission.

We have reviewed the referenced material and have the following comments and requests for information. We request a prompt written response by March 25, 2011.

1. For drug substance, based on available stability data, you have proposed an expiry date of (b) (4)-months. In addition a retest interval of (b) (4)-months is also proposed upon reaching the expiry date. Please clarify the proposed retest and the intent of this retest.
2. Lipiarmycin is controlled at NMT (b) (4) in the drug substance specification. Please lower the acceptance limit based on batch analysis and stability data.
3. Please provide the batch number of the drug substance used in the method validation study
4. Section 3.2.S.2.4 mentions (b) (4). However, your response dated March 08, 2011 proposes to (b) (4)
5. Please submit any validation data that may be available for the test (b) (4) to establish the (b) (4) of fidaxomicin. Also, please indicate if the test can discriminate (b) (4) if a mixture of (b) (4) is present.
6. You had indicated (IR response of March 01, 2011) that IR as a test for identity is being evaluated. When do you anticipate completing the validation study?

7. In response to our IR, you have included test for (b) (4) with an acceptance limit of (b) (4) in the drug substance specification. The proposed upper limit is acceptable but given the criticality of this quality attribute, please propose a lower limit as well.
8. Please comment on what prompted initiation of Design of Experiments study after the manufacture of the registration batches. Clearly indicate what, if any change(s) will be made to the commercial manufacturing process compared to the registration stability and clinical batches. The changes can be indicated, preferably by providing a comparative flow chart.
9. In the drug product specification, please lower the acceptance limit for total impurities of NMT (b) (4) based on batch analysis and stability data.

If you have any questions, call Althea Cuff, Regulatory Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Stephen Miller, Ph.D.
Acting 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/

STEPHEN P MILLER
03/11/2011



NDA 201699

**PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE**

Optimer Pharmaceuticals, Inc.
10110 Sorrento Valley Road, Suite C
San Diego, California 92121

ATTENTION: Marc Lesnick, Ph.D.
Director, Regulatory Affairs

Dear Dr. Lesnick:

Please refer to your New Drug Application (NDA) dated November 29, 2010, received November 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fidaxomicin Tablets, 200 mg.

We also refer to your December 13, 2010, correspondence, received December 14, 2010, requesting review of your proposed proprietary name, Difucid. We have completed our review of the proposed proprietary name, Difucid and have concluded that it is acceptable.

The proposed proprietary name, Difucid, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your December 13, 2010, 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 Brantley Dorch, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Fariba Izadi at (301) 796-0563.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
03/09/2011

Izadi, Fariba

From: Izadi, Fariba
Sent: Thursday, March 03, 2011 1:23 PM
To: 'Marc Lesnick'
Cc: 'Candice Durrence'
Subject: NDA 201699 (Fidaxomicin) Information Request

Dear Dr Lesnick,

We have the following information request from our Clinical team regarding IND 201699 (Fidaxomicin):

Please clarify the total number of subjects exposed to any dose of fidaxomicin. According to Table 2.3-1 in the integrated summary of safety, page 43, there were 675 subjects who received ≥ 1 dose of fidaxomicin. As per our calculation the number is 676. We arrived to this number by adding individual subjects who received at least one dose of fidaxomicin in Phase 1 (n=64), Phase 2 (n=48), and Phase 3 (n=564) studies.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

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/s/

FARIBA IZADI
03/04/2011

Izadi, Fariba

From: Marc Lesnick [mlesnick@optimerpharma.com]
Sent: Wednesday, March 02, 2011 1:58 PM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin Tablet) Information request

Fariba,

I confirm we've received your request.

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Wednesday, March 02, 2011 10:54 AM
To: Marc Lesnick
Cc: Candice Durrence
Subject: NDA 201699 (Fidaxomicin Tablet) Information request

Dear Dr. Lesnick,

We are reviewing your application for NDA 201699 (Fidaxomicin) and have the following information request from our Clinical Microbiology team:

In the fidaxomicin treatment group, it is noted that there was a *C. difficile* isolate from a patient who had recurring disease where *C. difficile* isolated during the recurrence had a higher fidaxomicin MIC than the baseline isolate. Were there any instances in the vancomycin population with recurring disease where the *C. difficile* isolate had a higher vancomycin MIC than the baseline isolate?

Best regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

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/s/

FARIBA IZADI
03/04/2011

Izadi, Fariba

From: Marc Lesnick [mlesnick@optimerpharma.com]
Sent: Monday, February 28, 2011 2:22 PM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin) Information request

Fariba-

We acknowledge receipt of the request, and will let you know a proposed response date after we speak with our team.

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Monday, February 28, 2011 8:11 AM
To: Marc Lesnick
Cc: Candice Durrence
Subject: NDA 201699 (Fidaxomicin) Information request

Dear Dr. Lesnick,

We are reviewing your application for NDA 201699 (Fidaxomicin) and have the following information request from our Clinical Pharmacology team.

Please provide missing bioanalytical study reports (not method validation reports) for plasma and fecal samples from Study OPT-80 1A-SD.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

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3/4/2011

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/s/

FARIBA IZADI
03/04/2011



NDA 201,699

INFORMATION REQUEST

Optimer Pharmaceuticals, INC.
Attention: Marc Lesnick, Ph.D.
Director, Regulatory Affairs
10110 Sorrento Valley Road, Suite C
San Diego, CA 92121

Dear Dr. Lesnick:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for for Difucid (Fidaxomicin) Tablet, 200 mg.

We also refer to your November 29, 2010, submission.

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.

(b) (4)



You have not designated the starting materials for the manufacture of the drug substance. For fermentation derived compounds, it has been the policy of the Agency to designate the cell banks and media used for (b) (4)

If you have any questions, call Althea Cuff, Regulatory Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Stephen Miller, Ph.D.
Acting 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/

STEPHEN P MILLER
02/10/2011

Izadi, Fariba

From: Marc Lesnick [mlesnick@optimerpharma.com]
Sent: Monday, February 07, 2011 4:41 PM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin)

Fariba-

Request acknowledged. When we have a better idea of when we can respond, I'll let you know.

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Monday, February 07, 2011 1:26 PM
To: Marc Lesnick
Cc: Candice Durrence
Subject: NDA 201699 (Fidaxomicin)

Dear Dr. Lesnick,

We are reviewing your NDA 201699 for Fidaxomicin and have the following information requests from our Clinical Pharmacology team.

Please provide:

- Bioanalytical report supporting extended stability of fecal samples at -70 °C for fidaxomicin and OP-1118.
- Listing of individual sample collection dates and corresponding analytical run dates for all pharmacokinetic fecal samples from the Phase 2A study and Phase 3 studies (101.1.C.003, 101.1.C.004).

Currently, stability of fidaxomicin and OP-1118 in fecal samples has been established for 93 days and 31 days, respectively, at -70 °C (Report MC04249). Please be advised that without adequate frozen stability data, labeling statements referring to pharmacokinetic data for fidaxomicin and OP-1118 in feces will be limited to descriptive terms.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

Reference ID: 2902515

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/s/

FARIBA IZADI
02/08/2011

Izadi, Fariba

From: Izadi, Fariba
Sent: Friday, February 04, 2011 5:14 PM
To: 'Marc Lesnick'
Cc: Candice Durrence
Subject: NDA 201699 (Fidaxomicin) Additional Comments.

Attachments: AdditionalCommenttoIR3.doc



AdditionalCommenttoIR3.doc (28...

Dear Dr. Lesnick,

Attached, please find additional comments from our Statistics team regarding your NDA 201699 (Fidaxomicin)

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

Please confirm receipt of this e-mail.

NDA 201699 (Fidaxomicin)

What to submit to FDA regarding the sensitivity analyses:

Please submit the following:

- All complete imputed datasets for each sensitivity analysis. For each imputed variable, include a flag variable in the dataset indicating whether the value was imputed.
- Code performing the imputation for each sensitivity analysis
- Summary of results from the sensitivity analyses (see next section)

What to describe in the summary of results from the sensitivity analyses:

In the summary of results from the sensitivity analyses, do the following (see Box 3 of Sterne et al 2009):

- Report the number of missing values for each variable of interest, or the number of cases with complete data for each important component of the analysis. Give reasons for missing values if possible.
- Describe the multiple imputation analyses as follows:
 - o Provide details of the imputation modeling: Report details of the software used and of key settings for the imputation modeling. It is recommended that at least 20 imputed datasets be created
 - o List the variables included in the imputation procedure. Provide rationale if certain variables were dropped or added to the model. How were non-normally distributed and binary/categorical variables dealt with?
 - o Compare observed and imputed values through assessments of goodness of fit.
 - o Discuss whether the variables included in the imputation model make the missing at random assumption plausible
- Provide exploratory figures checking for convergence of MCMC algorithm or Gibbs sampler in the imputation step.
- Compare the results of the different sensitivity analyses to each other and comment on any discrepancy in their conclusions.

References:

Horton, Nicholas J. and Ken P. Kleinman. (2007) Much Ado About Nothing: A Comparison of Missing Data Methods and Software to Fit Incomplete Data Regression Models. *The American Statistician* 61(1, February):79–90.

Sterne JA, White IR, Carlin JB, et al Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338. b2393. (doi: 10.1136/bmj.b2393).

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/s/

FARIBA IZADI
02/08/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 201699 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Dificid Established/Proper Name: Fidaxomicin Dosage Form: Tablet Strengths: 200 mg		
Applicant: Optimer Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: 11-29-10 Date of Receipt: 11-30-10 Date clock started after UN: 11-30-10		
PDUFA Goal Date: -5-30-2011		Action Goal Date (if different): 05-30-2011
Filing Date: January, 29, 2011		Date of Filing Meeting: December 20, 2011
Chemical Classification: (1,2,3 etc.) (original NDAs only) NME-1		
Proposed indication(s)/Proposed change(s): Treatment of <i>Clostridium difficile</i> infection and prevention of recurrences.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 064435				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	x			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	x			
Are all classification properties [e.g., orphan drug, OTC, 505(b)(2)] entered into tracking system? <i>If no, ask the document room staff to make the appropriate entries.</i>	x			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		x		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			

<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				x	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].				x	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?				x	
<p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm				x	
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			x		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?				x	
<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p>					

Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA</i> s/ <i>NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		x		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA</i> s <i>only</i>)?		x		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	x			
Index: Does the submission contain an accurate comprehensive index?	x			
Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i> s/ <i>NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLA</i> s/ <i>BLA efficacy supplements</i>) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)	x			
If no , explain.				

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

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

<i>section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			x	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			x	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	x			
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	x			
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	x			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <i>If no, request in 74-day letter</i>	x			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		x		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	x			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>		x		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	x			
Is the PI submitted in PLR format? ⁴	x			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			x	

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	x			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			x	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	x			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		x		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): July 13, 2005 <i>If yes, distribute minutes before filing meeting</i>	x			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): July 1, 2010 <i>If yes, distribute minutes before filing meeting</i>	x			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		x		

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 20, 2010

BLA/NDA/Supp #: 201699

PROPRIETARY NAME: Difucid

ESTABLISHED/PROPER NAME: Fidaxomicin

DOSAGE FORM/STRENGTH: 200 mg Tablet

APPLICANT: Optimer

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

BACKGROUND: Treatment of *Clostridium Difficile* and prevention of recurrences.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Fariba Izadi	Y
	CPMS/TL:	Frances Lesane	N
Cross-Discipline Team Leader (CDTL)	John Alexander		Y
Clinical	Reviewer:	Dmitri Iarikov	Y
	TL:	John Alexander	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial products)	Reviewer:	Fred Marsik	N
	TL:	Fred Marsik	N

Clinical Pharmacology	Reviewer:	Aryun Kim	Y
	TL:	Kim Bergman	Y
Biostatistics	Reviewer:	Rima Izem	Y
	TL:	Thamban Valappil	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wendy Schmidt	Y
	TL:	Wendy Schmidt	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Bala Shanmugam	Y
	TL:	Rapti Madurawe	N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Brantley Dorch, Loretta Holmes	Y
	TL:	Tselaine Jones-Smith	
OSE/DRISK (REMS)	Reviewer:	Mary Dempsey	Y
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Kassa Ayalew	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers, Quality Biopharmaceutics	Elsbeth Chikhale		Y
Other attendees: Lori Gorski, John Farley, Katie Laessig, Wiley Chambers, Ed Cox, Steve Miller, Susmita Samanta, Carmen Debellas			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date if known: April 5, 2011 <input type="checkbox"/> NO <input type="checkbox"/> To be determined

<p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	Reason:
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Ed Cox	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review and chemical classifications and other properties [e.g., orphan drug, OTC, 505(b)(2)], are entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)

<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

FARIBA IZADI
02/04/2011

Izadi, Fariba

From: Candice Durrence [cdurrence@optimerpharma.com]
Sent: Thursday, February 03, 2011 5:18 PM
To: Izadi, Fariba
Cc: Marc Lesnick
Subject: RE: NDA 201699 (Fidaxomicin) Information request.

Hi Fariba,
We confirm receipt of this email.

Thanks,

Candice Durrence

Regulatory Affairs Manager
Optimer Pharmaceuticals, Inc.
10110 Sorrento Valley Road, Suite C
San Diego, CA 92121
(858) 458-5561
www.optimerpharma.com

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Thursday, February 03, 2011 1:44 PM
To: Marc Lesnick
Cc: Candice Durrence
Subject: NDA 201699 (Fidaxomicin) Information request.

Dear Dr. Lesnick,

We are reviewing your submission for NDA 201699 (Fidaxomicin) and have the following information request.

Please submit any additional information you can obtain for subject 003-020002. We are interested in obtaining more information on the adverse event "GI bleed" and the circumstances of the patient's death. If you can, please provide a hospital discharge summary, emergency ward records for the day of death, or any other medical information you can obtain on these events.

Best Regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

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Reference ID: 2901049

2/4/2011

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FARIBA IZADI
02/04/2011

Izadi, Fariba

From: Candice Durrence [cdurrence@optimerpharma.com]
Sent: Thursday, February 03, 2011 1:41 PM
To: Izadi, Fariba
Cc: Marc Lesnick
Subject: RE: NDA 201699 (Fidaxomicin Tablet) Information request.

Hello Fariba,
The CRFs requested below, and those from the 1/21 information request, will be submitted through the ESG on Friday, February 11.

Thanks,

Candice Durrence
Regulatory Affairs Manager
Optimer Pharmaceuticals, Inc.
10110 Sorrento Valley Road, Suite C
San Diego, CA 92121
(858) 458-5561
www.optimerpharma.com

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Wednesday, February 02, 2011 1:50 PM
To: Marc Lesnick
Cc: Candice Durrence
Subject: NDA 201699 (Fidaxomicin Tablet) Information request.

Dear Dr Lesnick,

We are reviewing your submission for NDA 201699 (Fidaxomicin) and have the following information requests.

Please provide the following case report forms and case narratives (if available).

003-009049
003-011027
003-011056
003-058004
004-057028
004-057030
004-184001
004-189004
004-189008
004-189023
004-201017

Please let me know how long it will take to submit the case report forms.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881

Reference ID: 2900752

2/3/2011

E-mail: Fariba.Izadi@FDA.HHS.GOV

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Reference ID: 2900752

2/3/2011

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/s/

FARIBA IZADI
02/03/2011

Teleconference Date and Time: February 1, 2011
Application Number: NDA 201699
Product Name: Fidaxomicin Tablet
Indication: Treatment of C. difficile and prevention of recurrences.
Sponsor/Applicant Name: Optimer

Division of Anti-Infective and Ophthalmology Products (DAIOP) Attendees:

John Alexander, MD, MPH. Medical Team Leader
Dimitri Iarokov, MD. Medical Officer
Thamban Valappil, PhD Statistics Team Leader
Rima Izem, PhD Statistics Reviewer
Scott Komo, PhD Statistics Reviewer
Fariba Izadi, Pharm.D. Regulatory Health Project Manager

Optimer Attendees:

Marc Lesnick, PhD Director, Regulatory Affairs
Candice Durrence Manager, Regulatory Affairs
Sherwood Gorbach, MD Chief Medical Officer
Pamela Sears, PhD Executive Director, Biology and Pre-clinical Science
Tavette Neskoriik Manager, Clinical Operations
James Robinson, MS Associate Director, Biometrics

Background

A teleconference was held between DAIOP and Optimer to better clarify clinical and statistical information requests and Optimer's response to information requests.

Discussion

- 1- Clarification of answer (Sent by Optimer on 01-18-11) to Question A.1. There were several sources to data set XU (number of unformed stools per day) including, but not limited to, the take home worksheet. Correct?

Optimer's response: Yes

Was the take home worksheet information used for datasets EFPLUS and EFBM?

Optimer's response: The take home sheet was used in conjunction with the medical records. The CRF was used for the daily assessment of the unformed BM during the treatment period.

- 2 - Clarification of answer to Question A.4. You list two subset with discrepancies between datasets:

- a- Subset of subjects with rectal collection device volume (47 observations in 003 and 39 observations in 004)
- b- Subset of subjects with missing unformed bowel movements (112 observations in 003 and 0 observations in 004).

Are these the total numbers of discrepancies over the 10-day period?

Optimer's response: Yes.

Can you identify for a) the cause of the discrepancy (is it conversion from volume to number of unformed stools?)

Optimer's response: It is because of the conversion from rectal device to the conversion of bowel movement.

Do you mean in b) that some data that is set to missing in dataset XU has a value in dataset FU that is an imputed value (set to 3 or 4)?

Optimer's response: Yes

or do you mean that some of the data that is set to missing in dataset EFPLUS and EFBM has a value in XU?

Optimer's response: We will provide you with datasets identifying where discrepancies occur.

Which data set was used for the modified definition of cure end-point?

Optimer's response: Data set EFPLUS was used for reported results of study 003, dataset EF was used for reported results of study 004, dataset XU was used in integrated summary of efficacy.

3- Clarification to request B.1, B.2, B.3. In the last part of our request in B, we meant to ask descriptive information on extent of missing values in the dataset XU (number of daily unformed bowel movement), assuming that this is the dataset used to derived the modified cure endpoint. Could you please provide us with that?

Optimer's response: We will provide you will all descriptive information.

It is most important to have all the data that is collected two days prior to clinical cure assessment since those are the values used for deriving the modified definition of cure.

4- About Request C-2. We understand that one of the variables is missing, could you then produce a two way table with the remaining two variables instead of a three way table?

Optimer's response: We can provide a two way table.

FDA: Provide the list of subjects and assessment of the missing values.

Optimer asked for further clarification on Division's information request (Question # 3 sent on 01-21-11) See below:

Question 3: We found that some subjects in the MITT population were identified as non-recurrent although they took one of the following medications in the follow up period: Metronidazole, Flagyl, Vancomycin - oral, Vancocin – oral, Rifaximin, Xifaxan, Nitazoxanide, Alinia.

Please provide the CRFs (if they have not already been submitted to the NDA) of all subjects satisfying the above conditions. We are specifically interested in reasons why medication was administered: suspected recurrence of CDAD, prevention of recurrence of CDAD or other reasons.

The Division confirmed that all the CRFs should be provided, but there is no need for the Optimer to re-submit CRFs that have already been submitted to the NDA for other reasons.

In response to Optimer's question regarding the sensitivity analyses, (sent on 01-27-11) the Division confirmed that these analyses are planned on the global cure rate secondary endpoint in the MITT population in studies 003 and 004.

In regards to planned multiple imputation method in sensitivity analyses 3 and 4 (sent on 01-27-11), the Division confirmed that some variables may be dropped from the model if model does not converge due to colinearity between covariates.

The Division stated that Optimer can reduce the model with proper justification.

In response to Optimer's question, the Division clarified that the Sponsor can use any software package as long as they provide the Division with the information.

The Division clarified that there are no specific requirements regarding what type of software to use.

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FARIBA IZADI
02/08/2011

Izadi, Fariba

From: Izadi, Fariba
Sent: Thursday, January 27, 2011 2:05 PM
To: 'Marc Lesnick'
Cc: Candice Durrence
Subject: NDA 201699 (Fidaxomicin) Information request.

Attachments: IR Sensitivity Analyses Final Jan 27.doc



IR Sensitivity
Analyses Final ...

Dear Dr. Lesnick,

Attached, Please find the information request from our review team for NDA 201699 (Fidaxomicin).

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

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NDA 201699 (Fidaxomicin)

Information Request- Sensitivity analyses

Perform the following sensitivity analyses and send your results. These sensitivity analyses are related to the new sets of data we requested in the information request we sent you on 01/21/2011.

These analyses are planned on the global cure rate secondary endpoint and mitt population in studies 003 and 004. We first define some terms later used in the description of different subsets in each analysis, and then we describe each analysis in details.

Definition of terms

- Protocol defined recurrence assessment visit time period is study day 36 or 25 days after last day of treatment to study day 40.

- Unobserved values at recurrence assessment visit refer to recurrence outcomes of subjects who did not attend the recurrence assessment visit at the protocol defined recurrence assessment visit time period. These include outcome of subjects who died prior to recurrence assessment visit time period.

- Follow up period: Time after clinical cure assessment visit and before study day 36.

Sensitivity analysis 1:

Impute as recurrence the two following subsets of outcomes:

- 1) unobserved values at recurrence assessment visit, and
- 2) outcomes of subjects using disallowed medication during follow up period.

Derive the 95% confidence interval for the difference in rate using the method recommended by Agresti and Caffo (2000) as in protocol defined primary analysis.

Sensitivity analysis 2:

In Fidaxomicin arm, impute as recurrence the two following subsets of outcomes:

- 1) unobserved values at recurrence assessment visit and
- 2) outcomes of subjects using disallowed medication during follow up period.

In Vancomycin arm, leave outcomes as assessed by applicant in primary analysis.

Derive the 95% confidence interval for the difference in rate using the Agresti-Coull method as in protocol defined primary analysis.

Sensitivity analysis 3:

1) Impute as recurrence the two following subsets of outcomes:

- a) outcome of subjects using disallowed medication during follow up period for suspected recurrence of CDAD¹, and
 - b) outcomes of subjects who died prior to protocol defined recurrence assessment visit time.
- 2) Impute using multiple imputation methods the following two difference subsets of outcomes:
- a) outcome of subjects using disallowed medication during follow up period for unknown reason or other reasons than a suspected recurrence of CDAD, and

¹ Reason for prescribing disallowed medication is determined by clinical reviewer on a case by case basis using information from CRFs.

b) unobserved values for subjects alive at protocol defined recurrence assessment visit
Derive the 95% confidence interval for the difference in rate using multiple imputation method.

Sensitivity analysis 4:

- 1) Impute as recurrence the two following subsets of outcomes:
 - a) outcomes of subjects using disallowed medication during follow up period for a suspected recurrence of CDAD
 - b) outcomes of subjects who died prior to protocol defined recurrence assessment visit time for possibly related reason to CDIF² infection.
- 2) Impute using multiple imputation methods the following three subsets of outcomes:
 - a) outcomes of subjects using disallowed medication during follow up period for unknown reason or other reasons than a suspected recurrence of CDAD, and
 - b) outcomes of subjects who died prior to protocol defined recurrence assessment visit time for unrelated reason to CDIF infection, and
 - c) unobserved values for subjects alive at follow up period.

Derive the 95% confidence interval for the difference in rate using multiple imputation method.

Planned multiple imputation method in Sensitivity Analysis 3 and 4:

The multiple imputation method includes two steps, the imputation step and the analysis step using imputed datasets.

In the imputation step, outcomes in identified subsets are imputed using a logistic model predicting the probability of global cure with covariates of baseline characteristics, follow-up information for diarrhea, concomitant medication use, and timing variables such as length of treatment. More specifically, we plan to include the following variables in the logistic model: treatment assignment, study, study center, sex, race, age, weight, height, BMI, subject status, prior CDIF episodes, daily bowel movement at baseline or baseline disease severity, Diarrhea alone or other symptoms, prior use of CDI antibiotics, metronidazole failure, number of study days in treatment phase, concomitant systemic antibiotic medication during treatment phase, diarrhea at follow up visits after cure, serum albumin concentration (below 2.5 dl or not).

Note that:

- Since some follow up information for diarrhea is missing, these will be imputed as well. Imputation will use past observed follow up information and all other covariates
- A transformation (e.g. log or square root transformation) of some variables may be used to provide better fit or to insure convergence of fitting algorithm.
- Interaction between covariates may be included if they provide better fit without hurting the convergence.
- Some variables may be dropped from the model if model does not converge due to colinearity between covariates

20 datasets are generated in the imputation step

In the analysis step, estimates and confidence intervals are derived for each of the twenty datasets using the method recommended by Agresti and Caffo (2000) as in protocol defined primary analysis.

Finally, estimates and confidence intervals are combined into a summary inference about the difference of proportion using method described in Rubin and Schenker 1986 and Rubin 1987

² Whether death is related to CDIF is determined by clinical reviewer on a case by case basis using information from CRFs.

References:

Agresti A. Caffo BA. Simple and Effective confidence intervals for proportions and difference of proportions result from adding two successes and two failures. *The American Statistician*, 2000; 54:280-288.

Rubin, 1987 D.B. Rubin, *Multiple Imputation for Nonresponse in Surveys*, Wiley, New York (1987).

Rubin and Schenker, 1986 D.B. Rubin and N. Schenker, Multiple imputation for interval estimation from simple random samples with ignorable nonresponse, *J. Amer. Statist. Assoc.* **81** (1986), pp. 366–374.

Izadi, Fariba

From: Marc Lesnick [mlesnick@optimerpharma.com]
Sent: Thursday, January 27, 2011 2:05 PM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin) Information request.

Fariba-

We again acknowledge receipt.

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Thursday, January 27, 2011 11:05 AM
To: Marc Lesnick
Cc: Candice Durrence
Subject: NDA 201699 (Fidaxomicin) Information request.

Dear Dr. Lesnick,

Attached, Please find the information request from our review team for NDA 201699 (Fidaxomicin).

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

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FARIBA IZADI
01/28/2011

Izadi, Fariba

From: Marc Lesnick [mlesnick@optimerpharma.com]
Sent: Thursday, January 27, 2011 1:30 PM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin)

Fariba-

Receipt of request acknowledged.

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Thursday, January 27, 2011 10:31 AM
To: Marc Lesnick
Cc: Candice Durrence
Subject: NDA 201699 (Fidaxomicin)

Dear Dr. Lesnick,

We are reviewing your submission for NDA 201699 (Fidaxomicin) and have the following information request:

Please provide a **narrative** for subject 003-077-003. There is a case report form for this subject, but a narrative describing the events around the withdrawal due to an adverse event should be provided as well.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

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FARIBA IZADI
01/28/2011

From: Izadi, Fariba
Sent: Friday, January 21, 2011 5:07 PM
To: 'Marc Lesnick'
Cc: Candice Durrence
Subject: NDA 201699 (Fidaxomicin Tablet) -Information Request

Attachments: Information Request Jan 21 datasets.doc



Information
request Jan 21 dat..

Dear Dr. Lesnick,

Attached, please find additional information request from our review team. Please do not hesitate to contact me if you have any questions.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

Please confirm receipt of this e-mail.

NDA 201699 (Fidaxomicin)-Information Request

This letter has seven information requests with clarifying questions and request for submissions of new data sets. Requests 1 and 2 are general requests, requests 3 to 6 are specific to some protocol violations for the recurrence endpoint. Finally, request 7 pertains to an alternate definition for the recurrence and global cure secondary endpoints. Please address these requests within the next three weeks. For a timely turnaround, please submit your responses to the items as they become available. We are preparing a request for you to conduct some sensitivity analyses of the global response endpoint; we will send the request to you when it is complete.

- 1) Please provide reasons why some subjects who were randomized in pivotal trials 003 or 004 were not included in (1) the MITT population (2) the per protocol population for the cure phase (3) the per protocol population for the recurrence phase. Provide a line listing as well as a dataset for all randomized subjects in both trials with the following eight variables:
 - a) usubjid: subject id, using the same format as in the integrated summary of efficacy datasets.
 - b) studyid: study id
 - c) mitt: modified intent to treat population flag, using the same format as in the integrated summary of efficacy datasets.
 - d) mittReas: reasons why not in mitt population, character format.
 - e) pp: per protocol population flag for the cure phase using the same format as in the integrated summary of efficacy datasets.
 - f) ppReas: reasons why not in the per protocol population for the cure phase, character format.
 - g) ppRec: per protocol population for the recurrence phase flag, using the same format as in the integrated summary of efficacy datasets.
 - h) ppRecReas: reasons why not in the per protocol population for the recurrence phase, character format.

- 2) For each of the following timing variables, please clarify whether the date (resp. study day) is the date a subject attended the recurrence assessment visit (as in CRF), or whether the date (resp. study day) was imputed if subject was unable to attend the recurrence assessment visit. If any date or study day was imputed, append a flag variable to the same dataset and specify the algorithm used for the imputation
 - a) Variables xrdtc and xrdy in tabulation dataset xr from the integrated summary of efficacy.
 - b) Variables rassdt and bday from analysis dataset efrplus for study 003.
 - c) Variables recasdt and recady from analysis dataset ef for study 004.

The documentation in the define.pdf file indicates that variables rassdt and recasdt were collected from the CRF. However, these variables seem to have been imputed for some subjects who could not have attended the recurrence assessment visit (see request 5 below).

- 3) We found that some subjects in the mitt population were identified as non-recurrent although they took one of the following medications in the follow up period:
Metronidazole, Flagyl, Vancomycin - oral, Vancocin – oral, Rifaximin, Xifaxan, Nitazoxanide, Alinia.

Please provide the CRFs (if they have not already been submitted to the NDA) of all subjects satisfying the above conditions. We are specifically interested in reasons why medication was administered: suspected recurrence of CDAD, prevention of recurrence of CDAD or other reasons.

Our analysis found 48 of these subjects, they are listed in the Appendix. Please confirm that these 48 subjects are the only MITT subjects who met the above conditions. If not, provide the subject ID and CRF for any additional subjects satisfying the conditions above.

- 4) We found that diarrhea information from follow up visits at study days 17, 24, 31, and 36-40 is missing for a large number of subjects. For instance, we found that 110 globally cured subjects had no follow up data on any of these visits in study 003 in dataset FUPLUS. Was there an additional source of information for these subjects for follow up visits and if so, what is it? If the information on all follow up visits for these subjects is completely missing, provide reasons why.
- 5) We identified 30 subjects in the mitt population who died during the study but who were declared globally cured. The listing is shown in the Appendix. Please provide reasons for classifying these subjects as globally cured.
- 6) We identified 67 subjects in mitt population assessed as globally cured with their recurrence assessment day before study day 36 **and** less than 25 days after the last treatment day. Please identify subjects with such protocol violation of timing of recurrence visit window, reasons for the violation and reasons why they are assessed as globally cured.
- 7) Please provide a dataset with additional information for an exploratory endpoint of clinically suspected recurrence. We define clinically suspected recurrence as patients with diarrhea and the receipt of CDAD anti-infective therapy anytime between cure assessment and recurrence assessment visit, regardless of whether the toxin is positive or negative. This dataset should include the following variables:
- a) usbjid: subject id, using the same format as in the integrated summary of efficacy datasets.
 - b) studyid: study id, using the same format as in the integrated summary of efficacy datasets.
 - c) arm: randomized treatment arm, using the same format as in the integrated summary of efficacy datasets.
 - d) recSusp: suspected recurrence, categorical variable with categories of 'Yes', 'No' or 'Missing'.

Appendix:

A- List of subjects' id in mitt population, assessed as globally cured but took CDAD medication between cure and recurrence assessment visits:

"OPT-080-003-002-030"
"OPT-080-003-002-032"
"OPT-080-003-002-034"
"OPT-080-003-009-001"
"OPT-080-003-009-040"
"OPT-080-003-009-045"
"OPT-080-003-009-046"
"OPT-080-003-009-056"
"OPT-080-003-010-027"
"OPT-080-003-011-066"
"OPT-080-003-013-027"
"OPT-080-003-030-001"
"OPT-080-003-041-003"
"OPT-080-003-041-007"
"OPT-080-003-041-008"
"OPT-080-003-045-004"
"OPT-080-003-048-002"
"OPT-080-003-076-008"
"OPT-080-003-140-004"
"OPT-080-003-141-002"
"OPT-080-003-144-006"
"OPT-080-003-144-014"
"OPT-080-003-144-015"
"OPT-080-003-148-002"
"OPT-080-003-160-005"
"OPT-080-003-160-008"
"OPT-080-004-003-009"
"OPT-080-004-021-002"
"OPT-080-004-025-004"
"OPT-080-004-055-004"
"OPT-080-004-057-016"
"OPT-080-004-057-031"
"OPT-080-004-070-006"
"OPT-080-004-070-008"
"OPT-080-004-070-020"
"OPT-080-004-088-016"
"OPT-080-004-088-017"
"OPT-080-004-088-020"
"OPT-080-004-119-001"
"OPT-080-004-119-002"
"OPT-080-004-169-003"
"OPT-080-004-172-007"
"OPT-080-004-172-032"
"OPT-080-004-178-001"
"OPT-080-004-178-007"
"OPT-080-004-178-013"
"OPT-080-004-189-013"
"OPT-080-004-189-014"
"OPT-080-004-201-015"
"OPT-080-004-208-001"

B- List of subjects' id in mitt population, assessed as globally cured, who died during the study.

"OPT-080-003-001-016"
"OPT-080-003-007-001"
"OPT-080-003-009-001"
"OPT-080-003-009-024"
"OPT-080-003-009-056"
"OPT-080-003-011-050"
"OPT-080-003-013-030"
"OPT-080-003-016-008"
"OPT-080-003-017-002"
"OPT-080-003-017-004"
"OPT-080-003-017-008"
"OPT-080-003-136-003"
"OPT-080-003-136-004"
"OPT-080-004-030-001"
"OPT-080-004-049-004"
"OPT-080-004-055-004"
"OPT-080-004-057-016"
"OPT-080-004-064-001"
"OPT-080-004-069-009"
"OPT-080-004-070-026"
"OPT-080-004-088-020"
"OPT-080-004-088-028"
"OPT-080-004-092-002"
"OPT-080-004-093-003"
"OPT-080-004-169-014"
"OPT-080-004-172-007"
"OPT-080-004-172-014"
"OPT-080-004-172-023"
"OPT-080-004-178-015"
"OPT-080-004-180-011"

From: Marc Lesnick [mlesnick@optimerpharma.com]
Sent: Friday, January 21, 2011 5:20 PM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin Tablet) -Information Request
Request received.

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Friday, January 21, 2011 2:07 PM
To: Marc Lesnick
Cc: Candice Durrence
Subject: NDA 201699 (Fidaxomicin Tablet) -Information Request

Dear Dr. Lesnick,

Attached, please find additional information request from our review team. Please do not hesitate to contact me if you have any questions.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

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Reference ID: 2895569

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/s/

FARIBA IZADI
01/24/2011

Izadi, Fariba

From: Izadi, Fariba
Sent: Friday, January 14, 2011 2:45 PM
To: 'Marc Lesnick'
Cc: Candice Durrence
Subject: NDA 201699 (Fidaxomicin) Information request

Dear Dr. Lesnick,

(b) (4). When initially submitted as an IND, the product was described as belonging to the macrolide class. The definitions of a macrolide vary by source, but Dorland's Medical Dictionary (27th Ed.) defines a macrolide as:

1) A chemical compound characterized by a large lactone ring containing multiple keto and hydroxyl groups. 2) Any of a group of antibacterial antibiotics (e.g., erythromycin or oleandomycin) containing a macrolide ring linked glycosidically to one or more sugars. Macrolides are produced by certain species of *Streptomyces* and inhibit protein synthesis by binding to the 50S subunits of 70S ribosomes.

Additionally, Remington: The Science and Practice of Pharmacy (20th Ed.) states:

The macrolides are hydroxylated macrocyclic lactones containing 12 to 20 carbon atoms in the primary ring.

Please respond to the following information requests:

- 1) Does fidaxomicin meet the definition of a macrolide based on the chemical compound description in the definitions above?
- 2) Should the pharmacological classification for fidaxomicin be a macrolide antibacterial? If not, provide your justification for distinguishing fidaxomicin from the macrolides.
- 3) What other factors should be considered in determining the appropriate pharmacological class for fidaxomicin? For additional guidance, we refer you to the "Guidance for Industry and Review Staff: Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm186607.pdf>

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

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/s/

FARIBA IZADI
01/14/2011



NDA 201699

FILING COMMUNICATION

Optimer Pharmaceuticals, INC.
Attention: Marc Lesnick, Ph.D.
Director, Regulatory Affairs
10110 Sorrento Valley Road, Suite C
San Diego, CA 92121

Dear Dr. Lesnick:

Please refer to your New Drug Application (NDA) dated November 29, 2010, received November 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Difucid (Fidaxomicin) Tablet, 200 mg.

We also refer to your submission(s) dated December 01, 04, and 23, 2010.

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 **Priority**. Therefore, the user fee goal date is May 30, 2011.

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, midcycle, 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 requirement/commitment requests by May 03, 2011.

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.

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 acknowledge receipt of your request for a partial waiver and partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver or the partial deferral request is denied.

If you have any questions, call Fariba Izadi, Pharm.D., Regulatory Health Project Manager at (301) 796-0563.

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, M.D.
Deputy Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE A LAESSIG
01/21/2011

From: Marc Lesnick [mlesnick@optimerpharma.com]

Sent: Thursday, January 06, 2011 4:18 PM

To: Izadi, Fariba

Cc: Candice Durrence

Subject: RE: NDA 201699 (Fidaxomicin Tablet) Information Request

I acknowledge receipt of the request, and I'll get back to you with an estimated submission date when I hear from our CMC team.

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]

Sent: Thursday, January 06, 2011 1:13 PM

To: Marc Lesnick

Cc: Candice Durrence

Subject: NDA 201699 (Fidaxomicin Tablet) Information Request

Dear Dr. Lesnick,

We have an Information request from the review team regarding NDA 201699 (Fidaxomicin Tablet).

Please Provide the comparative dissolution profile data (*individual, mean, and plot*) for the comparator un-encapsulated vancomycin and the encapsulated vancomycin products used in the clinical studies (101.1.C.003 and 101.1.C.004).

Best regards,

Fariba Izadi, Pharm.D.

Regulatory Health Project Manager

Division of Anti-Infective and Ophthalmology Products

Phone: (301) 796-0563

Fax: (301) 796-9881

E-mail: Fariba.Izadi@FDA.HHS.GOV

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Reference ID: 2888579

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/s/

FARIBA IZADI
01/07/2011

Izadi, Fariba

From: Marc Lesnick [mlesnick@optimerpharma.com]
Sent: Wednesday, January 05, 2011 11:54 AM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin Tablet)

Thanks, Fariba. If the reviewers truly find they need any datasets regenerated, just let us know and of course we'll do them

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Wednesday, January 05, 2011 8:54 AM
To: Marc Lesnick
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin Tablet)

Dear Dr. Lesnick,

This is to inform you that it is not necessary to re-do the datasets. Please let me know if you need any additional information.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

From: Marc Lesnick [mailto:mlesnick@optimerpharma.com]
Sent: Tuesday, January 04, 2011 12:05 PM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: FW: NDA 201699 (Fidaxomicin Tablet)

Fariba-

We're busy working on the stat requests, but as you might have guessed, the holiday slowed us down. Can you let me know if the Clin Pharm reviewers are ok with the datasets as presented in the NDA (see email chain below), or if they would like them redone precisely as requested? Our stats team needs to know soon if we're going to include this in the next submission.

Thanks,

Reference ID: 2892276

1/14/2011

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Wednesday, December 29, 2010 8:16 AM
To: Marc Lesnick
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin Tablet)

Thank you. I will forward this to the team and let you know if they need any additional information.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

From: Marc Lesnick [mailto:mlesnick@optimerpharma.com]
Sent: Tuesday, December 28, 2010 5:02 PM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin Tablet)

Dear Fariba,

We're actively working on the FDA requests from December 23rd, below, and would like to point out to the Clin Pharm team that most of Question 1 already exists in the NDA. To be more precise, the PK datasets for the Phase 3 studies have been provided and can be found by looking in the Study Tagging File or the define.pdf for each study:

Study 101.1.C.003	File name: PK.xpt
Study 101.1.C.004	File name: PC.xpt

These datasets contain all of the requested information except weight and hepatic function. These two variables can be found in separate datasets (for 101.1.C.003: DMPLUS.xpt and LBPLUS.xpt; for 101.1.C.004: DM.xpt and LB.xpt). Further, the dose of FDX administered was always 200 mg for the Phase 3 studies and the actual exposure can be found in EXPLUS.xpt for 101.1.C.003 and EX.xpt for 101.1.C.004

We would also like to mention that within the ISE/ISS datasets, the pharmacokinetic data for the Phase 3 studies is in the ADXP.xpt file, with the demographic data located in the ADSL.xpt file and the laboratory information located in the ADLB.xpt file.

We are working to provide a SAS dataset for the Phase 2A study PK data, and on generating the special analysis

Reference ID: 2892276

1/14/2011

dataset to examine the affect of P-gp inhibitors on PK. We plan to provide these datasets by Jan 7th.

Please let me know if the Clin Pharm team is ok with the provided PK datasets from the two Phase 3 studies, or if they need to be regenerated with weight and hepatic function for their review.

Marc

Marc L. Lesnick, Ph.D.

Director, Regulatory Affairs

Optimer Pharmaceuticals

10110 Sorrento Valley Road, Suite C

San Diego, CA 92121

Ph: 858-458-5543

Fax: 858-909-0737

mlesnick@optimerpharma.com

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]

Sent: Thursday, December 23, 2010 10:45 AM

To: Marc Lesnick

Cc: Candice Durrence

Subject: FW: NDA 201699 (Fidaxomicin Tablet)

Dear Dr Lesnick,

We are reviewing your submission for NDA 201699 (Fidaxomicin Tablet) and have the following comments and information requests from our Clinical Pharmacology team.

1. Please Provide all pharmacokinetic data obtained from Phase 2A and Phase 3 studies in Microsoft Excel or SAS transfer files. Datasets should include the following:

- Study number
- Subject number
- Subject demographics and baseline characteristics including age, gender, weight, renal function (calculated creatinine clearance values and categories of mild, moderate, or severe renal impairment), and hepatic function (categories of toxicity grade ≤ 1 or ≤ 2)
- Dose of fidaxomicin administered
- Specimen collected (i.e., plasma or feces)
- Sampling day and time point (relative to the most recently administered dose)
- Concentration of fidaxomicin
- Concentration of metabolite OP-1118 (when available)

Perform and provide analysis of fidaxomicin (and OP-1118, if available) concentrations between subjects who did versus who did not receive known P-gp inhibitors from Phase 3 studies. An accompanying pharmacokinetic dataset which includes the use of P-gp inhibitors should also be provided.

Please confirm receipt of this e-mail.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

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FARIBA IZADI
01/14/2011

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:
CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)
Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

REQUEST DATE
January 04, 2011

IND NO.

NDA/BLA NO.
NDA 201699

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW)
Original

NAME OF DRUG
Fidaxomicin Tablet

PRIORITY CONSIDERATION
Yes

CLASSIFICATION OF DRUG
NME-1 Anti-biotic- New class-
(b) (4)

DESIRED COMPLETION DATE
(Generally 1 week before the wrap-up meeting)
April 7, 2011

NAME OF FIRM:
Optimer

PDUFA Date: May 30, 2011

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE (IFU)

TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
- LABELING REVISION

EDR link to submission:

\\CDSESUB1\EVSPROD\NDA201699\201699.enx

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS: **Revised Dates,**

Mid-Cycle Meeting: [Insert Date] March 8, 2011

Labeling Meetings: [Insert Dates] Labeling Meeting #1, April 19, 2011- #2 -April 26, 2011, #3 April 29, 2011.

Wrap-Up Meeting: [Insert Date] April 15, 2011

SIGNATURE OF REQUESTER Fariba Izadi

SIGNATURE OF RECEIVER

Reference ID: 2886992

METHOD OF DELIVERY (Check one)

eMAIL

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FARIBA IZADI
01/05/2011

Izadi, Fariba

From: Marc Lesnick [mlesnick@optimerpharma.com]
Sent: Thursday, December 23, 2010 2:32 PM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin Tablet)

Confirmed that email was received!

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Thursday, December 23, 2010 10:45 AM
To: Marc Lesnick
Cc: Candice Durrence
Subject: FW: NDA 201699 (Fidaxomicin Tablet)

Dear Dr Lesnick,

We are reviewing your submission for NDA 201699 (Fidaxomicin Tablet) and have the following comments and information requests from our Clinical Pharmacology team.

1. Please Provide all pharmacokinetic data obtained from Phase 2A and Phase 3 studies in Microsoft Excel or SAS transfer files. Datasets should include the following:

- Study number
- Subject number
- Subject demographics and baseline characteristics including age, gender, weight, renal function (calculated creatinine clearance values and categories of mild, moderate, or severe renal impairment), and hepatic function (categories of toxicity grade ≤ 1 or ≤ 2)
- Dose of fidaxomicin administered
- Specimen collected (i.e., plasma or feces)
- Sampling day and time point (relative to the most recently administered dose)
- Concentration of fidaxomicin
- Concentration of metabolite OP-1118 (when available)

Perform and provide analysis of fidaxomicin (and OP-1118, if available) concentrations between subjects who did versus who did not receive known P-gp inhibitors from Phase 3 studies. An accompanying pharmacokinetic dataset which includes the use of P-gp inhibitors should also be provided.

Please confirm receipt of this e-mail.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563

Reference ID: 2883525

12/27/2010

Fax: (301) 796-9881

E-mail: Fariba.Izadi@FDA.HHS.GOV

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/s/

FARIBA IZADI
12/27/2010

Teleconference with Optimer Pharmaceuticals, Inc. December 22, 2010

Division of Anti-Infective and Ophthalmology Products participants:

Dr. John Alexander, MD. MPH. Medical Team Leader
Dr. Sumathi Nambiar, MD. Deputy Division Director for Safety
Dr. Fariba Izadi, Pharm.D. Regulatory Health Project Manager

Optimer Pharmaceuticals, Inc. participants:

Dr. Sherwood Gorbach
Dr. Pam Sears
Dr. Xavier Frapaise
Dr. Mark Lesnick

Discussion:

In a teleconference held on December 22, 2010 with Optimer Pharmaceuticals, Inc., Optimer stated that after feedback from other health agencies, and their own assessment of the data presented, they have decided to modify their previous indication for NDA 201699 (Fidaxomicin Tablet) specifically, Optimer would like to replace the term (b) (4) with 'reduced rate of recurrences', since they find that to be more appropriate and accurate.

(b) (4)

Optimer asked for The Division's feedback, suggestion and language clarification with the label.

FDA Response:

The Division stated that since this NDA is still under review and the labeling will be discussed after the understanding of the perspective of the review itself, it is considered too early to discuss the labeling.

However, the team leader agreed with the reasons for changing the term (b) (4) (b) (4) with "reduced rate of recurrences". (b) (4)

FDA advised Optimer to formally submit these changes to the NDA as an amendment as soon as possible.

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/s/

FARIBA IZADI
12/27/2010

From: Izadi, Fariba
Sent: Wednesday, December 22, 2010 4:42 PM
To: 'Marc Lesnick'
Cc: 'Candice Durrence'
Subject: NDA 201699- Information Request

Attachments: Stat Information Request Dec 22 (2).doc



Stat Information
Request Dec 2...

Dear Dr. Lesnick,

Attached, please find the information requests from our statistics team regarding NDA 201699 (Fidaxomicin tablet). Please do not hesitate to contact me if you have any questions.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

Please confirm receipt of this e-mail.

NDA 201699 (Fidaxomicin Tablet)
Information Request:

- A. We have some clarification questions and requests regarding the data collection of subject's daily stool frequency, timing or volume.
- 1) Page 40 of Section 16.1.2 Sample Case Report Form shows the Subject Take Home Worksheet. Please specify how the data in this sheet was collected for inpatients and outpatients. More precisely, who provided the information (subject or healthcare professional?), when the data was collected (collected day by day or collected at hospital visit?), and how it was collected (in person or by phone?).
 - 2) Dataset XU in the integrated summary of efficacy reports in variable XURORRES the total number of unformed stools from the Subject Take Home Worksheet. Do the values '0' or '00' of this variable indicate that the data on unformed stools was collected **and** there were no unformed stools for corresponding subject on corresponding study day?
 - 3) Add to dataset XU in the integrated summary of efficacy the reported total number of stools (from Subject Take Home Worksheet) for each study day.
 - 4) Compare the values of variable XUORRES from dataset XU in integrated summary of efficacy for the 24 hours preceding the end of therapy visit to values of variable IBOWL in analysis dataset EFPLUS from study 003 (CDAD assessment at end of Therapy) and values of variable BMUNBOWN in analysis dataset EFBM from study 004 (CDAD assessment at end of therapy).
 - 5) Specify how missing values were handled for data collected from the Subject Take Home Worksheet (Page 40 of Section 16.1.2). That is, any partial imputation of some missing information in a provided sheet, or a full imputation on all information in a missing daily sheet.
- B. We also have requests for descriptive information of the extent of missing values for the primary endpoint, the two secondary endpoints as well as the Modified Cure endpoint.
- 1) Please provide a table with number of missing values for the primary endpoint, the two secondary endpoints as well as the Modified Cure endpoint.
 - 2) Please provide the baseline characteristics of subjects with missing values for the primary endpoint, the two secondary endpoints as well as the Modified Cure endpoint.
 - 3) Please provide a table with number of missing values by study center.

- C. Finally, we would like to see the following descriptive analyses to better compare the clinical cure definition in your protocol to clinical cure definition in the Vancomycin Tolevamer historical trials (from which the NI margin is derived)
- 1) Two-way table of clinical cure (primary endpoint) versus abdominal pain assessment at end of therapy visit. Abdominal test of cure categories are: No, Yes and mild, Yes and moderate, Yes and severe. This information is available from answers to Q8 and Q10 of CDAD assessment at end of therapy.
 - 2) Three-way table of clinical cure (primary endpoint) versus number of stools (in each of the two days prior to end of therapy visit) versus number of unformed stools (in each of the two days prior to end of therapy visit).

Izadi, Fariba

From: Marc Lesnick [mlesnick@optimerpharma.com]
Sent: Thursday, December 23, 2010 2:35 PM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201699- Information Request

Receipt confirmed!

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Wednesday, December 22, 2010 1:42 PM
To: Marc Lesnick
Cc: Candice Durrence
Subject: NDA 201699- Information Request

Dear Dr. Lesnick,

Attached, please find the information requests from our statistics team regarding NDA 201699 (Fidaxomicin tablet). Please do not hesitate to contact me if you have any questions.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

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Reference ID: 2883528

12/27/2010

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/s/

FARIBA IZADI
12/27/2010

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/s/

FARIBA IZADI
12/20/2010

Izadi, Fariba

From: Marc Lesnick [mlesnick@optimerpharma.com]
Sent: Tuesday, December 14, 2010 2:48 PM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin)- Information Request

Fariba-

Information Request received, and our team is currently assessing the time needed to address and submit the updated files.

Candice will send an email later with our planned response date.

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Tuesday, December 14, 2010 9:53 AM
To: Marc Lesnick
Cc: Candice Durrence
Subject: NDA 201699 (Fidaxomicin)- Information Request

Dear Dr. Lesnick,

We are reviewing your submission for NDA 201699 (Fidaxomicin) and have the following information requests from our review team.

The define.pdf files you provided for the analyses datasets in study 003, study 004 as well as the integrated summary of efficacy are not adequately documented. This makes it challenging for us to review your application. Please address this deficiency as follows:

- For all derived variables in all analyses datasets (study 003, study 004 and integrated summary of efficacy), provide (1) in column Origin, the name of all the source variable(s) with the name of their tabulation datasets (e.g. variable XUDY from dataset XU or alternatively XU.XUDY) (2) In the comments column, a description of the derivation algorithm (in plain language) and the name of the SAS program file doing the derivation. If you did not include the SAS program file doing the derivation in your submission, please provide it.
- For all categorical variables, provide in column Decodes the values each categorical variable takes. If any codes were used (e.g. code 1 for event and code 0 for censored), provide the key to the code as well.

To illustrate our request, we provide as an example the documentation for variable RESDIA from analysis dataset ADXE in the integrated summary of efficacy. The documentation for this variable mostly follows our specifications: (1) the Decodes column provides the required information, and (2) the Comments column provides a plain language description of the derivation algorithm. However, there are some deficiencies: (1) the column Origin does not specify the name of the source variables and the Comments column has a variable name without its tabulation dataset reference, and (2) the Comments column does not provide the name of the SAS program file deriving the variable.

varnum	Name	Label	Type	Length	Decodes	Origin	Comments
							1) Patients who never used rectal

Reference ID: 2877619

12/14/2010

1	RES DIA	Resolution of Diarrhea	Char 1	1= Event, 0= Censor	Derived	collection device: If ≤ 3 unformed bowel movements are observed for 2 consecutive days and it is sustained through the end of therapy/day 10 (XUDY). 2) Patients who only used rectal collection device: If the volume (over a 24-hour period) is decreased by 75% compared to admission and the 75% decrease is sustained until Day 10. 3) Patients who periodically used rectal collection device: Convert volume of stool to number of unformed bowel movements using formula - 60 cc (or ml) = 1 unformed bowel movement. Then use criteria specified in (1).
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Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

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/s/

FARIBA IZADI
12/14/2010

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Fariba Izadi, Pharm.D. Regulatory Health Project Manager Division of Anti-Infective and Ophthalmology Products Phone: (301) 796-0563 Fax: (301) 796-9881 E-mail: Fariba.Izadi@FDA.HHS.GOV
------------------------------	---

REQUEST DATE December 10, 2010	IND NO.	NDA NO. NDA 201699	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) Original
-----------------------------------	---------	-----------------------	---

NAME OF DRUG Fidaxomicin 200 mg Tablet	PRIORITY CONSIDERATION Yes	CLASSIFICATION OF DRUG NME-1 Antibiotic (b) (4)	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) April 20, 2011
---	-------------------------------	--	--

NAME OF FIRM: Optimer	PDUFA Date: May 30, 2011
--------------------------	--------------------------

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
--	--	---

EDR link to submission:

The network location is <\\CDSESUB1\EVSPROD\NDA201699\201699.enx>

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: March 7, 2011

Labeling Meetings: May 2, 2011, May 5, 2011, May 9, 2011

Wrap-Up Meeting: April 29, 2011

SIGNATURE OF REQUESTER: Fariba Izadi, Pharm.D. RPM.

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND
-----------------------	--

Reference ID: 2880120

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/s/

FARIBA IZADI
12/17/2010



NDA 201699

NDA ACKNOWLEDGMENT

Optimer Pharmaceuticals, INC.
Attention: Marc Lesnick, Ph.D.
Director, Regulatory Affairs
10110 Sorrento Valley road, Suite C
San Diego, CA 92121

Dear Dr. Lesnick:

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

Name of Drug Product: Fidaxomicin Tablet 200 mg

Date of Application: November 29, 2010

Date of Receipt: November 30, 2010

Our Reference Number: NDA 201699

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 January 29, 2011, 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 and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call Fariba Izadi, Pharm.D., Regulatory Health Project Manager at (301) 796-0563.

Sincerely yours,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Frances V LESANE
12/10/2010

Izadi, Fariba

From: Marc Lesnick [mlesnick@optimerpharma.com]
Sent: Tuesday, December 07, 2010 12:09 PM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin Tablets)-Request for Proposed proprietary name.

Fariba,

Thanks for the clarification. We'll start working on the submission following the new guidance. I'll give you a heads up on the timing of this submission when I know more.

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Tuesday, December 07, 2010 8:46 AM
To: Marc Lesnick
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin Tablets)-Request for Proposed proprietary name.

Dear Dr. Lesnick,

The package needs to be re-submitted again during the NDA phase by the company.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

From: Marc Lesnick [mailto:mlesnick@optimerpharma.com]
Sent: Tuesday, December 07, 2010 11:37 AM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin Tablets)-Request for Proposed proprietary name.

Fariba-

We've previously sent in a package for review of Difucid as proprietary name (see SN 133 to IND 64,435), and received a response from Carmen that the name was found to be acceptable (see attached email from Carmen).

Can this package from the IND be resubmitted by you, or do I need to put together something new?

Thanks for your guidance,

Reference ID: 2873737

12/7/2010

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Tuesday, December 07, 2010 8:24 AM
To: Marc Lesnick
Cc: Candice Durrence
Subject: NDA 201699 (Fidaxomicin Tablets)-Request for Proposed proprietary name.

Dear Dr. Lesnick,

Please refer to your new drug application submitted for Fidaxomicin Tablet on November 29, 2010. Please submit a request for review of the proposed proprietary name for approval as soon as possible. Attached is a draft Guidance for industry (contents of a complete submission for the evaluation of proprietary names). Please let me know if you need further assistance.

Best Regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

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Reference ID: 2873737

12/7/2010

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FARIBA IZADI
12/07/2010

Izadi, Fariba

From: Izadi, Fariba
Sent: Thursday, October 21, 2010 12:22 PM
To: 'Marc Lesnick'
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin)

Dear Dr. Lesnick,

Thank you for your prompt reply. It would be acceptable to submit these datasets to the NDA in early November, after the NDA is officially filed. It is preferred that a single dataset is created for both studies. You can create a separate folder containing dataset and associated file(s). These files can be placed into module 5.4 "datasets" as a separate file. Please let me know if you need further assistance.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov

Please confirm receipt of this e-mail.

From: Marc Lesnick [mailto:mlesnick@optimerpharma.com]
Sent: Wednesday, October 20, 2010 7:37 PM
To: Izadi, Fariba
Cc: Candice Durrence
Subject: RE: NDA 201699 (Fidaxomicin)

Fariba-

I've just met with our biostatistician and regulatory submission team, and they're working on a timeline for putting together the requested datasets. Our planned NDA submission date (November 5th) is coming up rapidly, and as you might imagine, we have completed and published over 99% of the NDA and are focused on performing all of the necessary formatting and QC checks. That said, we will try to include these datasets in the NDA as requested.

Two questions for you:

1. If it takes longer than anticipated to address this request, would it be acceptable to submit these datasets to the NDA in early November, after the NDA is officially filed?
2. Where in the NDA should we place these files? In the individual study areas in 5.3.5.1 Study Reports of Controlled Clinical Studies, or in 5.3.5.3 Reports of Analyses of Data from more than one study?

10/25/2010

Thanks for clarifying. We hope to know by early next week if we can submit these datasets as part of the NDA and still meet our current filing deadline; I will send you an email as soon as I know.

As a side note, please cc: Candice Durrence on regulatory correspondence such as this, in order to provide redundancy in the event I am unavailable.

Regards,

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Wednesday, October 20, 2010 2:06 PM
To: Marc Lesnick
Subject: NDA 201699 (Fidaxomicin)

Dear Dr. Lesnick,

Attached, please find a copy of the Dataset request document for NDA 201699 (Fidaxomicin tablet) . The purpose of this electronic submission is to facilitate the timely evaluation of data integrity and selection of appropriate clinical sites for FDA inspection as part of the application review process. Please submit a dataset for each of the two Phase 3 trials. Please let us know when you would be able to submit this information. Is it possible for you to submit these datasets with the clinical portion of the NDA?

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

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/s/

FARIBA IZADI
10/25/2010

Izadi, Fariba

From: Marc Lesnick [mlesnick@optimerpharma.com]
Sent: Tuesday, October 12, 2010 5:38 PM
To: Izadi, Fariba
Subject: RE: NDA 201,699 Difucid (fidaxomicin) question for clinical reviewer/biostatistician

Thanks!

Marc

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Tuesday, October 12, 2010 2:36 PM
To: Marc Lesnick
Subject: RE: NDA 201,699 Difucid (fidaxomicin) question for clinical reviewer/biostatistician

Dear Dr. Lesnick,

At present time, we are only requesting the program files used to generate the primary and important secondary analyses, as well as the program files used to generate the ADaM datasets. If the need arises, we may request additional program files later.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

From: Marc Lesnick [mailto:mlesnick@optimerpharma.com]
Sent: Monday, October 11, 2010 1:06 PM
To: Izadi, Fariba
Cc: Candice Durrence; Michael Monahan
Subject: NDA 201,699 Difucid (fidaxomicin) question for clinical reviewer/biostatistician

Fariba-

Here's a question from our publication team I'd like you to pass along to your clinical reviewer and/or biostatistician. As soon as you can get an answer, please pass it along!

"For the Fidaxomicin NDA, Optimer plans to submit the ISS/ISE tabulation datasets in CDSIC SDTM format as well as Analysis datasets in ADaM format. For the accompanying analysis program files, does the Division clinical/statistical reviewers want to receive all of the program files that were used to generate every ISS/ISE end-of-text tables, listings, and figures, or only those program files used to generate the ADaM datasets?"

Let me know if they need further clarification in order to answer this.

10/15/2010

Thanks,

Marc

Marc L. Lesnick, Ph.D.

Director, Regulatory Affairs

Optimer Pharmaceuticals

10110 Sorrento Valley Road, Suite C

San Diego, CA 92121

Ph: 858-458-5543

Fax: 858-909-0737

mlesnick@optimerpharma.com

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/s/

FARIBA IZADI
10/15/2010



IND 64,435

MEETING MINUTES

Optimer Pharmaceuticals, Inc.
Attention: Marc Lesnick, PhD
Director, Regulatory Affairs
10110 Sorrento Valley Road, Suite C
San Diego, CA 92121

Dear Dr. Lesnick:

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

We also refer to the meeting between representatives of your firm and the FDA on July 1, 2010. The purpose of the meeting was to discuss the proposed clinical and non-clinical data package planned for the NDA filing in 2010.

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

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

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, MD
Deputy Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Application Number: IND 64435
Product Name: Dificid (fidaxomicin) Tablets
Indication: *Clostridium difficile* associated diarrhea
Sponsor/Applicant Name: Optimer Pharmaceuticals

FDA ATTENDEES

Dr. Wiley Chambers	Acting Division Director
Dr. Katherine Laessig	Deputy Director
Dr. John Alexander	Clinical Team Leader
Dr. Dmitri Iarikov	Clinical Reviewer
Dr. Scott Komo	Statistical Reviewer
Dr. Thamban Valappil	Statistical Team Leader
Dr. Aryun Kim	Clinical Pharmacology Reviewer
Dr. Charles Bonapace	Clinical Pharmacology Team Leader
Dr. Wendelyn Schmidt	Pharmacology/Toxicology Team Leader
Dr. Frederic Marsik	Clinical Microbiology Team Leader
Dr. Nicole Mahoney	Staff Fellow
Dr. Carmen DeBellas	Regulatory Project Manager

SPONSOR ATTENDEES

	Optimer Pharmaceuticals, Inc.
Dr. Xavier Frapaise	Chief Scientific Officer
Dr. Sherwood Gorbach	Chief Medical Officer
Dr. Michael Corrado	Regulatory/Medical Officer
Dr. Pamela Sears	Executive Director, Biology and Pre-Clinical Science
Dr. Michael Hui	Senior Director, Quality Assurance
Mr. James Robinson	Associate Director, Biometrics
Dr. Marc Lesnick	Director, Regulatory Affairs
Ms. Candice Durrence	Manager, Regulatory Affairs

1.0 BACKGROUND

Dificid is being studied for the treatment of *Clostridium difficile* associated diarrhea. Optimer has completed one phase 3 non-inferiority study of Dificid using vancomycin capsules as a comparator and is completing a second Phase 3 study soon.

Optimer is planning to submit the NDA for Dificid in the third quarter of 2010. The purpose of the meeting was to discuss elements for the final preparation of the NDA documents for filing.

2. DISCUSSION

The Sponsor received the Agency's responses to the meeting background package questions prior to the meeting. The attached meeting minutes contain clarifications and discussion concerning the Agency's responses.

Question 1:

Optimer Pharmaceuticals has completed 6 clinical trials to demonstrate the safety and efficacy of Dificid for the treatment of *C. difficile* infections (CDI), including the two largest Phase 3 trials ever completed for this indication. In this briefing document, Optimer will submit an overview of the results of these studies and the statistical analysis plans (SAPs) for the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE), which include mock-tables and listing shells. As previously discussed with the Division, these Phase 3 studies used a non-inferiority study design, oral vancomycin as the comparator, and a non-inferiority margin of 10%. The justification for this non-inferiority margin was discussed at the meeting held with the Division on September 18, 2009, and was laid out in Investigational New Drug (IND) Amendment 160, submitted on October 16, 2009.

Does the Division have any comment on the adequacy of the proposed clinical package in order to support the safety and efficacy of Dificid for the proposed indication? Does the Division have any comment on the SAPs presented in the draft ISE/ISS?

Agency Response:

It is appropriate for the Sponsor to proceed to an NDA submission. Acceptability of a 10% NI margin as proposed would depend upon a detailed review of the NDA submission to make sure that patient characteristics are similar to the historical data. We note the existence of a second tolevamer trial (Bouza et al. presented at the 2008 European Congress of Clinical Microbiology and Infectious Diseases meeting) and recommend that this trial also be incorporated into your NI margin justification, although it is unlikely to significantly change the proposed NI margin.

In addition, please confirm for the efficacy analyses that:

- *Patients who receive the incorrect study medication will be classified into the treatment group they were randomized to, and,*
- *Patients who were randomized within the incorrect stratum will be classified into the stratum they were supposed to be randomized within.*

Clinical microbiology information in the NDA should be submitted as described in the guidance for industry “Providing Regulatory Submissions in Electronic Format Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.” Generally, the information on microbiology should be provided in two sections of the eCTD as follows:

- *Module 2, Section 2.7, Clinical Summary, subsection 2.7.2.4, Special Studies. This section should contain the microbiology summary report that contains the type of information with associated subheadings as described in this guidance. Thus, it contains the information used to justify the microbiology information included in the labeling.*
- *Module 5, Clinical Study Reports, subsection 5.3.5.4, Other Study Reports. This section should contain the nonclinical study and clinical trial reports used in the construction of the summary information provided in subsection 2.7.2.4. All of the study and trial reports used to construct the summary report presented in section 2.7.2.4 should be cross-linked to the summary report. Both of these sections should be cross-referenced to each other.*

Meeting Discussion:

The Sponsor agreed to all the recommendations made by the Agency in the responses above. In addition, the Agency agreed with the Sponsor’s proposal that the Phase 2A data set should not be included in the ISE and ISS. The Agency also agreed to the Sponsor’s proposal to place microbiologic isolate data that relates to efficacy by strain in section 2.7.3 and that links to section 2.7.2 are added to the eCTD.

Question 2:

In the September 18, 2009 Type C meeting with the Division, agreement was reached on the criteria to assess whether a thorough QT study in healthy subjects would provide meaningful information on the potential of fidaxomicin to induce corrected QT interval (QTc) prolongation in patients. In our last discussion on this topic, the Division stated that if plasma levels of fidaxomicin given to healthy subjects were not in the same range as values seen in CDI patients, a thorough QTc study in healthy volunteers would not be practical, and the impact of fidaxomicin on cardiac repolarization could be assessed from data gathered as part of the Phase 3 studies.

As part of our pharmacokinetic (PK) food effect study (Study OPT-80-005) we recently confirmed plasma PK levels in healthy adults using a sensitive bioanalytical assay for fidaxomicin, and summary tables are included in this Briefing Document. Fidaxomicin and OP-1118 (the main metabolite of fidaxomicin) levels in healthy subjects, even at double the therapeutic dose (400 mg), were in the low ng/mL range (10.6 ng/mL mean peak plasma concentration [C_{max}], and 25.5 ng/mL mean C_{max} , respectively), and most notably, the range in these individuals was much lower than that seen in patients with CDI. In our most recent Phase 3 study, the range of plasma concentrations observed in CDI patients included values that were approximately 10 times higher than the highest values observed in healthy subjects given twice the therapeutic dose in the PK food effect study OPT-80-005 (237 ng/mL for fidaxomicin and 871 ng/mL for OP-1118 [101.1.C.004] vs. 28.9 ng/mL for fidaxomicin and 77.4 ng/mL for OP-1118 [OPT-80-005]). This suggests that in healthy subjects we could not achieve systemic levels of fidaxomicin or its metabolite, OP-1118, that approach the levels seen in patients.

We have also included summary tables from the Phase 3 studies in this Briefing Document, which do not show any correlation between fidaxomicin treatment and corrected QTc interval prolongation.

Based on the lack of a QT prolongation effect in the Phase 3 studies, and the confirmation that systemic PK levels of fidaxomicin in healthy subjects are too low to mimic levels observed in patients, Optimer believes that a thorough QT study is not practical or necessary, and asks confirmation for a waiver.

Does the Division confirm that this data meets the criteria for a waiver discussed at the September Type C meeting?

Agency Response:

We agree a thorough QT study would not be practical or necessary for this product.

Meeting Discussion:

The Sponsor agreed with the response.

Formatting and Technical Questions

Question 4:

Optimer plans to submit the New Drug Application (NDA) in Electronic Common Technical Document (eCTD) format, and plans a rolling submission of modules as they are completed, per Fast Track approval granted October 30, 2003. Our proposed timeline for the submission of the modules is included in this Briefing Document (see Section 11). Also, we wish to make the Division aware that all individual study datasets will be submitted in their native format, but that only the ISS and ISE datasets will be submitted in Clinical Data Interchange Standards Consortium (CDISC) format (SDTM and ADaM datasets).

Does the Division agree these plans are acceptable?

Agency Response:

The Agency agrees with the proposed submission timing. The Agency would prefer to receive the individual study datasets in CDISC format, but your proposal is acceptable.

- *A random sample of treatment blinded case report forms (CRFs) will be requested with the NDA submission. If a listing of all randomized patients are provided to the Division prior to the NDA submission, a random sample will be generated and sent to the Sponsor so that these specific CRFs can be included in the NDA submission. The listing should include patient identification number and randomized treatment group.*
- *Prior to submission of the NDA, the Sponsor may wish to submit sample datasets for the Division's review. This is often helpful to uncover any issues with dataset formatting or content and facilitates the review process.*

Meeting Discussion:

The Sponsor agreed to the recommendations above and asked if the Agency required a set of CRFs (164 total) planned to be submitted in the NDA were sufficient. The Agency replied that a 10% random sample is preferred for clinical review. The Agency stated that additional CRFs can be in the same location with the rest of the CRFs.

The Agency stated that an Advisory Committee Meeting would be held sometime in mid-February or mid-March 2011.

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/s/

KATHERINE A LAESSIG
10/25/2010



IND 64,435

MEETING MINUTES

Optimer Pharmaceuticals, Inc.
Attention: Marc Lesnick, Ph.D.
Associate Director, Regulatory Affairs
10110 Sorrento Valley Road, Suite C
San Diego, CA 92121

Dear Dr. Lesnick:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OPT-80 (PAR 101).

We also refer to the meeting between representatives of your firm and the FDA on September 18, 2009. The purpose of the meeting was to discuss the results of a Phase 3 program.

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

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

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, M.D.
Deputy Director
Division of Anti-Infective and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 18, 2009
APPLICATION: IND 64,435
DRUG NAME: OPT-80 (PAR-101)
TYPE OF MEETING: Phase 3 Discussion

FDA ATTENDEES:

Division of Anti-Infective and Ophthalmology Products:

Dr. Wiley Chambers	Acting Division Director
Dr. Katherine Laessig	Deputy Director
Dr. Nasim Moledina	Clinical Reviewer
Dr. Thamban Valappil	Statistical Team Leader
Dr. Christopher Kadoorie	Statistical Reviewer
Dr. Frederic Marsik	Microbiology Team Leader
Dr. Charles Bonapace	Clinical Pharmacology Team Leader
Dr. Aryun Kim	Clinical Pharmacology Reviewer
Dr. Wendelyn Schmidt	Pharmacology/Toxicology Team Leader
Dr. Carmen DeBellas	Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Optimer Pharmaceuticals, Inc.

Dr. Xavier Frapaise	Chief Scientific Officer
Dr. Sherwood Gorbach	Chief Medical Officer
Dr. Michael Corrado	Clinical/Regulatory Consultant
Dr. Pamela Sears	Executive Director, Biology and Pre-Clinical Science
Dr. Ed Bryant	Biostatistical Consultant
Dr. Youe Kong Shue	Vice President, Clinical Development
Mr. James Robinson	Senior Manager, Biostatistics
Dr. Marc Lesnick	Associate Director, Regulatory

BACKGROUND:

Optimer has completed the enrollment and analysis of the first Phase 3 trial for the indication of *Clostridium difficile* infections, and will soon complete the second Phase 3 trial in the same indication. Optimer would like to discuss the results of the Phase 3 program with the Agency.

DISCUSSION:

The Sponsor received the Agency comments to questions submitted in the meeting package before the meeting. The discussion section of the meeting minutes will contain the Sponsor questions, Agency responses and meeting discussion concerning the Agency comments.

1.3. List of Questions for FDA

Question 1: Clinical Program

Optimer presents here the results of the completed first Phase 3 study of Difucid™ for the treatment of *Clostridium difficile* infection (CDI). Does the Division agree that, given the information provided, the results from this study combined with the ongoing second Phase 3 (101.1.C.004) study can form the basis for approval of Difucid for the indication of CDI, if the results from the ongoing Phase 3 study are positive?

Agency Response:

A summary of the results from study 101.1C.003 have been submitted but the basis of approval will be determined after the entire NDA database has been reviewed.

Meeting Discussion:

No meeting discussion.

Question 2: Secondary Endpoints for the Ongoing Phase 3 Study (Study 101.1.C.004)

Given the significance of Global Cure, defined similarly to “symptomatic cure” in the Cochrane review [Nelson, 2008] as cure without recurrence, as a relevant measure of true CDI cure, Optimer wishes to elevate the relative importance of this endpoint to a secondary endpoint in the ongoing 101.1.C.004 study with a gate-keeping strategy. A description of this strategy is included in Section 6.5.2.

Does the Division agree with the proposed plan to convert Global Cure from an exploratory endpoint to a secondary endpoint?

Agency Response:

The proposal to change Global Cure from an exploratory endpoint to a secondary endpoint is acceptable provided the Study 101.1.C.004 data are blinded. The statistical approach described for testing cure rate, recurrence rate and Global cure rate in a sequential manner is also acceptable in controlling the overall type I error rate.

Meeting Discussion:

The discussion concerning Global Cure ended in agreement with the proposal to use Global Cure as a secondary endpoint.

The Agency suggested that if a non-inferiority margin could not be justified the Sponsor should consider changing the primary endpoint to superiority of global cure from a non-inferiority of clinical cure.

The Sponsor commented that they are creating the non-inferiority justification by using Phase 3 Tolevamer study data. They would be using Tolevamer as a surrogate placebo.

Question 3: QTc Study

Optimer has discussed the requirement for a thorough QTc study with the Division at the End of Phase 2 meeting on July 17, 2007, and in a separate Type C meeting held on May 14, 2008. The minutes from these meetings can be found in Appendix 1. Optimer believes that the

pharmacokinetic (PK) and safety results from the completed Phase 3 study), in addition to the data previously submitted in support of the prior meetings, and the summary included, gives additional information for the Division's assessment.

Does the Division have any comment on the relevance of the additional safety information from our completed Phase 3 study on your assessment of the cardiovascular safety of Difidid?

Agency Response:

Although the Division recognizes the difficulty in properly assessing systemic exposure due to undetectable or nearly undetectable concentrations at many of the sampling time points, it is the Division's recommendation that a thorough QT study be performed if meaningful results can be obtained. The Division requests the sponsor to evaluate whether a thorough QT study may be possible in healthy subjects with the more sensitive LC-MS method (lower limit of quantification of 0.2 ng/mL versus the previous 5 ng/mL), particularly since it appears CDAD patients generally have higher exposures than healthy subjects and systemic concentrations obtained in healthy subjects may not exceed those observed in patients. If a thorough QT study is not possible, the Division recommends continuing with ECG monitoring in clinical trials, including the ongoing Study 101.1.C.004, as discussed in the Type C meeting held on 5/14/2008. This involves an ECG and simultaneous plasma pharmacokinetic sampling at pre-dose and at 3-5 hours post-dose on the first and last days of dosing, as well as at the time of early withdrawal or in case of a cardiac adverse event.

Meeting Discussion:

The Sponsor asked for clarification of the term "meaningful results" in the Agency responses.

The Agency stated that in order to obtain a clear understanding of any potential for cardiac safety issues the necessary systemic pharmacokinetic profile would need to be completed with more frequent pharmacokinetic sampling time points.

The Sponsor stated that a pharmacokinetic-food effect study with frequent pharmacokinetic samples and ECGs timed with blood draws at or near C_{max} is ongoing.

The Agency replied that if the results of this study showed lower systemic levels than previous studies and that the study is not feasible, a waiver of the QTc requirement may be considered.

Question 4: Non-clinical Program

Optimer is presenting a tabular listing of all of the non-clinical studies of fidaxomicin and its main metabolite, OP-1118, that are completed, in progress, or planned. We have included short summaries of the results for those studies that are completed, and estimated completion dates for the remainder.

Does the Division have any comment on the non-clinical program presented in this briefing package?

Agency Response:

The studies described appear appropriate to support the NDA filing. The adequacy of the studies will be a review issue.

Meeting Discussion:

No meeting discussion.

Question 5: Microbiological Breakpoints

Fidaxomicin has very low systemic absorption and it acts locally in the gastrointestinal (GI) tract. Since *Clostridium difficile* is found in nature as a wild type population only and no resistant populations exist, (b) (4) Quality control parameters, however, have been established so that laboratories that perform susceptibility testing can monitor the relationship of the *in vitro* minimum inhibitory concentration (MIC) test result to the clinical efficacy of Dificid.

(b) (4)

Agency Response:

While Fidaxomicin may be considered a topical drug and systemic breakpoints cannot be determined because the drug is concentrated in the intestine, MIC results can be useful in deciding if clinical failure is due to the infecting C. difficile organism being non-susceptible to Fidaxomicin. Therefore, while at this time it may not be possible to determine a resistant category based on MIC results one can determine based on surveillance data as well as data collected during clinical trials what MIC categorizes a C. difficile isolate as being susceptible to Fidaxomicin.

Meeting Discussion:

The Sponsor asked the Agency for help in how to propose a breakpoint for OPT-80 because there is no resistant population in the Phase 3 studies. See Agency response to Question 5. The Sponsor asked how information on the MIC of *C. difficile* isolates and clinical outcome would be stated in the drug label. The Agency indicated that there are a number of ways that this information could be presented. At the time of labeling negotiations this will be thoroughly discussed between the Agency and Sponsor.

Question 6: Fast-Track Submission Timelines

A timetable for pre-NDA meetings, and the commencement of the rolling submission, per the Fast-Track approval previously granted on September 3, 2003, is included as Appendix 2.

Does the Division wish to provide any feedback on this timeline or plan, as proposed?

Agency Response:

The timeline table is acceptable. You should note that the determination of whether the product qualifies for priority review will be made based on the results of the clinical studies. Therefore, we recommend that you submit the request for priority review with the submission of clinical studies in 2 Q 2010.

Meeting Discussion:

The Sponsor asked if the rolling submission can start before the Pre-NDA meeting is held. The Agency stated that it was acceptable.

Additional Clinical Microbiology Comments

1. Please provide in the NDA submission patient outcome for both the microbiologically evaluable population and per protocol population clinical and microbiologically outcome correlated with MIC.
2. Since it is the intention to include in vitro minimal inhibitory concentration testing quality control parameters in the package insert please summary reports and data used to determine the quality control parameters. These parameters need to be developed according to the method described in the Clinical and Laboratory Standards Institute (CLSI) document M23 A3 (2008).
3. In a previous submission (20 Aug 03) you indicated that you would determine frequencies of spontaneous resistance for *Clostridium difficile* using five recent clinical isolates. Please provide this information.
4. In cases of clinical failure please provide information of the susceptibility of the *C. difficile* associated with the CDI pre-therapy and post-therapy.
5. We strongly suggest that applicants provide microbiology information in the electronic common technical document (eCTD) as described in the guidance for industry Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.¹ Generally, the information on microbiology should be provided in two sections of the eCTD as follows:

Module 2, Section 2.7, Clinical Summary, subsection 2.7.2.4, Special Studies. This section should contain the microbiology summary report that contains the type of information with associated subheadings as described in this guidance. Thus, it contains the information used to justify the microbiology information included in the labeling.

Module 5, Clinical Study Reports, subsection 5.3.5.4, Other Study Reports. This section should contain the nonclinical study and clinical trial reports used in the construction of the summary information provided in subsection 2.7.2.4. All of the study and trial reports used to construct the summary report presented in section 2.7.2.4 should be cross-linked to the summary report. Both of these sections should be cross-referenced to each other.

¹ We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-64435	GI-1	OPTIMER PHARMACEUTICA LS-PAR PHARMACEUTICA LS INC	OPT-80, TIACUMICIN B, PAR- 101

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/s/

KATHERINE A LAESSIG
10/20/2009



IND 64,435

Advanced Biologics LLC
Attention: Annie Frimm
Director, Regulatory Affairs
580 Union Square Drive
New Hope, PA 18938

Dear Ms. Frimm:

Please refer to the Type C Guidance Meeting between representatives of your firm and FDA on 13 July 2005. The purpose of the meeting was to discuss your plan for further development of OPT-80 for use in the treatment of patients with *Clostridium difficile*-Associated Diarrhea (CDAD).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Carmen DeBellas, Regulatory Health Project Manager, at 301-827-2120.

Sincerely,

{See appended electronic signature page.}

Janice Soreth, M.D.
Director
Division of Anti-Infective and Ophthalmology
Products, HFD-520
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure



MEETING MINUTES

MEETING: Type C Guidance Meeting
DATE, TIME: 13 July 2005, 10:00-12:00 a.m. ET
LOCATION: CDER CORP S400 Conf Room

APPLICATION: IND 64,435
DRUG: PAR-101 (OPT-80, tiacumicin B)
INDICATION: Treatment of patients with *Clostridium difficile*-Associated Diarrhea (CDAD)
SPONSORS: Optimer Pharmaceuticals, Inc & Par Pharmaceutical Companies, Inc. Represented by Advanced Biologics LLC

OBJECTIVE:

- ⊕ To discuss data experienced in the Phase 2A dose ranging study
- ⊕ The sponsor would like to discuss plans for further drug development

BACKGROUND:

- Meeting Request: N-023-MR, dated 18 April 2005.
- Meeting Package: N-028-MP, dated 10 June 2005.
- Meeting Submission: N-029-MS, dated 30 June 2005.

**FOOD AND DRUG ADMINISTRATION (FDA) PARTICIPANTS:
Center for Drug Evaluation and Research (CDER),
Division of Anti-Infective and Ophthalmology Products (DAIOP)**

Mark Goldberger, M.D., M.P.H. – Director, Office of Antimicrobial Products (ODE IV)
Janice Soreth, M.D. - Director
John Alexander, M.D., M.P.H. - Clinical Team Leader
Thamban Valappil, Ph.D. – Acting Statistics Team Leader
Christopher Khedouri, Ph.D. – Statistics Reviewer
Charles Bonapace, Pharm.D. - Acting Clinical Pharmacology Team Leader
Jeffrey Tworzyanski, Pharm.D. - Clinical Pharmacology Reviewer
Robert Osterberg, Ph.D. - Pharmacology/Toxicology Team Leader
Wendy Schmidt, Ph.D. - Pharmacology/Toxicology Reviewer
Frederic Marsik, Ph.D. - Microbiology Team Leader
Kyong Hyon - Regulatory Health Project Manager
Carmen DeBellis, R.Ph. - Regulatory Health Project Manager

SPONSOR PARTICIPANTS:

Optimer Pharmaceuticals, Inc.:

Youe-Kong Shue, - Vice President, Pre-Clinical Development
Pamela Sears, Ph.D. - Director, Biology
Starr Shangle, - CRA
Dr. Sherwood Gorbach, - Consulting Medical Director

Par Pharmaceuticals Companies, Inc.:

Lynn Kramer, M.D. - Senior Vice President Development and Medical Affairs
Shankar Hariharan, Ph.D. - Executive Vice President & Chief Scientific Officer
Don Cilla, Pharm D. - Executive Director Clinical Pharmacology & Clinical Operations

(b) (6)

Advanced Biologics:

Michael Corrado, M.D. - President & CEO
Howard Solomon, M.D. - COO
Ken Phillips, Ph.D. - Statistician
Annie Frimm, - Director Regulatory Affairs

DISCUSSION:

The questions for discussion below were submitted to the FDA by Ms. Frimm in the Meeting Package dated 10 June 2005. Preliminary FDA Pharmacology/toxicology (a-d) responses were faxed to the Sponsor on 12 June 2005, prior to this Type C Guidance Meeting. After opening remarks, the participants of this meeting discussed the FDA responses. Advanced Biologics presented slides at relevant times throughout the meeting.

Question #1:

Are the timing and design of the proposed studies adequate for NDA filing?

FDA Response:

No, please submit the results prior to initiating the Phase 3 trials. Please note that the danger of targeting a PK level, especially if vehicles or doses change, is no longer relevant at the end of clinical development. It is always relevant to use a minimally maternally toxic dose as the highest dose. (This is stated with the understanding that you have had difficulties getting to a toxic dose.)

We concur with conducting pilot studies. We concur with the use of the i.v. route, Use of concurrent TK studies is also appreciated.

Additional Discussion:

The FDA asked what dose was going to be used for these studies. The sponsor responded that 20 ml/kg is the maximum volume for administration for rodents. The sponsor stated that the IV route would be used in rodents in order to get maximum exposure.

Question #2:

Both OPT-80 and its primary metabolite, OP-1118, demonstrate very low plasma levels, with no evidence of accumulation; therefore, Optimer/Par feel this short term telemeterized study will be sufficient to demonstrate PAR-101's cardiac safety in animals. Does the agency concur?

FDA Response:

The intravenous route is definitely preferable to the oral route. Please justify the dose levels and the use of infusion rather than bolus dosing. In conjunction with the data from the ³H mass balance/tissue distribution, the plasma levels may allow this data to be placed in context in the overall risk/benefit assessment.

Additional Discussion:

The FDA stated that a maximum dose would be acceptable in reproductive studies even though plasma levels of PAR-101 and the primary metabolite levels were lower compared to humans.

Question #3:

Optimer/Par will be conducting a ³H-OPT-80 mass balance and distribution study in beagles. No further ADME studies are planned. Does the agency concur that this will be sufficient information to support an NDA filing?

FDA Response:

Depending on the conduct and results of the study, this may be adequate. Please be aware that depending on the label location, it may be labile and incorporated into other compounds other than OPT-80 and its immediate metabolites, thus making the results less useful. It MAY be useful to include metabolite profiling in plasma and urine (LC/MS/MS).

Additional Discussion:

The sponsor clarified that the previous submission indicating (b) (4) was in error and should have indicated 90mg/dog. The Agency questioned if the selected dose would provide high enough levels of drug and metabolite in the various compartments to allow detection. The sponsor replied that the doses being used were comparable to human doses and that activity of the labeled drug would be monitored.

The sponsor outlined the location of the labeled drug and indicated the site was stable and that it was not expected to be moved by metabolism. The sponsor will get back to the Agency with a vehicle when it is chosen.

Question #4

Optimer/PAR will have conducted a comprehensive preclinical pharmacology and toxicology program as outlined in the background package. Other than those studies complete or listed as "Planned/In progress" no other preclinical testing is planned. Does the Agency concur that the preclinical program will support an NDA filing?

***FDA Response:** The problem with the overall toxicology program at this time is that there is still no clear profile of toxicity with OPT-80. Because of the inability to tie toxicology studies to metabolism, to good quality mass balance studies, an accurate picture of the effects cannot be drawn. Further, as a plethora of vehicles have been used (and it is not clear what the human clinical vehicle will be), vehicle effects are not elucidated. A good quality oral or intravenous study in the dog of 3 month duration (with doses that elicit frank toxicity) has been recommended.*

Additional Discussion:

The issue is elucidating the full toxic potential of the compound. One way to achieve the goal, given that their compound has a low solubility, is to increase the duration of exposure.

Question #5

Optimer/Par will have conducted a "thorough" QT/QTc study per FDA Guidance. Based on positive preclinical results, and assuming that this clinical study's results demonstrate no significant effect, does the Agency concur that this study, will be sufficient to support an NDA filing?

Discussion:

The Agency stated that the results of the dog mass balance study and the hERG study should be reviewed before recommending a human QTc study. Due to low concentrations of OPT-80 and its metabolite in healthy volunteers observed in the Phase 2A study, a QTc study in healthy volunteers may not provide meaningful data unless the plasma concentrations are similar to those seen in patients. The Agency suggested that a study with intensive QT monitoring may be performed in the sicker intended population (CDAD).

The sponsor replied that the formulation to be used in the efficacy QTc study may be different than the earlier trials. The sponsor is assessing ways of enhancing the absorption of the compound so concentrations in the healthy intended population. If a

QTc trial is required the sponsor will test the formulation in a dose escalation study prior to conducting the study. Assessing the QTc prolongation with the proposed formulation in the sicker intended population may be problematic due to confounders such as underlying conditions and additional medications. The sample size may be difficult to calculate.

Question#6

Based on the efficacy and safety data obtained from the Phase 2A study, Optimer/Par plan to conduct one single, multinational, pivotal Phase 3 trial. Is the proposed Phase 3 study design adequate for proof of efficacy for CDAD?

Discussion:

The Agency expressed concern that there are not sufficient data from the Phase 2A trial to choose a dose for the Phase 3 study since all the doses showed similar results. The Agency suggested another adequately sized Phase 2 trial be done using 2 doses of PAR-101 versus a comparator to be able to more confidently choose a single dose for the Phase 3 trial.

The sponsor suggested that the following be planned for the Phase 3 clinical trial:

- Sparse PK sampling;
- Real-time monitoring of safety and PK parameters;
- Independent review of data by a Data Safety Monitoring Board;
- Periodic FDA/Sponsor teleconferences/meetings;
- An interim safety analysis.

There was some discussion about comparators for the study. (b) (4)

The sponsor should use vancomycin in the Phase 3 trial to show the likely effects for comparison.

Conducting one pivotal trial that would demonstrate non-inferiority would not be sufficient. A second trial would be required. The Agency also stated that a single Phase 3 trial of non-inferiority that did not trend toward superiority would not give robust data for approval.

Question#7

Optimer/Par anticipates that by following this investigational plan they will have evaluated 350 subjects at the dose determined by their Phase 2A study. Is this an adequate population to support the safety for this indication for a drug which is virtually restricted to the gastrointestinal system?

Discussion:

The Agency stated that 300-600 patients on the clinical dose or higher would probably be sufficient to support safety, as long as there are no unanticipated safety problems identified. The Agency would actually prefer 500-600 patients. The Agency also stated that the number of patients needed to provide substantial evidence of efficacy (including additional phase 2 studies) would likely approach this range.

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/s/

John Alexander
8/22/2005 01:58:59 PM