

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201699Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

*****Pre-Decisional Agency Information*****

Date: April 21, 2011

To: Fariba Izadi, Pharm.D., Regulatory Project Manager
Division of Anti-Infective and Ophthalmology Products

Dmitri Iarikov, M.D., Ph.D., Medical Officer
Division of Anti-Infective and Ophthalmology Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications

Sheila Ryan, Pharm.D., Group Leader
Division of Drug Marketing, Advertising and Communications

Subject: NDA 201699
Dificid™ (fidaxomicin) tablets 200mg

As requested in your consult dated January 4, 2011, DDMAC has reviewed the draft labeling for Dificid™ (fidaxomicin) tablets 200mg.

Please note that a draft labeling review was sent via email to Fariba Izadi on April 13, 2011. The labeling has undergone substantial revisions since that date. This is an updated labeling review.

DDMAC's PI comments are based on the substantially complete version of the labeling titled, "# 2 Working copy NDA 201699 draft-labeling-text.doc" which was sent via email from Dr. Dmitri Iarikov on April 20, 2011.

DDMAC's comments are provided in the attached, marked-up version of the labeling.

If you have any questions about DDMAC's comments on the PI, please contact Christine Corser at 6-2653 or at Christine.Corser@fda.hhs.gov.

Thank you for the opportunity to provide comments on this label.

26 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/

CHRISTINE G CORSER
04/21/2011

MEMORANDUM

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

DATE: March 25, 2011

TO: John Alexander, M.D., Team Leader, DAIOP
Division of Anti-Infective and Ophthalmology Products

FROM: Kassa Ayalew, M.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA or BLA: NDA 201699

APPLICANT: Optimer Pharmaceuticals, Inc.
Marc Lesnick, Ph.D.
Director, Regulatory Affairs
mlesnick@optimerpharma.com
10110 Sorrento Valley Rd., Suite C
San Diego, CA 92121
Tel: 858-909-0736
Fax: 858-909-0737

DRUG: Difucid (fidaxomicin tablets)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATIONS: For the treatment of *Clostridium difficile* infection (CDI) and prevention of recurrences.

CONSULTATION REQUEST DATE: December 14, 2010

DIVISION ACTION GOAL DATE: April 1, 2011

PDUFA DATE: May, 30, 2011

I. BACKGROUND:

Optimer Pharmaceuticals, Inc. submitted a new drug application NDA 201699 for Dificid (fidaxomicin tablets), on November 29, 2010 for the indication of treatment of *C. Difficile* infection (CDI) and prevention of recurrences. To support the approval, the Applicant provided data from two well controlled clinical trials (n= 1147) (Study 101.1.C.003 and Study 101.1.C.004).

A consult from DAIOP was received on December 14, 2010 because the data generated from the above studies are considered pivotal and inspections of the clinical sites are essential to verify the quality of conduct of these studies for this NDA. The sites are selected due to enrollment of large numbers of study subjects, high number of INDs and lack of previous inspectional history.

Study 101.1.C.003 was a multi-national, multi-center, double-blind, randomized, parallel group study to compare the safety and efficacy of 200 mg PAR-101 taken q12h with 125 mg vancomycin taken q6h for ten days in subjects with *clostridium difficile*-associated diarrhea. A total of 629 subjects at 99 clinical sites in the US and Canada were randomized into the study.

Study 101.1.C.004 is similar in design to Study 101.1.C.003 and was conducted in 664 subjects in Belgium, France, Germany, Italy, Spain, Sweden, and the United Kingdom in addition to the US and Canada.

The sites requested for clinical inspections were the two domestic clinical investigators with the largest number of enrolled patients, Drs. Kathleen Mullane, Thomas Sheftel, and three foreign clinical investigators, Drs. Andre Poirier (Canada), Thomas, Louie (Canada) Roberto Esposito (Italy) and the sponsor (Optimer Pharmaceuticals, Inc.). Inspection of Dr. Thomas Sheftel (Site 11, Study 101.1.C.003) was initially scheduled along with the other 4 CI sites and the sponsor, however, it was subsequently cancelled due to scheduling conflicts and resource limitations. FDA's Atlanta District Office could not provide sufficient resources to conduct the inspection prior to late May 2011.

II. RESULTS (by Site): There was 5 sites inspected:

Name of CI, IRB, or Sponsor Location	Protocol # and # of Subjects:	Inspection Date	Final Classification
Kathleen Mullane, M.D. University of Chicago, 5841 S. Maryland Ave., M/C 5065 kmullane@medicine.bsd.uchicago.edu Chicago, IL 60637	Study 101.1.C.003/ Site # 9/n=56 Study No. 101.1.C.004/ Site # 178/n=20	January 19-February 1, 2011.	Pending (Interim classification: VAI)
Thomas Sheftel, M.D. Wellstar Infectious Disease, 55 Whitcher Street Marietta, GA 30060	Study 101.1.C.003 / Site # 11/n=43	N/A	Cancelled
Andre Poirier, M.D. Centre hospitalier régional de Trois-Rivières, 1991 du Carmel Trois-Rivieres QC, G8Z 3R9 Canada	Study 101.1.C.004/ Site # 189/ n=28	March 7, 2011-March 10, 2011	Pending (Interim classification: NAI)
Thomas, Louie, M.D. University of Calgary, Foothills Medical Center, AGW5, Infection Prevention and Control, 1403-29th Calgary, AB T2N 2T9 Canada	Study 101.1.C.003 / Site # 1/ n=88	February, 28, 2011-March 3, 2011	Pending (Interim classification: VAI)
Roberto Esposito, M.D. Policlinico di Modena, Clinica della Malattie Infettive e Tropicali via del Pozzo 71 Modena, IT, 41100	Study 101.1.C.004/ Site ID 69/n=21	February, 21, 2011-February, 24, 2011	Pending (Interim classification: VAI)
Optimer Pharmaceuticals, Inc. 10110 Sorrento Valley Rd., Suite C San Diego, CA 92121	Study 101.1.C.003: Kathleen Mullane, DO., Thomas Sheftel, M.D., Thomas Louie, M.D., Study 101.1.C.004: Kathleen Mullane, DO., Andre Poirier, M.D., Roberto Esposito, M.D.	January 19, 2011-February 1, 2011.	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary

communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Kathleen Mullane, M.D.

University of Chicago, 5841 S. Maryland Ave., M/C 5065
kmullane@medicine.bsd.uchicago.edu
Chicago, IL 60637

a. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811, between January 19- February 1, 2011.

A total of 76 subjects were enrolled into the 2 studies (Study 101.1.C.003 (n=56)/ Study No. 101.1.C.004 (n=20)) and 45 medical records were reviewed. For Study 101.1.C.003 a total of 580 patients were screened, 56 were enrolled, 54 completed the study and 1 subject withdrawn for AEs. For Study No. 101.1.C.004 a total of 258 patients were screened, 20 were enrolled, 19 completed the study and 2 subjects withdrawn for AEs. There was no evidence of under reporting of adverse events or protocol deviations. Primary efficacy endpoint was verifiable for all subject records reviewed.

The inspection evaluated informed consent and included review of source documents. Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequate adverse experience reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. General observations/commentary:

The inspection of Dr. Kathleen Mullane's site revealed that the studies were not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator, mainly for:

- I. Failure to adequately report all changes in research activity to Institutional Review Board prior to implementation. For example,
 - a) Specifically, regarding Protocol 003, approval to enroll additional subjects was not obtained on two occasions. Initial IRB approval was to enroll 10 subjects. At this site twelve subjects were enrolled before approval was sought to increase enrollment. The IRB did not approve enrollment of greater than 50 subjects at this site. The CI enrolled a total of 56 subjects.

DSI Reviewer Comments: The clinical investigator failed to obtain approval prior to enrollment of additional subjects on two occasions. IRB approval should have been obtained in accordance with the investigational plan. Dr. Mullane's response, dated 02/14/2011, to the Form FDA 483 issued acknowledged the finding identified during inspection and affirms

that all clinical trials at this site are now required to document accrual of subjects into electronic Clinical Trials Management System, and suggested that this documentation will allow better real time management of patient enrollment and easier PI monitoring of regulatory documentation. Although the clinical investigator failed to obtain an IRB approval about changes in the number of subjects, which is a regulatory violation, the violation is unlikely affect the overall reliability of safety and efficacy data from the site.

- II. Failure to use informed consent approved by the IRB and to properly document dates by the subject or the subject's legally authorized representative at the time of consent. For example,
- a) In study 003, 16 of 56 consents were not personally dated by the subject. The CI dated the consent forms.

DSI Reviewer Comments: *The clinical investigator should have ensured proper documentation of dates by the subject or the subject's legally authorized representative at the time of consent. This should have been conducted in accordance with the investigational plan. The CI's response, dated 02/14/2011, to the Form FDA 483 issued acknowledged the findings identified above and affirms that the CI no longer assists patients in completing the consent form. Although, the CI failed to obtain informed consent properly, the observed regulatory violation does not appear to significantly affect reliability of safety and efficacy data from the site.*

- b) In study 003, two subjects (subjects 049 and 050) signed the version 12 FEB 2008 of the consent form which was not the IRB approved consent form at the time of their enrollment (the IRB had approved a newer version on 06 MAR 2008).

DSI Reviewer Comments: *The CI's response, dated 02/14/2011, to the Form FDA 483 issued acknowledged the finding identified above. Subject 049 was enrolled 11APR08 and subject 050 on 08MAY08 using the 12FEB08 version of consent instead of the 06MAR08 version, in error. When this was noted, the subjects had completed the trial and follow-up period. The newer version of the consent form that was approved by the IRB on 06 MAR 2008 included information about addition of new sites to the study, notification of change in sponsor (b) (4) to Optimer with (b) (4) as the Contract Research Organization monitoring the trial, additional animal data which did not alter the risk profile of the study medication, and alteration in language of some of the inclusion and exclusion criteria for entry into the study that did not apply to subjects 049 and 050. Although, the CI failed to use the appropriate version of the informed consent, it appears that the newest version of the consent did not have major differences with the older version. The CI's response, dated 02/14/2011, to the Form FDA 483 issued acknowledged the finding identified above and states that since*

the conduct of this trial, the IRB has adopted a electronic system from which the latest version of the IRB approved and stamped consent form is available at all times from any institutional workstation for immediate download when initiating the consenting process with a study subject.

III. Failure to conduct the study in accordance with the signed statement of investigator and investigational plan. For example,

According to IB version 5.5, investigational product was to be stored at 36 to 46 °F. A memo dated 20AUG2008 further clarified that temperature logs were to be completed daily.

- a. For study 003 investigational storage temperatures were below the specified temperature range of 36-46°F from 31 MAR 2008 through 10 JUL 2008. For study 004 investigational drug temperatures were below 36°F on multiple occasions (17, 19, 22, and 29 SEP 2008; 6, 7, 13,14,16,21, and 29 OCT 2008, and 4 NOV 2008).

DSI Reviewer Comments: The clinical investigator reported to the sponsor to assess the impact of the temperature on the investigational product. The CI's response, dated 02/14/2011, to the Form FDA 483 issued acknowledged the finding identified above. The CI response also indicates that the sponsor provided approval that the study drug was eligible for distribution to the study subjects. Although the CI failed to store investigational drugs for multiple occasions within the permitted excursions according to the Investigator Brochure, based on the CMC review team, the 24-month stability data of drug product submitted by the sponsor demonstrates that the temperature excursions do not seem to affect product quality. This finding, which is a regulatory violation, is unlikely to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.

c. Assessment of data integrity:

Although regulatory violations were observed at this site, based on our review of the Form FDA 483, the establishment inspection report, the documents submitted with that report, and the 02/14/2011 written response to the Form FDA 483 Inspectional Observations, it is unlikely that the regulatory violations will significantly affect the overall reliability of safety and efficacy data from the site.

2. Thomas, Louie, M.D.

University of Calgary,
Foothills Medical Center,
AGW5, Infection Prevention and Control, 1403-29th
Calgary, AB T2N 2T9
Canada

a. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811, between February, 28, 2011-March 3, 2011.

At this site, a total of 340 subjects were screened, 89 subjects enrolled and 88 subjects completed the study (one subject withdrew consent). The inspection evaluated records of 53 subjects. There was no evidence of under reporting of adverse events or protocol deviations. Primary efficacy endpoint was verifiable for all subject records reviewed.

Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequate adverse experience reporting, and 5) handling of pharmacokinetic samples. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. General observations/commentary:

The inspection of Dr. Thomas Louie's site revealed that the studies were not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator, mainly for:

- I. Failure to conduct the study in accordance with the investigational plan. For example,
 - a. Subject # 001016 suffered an SAE that was reported as specified to the sponsor. However, the CI did not report this incident to IRB in a timely manner as specified under protocol section 10.2.2.1.
 - b. Subject # 001072 complained of fatigue and a cough at subsequent study visits. The CI did not record these events on the study iCRF. Under protocol section 10.2.1, all AEs, regardless of seriousness, severity, or perused relationship to study therapy, must be recorded using medical terminology in the source document and on the iCRF.
 - c. Per protocol section 4.2, Subjects are to have a *C. Difficile* positive test with in a 48 hour period of randomization. At least the following subjects were outside of this time period and enrolled in the study: Subjects #'d 001038, 001067, 001068, 001071, 001075, 001085, 001086, 001089.
 - d. Subject 001013 failed inclusion criteria by not having a *C. Difficile* positive test per protocol section 4.2. This subject was enrolled into and completed the study.
 - e. Per protocol section 9. 13, post-dose PK testing is to be performed within a

3-5 hour period of time. In at least the following Subjects, this testing was performed outside of this time frame: Subject #d 001007, 001008, 001015, 001019,001020,001035,001040,001071,001072,001073.

- f. Per protocol section 4.3, Subjects with any of the listed exclusion items shall be excluded from the study. The exclusion checklist for Subject 001018 had all the exclusion items checked 'Yes' and this subject was enrolled into and completed the study.

c. Assessment of data integrity:

Based on inspectional findings and the observations noted, efficacy and safety data obtained from this site are considered reliable.

Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

3. Optimer Pharmaceuticals, Inc.

10110 Sorrento Valley Rd.,
Suite C
San Diego, CA 92121

a. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.810, between January 19, 2011- February 1, 2011.

A review of all monitoring site visit reports for the selected six sites was conducted. Standard Operation Procedures for Monitoring and Monitoring Plans were reviewed and a few were collected. Optimer Pharmaceuticals, Inc. contracted selection and monitoring of clinical investigations to the CRO and therefore there was limited information available during the inspection.

The inspection evaluated the sponsor/monitor/CRO compliance program.

b. General observations/commentary:

The inspection of Optimer Pharmaceuticals, Inc.'s site revealed that the studies were not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator, mainly for:

- I. Failure to ensure proper monitoring of the study. For example,
 - a. Protocol violations that were identified during interim monitoring visit trip

reports were not reported to the sponsor's data tabulation submitted to the FDA.

- i. A Monitoring Visit Trip Report dated 5,6,7-Feb-2007 for clinical investigator site #001, revealed a protocol deviation for subject 001009 who did not have a post dose PK drawn on day one. This was not reported as a protocol deviation in the data tabulations.

***DSI Reviewer Comments:** Although the sponsor did not include this protocol deviation for subject 001009, who did not have a post dose PK drawn on day one, in the data listing under protocol deviation, based on DSI's review of the EIR and the Applicant's response, the protocol deviation has been documented and reported. In addition the observation was an isolated occurrence. This finding, which is a regulatory violation, is unlikely to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.*

- ii. A Monitoring Visit Trip Report dated 27-Apr-2007 for clinical investigator site #009 revealed a protocol deviation for subject 009005 who was on Flagyl (metronidazole) and Vancomycin while the subject was still on study. This was not reported as a protocol deviation in the data tabulations.

***DSI Reviewer Comments:** No other drugs potentially useful in the treatment of CDAD (e.g., oral vancomycin, metronidazole, etc.) should have been given during the trial unless they are specifically given because of a primary treatment failure or recurrence. Subject 009005 who received Flagyl (metronidazole) and Vancomycin while the subject was still in the study should have been reported as a protocol deviation in the data tabulations. The sponsor should have documented this protocol violation in the data listing under protocol deviation.*

Although the sponsor failed to report the protocol violation as required by the protocol, based on DSI's review of the EIR and the Applicant's response, the above violation was reported to FDA.

This finding, which is a regulatory violation, is unlikely to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.

- b. During the review of data tabulations against Case Report Forms for clinical investigator site #011, Subject No. 011069, a CDAD Assessment, End of Therapy, dated 13/May/2008, question 5, "Does the subject have WBC > 13,000/ mm³ revealed a response of "Missing". However there was a laboratory report dated 13/May 2008 which was imported into the database revealing the WBC results.

DSI Reviewer Comments: Applicant's response indicates that subject No. 011069 had WBC > 13,000/mm³. Although the clinical investigator initially reported as WBC measurement was "Missing", based on DSI's review of the EIR and the Applicant's response, the subject's WBC measurement was eventually reported to the sponsor. The finding is unlikely to impact data reliability, safety and welfare of subjects in the study.

c. Assessment of data integrity:

Although regulatory violations were observed at this site, it is unlikely based on the nature of the violations and the availability of alternative source documentation to confirm subject dosing, that they significantly affect the overall reliability of safety and efficacy data from the site.

4. Roberto Esposito, M.D.

Policlinico di Modena,
Clinica della Malattie
Infettive e Tropicali via del Pozzo 71
Modena, IT, 41100

a. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811, between February 21, 2011- February 24, 2011.

At this site, a total of 74 subjects were screened, 21 subjects were enrolled and 20 subjects completed the study (one subject withdrawn consent). The inspection evaluated informed consent and included review of source documents and hard copy reporting for 21 subjects. The primary efficacy endpoint data was verifiable.

Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequate adverse experience reporting, and 5) handling of pharmacokinetic samples. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. General observations/commentary:

The inspection of Dr. Roberto Esposito's site revealed that the studies were not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator, mainly for:

- I. Failure to conduct the study in accordance with the investigational plan. For example,

- a. Subject # 069009 took 6 doses of metronidazole from 04 Oct. 2008 to 06 October 2008. This subject was included in the study on 06 Oct.2008. This subject met the criteria to be excluded from the study under exclusion criteria # 6 which states concurrent use of this drug is allowed as long as it is no more than 24 hours of treatment at the time of enrollment.

***DSI Reviewer Comments:** Although the CI failed to exclude this subject from the study, based on DSI's review of the EIR and the Applicant's response dated February 25, 2011 (received March 10, 2011), the CI asked the sponsor for the Protocol Deviation Waiver regarding the Eligibility Criteria for this subject. This has been documented in the study subject's chart and the CI reported this subject as having failed to meet inclusion and exclusion criteria. The protocol deviation has been also documented and reported to the sponsor. This finding is unlikely to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.*

- b. Subject #069009 was treated for a urinary tract infection (UTI) on 17 October, 2008 within the post therapy follow up period of time for the research drug. The investigator did not report this condition as an adverse event.

***DSI Reviewer Comments:** The CI failed to report UTI as an adverse event. Based on DSI's review of the EIR and the Applicant's response dated February 25, 2011 (received March 10, 2011), although it is a regulatory violation, the finding was isolated and unlikely to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.*

- c. Subject #069009 was prescribed ciprofloxacin on 17 October 2008 for UTI during the post therapy follow up period of time for the research drug. The investigator did not report this drug as concomitant medication.

***DSI Reviewer Comments:** The CI failed to report ciprofloxacin as concomitant medication. Based on DSI's review of the EIR and the Applicant's response dated February 25, 2011 (received March 10, 2011), although it is a regulatory violation, the finding was isolated and unlikely to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.*

II. Failure to prepare or maintain accurate case history with respect to observations and data pertinent to the investigation. For example,

- a. Data reported in the Trial Master database at end of therapy for subject # 069009 was not accurate. The reporting criteria asks for a "Yes" or "No" response if the WBC count > 13,000/ul. The reported value was "No" , however the (b) (4) blood test results obtained for the collection date 15 Oct. 2008 had a WBC count value of 16,340/ul and the correct response

should have been recorded as “Yes:

***DSI Reviewer Comments:** The CI failed to report accurate WBC count for this subject at one point during the study. Based on DSI’s review of the EIR and the Applicant’s response to the Form FDA 483 issued (dated February 25, 2011 (received March 10, 2011)), which acknowledged the finding identified above, although it is a regulatory violation, the finding was isolated. The finding is also unlikely to impact data reliability, safety and welfare of subjects in the study.*

c. Assessment of data integrity:

Although regulatory violations were observed at this site, it is unlikely, based on the nature of the violations and the availability of alternative source documentation to confirm subject dosing, that they significantly affect the overall reliability of safety and efficacy data from the site.

Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

5. Andre Poirier, M.D.

Centre hospitalier régional de Trois-Rivières, 1991 du Carmel
Trois-Rivieres QC, G8Z 3R9
Canada

a. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811.

At this site, a total of 163 subjects were screened and 28 subjects enrolled and 26 subjects completed the study (subjects 189006 & 189009 were withdrawn; 189006 for SAE/Pneumonia & 189009 withdrawn due to false positive on C. diff Antitoxin test). The inspection evaluated informed consent and included review of source documents and hard copy reporting for 28 subjects. The efficacy endpoint data were verifiable.

Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequate adverse experience reporting, and 5) handling of pharmacokinetic samples. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. General observations/commentary:

The inspection of Dr. Andre Poirier’s site did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

c. Assessment of data integrity:

Based on the preliminary information provided for this site, data derived from Dr. Andre Poirier's site are considered acceptable.

Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The preliminary classification of Clinical Investigator inspections of Drs. Kathleen Mullane, Dr. Roberto Esposito are Voluntary Action Indicated (VAI), based on preliminary communications with the FDA field investigator. The preliminary classification of Clinical Investigator inspections of Dr. Andre Poirier is No Action Indicated (NAI). The inspection of Dr. Thomas Sheftel has been cancelled due to scheduling conflicts and resource limitations. Specifically, FDA's Atlanta District Office could not provide sufficient resources to conduct the inspection of Dr. Sheftel prior to late May 2011. The final classification of the sponsor/applicant, Optimer Pharmaceuticals, Inc. is VAI.

Notwithstanding inspection observations noted for Dr.'s Mullane and Esposito, as well as the sponsor, these findings are unlikely to importantly impact efficacy and safety data reliability. The data from this sponsor to the agency in support of NDA 201699 appear reliable based on available information.

The preliminary classifications are based on the preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

{See appended electronic signature page}

Kassa Ayalew, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D. for
Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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

/s/

KASSA AYALEW
03/25/2011

LAUREN C IACONO-CONNORS
03/25/2011



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: March 10, 2011

To: Wiley Chambers, MD, Director
Division of Anti-infective and Ophthalmology Products

Through: Irene Z. Chan, PharmD, BCPS, Acting Team Leader
Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Loretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name: Difucid (Fidaxomicin Tablets)
200 mg

Application Type/Number: NDA 201699

Applicant: Optimer Pharmaceuticals Inc.

OSE RCM #: 2010-2650

1 INTRODUCTION

This review evaluates the proposed container labels, carton and insert labeling for Difucid (Fidaxomicin Tablets), 200 mg. The labels and labeling were submitted on November 29, 2010.

2 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels and carton and insert labeling submitted as part of the November 29, 2010 submission (see Appendices A through C).

- Container labels, 20-count and 60-count
- Blister labels, 10-count
- Carton labeling for 20-count bottle, 60-count bottle, and 100-count blisters
- Insert labeling (no image)

3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels, carton labeling, and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 *Comments to the Division* for discussion during the review team’s label and labeling meetings. Section 3.2 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Brantley Dorch, at 301-796-0150.

3.1 COMMENTS TO THE DIVISION

A. General Comments

The Applicant has utilized trailing zeros in tables within the insert labeling (i.e., Tables 1, 2, 5, and 7). Trailing zeros can lead to 10-fold errors in dosing. DMEPA recommends removing all trailing zeros with the exception of when it is required to demonstrate the level of precision of the value being reported, such as for laboratory results, imaging studies that report size of lesions, or catheter/tube sizes.

B. Highlights Of Prescribing

1. The route of administration is not stated. The current statement is “Difucid (fidaxomicin tablets) (b) (4) Additionally, (b) (4) We recommend the statement be revised to read: “Difucid (fidaxomicin tablets) for oral use” as per 21CFR 201.57(a)(2).
2. Dosage and Administration—The route of administration is not included in the dosage and administration statement. Revise the statement to read: “200 mg tablet orally twice daily for 10 days with or without food”.

C. Full Prescribing Information

1. Section 2 Dosage and Administration, 2.1 (b) (4) does not state the route of administration. We recommend revising the statement to read:

“The recommended dose is one 200 mg Difucid tablet orally twice daily for 10 days with or without food.”

2. Section 7 contains the statement (b) (4) (b) (4). The dose designation “μg” (micrograms) is on the Institute for Safe Medication Practices (ISMP) “List of Error-Prone Abbreviations Symbols and Dose Designations” because it may be confused as “mg” (milligrams)¹. Therefore, the correct dose designation “mcg” (micrograms) should be used instead.
3. Sections 3 and 16 describe Difucid tablets as (b) (4). This description may be confusing and it appears it could be simplified to “oblong tablets”. However, we defer to CMC on the correct description of the tablets.
4. Section 16, *How Supplied/Storage and Handling*, has one notation for the NDC number. There are three packaging configurations (i.e., 20-count, 60-count, and 100-count) so the NDC number for each packaging configuration should be included in this section of the insert labeling.

3.2 COMMENTS TO THE APPLICANT

A. General Comments for all Container Labels and Carton Labeling

1. There is no statement of strength on the container labels and carton labeling. Place the statement of strength on the principal display panel immediately below the established name.
2. The net quantity statement is located in a prominent location on the principal display panel. 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.

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) (b) (4). These statements are unnecessary and add clutter to the labels.

¹ Institute for Safe Medication Practices. List of Error-Prone Abbreviations, Symbols, and Dose Designations. Available at <http://www.ismp.org/Tools/errorproneabbreviations.pdf>.

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.

5 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/

LORETTA HOLMES
03/10/2011

IRENE Z CHAN
03/10/2011

CAROL A HOLQUIST
03/10/2011

DSI CONSULT: Request for Clinical Inspections

Date: 12/14/2010

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP 2
Jean M. Mulinde, M.D., Acting Team Leader, GCP 2
Kassa Ayalew, M.D. Medical Officer
Division of Scientific Investigations
Office of Compliance/CDER

Through: Dmitri Iarikov, M.D., Medical Officer, DAIOP
John Alexander, M.D., M.P.H. Team Leader, DAIOP

From: Fariba Izadi, Pharm.D., Regulatory Health Project Manager/DAIOP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-201699

Optimer Pharmaceuticals (Regulatory Contact: Marc Lesnick, Ph.D.)

Phone: 858-9090-736

Email: mlesnick@optimerpharma.com

Drug Proprietary Name: Difucid (fidaxomaicin tablets)

NME or Original BLA (Yes/No): Yes

Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication: for the treatment of Clostridium difficile infections (CDI) and prevention of recurrences

PDUFA: 05-30-2011

Action Goal Date: 05-30-2011

Inspection Summary Goal Date: 4-01-2011 (Preliminary Comments for Inspection Sites sent before March 15, 2011 would be appreciated.)

DSI Consult

Reference ID: 2880103

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site ID 69 Roberto Esposito, M.D. Policlinico di Modena, Clinica della Malattie Infettive e Tropicali via del Pozzo 71 Modena, IT, 41100 Phone: 0039 059 422 3673 esposito.roberto@unimore.it	Study 101.1.C.0 04	n=21	Treatment of Clostridium difficile infection (CDI) and prevention of recurrences.
Site # 1 Thomas, Louie, M.D. University of Calgary, Foothills Medical Center, AGW5, Infection Prevention and Control, 1403-29th Calgary, AB T2N 2T9 Canada Phone: 403 944-1496 Fax: 403-944-2484 thomas.louie@calgaryhealthregion.ca	Study 101.1.C.0 03	n=88	Treatment of Clostridium difficile infection (CDI) and prevention of recurrences.
Site # 189 Andre Poirier M.D. Centre hospitalier régional de Trois-Rivières, 1991 du Carmel Trois-Rivieres Canada andre_poirier_chrtr@ssss.gouv.qc.ca Phone # 819 697 3333 #68881 Fax # 819 371 5007	Study 101.1.C.0 04	n=28	Treatment of Clostridium difficile infection (CDI) and prevention of recurrences.
Site # 11 Thomas Sheftel, M.D. Wellstar Infectious Disease, 55 Witcher Street Marietta,GA Thomas.Sheftel@wellstar.org 770-429-0083 770-425-0137	Study 101.1.C.0 03	n=43	Treatment of Clostridium difficile infection (CDI) and prevention of recurrences.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site # 9/ site # 178/ Kathleen Mullane, M.D. University of Chicago, 5841 S. Maryland Ave., M/C 5065 kmullane@medicine.bsd.uchicago.edu Chicago, IL 60637 Phone #: 773-702-3756 Fax #: 773-702-8998	Study 101.1.C.003	n=56	Treatment of Clostridium difficile infection (CDI) and prevention of recurrences.
Sponsor: Optimer Pharmaceuticals, Inc. Marc Lesnick, Ph.D. Director, Regulatory Affairs mlesnick@optimerpharma.com 10110 Sorrento Valley Rd., Suite C San Diego, CA 92121 Tel: 858-909-0736 Fax: 858-909-0737	Study 101.1.C.003	n=20	Treatment of Clostridium difficile infection (CDI) and prevention of recurrences.
Study 101.1.C.004	Study 101.1.C.004		

III. Site Selection/Rationale

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify): *Dr. Roberto Esposito's site had higher 100% cure rate, Dr. Andre Poirier's site cure rate was 93%.*
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): inspection history, number of INDS in CDER Database, NME

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other : inspection history, number of INDS in CDER Database

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

The documentation of the following needs to be verified:

1. The number of unformed bowel movements at study day 1 and day 3 (dataset XU.xpt; variable XUOPRES in data tabulation dataset)
2. The presence of either toxin A or B of *Clostridium difficile* in the stool within 48 hours of randomization

Should you require any additional information, please contact Fariba Izadi, Pharm.D., Regulatory Health Project Manager at 301-796-0563 or Dimitri Iarikov, M.D. Medical Officer, at 301-796-2292.

Concurrence: (as needed)

Medical Team Leader

Medical Reviewer

Division Director (for foreign inspection requests or requests for 5 or more sites only)

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
12/17/2010

KATHERINE A LAESSIG
12/17/2010