

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201699Orig1s000**

**CHEMISTRY REVIEW(S)**

**NDA 201-699**

**DIFICID™**  
**(fidaxomicin) tablets, 200 mg**

**Optimer Pharmaceuticals, Inc.**

**Balajee Shanmugam, Ph.D**  
**Division of Pre-Marketing Assessment, Branch V**  
**ONDQA**

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# Chemistry Review Data Sheet

1. NDA 201-699
2. REVIEW #:2
3. REVIEW DATE: 05-MAY-2011
4. REVIEWER: Balajee Shanmugam, Ph.D.
5. PREVIOUS DOCUMENTS: NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed  
Amendment

Document Date  
03-May-2011

7. NAME & ADDRESS OF APPLICANT:

Name: Optimer Pharmaceuticals, Inc.  
Address: 10110, Sorrento Valley Road, Suite C, San Diego,  
CA 92121.  
Representative: Marc Lesnick, Ph.D.  
Telephone: 858-909-0736 ext. 166

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: DIFICID™
- b) Non-Proprietary Name (USAN): fidaxomicin
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b) (1)

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 200 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

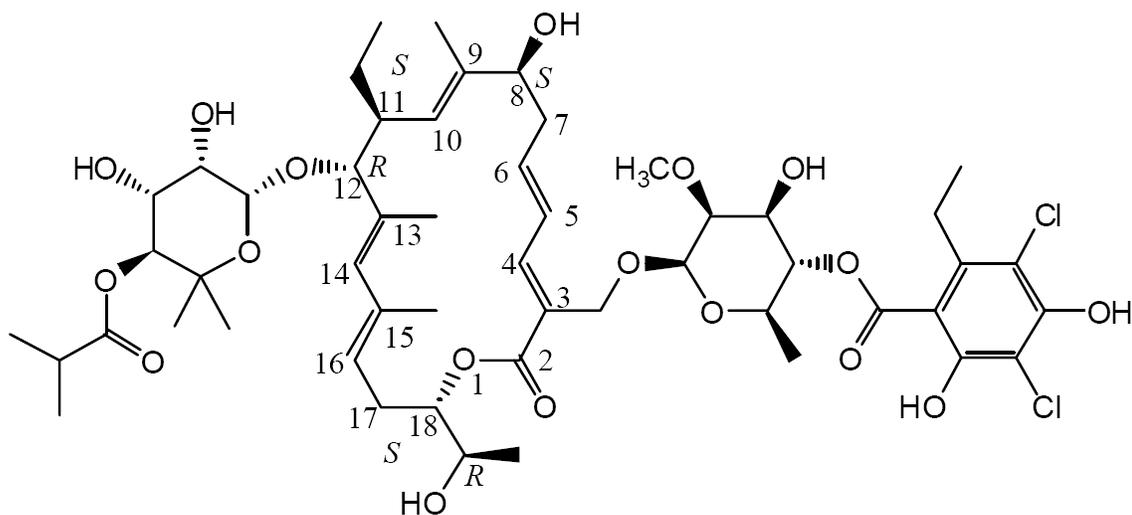
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Fidaxomicin – Oxacyclooctadeca-3,5,9,13,15-pentaen-2-one, 3-[[[6-deoxy-4-*o*-(3,5-dichloro-2-ethyl-4,6-dihydroxybenzoyl)-2-*o*-methyl- $\beta$ -D-mannopyranosyl]oxy]methyl]-12-[[6-deoxy-5-C-methyl-4-*o*-(2-methyl-1-oxopropyl)-  $\beta$ -D-*lyxo*-hexopyranosyl]oxy]-11-ethyl-8-hydroxy-18-[(1*R*)-1-hydroxyethyl]-9,13,15-trimethyl-, (3*E*, 5*E*, 8*S*, 9*E*, 11*S*, 12*R*, 13*E*, 15*E*, 18*S*)

Molecular formula: C<sub>52</sub>H<sub>74</sub>Cl<sub>2</sub>O<sub>18</sub>

Molecular weight: 1058.04

CAS: 380636-75-9



## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

Please see CMC review #1

### B. Other Documents:

## 18. STATUS:

Please see CMC review #1

Chemistry Assessment Section

# The Chemistry Review for NDA 201-699

## The Executive Summary

### Recommendation and Conclusion on Approvability

The NDA has provided sufficient/adequate information to assure identity, strength, purity and quality of the drug product. An overall "Acceptable" recommendation of the site has been made by the Office of Compliance. The revised labels are acceptable. Therefore, from the CMC perspective, there is no change to our earlier recommendation of Approval of the NDA.

### Chemistry Assessment

Please refer to chemistry review 1 by this reviewer for details on drug substance and drug product. Since writing the first chemistry review, Optimer submitted the revised carton and container label (amendment dated 03-May-2011) and is the subject of this review. (b) (4)

The company accepted the recommendation and submitted the revised labels.

(b) (4)

## Chemistry Assessment Section

(b) (4)

Reviewer Comments

The revised labels have incorporated the recommendation and are adequate.

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/s/  
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BALAJEE SHANMUGAM  
05/09/2011  
N201699CMCReview2

RAPTI D MADURawe  
05/09/2011

# MEMORANDUM

**Date:** April 15, 2011

**To:** NDA 201-699

**From:** Terrance Ocheltree, Ph.D., R. Ph.  
Division Director  
Division II, ONDQA

**Subject:** Tertiary review of ONDQA recommendation for NDA 201-699 Difacid™ (fidaxomicin) Tablets, 200 mg.

I have assessed the ONDQA reviews of NDA 201-699 by Balajee Shanmugam, Ph.D. and Elsbeth Chikhale, PhD. Both the CMC and Biopharmaceutics reviews were finalized on April 14, 2011 with a recommendation for Approval. On December 30, 2010 the Office of Compliance recommended “Acceptable” for the proposed manufacturing and testing sites, as shown in EES on April 15, 2011. Sufficient information has been provided to assure identity, strength, purity and quality.

As part of a post marketing commitment the applicant has agreed to include a test for the <sup>(b) (4)</sup> in the drug substance specification and submit a change-being-effect (CBE-0) supplement within six (6) months of the application approval when the method has been validated. During this time (6 months post approval), the applicant will test for <sup>(b) (4)</sup>

NDA 201-699 is an immediate release film coated tablet containing 200 mg of fidaxomicin indicated for the treatment of *clostridium difficile* associate with diarrhea. The proposed commercial packaging is a 30 cc and 60 cc HDPE bottles, with a child-resistant closure and blister pack. A 24 months expiration period has been requested and granted when the product is stored at 25°C (77°F) with excursions permitted to 15-30°C.

I concur with the “Approval” recommendation from a CMC perspective and the CMC related post marketing commitment.

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/s/  
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TERRANCE W OCHELTRIE  
04/18/2011

**NDA 201-699**

**DIFICID™**  
**(fidaxomicin) tablets, 200 mg**

**Optimer Pharmaceuticals, Inc.**

**Balajee Shanmugam, Ph.D**  
**Division of Pre-Marketing Assessment, Branch V**  
**ONDQA**

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# Chemistry Review Data Sheet

1. NDA 201-699
2. REVIEW #: 1
3. REVIEW DATE: 10-MAR-2011
4. REVIEWER: Balajee Shanmugam, Ph.D.
5. PREVIOUS DOCUMENTS: NA
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original (rolling submission)	04-Nov-2010
Amendment	29-Nov-2010
Amendment	01-Dec-2010
IR Response	04-April-2011
IR Response (email)	11-April-2011

7. NAME & ADDRESS OF APPLICANT:

Name: Optimer Pharmaceuticals, Inc.  
Address: 10110, Sorrento Valley Road, Suite C, San Diego,  
CA 92121.  
Representative: Marc Lesnick, Ph.D.  
Telephone: 858-909-0736 ext. 166

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: DIFICID™

- b) Non-Proprietary Name (USAN): fidaxomicin  
c) Code Name/# (ONDC only):  
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
  - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b) (1)

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 200 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

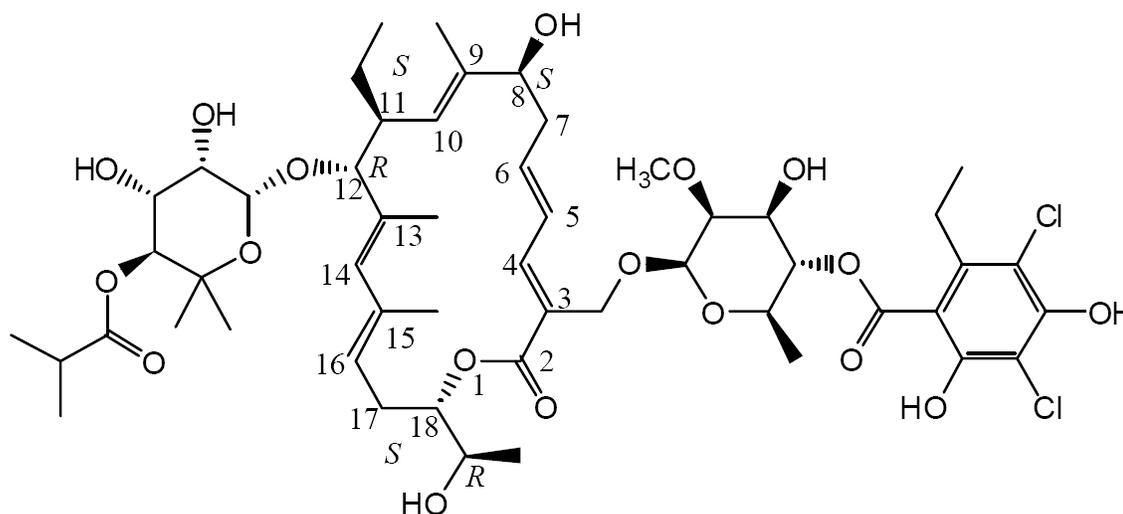
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Fidaxomicin – Oxacyclooctadeca-3,5,9,13,15-pentaen-2-one, 3-[[[6-deoxy-4-*o*-(3,5-dichloro-2-ethyl-4,6-dihydroxybenzoyl)-2-*o*-methyl- $\beta$ -D-mannopyranosyl]oxy]methyl]-12-[[6-deoxy-5-C-methyl-4-*o*-(2-methyl-1-oxopropyl)-  $\beta$ -D-*lyxo*-hexopyranosyl]oxy]-11-ethyl-8-hydroxy-18-[(1*R*)-1-hydroxyethyl]-9,13,15-trimethyl-, (3*E*, 5*E*, 8*S*, 9*E*, 11*S*, 12*R*, 13*E*, 15*E*, 18*S*)

Molecular formula: C<sub>52</sub>H<sub>74</sub>Cl<sub>2</sub>O<sub>18</sub>

Molecular weight: 1058.04

CAS: 380636-75-9



**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS	
(b) (4)	IV	[REDACTED]	[REDACTED]	(b) (4)	4	Adequate	15-Feb-2011	N/A
	III			3, 4	Adequate	27-Feb-2011	N/A	
	III			3, 4	Adequate	1-March-2011	N/A	
	III			3, 4	Adequate	1-March-2011	N/A	
	III			4	Adequate	2-March-2011	N/A	
	III			3,4	Adequate	2-March-2011	N/A	
	III			3,4	Adequate	2-March-2011	N/A	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

## 18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	13-AUG-10	
Pharm/Tox	Acceptable	28-MAR-11	W. Schmidt
Biopharm	Acceptable	13-APR-11	E. Chikhale
Methods Validation	Not requested	-	
EA	Categorical exclusion	31-JAN-2011	B. Shanmugam
Microbiology	NA	-	-

# The Chemistry Review for NDA 201-699

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The NDA has provided sufficient/adequate information to assure identity, strength, purity and quality of the drug product. An overall “Acceptable” recommendation of the site has been made by the Office of Compliance. Labeling is currently under negotiation but from chemistry standpoint it is adequate. Therefore, from the CMC perspective, this NDA is recommended for approval.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

For Phase 4 CMC commitment, per Agency’s recommendation, the company has agreed to include a test for (b) (4) in the drug substance specification by submitting a supplement (CBE-0) within 6-months of approval of the application. Though not part of the Phase 4 commitment, the firm should, as committed in the submission, continue to monitor the stability of the drug product.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Fidaxomicin is formulated as an immediate release tablet containing 200 mg of fidaxomicin. The tablets are white to off-white film coated, (b) (4) tablet, debossed with “FDX” on one side and “200” on the other side. The manufacture of the drug product involves (b) (4)

The drug product stability data provided for the 200 mg dosage strength supports the requested expiration date of 24-months when stored at 20°C-25°C.

The drug substance fidaxomicin, a new molecular entity, is a macrolide antibacterial agent which acts by inhibiting transcription and more specifically, RNA polymerase. Fidaxomicin is oxacyclooctadeca-3,5,9,13,15-pentaen-2-one, 3-[[[6-deoxy-4-*o*-(3,5-dichloro-2-ethyl-4,6-dihydroxybenzoyl)-2-*o*-methyl-β-D-mannopyranosyl]oxy]methyl]-12-[[[6-deoxy-5-*C*-methyl-4-*o*-(2-methyl-1-oxopropyl)-β-D-*lyxo*-hexopyranosyl]oxy]-11-ethyl-8-hydroxy-18-[(1*R*)-1-hydroxyethyl]-9,13,15-trimethyl-, (3*E*, 5*E*, 8*S*, 9*E*, 11*S*, 12*R*, 13*E*, 15*E*, 18*S*). The drug substance occurs as a white to off-white powder and is poorly soluble in (b) (4). Fidaxomicin has poor solubility, poor permeability and absorption (BCS Biopharmaceutics Classification System, Class IV). Fidaxomicin is produced by fermentation by the actinomycete, *Dactylosporangium aurantiacum* (b) (4)

## Executive Summary Section

**B. Description of How the Drug Product is Intended to be Used**

Dificid™ is indicated for the treatment of *Clostridium difficile* associated diarrhea. The intended dosing for fidaxomicin is one 200 mg tablet twice a day. Fidaxomicin will be available in 200 mg strength. The requested expiration date of 24-months for product stored at 20°C-25°C is supported by adequate stability data.

**C. Basis for Approvability or Not-Approval Recommendation**

The original submission and the subsequent amendments submitted by the firm have provided adequate information describing the CMC for Dificid™ (fidaxomicin tablets).

The drug substance has been well characterized and the manufacturing process is well documented. The specification will ensure adequate control of the quality attributes and stability of the drug substance justifies the proposed expiry date. The impurities are qualified by toxicological studies and are discussed in this review. The acceptance criteria for some of the quality attributes have been successfully negotiated with the applicant, the details of which are provided in Section S.4.1.

The manufacture of the drug product has been adequately described. Dissolution, an important tablet performance quality attribute was reviewed by Dr. Elsbeth Chikhale, and was found to be adequate. All issues regarding the drug product specifications have been adequately negotiated with the applicant. The company has established key process parameters in the manufacture of the drug product. The applicant will continue to monitor the stability of the drug substance and drug product. All facilities provided in this NDA have been recommended Acceptable by the Office of Compliance.

In accordance to 21 CFR 314.50, the application provides adequate information on manufacturing and packaging procedures, in-process controls, methods, and specifications.

**III. Administrative****A. Reviewer's Signature**

{see Electronic Signature Page}

**B. Endorsement Block**

Balajee Shanmugam/  
Rapti Madurawe/

**C. CC Block**

Fariba Izadi/

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/s/  
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BALAJEE SHANMUGAM

04/14/2011

CMCReview

RAPTI D MADURAWA

04/14/2011

I concur with the primary reviewer's assessment that NDA 201,699 has provided adequate information to assure identity, strength, purity and quality of the drug product. I therefore concur with the recommendation of NDA approval from the CMC perspective.

Initial Quality Assessment  
Branch IV  
Pre-Marketing Assessment Division II

<b>OND Division:</b> DAIOP	
<b>NDA:</b>	201,699
<b>Applicant:</b>	Optimer Pharmaceuticals, Inc.
<b>Stamp Date:</b>	November 30, 2010
<b>PDUFA Date:</b>	May 30, 2011 (Priority review granted)
<b>Trademark:</b>	Dificid™
<b>Established Name:</b>	Fidaxomicin
<b>Dosage Form:</b>	Tablet, immediate release
<b>Route of Administration:</b>	Oral
<b>Indication:</b>	Treatment of <i>Clostridium difficile</i> infection (CDI) and reduction of recurrence when used to treat initial CDI
<b>PAL:</b> Rapti D. Madurawe	
	YES      NO
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/> <input type="checkbox"/>
<b>Comments for 74-Day Letter:</b>	<input type="checkbox"/> <input checked="" type="checkbox"/>

## Summary and Critical Issues:

### A: Summary

#### Introduction

NDA 201,699 provides for the new molecular entity, fidaxomicin. The drug substance, fidaxomicin, is an antibiotic obtained by fermentation. The drug product is an immediate-release film-coated tablet for oral use containing 200 mg of fidaxomicin per tablet. The drug product is packaged in two bottle configurations, 20-count and 60-count tablets per bottle, and in a blister pack configuration (b) (4).

Fidaxomicin is also known as tiacumicin B and by the code names OPT-80 and PAR-101. Fidaxomicin was developed under IND 64,435 (tablet) and (b) (4) (oral suspension).

NDA 201,699 was submitted as a rolling submission in the eCTD format. The NDA was granted a priority review.

The applicant refers to fidaxomicin as a novel antibiotic agent and the first representative of a new class of antibacterial called (b) (4). From a chemical structure perspective, fidaxomicin is a macrolide containing an 18-membered (b) (4) ring. Fidaxomicin, if approved, would be the first 18-member macrolide. (b) (4)

(b) (4)

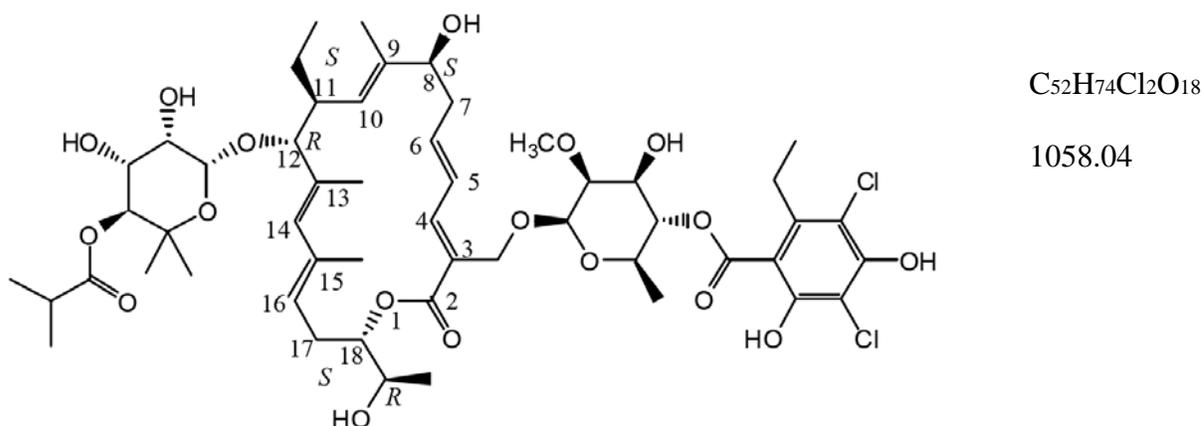
At the time of writing this IQA, the antibiotic class of fidaxomicin is not agreed upon and is under discussion with the applicant.

This initial assessment contains a brief summary of the NDA information. Critical issues and other potential review issues are discussed in section B and C, respectively.

## Drug Substance

Fidaxomicin drug substance (DS) is a white to off-white powder. Its structure is shown in Figure 1. Fidaxomicin is a new molecular entity obtained by the fermentation of *Dactylosporangium aurantiacum*. Although the applicant states the main constituent of fidaxomicin is (R)-Tiacumicin B, with the balance being a group of closely related analogs, NDA 201-699 provides for a single molecular entity, fidaxomicin.

**Figure 1: Structure of Fidaxomicin DS**



The drug substance (DS) is manufactured by

(b) (4)

(b) (4)

The applicant has determined fidaxomicin to be a BCS Class IV compound (low solubility, low permeability) by an in vitro BCS study.

(b) (4)

The DS is freely soluble in  
Solubility information in other organic solvents is included in the NDA.

(b) (4)

The structure of fidaxomicin is characterized by

(b)

(4)

. Its

Initial Quality Assessment

stereochemistry is determined by 1D and 2D homonuclear and heteronuclear NMR. (b) (4)

The applicant claims that fidaxomicin as manufactured by their current process does not exhibit (b) (4)

(b) (4)

(b) (4)

Early pre-clinical DS batches were made at (b) (4) Phase 1 and Phase 2 DS batches were made by (b) (4) Three Phase 3 DS batches were made at (b) (4) the commercial manufacturing site, at a batch size of (b) (4) These are also the primary DS registration batches and the yield indicates they were manufactured at the commercial scale. Various toxicity studies were conducted with DS batches from (b) (4)

DS specifications are shown in Table 1. (b) (4) (b) (4)

**Table 1: Proposed DS Specification**

(b) (4)



The DS has many related substance impurities. (b) (4)  
Fourteen impurities are included in the DS specification. Structures of 13 (b) (4) impurities, 4 degradants (b) (4) and 4 (b) (4) impurities are identified. Although several impurities have biological activity, activity (based on MIC) is (b) (4) than fidaxomicin. Therefore, control of the impurity profile is relevant to fidaxomicin activity. Curiously, impurity (b) (4) This impurity has (b) (4)

The applicant proposes a retest date of (b) (4) (b) (4)-months for DS stored in (b) (4). The retest date may be extended based on the ongoing 60-month stability study. Primary stability data provided for the 3 registration batches are, 36-months refrigerated (2 to 8°C), 36-months frozen (-25 to -10°C), 24-months 25°C/60% RH and 6 months 40°C/75% RH. Three months of stability data are also provided for two commercial scale batches. Assay, total related substances and (b) (4) were within specification after (b) (4) (b) (4) (b) (4). It seems unlikely that the stability period would extend beyond (b) (4).

Forced degradation studies were conducted with both (b) (4) fidaxomicin. The degradation study report was not found in the NDA during this initial assessment. If it is not located, the applicant should submit it to the NDA.

## Drug Product

The drug product (DP) is an immediate release, tablet for oral use containing 200 mg of fidaxomicin. Each commercial tablet is a white to off-white film coated, (b) (4) (b) (4) tablet. The tablet is debossed with the “FDX” on one side and “200” on the other side. Tablets are packaged in 30 cc and 60 cc bottles (20-count and 60-count, respectively) and in a 10-count blister pack containing (b) (4) aluminum foil blister cards with aluminum foil

Initial Quality Assessment

lid/white paper backing ( (b) (4) per blister card). The bottles are white, high density polyethylene (HDPE), with tamper-evident, induction-sealed, (b) (4) child-resistant caps and a desiccant.

The commercial DP manufacturing facility is Patheon Inc., Mississauga, Ontario, Canada. The commercial DP formulation and batch formula is given in Table 2.

**Table 2: Drug Product Formulation and Commercial Batch Formula**

Component	Function(s)	Quality Standard	mg/Tablet	Batch Formula		
				% (w/w)	ka/batch (b) (4)	
Fidaxomicin (powder)	Active Ingredient	In house	200.0 <sup>1</sup>	(b) (4)	(b) (4)	
Microcrystalline Cellulose	(b) (4)	USP/NF, PhEur, JP	(b) (4)			
Pregelatinized Starch		USP/NF, PhEur, JP				
Hydroxypropyl Cellulose		USP/NF, PhEur, JP				
Butylated Hydroxytoluene		USP/NF, PhEur				
Sodium Starch Glycolate		USP/NF, PhEur, JP				
Magnesium Stearate		USP/NF, PhEur, JP				
(b) (4)		USP				-
(b) (4)						
(b) (4)		NF				-
(b) (4)		(b) (4)				
(b) (4)	(b) (4)	DMF (b) (4)	(b) (4)			
<b>Total tablet weight: 360</b>						

The registration stability DP batches, (b) (4), were manufactured at Patheon (the commercial site). (b) (4) manufactured some of the Phase 3 and Phase 2 DP batches. There are changes to the formulation (b) (4) and the manufacturing processes amongst the various Phase 3 batches used. The quantitative formulas of the Phase 3 DP

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batches, tabular comparison of the manufacturing processes (including process parameters), dissolution profiles and batch data are needed to establish the linkage between the bioavailability/Phase 3 batches and the commercial batches. Some of this information is not located in the NDA or lacks sufficient detail.

The commercial batch size is (b) (4) Tablets are manufactured by (b) (4)

(b) (4)

The applicant does not claim this to be a QbD NDA. A design space is not specified in the manufacturing process description. (b) (4)

(b) (4)

DP packaging was described above. DMFs referenced for the packaging components and excipients are DMF (b) (4) (30 cc Bottle), DMF (b) (4) (60 cc Bottle), DMF (b) (4) (CR Closure 30 cc Bottle), DMF (b) (4) (CR Closure 60 cc Bottle), DMF (b) (4) (Desiccant), DMF (b) (4) (Aluminum Blister Film and Lidding Foil) and DMF (b) (4)

DP specifications are given in Table 3 and are discussed under review comments. The BHT Assay has different release and stability acceptance criteria (b) (4)

The dissolution criterion proposed for this immediate-release tablet is low ( $Q_{(4)}/45$  min). There is no specification for (b) (4) (b) (4) Five degradants are specified. Batch data at release shows the presence of many related substance impurities in the drug product. As batch and stability data identifies impurities by its RRT, how they are linked to the specification could not be evaluated. Impurity (b) (4) which is not included in the specified impurities, occurs at a level of (b) (4) in the single commercial scale/process DP batch (b) (4) manufactured.

**Table 3: Proposed DP Specification**

(b) (4)



DP stress studies under light and freeze-thaw conditions are reported to show no significant changes to the DP quality. (b) (4)

The expiration period proposed for the DP is 24-months when stored at controlled room temperature conditions. The amount of stability data provided is 24 months of long-term ( 25°C/60% RH, also 5°C) and 6 months of accelerated (40°C/75% RH) for the 3 registration stability batches. It is unclear if the (b) (4) blister card used for stability is the same as the commercial blister card. Accelerated stability data show adverse trends for Assay, BHT,

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related substances (b) (4) Dissolution does not appear to be affected, but is harder to determine without a detailed assessment.

Note that both the fidaxomicin tablets and the comparator, vancomycin tablets, used in the pivotal clinical studies (101.1.C.003 and 101.1.C.004) were encapsulated for blinding purposes. Hence, a comparison of the dissolution of encapsulated and unencapsulated tablets is required for both fidaxomicin DP and the comparator.

***B: Critical issues for review***

## 1. DP dissolution

(b) (4)

### 3. Equivalency of clinical, bioavailability and commercial DP batches

DOE studies were conducted after the manufacture of the clinical DP batches (these are also the registration batches). Hence, the commercial DP manufacturing process may be different from that of the clinical process. The various Phase 3 clinical batches had formulation differences and were made by two different manufacturers (b) (4). There could be differences in the manufacturing processes used by (b) (4). The formulations, manufacturing processes, dissolution and batch data need to be compared for equivalency of the clinical lots (to one another) as well as the commercial DP lot. The applicant should provide a side-by-side comparison of the manufacturing process and the process parameters in a tabular format. The narrative description currently provided lacks the process details to enable comparison. The commercial manufacturing process provided should be updated with the process parameters.

### 4. DS impurity profile qualification

Due to the numerous related substances in the DS, lack of resolution of some impurity peaks, and the use of different manufacturers for the non-clinical and commercial DS, adequate qualification of the impurity profile should be discussed with the PharmTox reviewer. As different impurities have different MICs (not as active), (b) (4)  
(b) (4)

### 5. DS manufacturing process

DS manufacturing process is complex with multiple unit operations. Only a superficial description is given with no process parameters. Many critical processes, such as (b) (4)

[Redacted] (b) (4)

**C: Other potential review issues**

Miscellaneous review issues noted during the initial assessment are as follows

1. Drug Substance

[Redacted] (b) (4)

- (c) Notable omissions in the DS specification are tests for [Redacted] (b) (4). These attributes are critical for DS quality and should be added to the DS specification. An IR test for identity is also recommended. The DS manufacturing is out-sourced currently and additional suppliers could be added later.
- (d) An expiration date (instead of retest date) is recommended for the DS.

2. Drug Product

- (a) The scaled-down factors evaluated in the DOE appears to [Redacted] (b) (4).  
[Redacted] (b) (4)
- (b) Is the blister pack used in the stability study the same as the commercial DP.
- (c) Stress test data should be provided, if not given in the NDA.
- (d) Why was an [Redacted] (b) (4).  
[Redacted] (b) (4)
- (e) Significant detail on the DP manufacturing process and in-process controls are needed.
- (f) The completed batch record submitted in the NDA may not be representative of the commercial DP manufacturing process as further process development studies was conducted afterwards.

(g) Although (b) (4) was monitored under DP stability, it is not included in the proposed DP specification. (b) (4) should be added to the DP specification.

***D: Comments for 74-Day Letter***

None. Critical issues noted above are intended for internal ONDQA use and require further evaluation before conveying them to the applicant.

Rapti D. Madurawe, Ph.D.  
Pharmaceutical Assessment Lead

\_\_\_\_\_  
Date

Stephen R. Miller  
Branch Chief

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Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RAPTI D MADURAWA  
02/14/2011

STEPHEN P MILLER  
02/15/2011