CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213138Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA #213138
Assessment # 2

Drug Product Name	DIFICID (fidaxomicin) For Oral Suspension
Dosage Form	Granules for Oral Suspension
Strength	40 mg/mL (after reconstitution)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Cubist Pharmaceuticals
US agent, if applicable	Merck Sharp and Dohme Corp.

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0011	12/17/2019	Quality
eCTD 0012	01/02/2020	Quality
eCTD 0013	01/10/2020	Quality
eCTD 0014	01/10/2020	Quality

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	IV		(b) (4)	Adequate	1/14/2020	Reviewed by Shalini Anand

B. OTHER DOCUMENTS: ***IND, RLD, RS, Approved NDA***

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ) at this time. The Overall Manufacturing Inspection recommendation was entered as Approve on 12/18/2019.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Refer to Review #1 for a detailed background of the overview of the product.

The CMC Integrated Quality Review #1 (Review #1) on 1/02/2020 recommended this NDA for a CR due to a pending IR with issues relating to the drug product shelf life and a requested test (b) (4). In addition, the referenced DMF (b) (4) (mixed berry flavor) was under review at the time of Review #1.

The applicant provided a response to the pending IR, and an addendum to the drug product review was completed. This NDA is now recommended for **approval** from a CMC perspective.

B. Quality Assessment Overview

Drug Substance: Adequate

Refer to Review #1.

Drug Product: Adequate

Refer to Review #1 for the complete details of the drug product. At the time of Review #1, there were pending issues relating to the assigned

shelf life of the product, (b) (4), and the referenced DMF (b) (4) for the mixed berry flavor.

DMF (b) (4), which describes the mixed berry flavor, is now adequate to support this NDA. The applicant also included the requested (b) (4). The (b) (4) was found acceptable in the drug product review.

Following review of the additional stability data, this product is granted a **9-month** shelf life. The applicant also committed to submitting a CBE-30 Supplement to extend the drug product shelf life when additional long-term data becomes available.

This NDA is currently recommended for Approval from a drug product perspective. For additional details, refer to the drug product review by Shalini Anand.

Labeling: Adequate

Refer to Review #1.

Manufacturing: Adequate

Refer to Review #1.

Biopharmaceutics: Adequate

Refer to Review #1.

Microbiology (if applicable): Adequate

Refer to Review #1

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay of fidaxomicin/ stability (impurities/ degradation products	Process, raw materials	M		Acceptable	

Physical Stability	Process, raw materials, formulation	M	(b) (4)	Acceptable; however, the applicant committed to submit a supplement to extend the shelf life	Adequate. The product is granted a 9-month shelf life
Content Uniformity	Process, raw materials	L		Acceptable	
(b) (4)	Process	L		Acceptable	
Microbial Limits	Process, raw materials, formulation	L		Acceptable	Applicant should perform AET on at least 1 primary stability batch at the end of proposed shelf life.
Dissolution	Process, formulation, raw materials	L		Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

Application Technical Lead Name and Date:

Erika E. Englund, Ph.D.

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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA #213138
Assessment # 1

Drug Product Name	DIFICID (fidaxomicin) For Oral Suspension
Dosage Form	Granules for Oral Suspension
Strength	40 mg/mL (after reconstitution)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Cubist Pharmaceuticals
US agent, if applicable	Merck Sharp and Dohme Corp.

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0001	7/24/2019	All
eCTD 0003	10/15/2019	Quality
eCTD 0005	10/22/2019	Quality
eCTD 0006	10/23/2019	Quality
eCTD 0007	11/15/2019	Quality
eCTD 0008	11/12/2019	Quality
eCTD 0009	11/20/2019	Quality
eCTD 0010	12/4/2019	Quality
eCTD 0011	12/17/2019	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	NA	NA
Drug Product	Shalini Anand	Thomas Oliver
Manufacturing	Jiao Yang	Arwa El Hagrasy
Microbiology	Nutan Mytle	Neal Sweeney
Biopharmaceutics	Zhuojun Zhao	Elsbeth Chikhale
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Erika Englund	
Laboratory (OTR)	NA	

Environmental	Refer to DP review	

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	IV		(b) (4)	Active		Under review

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	201699	Tablet
IND	(b) (4)	Oral Suspension
IND	64435	Tablet

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH-ODE	NA			
CDRH-OC	NA			
Clinical	NA			
Other	NA			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has **not** provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for a **Complete Response** by the Office of Pharmaceutical Quality (OPQ) at this time. The Overall Manufacturing Inspection recommendation was entered as Approve on 12/18/2019.

Due to the failures (b) (4) in the drug product accelerated stability studies, a drug product shelf life can not be assigned at this time. In addition, DMF (b) (4) is currently under review for the mixed berry flavor. An information request was sent regarding the stability failures and supporting information in the DMF. An addendum will be written to this IQA following review of the responses by the drug product reviewer.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Fidaxomicin is a macrolide antibacterial. NDA 201699 (fidaxomicin tablets) was approved on 5/27/2019 for the treatment of Clostridium difficile-associated diarrhea (CDAD) in adults (≥ 18 years of age). NDA 213138 describes immediate release fidaxomicin granules for oral suspension, and extends the indication to pediatric patients (6 months to < 18 years of age). The weight-based dosing of the granules ranges from 80 mg to 200 mg administered twice daily.

Fidaxomicin granules for oral suspension is formulated as white to yellowish white granules, and is supplied in a 150 mL amber glass bottle with a plastic child resistant cap. The product is to be reconstituted with 130 mL of water resulting in a 40 mg/mL suspension. A single bottle provides at least 10 days of dosing at 200 mg/day. The proposed storage time of the product is 12 days.

The CMC information (including environmental assessment) for the new fidaxomicin formulation is submitted in NDA 213138 (Module 3). The labeling information for fidaxomicin tablets and granules is provided in the efficacy supplement NDA 201699/S-012.

Proposed Indication(s)	Clostridium difficile-associated diarrhea (CDAD). Dificid is currently approved for adults (≥ 18 years of age). NDA 213138 was submitted to extend the

including Intended Patient Population	indication to pediatric patients (from 6 months to < 18 years of age).
Duration of Treatment	10 days.
Maximum Daily Dose	The recommended dosing for pediatric patients is weight based with 200 mg twice daily being the maximum daily dose.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

There was no separate drug substance review for this NDA. Since this new NDA references the approved NDA 201699 for all drug substance information, there is no drug substance DMF, and both NDAs have the same applicant, no API review assignment is needed. Refer to the 7/25/2019 e-mail communication from the drug substance branch chief, Suong Tran.

Drug Product: Inadequate

Before the development of the commercial packaging, the product had been manufactured in a 150 mL amber glass bottle with a plastic cap. 36 months of long-term stability data had been submitted for these batches (primary stability batches, PSS); however, (b) (4) .

The proposed commercial drug product will be supplied in a 150 mL amber glass bottle with a CR cap enclosed in a laminate aluminum foil pouch inside a folding carton. (b) (4) 6 months of stability data has been provided for this configuration (formal stability batches, FSS).

FSS batches failed (b) (4) at 6 months under accelerated stability conditions. No (b) (4) was reported for the PSS batches. Since the formulation for the PSS and FSS batches is the same, it is not clear at this time why (b) (4) was reported for the product with (b) (4) . An information request was sent to the applicant on December 18, 2019. The shelf life of the product will be evaluated following response to this IR.

In addition, DMF (b) (4) which describes the mixed berry flavor is currently under review. The addendum to this IQA will also cover the adequacy of this DMF to support the NDA.

This NDA is currently recommended for a Complete Response from a drug product perspective. For additional details, refer to the drug product review by Shalini Anand.

Labeling: Adequate

The labeling recommendations were communicated to the OND PM.

Manufacturing: Adequate

(b) (4)

The facilities are determined to be acceptable and the overall manufacturing inspection recommendation (OMIR) is approval to support the application.

This NDA is recommended for approval from a manufacturing perspective. For additional details, refer to the review by Jiao Yang.

Biopharmaceutics: Adequate

The biopharmaceutics review evaluated the data supporting the proposed dissolution method, acceptance criterion justification as well as the bridging between drug product (DP) manufacturing sites of the proposed commercial drug product and the clinical batches. Based on the provided data, the dissolution method and acceptance criteria (Q =(b) (4)% in 30 min) was found acceptable. The applicant also provided adequate dissolution data to support the bridging between the commercial drug product manufacturing site (Almac) and the clinical drug product manufacturing site (Astellas).

This NDA is recommended for approval from a biopharmaceutics perspective. For additional details, refer to the review by Zhuojun Zhao.

Microbiology (if applicable): Adequate

The drug product is supplied as granules for oral suspension, and reconstituted with 130 mL of water. (b) (4) , and the applicant proposed

that the reconstituted product could be stored for 12 days at 2-8 °C. An Antimicrobial Effectiveness Test (AET) was performed with reconstituted oral suspension (b) (4), and tested at days 14 and 28. The applicant also committed to conducting antimicrobial effective testing on at least one primary stability batch at the end of the proposed shelf life. The microbiology review found the AET and commitment acceptable. Since the AET data for the reconstituted drug product covered a 28-day storage period, a separate reconstitution/storage microbiological challenge study was not necessary to support a 10-day storage period.

This NDA is recommended for approval from a microbiology perspective. For additional details, refer to the review by Nutan Mytle.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay of fidaxomicin/ stability (impurities/ degradation products	Process, raw materials	M		Acceptable	
Physical Stability	Process, raw materials, formulation	M	(b) (4)	Not Acceptable	The applicant reported (b) (4) in the accelerated stability studies. The IR response is pending
Content Uniformity	Process, raw materials	L		Acceptable	

(b) (4)	Process	L	(b) (4)	Acceptable	
Microbial Limits	Process, raw materials, formulation	L		Acceptable	Applicant should perform AET on at least 1 primary stability batch at the end of proposed shelf life.
Dissolution	Process, formulation, raw materials	L		Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

The deficiencies, if applicable, will be captured in the IQA addendum

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

Application Technical Lead Name and Date:

Erika E. Englund, Ph.D.

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	DIFICID® (fidaxomicin) for oral suspension	Adequate.
Established name(s)	Fidaxomicin for oral suspension	Adequate.
Route(s) of administration	Oral	Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4) for oral suspension, 40 mg/mL (after reconstitution (b) (4))	Adequate.
Controlled drug substance symbol (if applicable)	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

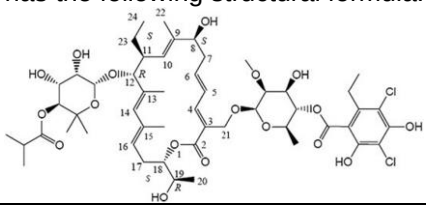
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	(b) (4) fidaxomicin granules is reconstituted with 130 mL of (b) (4). The suspension concentration after reconstitution is 40 mg/mL. The reconstituted suspension is stable for 12 days if stored under refrigeration (2°C to 8°C or 36°F to 46°F).	Inadequate The supporting in-use stability data is provided in quality submission dated 07/24/2019. The recommendation is to use "purified water" instead of "(b) (4)" The "(b) (4)", may be too restrictive and unnecessary. A hospital pharmacy would typically have (b) (4) on hand, but not the retail pharmacies.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	White to yellowish white granules for oral suspension	Adequate.
Strength(s) in metric system	Each 5 mL of oral suspension contains 200 mg of fidaxomicin (40 mg of fidaxomicin per mL)	Recommendation from DMEPA- consistent use of the strength statement as "40 mg/mL (200 mg/5 mL)" throughout the PI.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	Adequate.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	White to yellowish white granules (before reconstitution). White to yellowish white oral suspension (after reconstitution)	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 Description

Item	Information Provided in the NDA	Assessor's Comments
Proprietary and established name(s)	DIFICID (fidaxomicin) for oral suspension, fidaxomicin for oral suspension	Adequate
Dosage form(s) and route(s) of administration	Granules for oral suspension	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	Adequate.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	inactive ingredients: citric acid, microcrystalline cellulose, mixed berry flavor, sodium benzoate, sodium citrate, sodium starch glycolate, sucralose, and xanthan gum.	Adequate.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	Antibacterial Drug	Adequate.
Chemical name, structural formula, molecular weight	The chemical name of 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-Omethyl-β-D- mannopyranosyl]oxy]methyl]-12-[[6-deoxy-5-C-methyl-4-O-(2-methyl-1-oxopropyl)-β-D-lyxohexopyranosyl] oxy]-11-ethyl-8 -hydroxy-18-[(1R)-1-hydroxyethyl]-9,13,15-trimethyl-, (3E,5E,8S,9E,11S,12R,13E,15E,18S)-. (b) (4) It has the following structural formula: 	Adequate.
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	-	-

1.2.4 Section 16 HOW SUPPLIED/STORAGE AND HANDLING section

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	DIFICID granules for oral suspension is supplied as 150 mL amber glass bottles of 9.53 g of granules that contain 5.45 g of fidaxomicin	Adequate.
Strength(s) in metric system	The concentration of fidaxomicin is 200 mg per 5 mL (40 mg/mL) in the reconstituted oral suspension.	Recommendation from DMEPA- consistent use of the strength statement as "40 mg/mL (200 mg/5 mL)" throughout the PI.
Available units (e.g., bottles of 100 tablets)	After reconstitution, the total oral suspension volume is 136 mL per bottle. NDC 52015-7002 (b) (4)	A recommendation Is communicated to OND for including a statement 'Discard excess/ unused volume after 12 days'
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See above	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store in the original package. Do not open pouch until time of use	The foil pouch is (b) (4)
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store DIFICID granules for oral suspension at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F- 86°F). Once reconstituted, store DIFICID oral suspension refrigerated at 2°C-	Adequate. The supporting in-use stability data is provided in quality submission dated 07/24/2019.

	8°C (36°F-46°F) for up to 12 days. Store capped in the original bottle.	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	Yes	Adequate.

1.2.3 Other Sections of Labeling

1.2.4 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for Merck & Co. Inc.	Adequate.

Reviewer's Assessment of Package Insert: Ina*dequate*

Section 2- Dosage and administration-

The supporting in-use stability data for reconstituted suspension under refrigeration (2°C to 8°C or 36°F to 46°F) for 12 days is provided in section 3.2.P.8.

DMEPA recommendation is to use "purified water" instead of "(b) (4)" for dosage and administration section. The "(b) (4)" may be too restrictive and unnecessary. A hospital pharmacy would typically have (b) (4) on hand, but not the retail pharmacies.

The recommendation was communicated to change the terminology "oral dosing (b) (4)" to "oral dosing syringe." The compatibility studies (as provided in section 3.2.P.2) are conducted with oral syringes.

Section 16- How supplied/Storage and Handling-

The proposed fill weight of the granules is 9.53 g/ bottle. The total suspension volume after reconstitution with 130 mL of water will be 136 mL/bottle. For 200 mg dosing/ twice a day, with suspension concentration of 40 mg/mL, patient needs only 100 mL of suspension for 10 days of dosing (recommended dosing on the label). So, a recommendation was communicated to OND for including a statement - discard the excess or unused volume.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):
The storage instructions in the Patient Information are appropriate, and instructions are included to keep DIFICID in original child-resistant bottle and store Dificid oral suspension in the refrigerator between 36°F to 46°F (2°C to 8°C)

The recommendation is communicated to OND for including a statement -discard the excess or unused suspension.

DMPP recommended is to change the terminology “oral dosing (b) (4)” to “oral dosing syringe to be consistent with PI. The compatibility studies (as provided in section 3.2.P.2) are conducted with oral syringes.

3.0 CARTON AND CONTAINER LABELING

IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 22, 2019

3.1 Container Label

(b) (4)

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Item	Information provided in the container label(s)	Information provided in the carton label(s)
Proprietary name, established name, and dosage form (font size and prominence	DIFICID (fidaxomicin) for oral suspension	DIFICID (fidaxomicin) for oral suspension
Dosage strength	40 mg/mL	40 mg/mL
Route of administration	Oral	Oral
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	Each mL contains 40 mg of Fidaxomicin after reconstitution with 130 mL (b) (4) (136 mL total volume after reconstitution)	Each mL contains 40 mg of Fidaxomicin after reconstitution with 130 mL (b) (4) (136 mL total volume after reconstitution)
"Rx only" displayed on the principal display	Yes	Yes
NDC number	NDC 52015-7002-1	NDC 52015-7002-2 *Recommendation from DMEPA- One carton containing one unit should have the same NDC number (last digit (s)of the NDC). Therefore, update the NDC number for pouch and carton labelling to be 5015-7002-1
Lot number and expiration date	Yes	Yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Refrigerate reconstituted suspension at 2°C-8°C (36°F-46°F) for up to 12 days.	Store in original package. Do not open pouch until time of use Before Reconstitution- at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F). After reconstitution- store refrigerated at 2°C-8°C (36°F-46°F) for up to 12 days.
Bar code	Yes	Yes

Item	Information provided in the container label(s)	Information provided in the carton label(s)
Name of manufacturer/distributor	The manufacturer name is included: **Merck & Co., Inc.**	The manufacturer name is included: **Merck & Co., Inc.**
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	Yes	Yes
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	- Must be reconstituted by a Pharmacist before dispensing	-Must be reconstituted by a Pharmacist before dispensing -Discard unused portion (b) (4) after 12 days

Assessment of Carton and Container Labeling:

The inactive ingredients are listed as per the information provided in section 3.2.P.1.
There is a description of the storage of the granules, at controlled room temperature before reconstitution and under refrigeration after reconstitution with water. This is acceptable. The carton also describes that the reconstituted suspension is stable for 12 days at refrigerated conditions. The supporting in use stability studies are provided in section 3.2.P.8.
The name of the product is consistent with the PI.

The following comments (from DMEPA) will be sent-

1. The revised National Drug Code (NDC) on the container label, as well as the pouch and carton labeling include different NDC package code numbers. One carton containing one unit should have the same NDC number (last digit (s)of the NDC). Therefore, to align with your proposed prescribing information (PI), as well the container label, update the NDC number for pouch and carton labelling to be 5015-7002-1
2. The proposed container label, as well as the pouch and carton labeling include the statement, “Each mL contains 40 mg fidaxomicin after reconstitution with 130 mL (b) (4).” However, (b) (4) is not required to reconstitute Dificid granules and (b) (4) may not be readily available in retail pharmacies. Please revise the statement to read, “Each mL contains 40 mg fidaxomicin after reconstitution with 130 mL Purified Water.”

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Refer to discussion above and recommendations in OND labeling.

Primary Labeling Reviewer Name and Date:

Shalini Anand, Ph.D.

12/19/2019

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Thomas F. Oliver, Ph.D.

12/23/2019

Shalini Anand

Digitally signed by Shalini Anand
Date: 12/23/2019 09:55:29AM
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Thomas Oliver

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Comments: just signed!

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	213138
Assessment Cycle Number	#1
Drug Product Name/ Strength	DIFICID (fidaxomicin) For Oral Suspension, 40 mg/mL after reconstitution
Route of Administration	Oral
Applicant Name	Cubist Pharmaceuticals LLC
Therapeutic Classification/ OND Division	Antimicrobial/DAI
RLD/RS Number	Cross Referenced Applications: NDA 201699/S-012 (tablet) and IND (b) (4), IND 064435 (tablet)
Proposed Indication	For the treatment of clostridium difficile-associated diarrhea (CDAD)
Primary Assessors	Zhuojun Joan Zhao, Ph.D.
Secondary Assessors	Elsbeth Chikhale, Ph.D.
Assessment	**Adequate**
Recommendation	Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 213138 for DIFICID (fidaxomicin) For Oral Suspension is recommended for **APPROVAL**.

Assessment Summary:

DIFICID (fidaxomicin) for oral suspension is a new, immediate release, pediatric formulation of fidaxomicin. The drug product is formulated as white to yellowish white granules supplied in a 150 mL amber glass bottle. Each bottle is filled with 9.53 g of the granule formulation that contains 5.45 g fidaxomicin. The granules in the bottle are to be reconstituted with 130 mL (b) (4) resulting in a 40 mg/mL fidaxomicin suspension. A single bottle provides for at least 10 days of dosing at 200 mg per day.

The Applicant conducted a Phase 3 study SUNSHINE 2819-CL-0202 comparing the safety and efficacy of the proposed fidaxomicin granules for suspension, DIFICID® tablets, and vancomycin in pediatric patients with *clostridium difficile*-associated diarrhea. Both this NDA 213138 (fidaxomicin for oral suspension) and efficacy supplement 12 under NDA 201699 (fidaxomicin tablets) are submitted to fulfill PMR 1757-002 for NDA 201699.

This review evaluates the data supporting the proposed dissolution method, acceptance criterion justification as well as the bridging between drug product (DP) manufacturing sites of the proposed commercial drug product and the clinical batches.

Dissolution method and Acceptance Criterion:

Based on the provided data, the following dissolution method and acceptance criterion are acceptable as QC method for drug product batch release and stability testing:

USP Apparatus	Rotation Speed	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim)
USP II (Paddle)	40 RPM	2.0% Tween in Water	900 mL	Q= (b) (4)% in 30 minutes

Bridging Formulations:

The Applicant provided adequate dissolution data to support the bridging between the commercial DP manufacturing site (Almac) and the clinical batches DP manufacturing site (Astellas).

Document(s) Assessed	Date Received
0001 (1)	**July 24, 2019**
0007 (7)	**November 5, 2019**
0009 (9)	**November 20, 2019**
0011 (11)	**December 17, 2019**

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues: None

B.1 DRUG SUBSTANCE SOLUBILITY

The drug substance, Fidaxomicin, shows very limited aqueous solubility from pH 1.2 to 6.8.

(b) (4)

B.2 DISSOLUTION METHOD

The Applicant evaluates the dissolution performance of fidaxomicin suspension at the proposed highest dose or worst case, 200 mg, which corresponds to 5 mL of oral

suspension. The proposed dissolution conditions are similar to those of the approved dissolution method for Fidaxomicin 200 mg tablet (NDA 201699)[1], shown in Table 2.

Table 2: Dissolution Methods for Fidaxomicin Suspension and Tablets

Dissolution Methods for Fidaxomicin products			
Parameter	For Suspension (NDA 213138)		Approved for Tablets (NDA 201699)[1]
Apparatus	USP II (Paddle)		
Rotation Speed (RPM)	40 (revised)	(b) (4) (initially proposed)	75
Medium & Volume	900 mL 2.0% Tween in water		

The Applicant justified the selection of the dissolution methodology below[2]:

(b) (4)

[redacted]

[1] DARRTS: NDA 201699 REV-QUALITY-03 (General Review), final date 04/14/2011

[2] \\cdsesub1\evsprod\nda213138\0011\m3\32-body-data\32p-drug-prod\5119-granulesos\32p5-contr-drug-prod\32p56-justif-spec\justification-of-specifications.pdf

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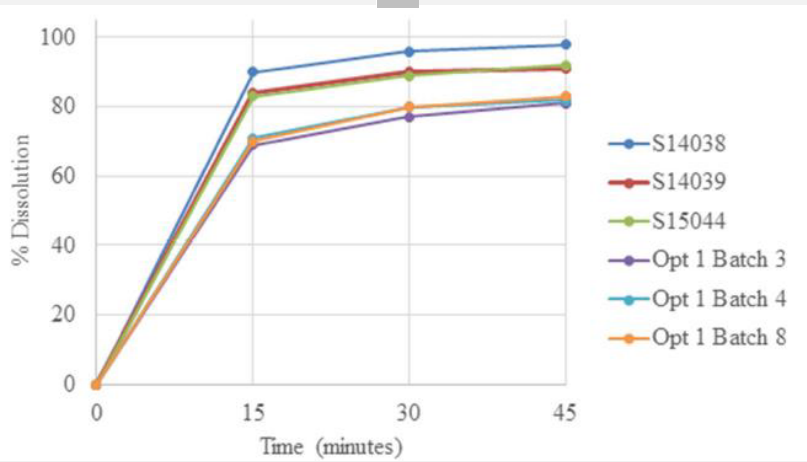
Discriminating Power of the Method:
During the development of the proposed drug product, the Applicant evaluated the effect of granulation variables on dissolution profiles using the original dissolution method (i.e. (b) (4) rpm rotation speed).

The dissolution profiles of Fidaxomicin with a set of samples manufactured under insufficient granulation (Lot No. Opt 1 Batch 3, Opt 1 Batch 4 and Opt 1 Batch 8) and a set of samples from the target granulation conditions (Registration Batches, Lot No. S14038, S14039 and S15044) are shown in Figure 2. The Applicant claims that these two set of profiles were different and it was feasible to distinguish between the two set of batches at 30 minutes, which is equivalent to the proposed evaluation time point according to the revised acceptance criterion of Q = (b) (4)% at 30 minutes.

Figure 2. Discrimination Power of the Initially Proposed Dissolution Test Methods (@ (b) (4) rpm)



No new discriminating power study was provided for the revised dissolution method (40 rpm rotation speed). It is expected that the revised dissolution method with reduced rotation speed should have similar, if not better, discriminating power on granulation variables compared to the initially proposed (b) (4) rpm) dissolution method.

Assessment: *{Adequate}*
Based on the provided information in both amendments dated November 20, 2019 (Appendix 1) and December 17, 2019 (Appendix 2), the Applicant has adequately demonstrated the suitability of the revised dissolution method (i.e. 900 mL 2.0% Tween in water using USP II (Paddle) at 40 RPM) for batch release and stability testing.

The discriminating power of the proposed dissolution method with regards to process granulation variations is limited and no other parameters were investigated.

The Applicant did not include the sample preparation procedure for dissolution in the Analytical Procedure Dissolution (module 3.2.P.5.2) of the original submission. The Applicant was recommended to revise the sample preparation (b) (4)

[redacted] in IR letters dated October 24, 2019 (Appendix 1) and December 5, 2019 (Appendix 2). In the Amendment dated December 17, 2019, the Applicant updated analytical procedures accordingly in 3.2.P.5.2.3 (Appendix 2). .

Based on the totality of the dissolution data, the revised dissolution method (40 rpm) and revised sample preparation instructions [redacted] are found acceptable.

B.3 DISSOLUTION ACCEPTANCE CRITERIA

The Applicant initially proposed a dissolution acceptance criterion of Q=[redacted]% at [redacted] minutes using the initial dissolution method (i.e [redacted]RPM).

Based on the dissolution data for the registration batches shown in Table 8, the Applicant's revised dissolution acceptance criterion of Q=[redacted]% (Q) at 30 minutes is found acceptable during the review cycle (Appendix 2).

Assessment: *{Adequate}*

The revised dissolution acceptance criterion of NLT [redacted]% (Q) in 30 minutes is acceptable.

B.12 BRIDGING OF FORMULATIONS

The PK of fidaxomicin in pediatric patients [redacted] is based on the results of one Phase 2a study (OPT-80-206) and one Phase 3 study (SUNSHINE). The relative (% of total) composition of the proposed commercial formulation is the same as the phase 3 clinical formulation (Table 6), however, the total granule fill weight is changed.

Table 6: Commercial Market Image

Ingredient	Phase 3 Image g/bottle	Final US Commercial Image g/bottle
FIDAXOMICIN	4.400	5.446
Cellulose, microcrystalline	[redacted]	
Sodium starch glycolate		
Xanthan gum		
Citric Acid		
Sodium citrate		
Sodium benzoate		
Sucralose		
Mixed berry flavor		
Final fill weight	7.700	9.530

The clinical batches used in Phase 3 study SUNSHINE 2819-CL-0202 were manufactured by Astellas. The proposed commercial drug product manufacturer is Almac Pharma. The Applicant provided dissolution testing results using the initial proposed dissolution method for the representative batches (Phase 3 clinical batches (C14006 and C15063 manufactured at Astella), [redacted] batches (S14038A, S14039A and S15044A) and Almac DP batches (W046915, W046916, W046917 and W040260).

Table 7: Dissolution Results of Representative Fidaxomicin Granules for Oral Suspension Batches

Batch #	Purpose	Fill level (g/bottle)	Dissolution (%LC)		
			15 min	30 min	45 min
C14006	Phase 3 clinical	7.70	91 (b) (4)	97 (b) (4)	98 (b) (4)
C15063	Phase 3 clinical	7.70	87	94	96
S14038A	Primary Stability	7.70	101[a], 96[b] (b) (4)	107[a], 107[b] (b) (4)	107[a], 109[b] (b) (4)
S14039A	Primary Stability	7.70	92 (b) (4)	97 (b) (4)	100 (b) (4)
S15044A	Primary Stability	7.70	90	96	99
W046915	Formal Stability	9.53	85	100	102
W046916	Formal Stability	9.53	85	97	101
W046917	Formal Stability	9.53	86	96	100
W040260	Process Qualification	7.70	84	93	96

a1st analysis; b.2nd analysis; range is from both analysis data

Assessment: *{Adequate}*

As phase 3 clinical and other (b) (4) *batches were expired batches during the review cycle, no comparative dissolution profiles using the revised dissolution method were available. However, as shown in Table 7, similar dissolution profiles were observed between the batches made by Astellas and Almac using the initial dissolution method. No f2 values were calculated due to the rapid release. The Applicant's bridging study between the DP manufacturing sites is found acceptable.*

B. 13 BIOWAIVER REQUEST

Assessment: *N/A*

A biowaiver request is not submitted nor required for this NDA.

R. REGIONAL INFORMATION

Comparability Protocols: N/A

Post-Approval Commitments: N/A

Lifecycle Management Considerations: N/A

APPENDIX 1: Biopharmaceutics Information Request dated October 24, 2019 and the Applicant's Response on November 5, 2019 and November 20, 2019

Biopharmaceutics Request Comments:

1. Provide the complete dissolution profile data (n=12 bottles, individual, mean, SD, profiles) using the following dissolution methods for your registration batches (W046915, W046916 and W046917).

USP Apparatus	*Rotation Speed*	*Medium*	*Volume*
USP II (Paddle)	(b) (4) *RPM*	*Water with 2.0% Tween*	*900 mL*
	40 RPM		

The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim).

2. Your Analytical Procedure-Dissolution in 3.2.P.5.2 does not include the sample preparation procedure. Provide an updated analytical procedure " (b) (4) *" for batch release and stability dissolution testing.*

Applicant's Response to Biopharmaceutics Comment 1:

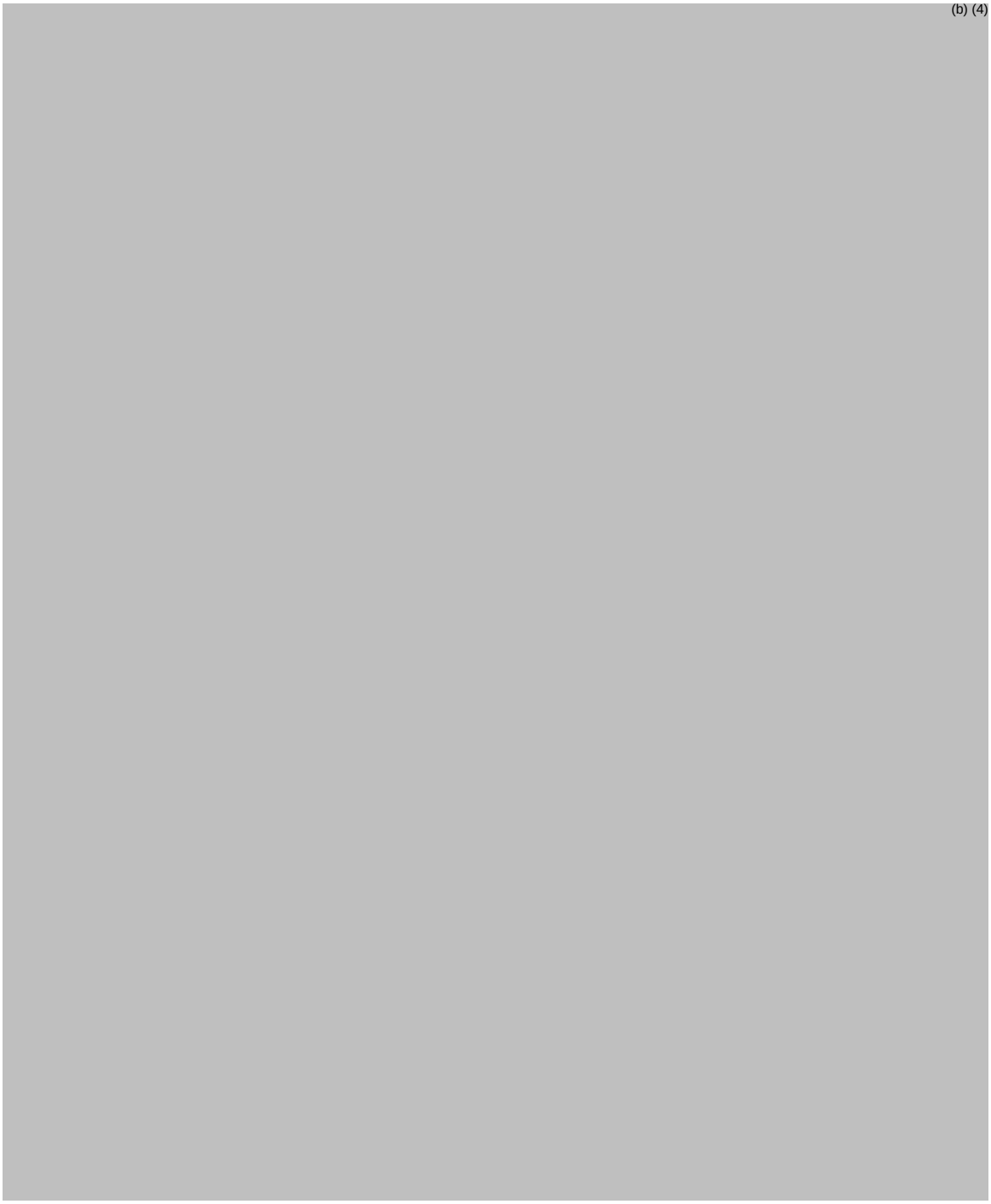
The dissolution data (n=12 bottles) for the three registration batches using USP Apparatus II (Paddle) in water with 2.0% Tween in volume of 900mL with rotation speed of (b) (4) RPM and 40RPM are provided in the amendment[3].

Reviewer Note:

Based on the provided data in the original submission[4] and the current amendment[3], the dissolution profiles using rotation speeds, (b) (4) 40 and (b) (4) RPM are shown below for each registration batch:

[3] \\cdsesub1\evsprod\nda213138\0009\m1\ us\cmc\quality-information-amendment-20nov2019.pdf

[4] \\cdsesub1\evsprod\nda213138\0003\m3\32-body-data\32p-drug-prod\5119-granulesos\32p8-stab\stability-data-2.pdf



Based the above comparison, the FDA recommend the following dissolution method and acceptance criterion to the proposed drug product.

USP Apparatus	Rotation Speed	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim)
USP II (Paddle)	(b) (4) RPM	2.0% Tween in Water	900 mL	Q= (b) (4) % in 30 minutes

Applicant's Response to Biopharmaceutics Comment 2:

Dissolution testing is performed by taking (b) (4) (see section 3.2.P.3.3 Description of Manufacturing Process and Controls - 40mg/ml). Additionally, dissolution study results presented below demonstrate that testing results of samples from different bottles (b) (4).

A development batch (ENQ2636/AIRB/001/01/P01) manufactured using the same scale and process as the FSS batches was used to perform comparative dissolution study, by testing the sample units from different bottles of reconstituted suspension (b) (4). The results shown below demonstrate that sample units from different bottles (b) (4)

%Dissolved at (b) (4) min		
Bottle Number or Replicates	(b) (4)	(b) (4)
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Min	**103**	
Max	**107**	
Mean	**105**	
SD	**1.4**	
%RSD	**1.3**	

Part B of section 3.2.P.5.2.3 Analytical Procedures – Dissolution has been updated to include sample preparation procedure and is copied below:

B. Dissolution Parameters for Sample Preparation

Apparatus:	USP No. 2 (paddles)
Rotation Speed:	(b) (4) rpm
Dissolution Medium:	2.0% Tween 80 in water (v/v)
Medium Volume:	900 mL
Medium Temperature:	37 °C
Sampling Time:	(b) (4) minutes
Sample Size:	5 mL of oral suspension (equivalent to one maximum dose)¥. (b) (4)
Sample Clarification:	Filter through a 10 µm or 35 µm full flow filter or equivalent.
¥ 40 mg/mL Fidaxomicin oral suspension was prepared by addition of 130 mL water into the bottle with 9.53 g fidaxomicin granules followed by shaking.	

Reviewer Note:

The Applicant's response is not satisfactory. The FDA would reiterate that dissolution testing should be conducted (b) (4) for batch release and stability dissolution testing.

APPENDIX 2: Biopharmaceutics Information Request dated December 5, 2019 and the Applicant's Response on December 17, 2019

1. Based on the dissolution data submitted in your response dated November 20, 2019, the following dissolution method and acceptance criterion are recommended for your proposed Fidaxomicin for oral suspension

USP Apparatus	***Rotation Speed***	***Medium***	***Volume***	***Cumulative % of Drug Dissolved (Label Claim)***
USP II (Paddle)	(b) (4) *RPM*	*2.0% Tween in Water*	*900 mL*	*Q=* (b) (4) *% in 30 minutes*

Update your drug product release and stability specifications accordingly. In addition, be advised, that the recommended dissolution acceptance criterion is based on n=12 and therefore, sometimes stage 2 and occasionally stage 3 testing maybe needed.

2. We have reviewed the dissolution sample preparation study data/information in your response dated November 5, 2019. However, your proposed analytical procedure for dissolution sample preparation is not acceptable. (b) (4) *Provide an updated analytical procedure for batch release and stability dissolution testing.*

Applicant's Response to Biopharmaceutics Comment 1:
The Applicant agrees to change the dissolution specification to Q= (b) (4)% in 30 minutes from the previously proposed Q= (b) (4)% in (b) (4) minutes. Updated sections (2.3.P.5 and 3.2.P.5.1) are provided with this submission.

Upon further review of the data and to avoid potential false positive dissolution failures based on the nature of the formulation and the observed lack of full dispersion at (b) (4) RPM, the applicant proposes to reduce the rotation speed to 40 RPM versus the recommended (b) (4) RPM. The proposed range is within the acceptable range of 25-50 RPM for a suspension dissolution method according to USP <1092>, The Dissolution Procedure: Development and Validation.

Reviewer Note:
The Applicant's response is satisfactory. Based on the provided dissolution data using (b) (4) and 40 RPM in Table 8, the Applicant's revised dissolution method and acceptance criterion are found acceptable.

Applicant's Response to Biopharmaceutics Comment 2:

Part B of section 3.2.P.5.2.3 Analytical Procedures – Dissolution has been updated to specify the sampling [redacted] (b) (4) below:

B. Dissolution Parameters for Sample Preparation

Apparatus:	USP No. 2 (paddles)
Rotation Speed:	40 rpm
Dissolution Medium:	2.0% Tween 80 in water (v/v)
Medium Volume:	900 mL
Medium Temperature:	37 °C
Sampling Time:	30 minutes
Sample Size:	5 mL of oral suspension (equivalent to one max dose)¥. Each sample units for dissolution testing is taken from a separate single bottle by syringe with suspension weight recorded.
Sample Clarification:	Filter through a 10 µm or 35 µm full flow filter or equivalent
¥ 40 mg/mL Fidaxomicin oral suspension was prepared by addition of 130 mL water into the bottle with 9.53 g fidaxomicin granules followed by shaking.	

The updated section 3.2.P.5.2.3 Analytical Procedures – Dissolution is provided in Module 3.2. P Drug Product of this response.

Reviewer Note:

The Applicant's response is satisfactory.

Zhuojun Zhao

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Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 12/27/2019 06:13:19PM
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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	Dificid® (Fidaxomicin)
NDA Number	213138
Assessment Cycle Number	1
Drug Product Name/ Strength	Dificid for oral suspension/40mg/mL after reconstitution
Route of Administration	oral
Applicant Name	Cubist Pharmaceuticals, LLC; c/o Merck Sharp & Dohme Corp.
Therapeutic Classification/ OND Division	DAIP (Priority review)
Manufacturing Site	Almac Pharma Services Limited, UK
Method of Sterilization	Non-sterile drug product

Assessment Recommendation: **Adequate**

Assessment Summary: No microbiology deficiencies were identified. The applicant demonstrates an adequate level of microbiological control for the manufacturing process and drug product. This submission is recommended for approval on the basis of product quality microbiology.

List Submissions being assessed (table):

Document(s) Assessed	Date Received	Assigned to Reviewer
7/24/2019	7/24/2019	7/25/2019
10/22/2019*	10/22/2019	10/23/2019

*IR Response

Highlight Key Issues from Last Cycle and Their Resolution: NA

Remarks: An 'eCTD submission'. This review also includes review of responses received on 10/22/2019 to IR issued by Agency on 10/10/2019.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): NA

Supporting Documents: NA

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** The drug product Fidaxomicin granules for oral suspension is formulated as white to yellowish white granules, and is supplied in a 150 mL amber glass bottle with a plastic child resistant cap.

- **Drug product composition –**

Ingredients	Pharmaceutical function	Quantity/mL (mg/5 mL)	Quantity (g/bottle)
Fidaxomicin (In house)	Active pharmaceutical ingredient	200.0	5.446
Cellulose, microcrystalline (USP/NF)	(b) (4)		
Sodium starch glycolate (USP/NF)			
Xanthan gum (USP/NF)			
Citric acid (USP/NF)			
Sodium citrate (USP/NF)			
Sodium benzoate (USP/NF)			
Sucralose (USP/NF)			
Mixed berry flavor (In house)			
Total		350.0	9.530

- **Description of container closure system –** (container-closure-system.pdf) The container closure system for the drug product is (b) (4) amber glass bottle which is capped with plastic child resistant cap with (b) (4) liner.

  Bottle: 150 mL amber glass bottle manufactured by (b) (4) .

  Cap: 28 mm, white child resistance with (b) (4) liner manufactured by (b) (4).

  Foil pouch: Laminate aluminum foil pouch. This is secondary packaging. The amber glass bottle is placed in laminated aluminum foil pouch which is sealed (b) (4) .

Assessment: *Adequate*

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Since the drug products are non-sterile oral granules, CCIT is not applicable. However, applicant states that the oral suspension prepared by reconstituting the granules is multiple oral dosage form (b) (4) . Antimicrobial effectiveness tests were conducted (drug-product-5119-granulesos-2.pdf) on granules suspended in (b) (4) as directed in the label instruction.

The AET test for reconstituted granules solution showed microbiological stability for 28 days (b) (4) . However, the sponsor initially did not submit microbiological evaluation of the reconstituted oral suspension (an IR was issued). Oral suspension is multiple dosage form (b) (4) . The suspension will be stored for 10 days at 2-8°C.

Assessment:

IR to sponsor (10/10/2019): *1. Based on the proposed package insert and container label, the reconstituted DIFICID® for oral suspension drug product is an aqueous multiple dosage form. As per section 2.5-pharmaceutical-development.5.pdf, antimicrobial effectiveness testing of DIFICID® granules showed antimicrobial activity (b) (4) over stability storage period. However, the studies showing antimicrobial effectiveness of the reconstituted oral suspension have not been submitted. Therefore, please provide data demonstrating antimicrobial effectiveness (i.e., USP <51> or equivalent) of the formulation (b) (4) for release or stability.*

IR Response (10/22/2019): AET test was performed with reconstituted oral suspension (b) (4) . Up-to 6 log reduction was observed from initial count on days 14 and 28.

Sample	Test organism	Number of CFU/g			Log reduction		Criteria fulfilled
		Initial	14 days	28 days	14 days	28 days	(Y/N)
1282-003 (0.20 %)‖	*S. aureus*	$7.5*10^6$	<10	<10	6	6	Y
	P. aeruginosa	$6.8*10^6$	<10	<10	6	6	Y
	C. albicans	$4.8*10^6$	<10	<10	6	6	Y
	E. Coli	$4.1*10^6$	<10	<10	6	6	Y
	A. brasiliensis	$2.3*10^6$	20	20	5	5	Y

2. Provide a commitment to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (reference ICH Q1A Stability Testing of New Drug Substances and Products).

IR Response (10/22/2019): The applicant commits to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life.

Assessment: Adequate

P.3 MANUFACTURE

P.3.1 MANUFACTURERS

Manufacture, packaging, labeling, testing, and stability testing:
Almac Pharma Services Limited
Seagoe Industrial Estate, Portadown, Craigavon, BT63
5UA, United Kingdom

Assessment: *Adequate*

P.3.3 DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS CONTROLS

Overall Manufacturing Operation (manuf-process-and-controls.pdf)
Flow diagram taken as is from application:

Components	Stage	In-Process Control
(b) (4)		

Assessment: ***Adequate***

P.5 CONTROL OF DRUG PRODUCT

P.5.1 SPECIFICATION

Test	Release and Shelf-Life (Granules) Acceptance Criteria	Test Method	Batch # 12-0005 (Clin study) C14006, C15063

Microbial Limits	Total aerobic microbial count (TAMC): (b) (4) CFU/g Total combined yeasts and molds count (TYMC): (b) (4) CFU/g *Escherichia coli*: (b) (4)	USP <61> and <62>	<100 CFU/g <100 CFU/g *E. coli*: Absent *Salmonella spp*: Absent *Pseudomonas aeruginosa*: Absent *S. aureus:* Absent *S. enteric*: Absent *C. albicans*: Absent

Assessment: *Adequate*

P.8 STABILITY

P.8.1 STABILITY SUMMARY AND CONCLUSION

Stability Batches: S14038A, S14039A, S15044A,
Executed batches: W046915, W046916, W046917:

		W046915	W046916	W046917
Microbial limits	Total aerobic microbial count: (b) (4) CFU/g	<100 CFU/g	<100 CFU/g	<100 CFU/g
	Total combined yeasts and molds count: (b) (4) CFU/g	<10 CFU/g	<10 CFU/g	<10 CFU/g
	Escherichia coli: (b) (4) (b) (4) g)	Absent (b) (4))	Absent (b) (4) g)	Absent (b) (4) g)

Proposed Storage Statement (before reconstitution):
Store in the original package. Do not open pouch until time of use. Store at 20-25°C (68-77°F), excursions permitted between 15-30°C (59-86°F).
Proposed Storage Statement (after reconstitution): (P2-pharmaceutical-development-2.pdf, 15/16)
Store in the original (b) (4). Store refrigerated, 2-8°C (36-46°F) up to 12 days

A shelf life of (b) (4) months is proposed for Fidaxomicin granules for oral suspension, when packed in the proposed container closure system and stored at 25°C.

Assessment: *Adequate*

P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

Test	Long Term 25°C/60% RH	Accelerated conditions 40°C/75% RH
Microbial limits testing	0, 6, 12, 24 and 36 months	0 months

Assessment: ***Adequate***

P.8.3 STABILITY DATA

Microbial limits were tested on Lots 15S0168A, 15S0168C, 15S0183B at long term conditions (25°C/60% RH). All results met the acceptance criteria

Assessment: As described above the applicant commits to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life.

Adequate

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information

- Post-dilution/constitution hold time (description-and-composition.pdf, 1/1)

The content of the bottle will be reconstituted with 130 mL of (b) (4). The total volume of suspension in the bottle after reconstitution with (b) (4) is 136 mL. The Fidaxomicin concentration of resulting oral suspension is 40 mg/mL. This provides a sufficient volume of the suspension for the period of 10 days of dosing at 200 mg Fidaxomicin twice a day. Suspension is stored in refrigerator (5°C) until use (3.2.P.8.1-stability summary and conclusion-Astellas.pdf, page 3/5) Applicant is cross referencing both INDs for fidaxomicin #064,435 and # (b) (4) for the tablet and oral suspension, respectively. In IND (b) (4), applicant states that a study was conducted, and results show that In-use stability of suspension is stable for 12 days at 2-8°C after reconstitution. (pharmaceutical-devlopment-2.pdf). No further study details were provided (IND (b) (4)). In IR response, dated 10/23/2019, applicant has provided AET results performed for reconstituted oral suspensions and results showed that oral suspension had up-to 6 log reduction in microorganism tested (b) (4) and the reconstituted drug product does not support microbial growth over the in-use/storage period.

Assessment: As the provided AET data for the reconstituted drug product covered a 28-day storage period, a separate reconstitution/storage

microbiological challenge study to support a 10-day storage period for the reconstituted granules is not necessary.

Adequate

MICROBIOLOGY LIST OF DEFICIENCIES: NA

Primary Microbiology Assessor Name and Date:
Nutan Mytle, Ph.D. 10/29/2019

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Neal J. Sweeney, Ph.D. 11/01/2019

Nutan Mytle

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Neal Sweeney

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Date: 11/14/2019 03:00:07PM
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