CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 209356

Name: Sucralfate Suspension, 1 g/10ml

Sponsor: Amneal Pharmaceuticals LLC

Approval Date: December 02, 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA209356Orig1s000

CONTENTS

Reviews / Information Included in this Review

Approval Letter	
Tentative Approval Letter	
Labeling	
Labeling Review(s)	
Medical Review(s)	
Chemistry Review(s)	**X**
Pharm/Tox Review	
Bioequivalence Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Other Review(s)	
Administrative & Correspondence Documents	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209356

CHEMISTRY REVIEWS

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Complete Response-Minor
☐ Complete Response-Major
☐ Complete Response-Major-Facilities Only

ANDA 209356
Assessment # 3

Drug Product Name	Sucralfate
Dosage Form	Suspension
Strength	1g/10 ml
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Ameal Pharmaceutical, Ltd.
US agent, if applicable	Alpesh Patel

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original ANDA (eCTD 0000)	05/27/2016	Drug Product, Process, Biopharmaceutics
Quality/Response to Information Request (eCTD 0001)	07/06/2016	Drug Product, Process, Biopharmaceutics
Quality/Response to Information Request (eCTD 0002)	10/28/2016	Drug Product (Samples Request)
Amendment (eCTD 0006)	04/10/2018	Drug Product, Process, Biopharmaceutics
Amendment (eCTD 0008)	02/22/2019	Bioequivalence
Quality/ Response to Complete Response (eCTD 0009)	06/03/2019	Drug Substance, Drug Product, Facilities
Quality/Quality Information (eCTD 0010)	08/07/2019	Drug Substance
Amendment (eCTD 0011)	11/05/2019	Drug Product
Amendment (eCTD 0012)	11/21/2019	Drug Product

eCTD 0003, 0005 include administrative information. eCTD 0004 includes mid-cycle meeting request with BE. eCTD 0007 includes labeling information.

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Steve Kinsley	Erin Skoda
Drug Product	Hongmei Li	Asif Rasheed
Manufacturing	Ruth Herzog	Jane Chang/Kamal Tiwari
Biopharmaceutics	Kelly Kitchens	Tien Mien Chen
Regulatory Business Process Manager	Jaimie Jones	
Application Technical Lead	Asif Rasheed	
Laboratory (OTR)	n/a	

Environmental	n/a	

QUALITY ASSESMENT DATA SHEET

IQA ANDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	Type II	(b) (4)		Adequate	10/8/2019	By Steven Kinsley
	Type III			Adequate	09/10/2012 by Nina Ni	Referred by several approved ANDAs on dartts
	Type III			Adequate	10/11/2013 by Andrew J Langowski	Referred by several approved ANDAs on dartts
	Type III			Adequate	1/24/2012 by Gene W Holbert	Referred by several approved ANDAs on dartts
	Type III			Adequate	08/20/2014 by Sulene Han	Referred by several approved ANDAs on dartts
	Type III			Adequate	2/10/2012 by Gene W Holbert	Referred by several approved ANDAs on dartts
	Type III			Adequate	04/22/2016 by Joel Hathaway	Referred by several approved ANDAs on dartts
	Type III			Adequate	09/09/2014 by Sherita McLamore	Referred by several approved

(b) (4)		(b) (4)			ANDAs on dartts
	Type III		Adequate	03/18/2016 by Rajiv Agarwal	Referred by several approved ANDAs on dartts

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

Document	Application Number	Description
	NDA 019183	RLD **CARAFATE®** suspension
	(b) (4)	

2. CONSULTS n/a

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

EXECUTIVE SUMMARY (APPROVALS ONLY)

IQA ANDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

ANDA 209356, Sucralfate Oral Suspension, 1 g/10 mL is recommended for approval with 24-month expiry date. All quality issues for drug substance, drug product, process and facilities have been adequately resolved in Quality Reviews 1 through 3.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Drug product (DP) Sucralfate suspension is indicated in short-term treatment (up to 8 weeks) of active duodenal ulcer. The recommended adult oral dosage for duodenal ulcer is 1 g four times per day on an empty stomach. Sucralfate Suspension contains sucralfate and sucralfate is an α-D-glucopyranoside, β-Dfructofuranosyl-, octakis-(hydrogen sulfate), aluminum complex. In vitro observations suggest that sucralfate's antiulcer activity is the result of formation of an ulcer-adherent complex that covers the ulcer site and protects it against further attack by acid, pepsin, and bile salts. There are approximately 14 to 16 mEq of acid-neutralizing capacity per 1g dose of sucralfate. Although the mechanism of sucralfate's ability to accelerate healing of duodenal ulcers remains to be fully defined, it is known that it exerts its effect through a local, rather than systemic action.

Final recommended dissolution method/specification acknowledged by Firm?	☒ Yes ☐ No ☐ N/A
Are there comparability protocols provided? If yes, how many?	☐ Yes How many:_____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	☐ Yes ☐ No *(see comments) ☒ N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	☒ Yes ☐ No *(see comments) ☐ N/A

Proposed Indication(s) including Intended Patient Population	Short-term (up to 8 weeks) treatment of active duodenal ulcer
Duration of Treatment	Up to 8 weeks
Maximum Daily Dose	4 g
Alternative Methods of Administration	None

B. Quality Assessment Overview (Please note: ATLs should check the most recent policy alert list)

Drug substance (DS) Sucralfate is a synthetic sulfate oligosaccharide aluminum complex derived from sucrose. Sucralfate has an official monograph in USP and EP. (b) (4)

(b) (4)

Drug product (DP) Sucralfate is an oral suspension and non-compendial. Firm provided comparable physicochemical properties between the generic product and the RLD product during pharmaceutical development and in justification for DP specification. The firm updated stability study data up to 24 months under room temperature conditions, and the data is within the proposed specification.

(b) (4)

The dissolution method was determined to be adequate. The Applicant's proposed dissolution acceptance criteria – NLT (b) (4)% (Q) in 30 minutes, and NLT (b) (4) in 30 minutes – are also adequate.

Sucralfate suspension 1 g/10 mL is supplied as a pink suspension available in bottles of 14 fl oz (NDC 65162-062-05).

Recommended storage condition for the drug product is: Store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature].

C. Risk Assessment

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #3	Comments*
API sameness [for biowaiver]	(b) (4)			
Physical stability (solid state)				

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #3	Comments*
Physical Stability (Sedimentation for suspension only)	(b) (4)			
Physical Stability (Particle size growth for suspension only)				
Chemical stability				
pH				
Assay				
Content uniformity				
Dosing Accuracy				

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #3	Comments*
Microbial limits	(b) (4)			
Preservative Content				
Leachable				
Dissolution				

Application Technical Lead Name and Date: Asif Rasheed, 11/22/2019

Asif Rasheed

Digitally signed by Asif Rasheed
Date: 11/26/2019 04:55:19PM
GUID: 54943563003295d5fb908e815949f79d

Recommendation: Approval

ANDA 209356

Review # 3c

Drug Name/Dosage Form	**Sucralfate Suspension**
Strength	**1 g/10 mL**
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Amneal Pharmaceuticals LLC
US agent, if applicable	NA

Quality Review Data Sheet

1. **RELATED/SUPPORTING DOCUMENTS**

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	*10/17/2019*	*By Steven Kinsley*
	Type III			Adequate	09/10/2012 by Nina Ni	Referred by several approved ANDAs on dartts
	Type III			Adequate	10/11/2013 by Andrew J Langowski	Referred by several approved ANDAs on dartts
	Type III			Adequate	1/24/2012 by Gene W Holbert	Referred by several approved ANDAs on dartts
	Type III			Adequate	08/20/2014 by Sulene Han	Referred by several approved ANDAs on dartts
	Type III			Adequate	2/10/2012 by Gene W Holbert	Referred by several approved ANDAs on dartts

(b) (4)	Type III	(b) (4)	Adequate	04/22/2016 by Joel Hathaway	Referred by several approved ANDAs on dartts
	Type III		Adequate	09/09/2014 by Sherita McLamore	Referred by several approved ANDAs on dartts
	Type III		Adequate	03/18/2016 by Rajiv Agarwal	Referred by several approved ANDAs on dartts
	Type IV		Adequate	By Hongmei Li	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
	NDA 019183	RLD **CARAFATE®** suspension
	(b) (4)	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Quality Review Team

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Bioequivalence	complete	Adequate	11/18/2019	Manjinder Kaur
Biopharmaceutics	complete	Adequate	8/20/2018	Kelly Kitchens
Labeling	complete	Adequate	6/11/2019	Esther Park
Other				

Updated risk Assessment:

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	*Initial FMECA RPN*	*Comment*	*Updated FMECA RPN*	*Comment*
API sameness [for biowaiver]	(b) (4)			
Physical stability (solid state)				
Physical Stability (Sedimentation for suspension only)				
Physical Stability (Particle size growth for suspension only)				
Chemical stability				
pH				
Assay				
Content uniformity				
Dosing Accuracy				

	(b) (4)
Microbial limits	
Preservative Content	
Leachable	
Dissolution	

DRUG SUBSTANCE - Sucralfate

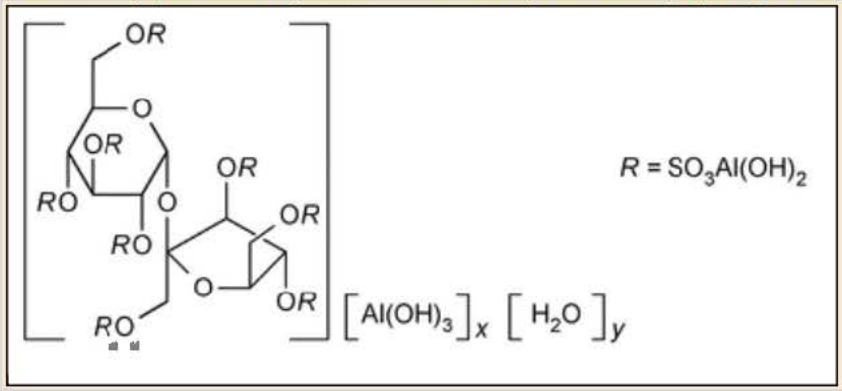
Product Background:

ANDA: 209356 Sucralfate suspension, 1 g/10 mL

Drug substance: Sucralfate, USP

Chemical Name and Structure: Sucralfate, USP

α-D-Glucopyranoside, β-D-fructofuranosyl-, octakis(hydrogen sulfate), aluminum complex



DMF #: (b) (4)

Applicant Name/DMF Holder: Amneal Pharmaceuticals/ (b) (4)

Review Summary: Adequate

Drug substance (DS) Sucralfate is a synthetic sulfate oligosaccharide aluminum complex derived from sucrose. Sucralfate has an official monograph in USP and EP. (b) (4) (b) (4) (b) (4) (b) (4) 1st generic ANDA application for sucralfate suspension. *Currently DMF* (b) (4) *was found adequate, reviewed by Steven Kinsley (10/17/2019), however, no evaluation to address API sameness in DMF review. API sameness study was performed per PSG recommendation and provided in the application, which is found adequate.* (b) (4) (b) (4) *Module 3.2.S.2.6 -Manufacturing Process Development of this Amendment.* (b) (4) (b) (4) *which is found satisfactory.*

The firm's DS specifications are based on the USP monograph and DS in the DMF, found acceptable.

List Submissions being reviewed (table):

Document	*Date*
Multiple categories/subcategories	*02/22/2019*
Multiple categories/subcategories (S0009)	*06/03/2019*

Multiple categories/subcategories (S0010)	*08/07/2019*
Multiple categories/subcategories (S0011)	*11/05/2019*
Multiple categories/subcategories (S0012)	*11/21/2019*

Document reviewed in Review#2	*Date*
Multiple categories/subcategories	*04/10/2018*
Document reviewed in Review#1	*Date*
Original ANDA	*05/27/2016*
Quality/Response to Information Request	*07/06/2016*
Quality/Response to Information Request (S0002)	*10/28/2016*

Highlight Key Outstanding Issues from Last Cycle:

- perform Spectroscopic characterizations per FDA draft guidance to demonstrate API sameness

Concise Description Outstanding Issues Remaining: None

Chemistry Review Part I: Applicant's Response to CR#2 Deficiencies

Deficiencies sent in CR2 on 02/07/2019:

We acknowledge you provided analysis study for API composition, elemental analysis and C/S and C/Al ratio as well as acid neutralizing capacity. However, there are no characterization study of DSC, TGA and UV for the drug substance used in the drug product. Please be aware that FDA draft guidance for Sucralfate suspension is official on Oct 2017. Please perform Spectroscopic characterizations per FDA draft guidance to demonstrate API sameness.

Firm's response on 06/03/2019:

Please note that Comparative Physicochemical Characterizations, Study No. 062-IV-CH was conducted as per the October 2017, Product Specific Bioequivalence Recommendation Guidance (BE Guidance) for sucralfate. The study report was provided in Module 5.3.1.3 of the Complete Response Amendment dated April 10, 2018 (Sequence# 0006).

For the API Sameness characterization, the study included the following tests:

(b) (4)

(b) (4)

Asserssor's assessment: Satisfactory

Physicochemical Characterizations Study report No. 062-IV-CH is located at Module 5.3.1.3 submitted on 04/10/2018.

Product samples used:

Details	API	Test Product	Reference Product

(b) (4)

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(b) (4)

Assessor's assessment: Satisfactory

(b) (4)

(b) (4) the information provided is found acceptable.

==========

Part II: Chemistry Review #2

S.1 General Information: Satisfactory per Review#1

S.2 Manufacture: Satisfactory

Please refer to DMF (b) (4)

Reviewer's Assessment: Satisfactory

(b) (4)

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(b) (4)

S.5 Reference Standard: Satisfactory per Review#2

S.6 Container Closure: Satisfactory per Review#1

S.7 Stability: Satisfactory per Review#1

List of Deficiencies:

None.

Primary Drug Substance Reviewer Name and Date: Hongmei Li, 9/30/2019; 11/08/2019; 11/22/2019

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Asif Rasheed, 10/29/2019, 11/22/2019

DRUG PRODUCT – Sucralfate Oral Suspension

Product Background:

Drug product (DP) Sucralfate suspension is indicated in short-term treatment (up to 8 weeks) of active duodenal ulcer. The recommended adult oral dosage for duodenal ulcer is 1 g four times per day on an empty stomach. Sucralfate Suspension contains sucralfate and sucralfate is an α-D-glucopyranoside, β-Dfructofuranosyl-, octakis-(hydrogen sulfate), aluminum complex. In vitro observations suggest that sucralfate's antiulcer activity is the result of formation of an ulcer-adherent complex that covers the ulcer site and protects it against further attack by acid, pepsin, and bile salts. There are approximately 14 to 16 mEq of acid-neutralizing capacity per 1g dose of sucralfate. Although the mechanism of sucralfate's ability to accelerate healing of duodenal ulcers remains to be fully defined, it is known that it exerts its effect through a local, rather than systemic action.

DP Sucralfate Suspension for oral administration contains 1 g of sucralfate per 10 mL. Sucralfate Suspension also contains: colloidal silicon dioxide NF, FD&C Red #40, glycerin USP, methylcellulose USP, methylparaben NF, microcrystalline cellulose NF, purified water USP, simethicone USP sorbitol solution USP, and (b) (4) Cherry Flavor.

Sucralfate Suspension, 1 g/10 mL is a pink suspension supplied in bottles of 14 fl oz. It should be stored under controlled room temperature.

There is no USP monograph for Sucralfate suspension, and RLD is Carafate (sucralfate) suspension 1g/10 mL, NDA 019183, approved in 1993 and held by Forest lab Inc.

==========

ANDA: 209365

Drug Product Name / Strength: Sucralfate Suspension, 1 g/10 mL

Route of Administration: Oral

Applicant Name: Amneal Pharmaceuticals Inc.

Review Summary: Adequate

DP Sucralfate suspension does not have a USP monograph. BE guidance for sucralfate suspension was revised and become available in Oct 2017. The BE guidance includes recommendations for demonstration of API sameness, Q1/Q2 formulation as RLD, comparative physicochemical characterization of the test and RLD product, and acceptable bioassays. API

sameness refers to drug substance section; and bioassay evaluation will be covered by bioequivalence review.

This ANDA proposed Q1/Q2 formulation except for flavor and color, which is found acceptable. The firm proposed DP specifications based on Sucralfate Tablet USP monograph and the stability data of the exhibit batches. The firm provided comparable physicochemical properties between the generic product and the RLD product during pharmaceutical development and in justification for DP specification. The firm updated stability study data up to 24 month under room temperature conditions, and the data is within the proposed specification.

It is noted that Acid Neutralizing Capacity is (b) (4) in RLD specification, and approx. 14 to 16 mEq per RLD product labeling insert, (b) (4)

(b) (4)

List Submissions being reviewed (table):

Document	*Date*
Multiple categories/subcategories	*02/22/2019*
Multiple categories/subcategories (S0009)	*06/03/2019*
Multiple categories/subcategories (S0010)	*08/07/2019*
Multiple categories/subcategories (S0011)	*11/05/2019*
Multiple categories/subcategories (S0012)	*11/21/2019*

Document reviewed in Review#2	*Date*
Multiple categories/subcategories	*04/10/2018*
Document reviewed in Review#1	*Date*
Original ANDA	*05/27/2016*
Quality/Response to Information Request	*07/06/2016*
Quality/Response to Information Request (S0002)	*10/28/2016*

Highlight Key Outstanding Issues from Last Cycle:

- minor deficiencies for acid neutralizing capacity and aluminium in DP release and stability specification
- comparative study for viscosity with (b) (4) t addition of acid
- Comparative aluminum release at pH 1.2

Concise Description Outstanding Issues Remaining: None

Chemistry Review Part I: Applicant's Response to CR#2 Deficiencies

(b) (4)

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(b) (4)

R Regional Information: satisfactory per review #1

List of Deficiencies

None.

Primary Drug Product Reviewer Name and Date: Hongmei Li, 7/1/2019; 9/30/2019; 11/8/2019; 11/22/2019

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

Asif Rasheed, 10/29/2019, 11/22/2019

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

LABELING

{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A

If "No," explain.

For OTC Drugs and Controlled Substances: NA

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es): NA

ANDA Strength	Length (mm)	Imprint Code

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

None

List of Deficiencies: None

Primary Drug Product Reviewer Name and Date: Hongmei Li/09/30/2019

Secondary Drug Product Reviewer Name and Date: Asif Rasheed, 10/29/2019

Asif Rasheed

Digitally signed by Asif Rasheed
Date: 11/22/2019 02:08:34PM
GUID: 54943563003295d5fb908e815949f79d

Hongmei Li

Digitally signed by Hongmei Li
Date: 11/22/2019 02:08:57PM
GUID: 54c94ca000084932f06afe87774bef34

PROCESS

Product Background: Drug product Sucralfate Suspension is indicated for short-term (up to 8 weeks) treatment of active duodenal ulcer. Sucralfate is also used for the treatment of gastroesophageal reflux disease (GERD) and stress ulcers.

ANDA: 209356

Drug Product Name / Strength: Sucralfate Suspension / 1g/10mL

Route of Administration: Oral

Applicant Name: Amneal Pharmaceutical, Ltd.

Review Recommendation: ***Adequate***

Review Summary:

(b) (4)

(b) (4) A second cycle review resulted in no deficiencies and process review is adequate.

List Submissions being reviewed (table):

➢ Document(s) Reviewed (SD-#)	➢ Date Received
Amendment (SD-7)	**April 10, 2018**
New/ANDA (SD-1)	**May 27, 2016**

Highlight Key Outstanding Issues from Last Cycle:

The firm had adequately addressed process deficiencies identified during the first review cycle regarding in-process controls and compliance with 21 CFR 177.

Concise Description Outstanding Issues Remaining:
None.

List Number of Comparability Protocols: None

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(b) (4)

R2 Assessment: Adequate

Summary of Process Validation Studies Conducted: N/A

Assessment of Microbiological Controls: Please refer to DP review

Comparability Protocols: None

Post-Approval Commitments: N/A

Lifecycle Management Considerations: N/A

List of Deficiencies: None.

Primary Process Reviewer Name and Date:

Ruth Herzog
2/2/2017, 5/7/2018

Secondary Reviewer Name and Date:

Kamal Tiwari
7/3/2017, 09/21/2018

Ruth Herzog

Digitally signed by Ruth Herzog
Date: 9/21/2018 09:23:02AM
GUID: 525daa8500038fae65842c9cebffd2d6

Kamal Tiwari

Digitally signed by Kamal Tiwari
Date: 9/21/2018 08:31:29AM
GUID: 508da7040002897e4750ca8cb60b8dc8

BIOPHARMACEUTICS REVIEW for ANDA SUBMISSIONS	
Application No.	209356-ORIG-1-AMEND-7
Product Name	Sucralfate Suspension
Applicant	Amneal Pharmaceuticals
Dosage Form/Strengths	Suspension, 1 g/10 mL
Route of Administration	Oral
Indication for Use	Short-term (up to 8 weeks) treatment of active duodenal ulcer
Submission Date	April 10, 2018
Review Date	August 15, 2018
Primary Reviewer	Kelly M. Kitchens, Ph.D.
Secondary Reviewer	TienMien Chen, Ph.D.
Recommendation	**ADEQUATE**

1. REVIEW SUMMARY:

Background:
The Applicant is seeking approval of Sucralfate Suspension, 1 g/10 mL, under the 505(j) path. The reference listed drug (RLD), Carafate® (sucralfate) suspension, was approved under NDA 19183 for the 1 g/10 mL strength.

The original Biopharmaceutics review for this ANDA was completed by Dr. Kelly Kitchens on July 7, 2017.

Submission:
This resubmission is in response to the Complete Response (CR) letter dated August 24, 2017. The Biopharmaceutics deficiencies identified in the CR letter were: submit the complete dissolution data for all exhibit batches; submit the aluminum dissolution data as both mass (in milligrams) and as % release.

Review's Objective:
The Biopharmaceutics review is focused on the adequacy of the Applicant's response to the Biopharmaceutics deficiencies regarding the dissolution data.

Reviewer's Assessment:
The dissolution method was previously determined to be adequate (see the Biopharmaceutics Review by Dr. Kelly Kitchens dated July 7, 2017 in Panorama). The Applicant's proposed dissolution acceptance criteria – NLT (b) (4)% (Q) in 30 minutes, and NLT (b) (4) in 30 minutes – are also adequate.

Conclusion and Recommendation:
From the Biopharmaceutics perspective, ANDA 209356 for Sucralfate Suspension, 1 g/10 mL, is recommended for approval.

2. REVIEW:

a) List Submissions being reviewed:

April 10, 2018	Resubmission 1st major – complete response amendment

b) Highlight Key Outstanding Issues from Last Review Cycle: The Applicant was requested to submit the complete dissolution data for all the exhibit batches, and to report the dissolution data as both mass (in milligrams) and as % release.

c) Concise Description of Outstanding Issues: there are no outstanding issues

d) Dissolution method and acceptance criteria proposed by the Applicant:

Method Source	USP Apparatus	Speed (RPMs)	Medium/ Temperature	Volume (mL)	Sampling Times (min)	Acceptance Criteria
FDA	II (paddle)	75	0.01 N HCl/0.067 M KCl, pH 1.0	900	10, 20, 30, 45	NLT (b) (4)% (Q) of the theoretical amount of Aluminum is dissolved in 30 minutes
						NLT (b) (4) of Aluminum is dissolved in 30 minutes

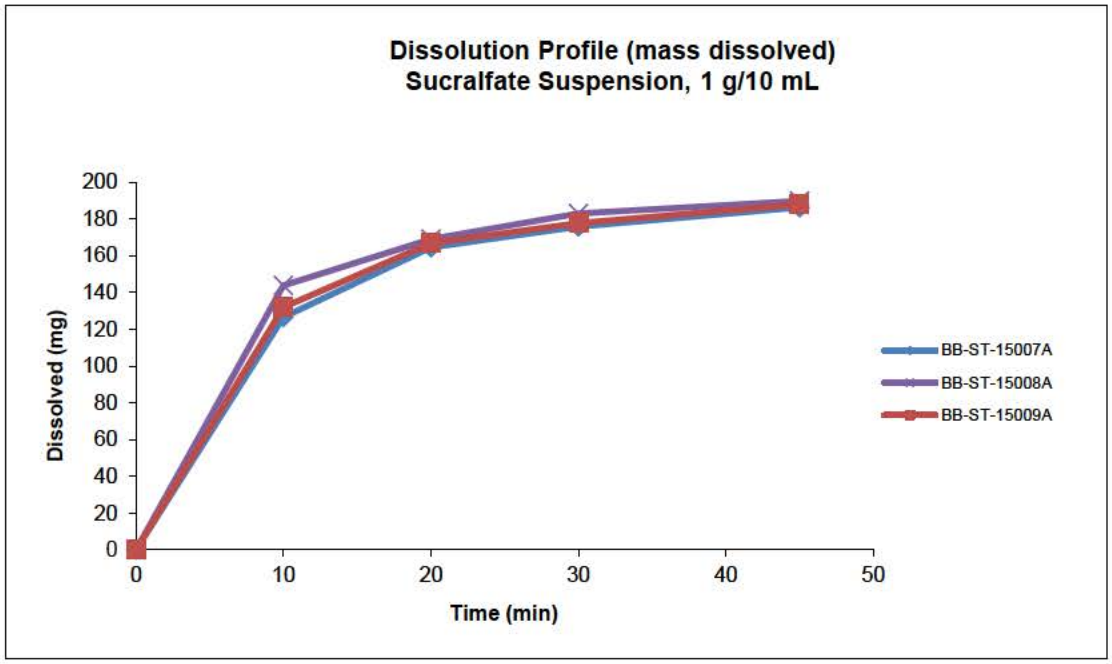
e) In Vitro Dissolution Data

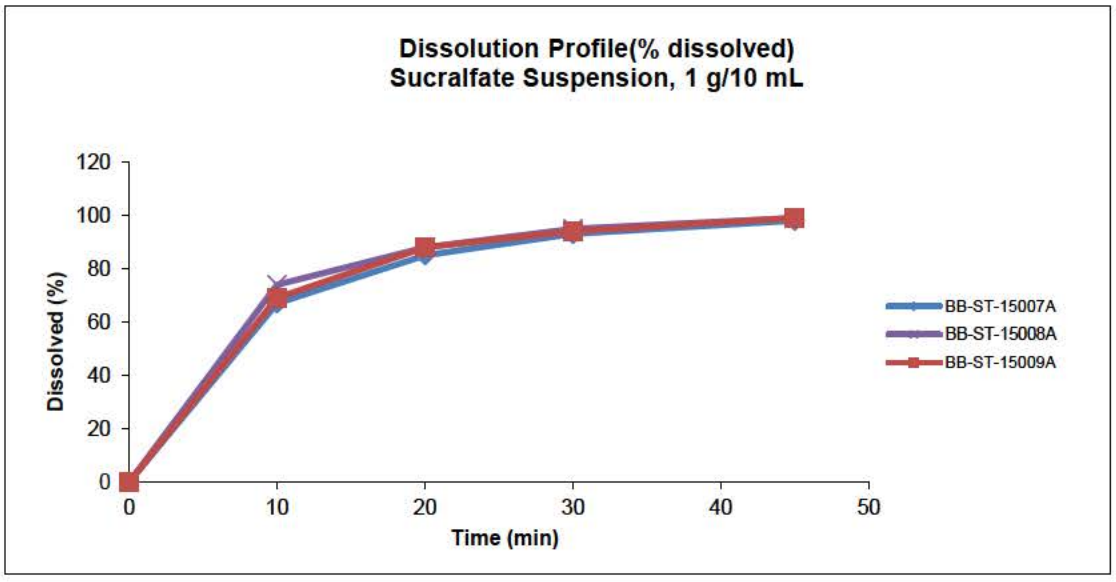
Table 1: Summary of mean in vitro dissolution data for the proposed drug product

Time (minutes)	Mass/% Dissolution		
	Batch No.		
	BB-ST-15007A	BB-ST-15008A*	BB-ST-15009A
10	126.490 mg / 67%	143.742 mg / 74%	131.960 mg / 69%
20	162.402 mg / 85%	169.035 mg / 88%	166.802 mg / 88%

30	175.819 mg / 93%	182.852 mg / 95%	177.762 mg / 94%
45	186.250 mg / 98%	189.748 mg / 99%	187.935 mg / 99%

*Biobatch





See Appendix 1 for the complete dissolution data of the test product exhibit batches.

3. REVIEWER'S ASSESSMENT:

Dissolution Method: Adequate. Sucralfate is a synthetic sulfate oligosaccharide aluminum complex derived from sucrose. Therefore, Aluminum is the measured analyte from the dissolution samples.

Dissolution Acceptance Criteria: Adequate

4. BIOPHARMACEUTICS COMMENTS:

See Appendix 2 for details of the CR letter deficiencies and the Applicant's responses.

The Applicant provided the requested data, and the Applicant's responses are acceptable.

5. CONCLUSION and RECOMMENDATION:

The following dissolution method and acceptance criteria are adequate for the test product:

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance Criteria
II (paddle)	75	0.01 N HCl/0.067 M KCl, pH 1.0	900	NLT (b) (4)% (Q) of the theoretical amount of Aluminum is dissolved in 30 minutes
				NLT (b) (4) of Aluminum is dissolved in 30 minutes

This ANDA is recommended for approval.

6. SIGNATURE BLOCK:

Primary Biopharmaceutics Reviewer:
Kelly M. Kitchens, Ph.D., August 15, 2018

Secondary Biopharmaceutics Reviewer: I concur. 08/20/18
TienMien Chen, Ph.D.,
Acting Biopharm. Lead,
DB/ONDP/OPQ

APPENDIX 1

Dissolution Data Tables

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

APPENDIX 2

Applicant's Complete Response

1. The detailed dissolution profile data at release for the other exhibit batches using the proposed dissolution method, however, could not be located in this submission. Therefore, submit the complete dissolution profile data (individual, mean of n=12, %RSD, range, and mean profile) and batch information (batch no., manufacturing dates, site, size, and date of dissolution testing) for all the exhibit batches, including batches BB-ST-15007A and BB-ST-15009A. These dissolution data are needed to establish an appropriate dissolution acceptance criterion.

Applicant's Response:
Amneal acknowledges the Agency's comment. The complete dissolution profile data (individual, mean of n=12, %RSD, range, and mean profile) and batch information (batch no., manufacturing dates, site, size, and date of dissolution testing) for all the exhibit batches are provided in Report # 062-DS-OGD in Module 5.3.1.3.

2. We request that you submit the aluminum dissolution data as both
    a. Mass in milligrams; and
    b. % release of aluminum based on total aluminum present in the dosage form.

    The dissolution acceptance criteria should be expressed as both mass released and % released.

Applicant's Response:
Amneal acknowledges the Agency's comment. The aluminum dissolution data as both Mass in milligrams; and % release of aluminum based on total aluminum present in the dosage form, for all the exhibit batches are provided in Report # 062-DS-OGD in Module 5.3.1.3.

Based on the results Amneal proposes the following acceptance criteria for dissolution.
NLT (b) (4)% (Q) of the theoretical amount of Aluminum in 30 minutes;
NLT (b) (4) of Aluminum in 30 minutes.

Please refer to Module 3.2.P.5.1 for the revised drug product release/stability specifications.

v

Kelly Kitchens

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Date: 8/20/2018 04:35:43PM
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Tien Mien Chen

Digitally signed by Tien Mien Chen
Date: 8/20/2018 04:36:45PM
GUID: 508da7240002a26723d38018ce005126

FACILITIES

Product Background:	**First Review;** Indicated for the treatment of active duodenal ulcers.
NDA/ANDA:	ANDA 209356
Drug Product Name/Strength:	**First Generic;** Sucralfate Suspension, 1 g/10 mL
Route of Administration:	Oral
Applicant Name:	AMNEAL PHARMACEUTICALS

Review Summary: **ADEQUATE**

List Submissions being reviewed (table):

Submission(s) Reviewed	Date Received
Submission amendment (Administrative / Last 356h form)	25-JUL-2017
Submission amendment (Response to IR)	06-JUL-2016
Original submission	27-MAY-2016

Highlight Key Outstanding Issues from Last Cycle: Not Applicable

Concise Description Outstanding Issues Remaining: None

10 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

QUALITY ASSESSMENT

Primary Facilities Reviewer Name and Date:

ADEQUATE

Frank Wackes, 27JULY2017
Consumer Safety Officer, OPQ/OPF/DIA/IABII

Secondary Reviewer Name and Date:

I concur with the acceptable recommendation.

Christina Capacci-Daniel, PhD – 11August2017
Acting QAL, OPQ/OPF/DIA/IABII

Frank Wackes

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Christina Capacci-Daniel

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Asif Rasheed

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