CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209589Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 209589
Review # 1

Drug Name/Dosage Form	Clenpiq (sodium picosulfate, magnesium oxide, and anhydrous citric acid) Solution
Strength	10mg/3.5g/12g
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Ferring Pharmaceutical, Inc.
US agent, if applicable	Not applicable

1	Original Submission	01/31/2017
2	Proprietary Name Request	03/13/2017
3	Response to Clinical Information Request	03/30/2017
4	Response to Quality Information Request: Facilities	04/05/2017
5	Labeling: Package Insert Draft	05/05/2017
6	Response to Quality Information Request: Microbiology and Biopharm	05/19/2017
7	Response to Quality Information Request: Drug Substance, Drug Product, and Process	05/26/2017
8	Clinical: Safety Update	05/26/2017
9	Response to Quality Information Request: Biopharm	06/16/2017
10	Response to Quality Information Request: Drug Product and Process	06/29/2017
11	Response to Quality Information Request: Drug product-Correction to Assya and Degradation Product Calculation	09/29/2017
12	Response to Quality Information Request: Post-Approval Stability Commitment and Environmental Assessment	10/05/2017
13	Label and Labeling: Package Insert Draft, Container closure, and Carton	10/25/2017
14	Labeling: Package Insert Draft	11/02/2017

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Sukhamaya 9sam) Bain, Ph.D.	Donna F. Christner, Ph.D.
Drug Product	Hamid Shafiei, Ph.D.	Moo-Jhong Rhee, Ph.D.
Process	Kejun Cheng Ph.D.	N. Chidambaram, Ph.D.
Microbiology	Eric Adeeku, Ph.D.	Erika Pfeiler, Ph.D.
Facility	Carl Lee	B.J. Ryan
Biopharmaceutics	Vincent (Peng) Duan, Ph.D.	Tien-Mien Chen, Ph.D.
Regulatory Business Process Manager	Oumou K. Barry, MHA, MT, ASCP	Hamet Toure, PharmD, MPH
Application Technical Lead	Hamid Shafiei, Ph.D.	Not applicable
Laboratory (OTR)	Not applicable	Not applicable
ORA Lead	Zachery Miller	Not applicable
Environmental	Hamid Shafiei, Ph.D.	Moo-Jhong Rhee, Ph.D.

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	11-APR-2017	Reviewed By: Sukhamaya Bain, Ph.D.
	Type II			Adequate	05-OCT-2017	Reviewed By: Sukhamaya Bain, Ph.D.
	Type II			Adequate	07-APR-2017	Reviewed By: Sukhamaya Bain, Ph.D.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	202535	RLD: PREPOPIK for Oral Solution

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, purity, strength and quality of the drug substance and drug product.

All labels/labeling issues have been resolved.

The Office of Process and Facility has made an overall "Acceptable" recommendation regarding the facilities involved in this NDA.

Therefore, from the OPQ perspective, this NDA is recommended for **APPROVAL** with the drug product expiration dating period of **18 months**.

II. Summary of Quality Assessments

A. Product Overview

Ferring Pharmaceutical, Inc. has submitted this 505(b)(2) new drug application for CLENPIQ™ (sodium picosulfate, magnesium oxide and anhydrous citric acid) Oral Solution, 10mg/3.5g/12g. CLENPIQ™ Oral Solution is a stimulant and osmotic laxative indicated for the cleansing of colon in preparation to colonoscopy. CLENPIQ™ Oral Solution contains identical amounts of the same three active ingredients used in the approved drug product, PREPOPIK® for oral solution (NDA 202535), but it is reformulated as a solution ready for oral consumption. PREPOPIK® is marketed as two packets powder in a carton for the two-dose regimen as prescribed. The content of each PREPOPIK® packet is to be dissolved in cold water prior to oral administration.

The applicant has stated that CLENPIQ™ Oral Solution was developed to eliminate the reconstitution step and to reduce any potential for dosing inadequacies associated with the patient's failure to fully dissolve the entire content of the packet before taken orally.

CLENPIQ™ Oral Solution is supplied in a carton containing two (b) (4) (b) (4) bottles enclosed with a (b) (4) caps, each holding 160mL of cranberry-flavored, colorless to slightly yellow, clear oral solution, along with an eight-ounce cup for measuring fluids for hydration. Each bottle contains 10mg sodium picosulfate, 3.5g magnesium oxide, and 12g anhydrous citric acid.

The applicant of this application is also the owner of the approved NDA 202535 for PREPOPIK®.

Proposed Indication(s) including Intended Patient Population	**Indicated for cleansing of the colon in preparation for colonoscopy**
Duration of Treatment	**Two dose to be taken within 24 hour prior to colonoscopy procedure**
Maximum Daily Dose	**Two 160mL bottles for oral administration. Each bottle contains 10mg of sodium picosulfate, 3.5g of magnesium oxide, and 12g of anhydrous citric acid**
Alternative Methods of Administration	**Not applicable**

B. Quality Assessment Overview

Drug Substance:

Sodium picosulfate -

4,4'-[(pyridin-2-yl)methylene]diphenyl bis(sodium sulphate) monohydrate

is a (b) (4)

(b) (4)

Anhydrous citric acid –

1,2,3-propanetricaboxylic acid, 2-hydroxy

(b) (4)

Magnesium oxide –

MgO

(b) (4)

The CMC information for the three active ingredients, sodium picosulfate, anhydrous citric acid, and magnesium oxide that are provided in DMF (b) (4), DMF (b) (4) and

DMF (b) (4) respectively, have been reviewed by the Drug Substance Reviewer, Dr. Sam Bain. Dr. Bain has found the three referenced DMFs adequate and has recommended the **approval** of this new drug application from the drug substance perspective.

Drug Product:

Ferring Pharmaceutical, Inc. has developed CLENPIQ™ (sodium picosulfate, magnesium oxide, and anhydrous citric acid) Oral Solution, 10mg/3.5g/12g as an alternative dosage form of their currently approved drug product, PREPOPIK® for Oral solution. The new solution formulation adds more convenience to the patient administration since it is ready for oral use without needing reconstitution in cold water prior to administration as is required for PREPOPIK®. It also believed that the elimination of the reconstitution step may reduce any potential for dosing inadequacies arising from the patient's failure to fully dissolve the entire content of each packet before it is taken.

CLENPIQ™ Oral Solution contains the identical amounts of the same three active ingredients, sodium picosulfate, magnesium oxide, and anhydrous citric acid as PREPOPIK®, but it is formulated with different inactive ingredients (b) (4) (b) (4)

The to-be-marketed CLENPIQ™ Oral Solution is to be packaged in a carton containing two bottles that supplies the drug product for the same two-dose regimen prescribed for PREPOPIK®. Each bottle contains 160mL of cranberry-flavored, colorless to slightly yellow, clear oral solution and is indicated for colon cleansing in preparation for colonoscopy. Each 160mL contains 10mg of sodium picosulfate, 3.5g magnesium oxide, and 12g of citric acid.

The pharmaceutical/formulation development for this drug product was mainly focused on the selection of compatible excipients and container closure system. The excipients selection was aimed at (b) (4) (b) (4)

The proposed drug product specification as well as the methods used in the release and stability testing of the drug product have been reviewed by Biopharm, Microbiology, and ONDP reviewers and have been found to be appropriately validated and adequate for determining the identity, strength, purity, and quality of the drug product at release and throughout the proposed shelf-life of 18 months. In support of the proposed expiration dating period of 18 months, sufficient accelerated, intermediate, and long-term stability data have been submitted in the application. The stability results clearly show that the drug product will be stable in the proposed packaging configuration for at least 18 months when stored under the ICH-defined long-term conditions. Therefore, expiration dating period of 18 months is granted.

In summary, the Drug Product Reviewer/ATL, Dr. Hamid Shafiei has concluded that from the drug product perspective, the applicant has submitted sufficient CMC information that illustrates the applicant can routinely manufacture CLENPIQ™ Oral Solution with consistent quality from batch to batch with the desired quality attributes. Therefore, from the ONDP standpoint, Dr. Shafiei has recommended the **approval** of this new drug application.

Process

From the process point of view, the applicant has performed adequate risk assessment of each pivotal manufacturing process step that can impact the quality of the final drug product. Based on the understanding of the manufacturing process and the risks associated with each manufacturing step, the applicant has implemented appropriate controls and in-process testing. (b) (4)

(b) (4)

In summary, the process reviewer, Dr. Kejun Cheng, has concluded that the applicant has adequately addressed the deficiencies delineated in the information requests and has provided sufficient information that supports the proposed manufacturing process for CLENPIQ™ Oral Solution described in the application. Dr. Cheng has recommended the **approval** of this application from the manufacturing process point of view.

Biopharm

The proposed drug product is a pre-mixed oral solution, and therefore, the Biopharm review has been mainly focused on acceptability the applicant's request for biowaiver. The applicant has justified requesting for a biowaiver based on the assertion that CLENPIQ™ Oral Solution contains the same active ingredients as the approved drug product, PREPOPIK® for Oral solution and that the new solution formulation does not contain any inactive ingredient that may significantly affect absorption or systemic and/or local availability. In support of this claim the applicant has submitted results from comparative solubility under relevant physiological pH of (b) (4) comparative permeability, laxative effect in rat, osmolality, and electrolyte studies. The applicant has provided appropriate information to justify that it would be unlikely that the addition of the proposed amounts of malic acid, EDTA, and sucralose to the

formulation of the drug product have any impacts the drug absorption or cause any safety issues.

In summary, the Biopharm Reviewer, Dr. Vincent (Peng) Duan has concluded that the information provided adequately bridges the bioavailability/bioequivalence between CLENPIQ™ Oral Solution and PREPOPIK® for Oral solution. Therefore, Dr. Duan has found the request for biowaiver acceptable and has recommended the **approval** of this application from the Biopharm standpoint.

Microbiology

CLENPIQ™ Oral Solution is a non-sterile drug product and is tested for bioburden according to USP <61> and USP <62> (b) (4) The proposed USP adopted methods has been validated to confirm that the methods can determine bioburden (b) (4) effectiveness for this drug product. The proposed methods and method validation as well as acceptance limits for bioburden have been reviewed and evaluated by the Microbiology Reviewer, Dr. Eric Adeeku. Dr. Adeeku has concluded that the proposed test methods are appropriate for their intended purpose and that the applicant has demonstrated adequate level of (b) (4) Dr. Adeeku has recommended the **approval** of this application from the Microbiology perspective.

Facilities

Facilities involved in this application has been reviewed by the Facilities Reviewer, Carl Lee. Mr. Lee has concluded that "There appears to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facilities and their previous inspection results, history, and relevant experience. The facilities are determined **acceptable** in their identified functions and responsibilities to support approval of NDA 209589 for manufacturing of Clenpiq™ (sodium picosulfate, magnesium oxide, and anhydrous citric acid) oral solution".

Environmental Assessment

The applicant has requested categorical exclusion from the preparation of the environmental assessment according to 21 CFR § 25.31(a), In support of this request, the applicant has determined the EIC for each of the active ingredients based on the maximum anticipated production according to estimated (b) (4) sales forecast. The calculated EIC for each of the active ingredients falls far below 1ppb, the limit that triggers preparation of the environmental assessment. The request for the categorical exclusion has been reviewed by the Drug Product Reviewer/ATL, Dr. Hamid Shafiei. Dr. Shafiei has found the applicant's request for categorical exclusion per 21 CFR § 25.31(a) is deemed valid and has **granted** the categorical exclusion to this new drug application.

C. Special Product Quality Labeling Recommendations (NDA only)

Not applicable

D. Final Risk Assessment (see Attachment)

Since, this drug product is manufactured by the same manufacturer of the currently approved drug product, PREPOPIK® for Oral solution, no overall risk assessment is provided here. However, relevant risk evaluations/risk assessments associated with the proposed manufacturing process/equipment and facilities are separately captured and discussed in the Process and the Facilities review chapters of this integrated quality assessment.

Overall Assessment by the Application Technical Lead (ATL):

Based on the assessments and approval recommendation from each OPQ review discipline, this 505(b)(2) new drug application is recommended for **Approval** from the OPQ perspective with an expiration dating period of **18 months**.

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

LABELING

R Regional Information

1.14 Labeling

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section

CLENPIQ™ (sodium picosulfate, magnesium oxide, and anhydrous citric acid) oral solution
Initial U.S. Approval: 2012

----------DOSAGE FORMS AND STRENGTHS ----------
CLENPIQ oral solution: Each bottle contains 10 mg of sodium picosulfate, 3.5 g of magnesium oxide, and 12 g of anhydrous citric acid in 160 mL of solution (3)

Item	Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	CLENPIQ™ (sodium picosulfate, magnesium oxide, and anhydrous citric acid) **Satisfactory**
Dosage form, route of administration	oral solution **Satisfactory**
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (201.57(a)(8))	
Whether the drug product is scored	N/A

(b) "Full Prescribing Information" Section

2: Dosage and Administration

Special instructions:

- The preferred method is the "Split-Dose" method and consists of two separate doses: the first dose during the evening before the colonoscopy and the second dose the next day, during the morning prior to the colonoscopy [see Dosage and Administration (2.2)].

- The alternative method is the "Day Before" method and consists of two separate doses: the first dose during the afternoon or early evening before the colonoscopy and the second dose 6 hours later during the evening before the colonoscopy [see Dosage and Administration (2.3)].

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	• The preferred method is the "Split-Dose" method and consists of two separate doses: the first dose during the evening before the colonoscopy and the second dose the next day, during the morning prior to the colonoscopy [see Dosage and Administration (2.2)]. • The alternative method is the "Day Before" method and consists of two separate doses: the first dose during the afternoon or early evening before the colonoscopy and the second dose 6 hours later during the evening before the colonoscopy [see Dosage and Administration (2.3)]. **Satisfactory**

3: Dosage Forms and Strengths

Oral solution: Each bottle contains 10 mg of sodium picosulfate, 3.5 grams of magnesium oxide, and 12 grams of anhydrous citric acid in 160 mL of colorless to slightly yellow, clear solution.

Item	**Information Provided in NDA**
Available dosage forms	Solution **Satisfactory**
Strengths: in metric system	10 mg of sodium picosulfate, 3.5 grams of magnesium oxide, and 12 grams of anhydrous citric acid in 160 mL of colorless to slightly yellow, clear solution **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	160 mL of colorless to slightly yellow, clear solution **Satisfactory**

#11: Description

CLENPIQ (sodium picosulfate, magnesium oxide, and anhydrous citric acid) oral solution is a stimulant and osmotic laxative that is provided as a cranberry-flavored, colorless to slightly yellow, clear oral solution, and is supplied as two bottles in each carton.

Each bottle of CLENPIQ contains 10 mg sodium picosulfate, USP; 3.5 g magnesium oxide, USP; and 12 g anhydrous citric acid, USP. The product also contains the following inactive ingredients:

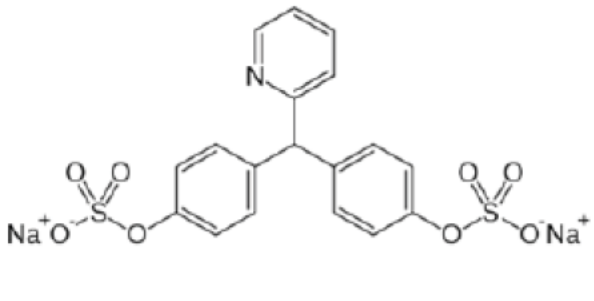
Acesulfame potassium, cranberry flavor, disodium edetate, malic acid, sodium benzoate, sodium hydroxide, sodium metabisulfite, sucralose, and water. The cranberry flavor contains glyceryl triacetate (triacetin), maltodextrin and sodium octenyl succinated starch.

The following is a description of the three active ingredients contained in CLENPIQ:

Sodium picosulfate is a stimulant laxative.

Sodium Picosulfate

- Chemical name: 4,4′-(2-pyridylmethylene) diphenyl bis(hydrogen sulfate) disodium salt, monohydrate
- Chemical formula: $C_{18}H_{13}NNa_2O_8S_2 \cdot H_2O$
- Molecular weight: 499.4
- Structural formula:



Sodium picosulfate

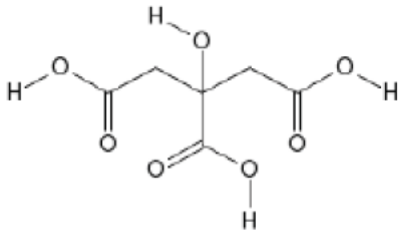
Magnesium citrate, which is formed in solution by the combination of magnesium oxide and anhydrous citric acid, is an osmotic laxative.

Magnesium Oxide

- Chemical name: Magnesium oxide
- Chemical formula: Mg O
- Molecular weight: 40.3
- Structural formula: Mg O

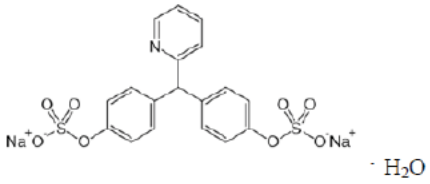
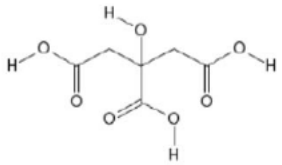
Anhydrous Citric Acid

- Chemical name: 2-hydroxypropane-1,2,3-tricarboxylic acid
- Chemical formula: C6H8O7
- Molecular weight: 192.1
- Structural formula:



Anhydrous citric acid

Item	Information Provided in NDA
Proprietary name and established name	CLENPIQ (sodium picosulfate, magnesium oxide, and anhydrous citric acid) **Satisfactory**
Dosage form and route of administration	Oral solution **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Each bottle of CLENPIQ contains 10 mg sodium picosulfate, USP; 3.5 g magnesium oxide, USP; and 12 g anhydrous citric acid, USP. The product also contains the following inactive ingredients: Acesulfame potassium, cranberry flavor, disodium edetate, malic acid, sodium benzoate, sodium hydroxide, sodium metabisulfite, sucralose, and water. The cranberry flavor contains glyceryl triacetate (triacetin), maltodextrin and sodium octenyl succinated starch. **Satisfactory**

Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	CLENPIQ (sodium picosulfate, magnesium oxide, and anhydrous citric acid) oral solution is a stimulant and osmotic laxative **Satisfactory**
Chemical name, structural formula, molecular weight	<u>Sodium Picosulfate</u> • Chemical name: 4,4´-(2-pyridylmethylene) diphenyl bis(hydrogen sulfate) disodium salt, monohydrate • Chemical formula: C18H13NNa2O8S2·H2O • Molecular weight: 499.4 • Structural formula:  Sodium picosulfate Magnesium citrate, which is formed in solution by the combination of magnesium oxide and anhydrous citric acid, is an osmotic laxative. <u>Magnesium Oxide</u> • Chemical name: Magnesium oxide • Chemical formula: Mg O • Molecular weight: 40.3 <u>Anhydrous Citric Acid</u> • Chemical name: 2-hydroxypropane-1,2,3-tricarboxylic acid • Chemical formula: C6H8O7 • Molecular weight: 192.1 • Structural formula:  Anhydrous citric acid **Satisfactory**
If radioactive, statement of important nuclear characteristics.	N/A

Other important chemical or physical properties (such as pKa or pH)	a cranberry-flavored, colorless to slightly yellow, clear oral solution, and is supplied as two bottles in each carton **Satisfactory**

#16: How Supplied/Storage and Handling

How Supplied

CLENPIQ is supplied in a carton containing two bottles, each holding 160 mL of cranberry-flavored, colorless to slightly yellow, clear oral solution, along with an eight-ounce cup for measuring fluids for hydration. Each bottle contains 10 mg sodium picosulfate, 3.5 g magnesium oxide, and 12 g anhydrous citric acid.

CLENPIQ Cranberry flavor: NDC# 55566-6700-1.

Storage

Store CLENPIQ at 25°C (77°F). Excursions permitted at 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Do not refrigerate or freeze.

Item	Information Provided in NDA
Strength of dosage form	CLENPIQ is supplied in a carton containing two bottles, each holding 160 mL of cranberry-flavored, colorless to slightly yellow, clear oral solution, along with an eight-ounce cup for measuring fluids for hydration. Each bottle contains 10 mg sodium picosulfate, 3.5 g magnesium oxide, and 12 g anhydrous citric acid. **Satisfactory**
Available units (e.g., bottles of 100 tablets)	CLENPIQ is supplied in a carton containing two bottles, each holding 160 mL **Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	A cranberry-flavored, colorless to slightly yellow, clear oral solution **Satisfactory**
Special handling (e.g., protect from light)	N/A
Storage conditions	Store CLENPIQ at 25°C (77°F). Excursions permitted at 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Do not refrigerate or freeze. **Satisfactory**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured by: ASM Aerosol-Service AG Industriestrasse 11, CH - 4313 Möhlin Switzerland Manufactured for: Ferring Pharmaceuticals Inc. Parsippany, N.J. 07054 **Satisfactory**

Reviewer's Assessment:

The ONDP perspective packaged insert is deemed **satisfactory.**

2. *Immediate Container Label*

(b) (4)

Item	Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	CLENPIQ™ (sodium picosulfate, magnesium oxide, and anhydrous citric acid) The font of the established name should be at least 50% of the tradename and also its color should be as prominent as the tradename. **Unsatisfactory**
Dosage strength	10 mg/3.5 g/12 g per 160-mL bottle **Satisfactory**
Net contents	160 mL **Satisfactory**
"Rx only" displayed prominently on the main panel	Displayed **Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Displayed **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	Not provided. **Unsatisfactory**
Storage conditions	Store at 25° C (77°F); Excursions permitted at 15-30°C (59-86°F) [See USP controlled room temperature]; Do not refrigerate or freeze. **Satisfactory**
Bar code (21CFR 201.25)	Not displayed **Unsatisfactory**
Name of manufacturer/distributor	Provided **Satisfactory**
And others, if space is available	CLENPIQ™ is a ready-to-drink oral solution that doesn't need to be diluted. Both bottles are required for a complete bowel preparation. **Satisfactory**

Reviewer's Assessment:

The following revision should be made to the immediate container (bottle) label:

- The font size for the established name should be at least 50% of the tradename, and its color also should be as prominent as the tradename.
- Add lot number and expiration date
- Add bar code.

Conclusion: The immediate container label needs to be revised and therefore, it is **unsatisfactory.**

3. Carton Labeling

(b) (4)

Item	Information Provided in NDA
Proprietary name, established name (font size, prominence)	CLENPIQTM (sodium picosulfate, magnesium oxide, and anhydrous citric acid) The font size should be at least 50% of the tradename and as prominent as the tradename. **Unsatisfactory**
Dosage strength	10 mg/3.5 g/12 g per 160-mL bottle **Satisfactory**
Net quantity of dosage form	Two (2) 160-mL bottles **Satisfactory**
"Rx only" displayed prominently on the main panel	Displayed **Satisfactory**
Lot number and expiration date	Not provided. **Unsatisfactory**
Storage conditions	Store at 25° C (77°F); Excursions permitted at 15-30°C (59-86°F) [See USP controlled room temperature] Do not refrigerate or freeze. **Satisfactory**
Bar code (21CFR 201.25)	Displayed **Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Displayed **Satisfactory**
Manufacturer/distributor's name	Displayed **Satisfactory**
Quantitative ingredient information (injectables)	N/A
Statement of being sterile (if applicable)	N/A
"See package insert for dosage information"	Read the instructions in the enclosed Medication Guide AT LEAST 2 DAYS BEFORE your colonoscopy and again right before taking CLENPIQ™. **Satisfactory**
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Displayed. **Satisfactory**

Reviewer's Assessment:

The following revision should be made to the carton label:

- The font size of the established name should be at least 50% of the tradename and also it should be as prominent as the tradename.
- Add lot number and expiration date to the carton label.

Conclusion: The carton label needs to be revised and therefore, it is **unsatisfactory**.

List of Deficiencies:

1) ***Immediate container label:***
   - *The font size of the established name should be at least 50% of the tradename and also it should be as prominent as the tradename.*
   - *Add lot number and expiration date*
   - *Add bar code.*

2) ***Carton label:***
   - *The font size of the established name should be at least 50% of the tradename and also it should be as prominent as the tradename.*
   - *Add lot number and expiration date to the carton label.*

Overall Assessment and Recommendation:

This NDA is not recommended for approval until the label/labeling issues are appropriately resolved.

Primary Labeling Reviewer: Hamid Shafiei, Ph.D., Branch V/DNDP II/ONDP

Secondary Reviewer:

I agree with Dr. Shafiei's assessment on the labeling and labels and concur with his recommendation that this application is not ready for approval in its present form per 21 CFR 314.125(b)(6).

Moo-Jhong Rhee, Ph.D., Chief Branch V/DNDP II/ONDP

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 10/13/2017 03:59:44PM
GUID: 507d824300005f344cf8b5e5989f0057

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 10/13/2017 04:11:17PM
GUID: 502d0913000029f9798ca689a802fa55

Memorandum

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

Date: **October 25, 2017**
From: **Hamid Shafiei, Ph.D.**
Drug Product Reviewer, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: **CMC Label/Labeling Review #1 of NDA 209589**

Subject: **Review of the Resubmitted Immediate Container and Carton Labels**

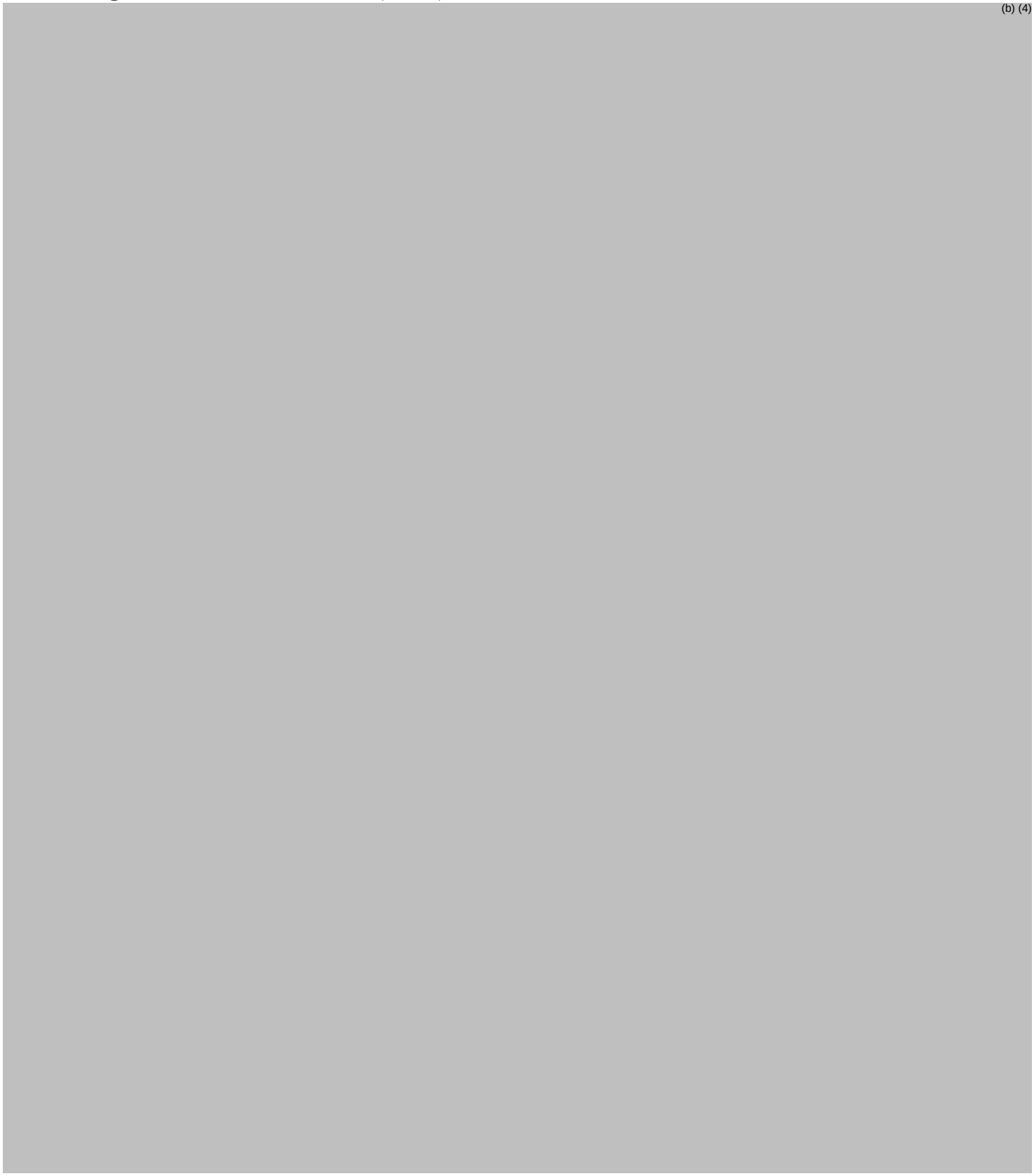
During the Review # 1 of the label/labeling of NDA 209589 for Clenpiq (sodium picosulfate, magnesium oxide, anhydrous citric acid Oral Solution, 10mg/3.5g/12g, the following deficiencies were noted:

1) ***Immediate container label:***
   - *The font size of the established name should be at least 50% of the tradename and also it should be as prominent as the tradename.*
   - *Add lot number and expiration date*
   - *Add bar code.*

2) ***Carton label:***
   - *The font size of the established name should be at least 50% of the tradename and also it should be as prominent as the tradename.*
   - *Add lot number and expiration date to the carton label.*

In an amendment dated October 25, 2017, the applicant has resubmitted revised immediate container and carton labels. The labels are presented in Figures 1 and 2.

Figure 1: Immediate Container (Bottle) Label



Review Comments and Evaluation

Lot number, expiration date, and bar code have been added to the immediate container label. The font size and prominence of established name vs trade name have been appropriately addressed.

Lot number and expiration date have been added to the carton label. The font size and prominence of the established name vs trade name have been appropriately addressed.

Recommendation:

The resubmitted immediate container (bottle) and carton labels are deemed satisfactory from the ONDP perspective. All label/labeling deficiencies have been adequately addressed. This application is now recommended for approval from the label/labeling standpoint.

Hamid R. Shafiei, Ph.D.
Drug Product Reviewer
Branch V, Division II, ONDP

Moo-Jhong Rhee, Ph.D.
Chief, Branch V, Division II, ONDP

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 10/25/2017 03:34:21PM
GUID: 507d824300005f344cf8b5e5989f0057

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 10/25/2017 03:38:11PM
GUID: 502d0913000029f9798ca689a802fa55

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

BIOPHARMACEUTICS

IQA Review Guide Reference

Product Background:

NDA: 209589

Drug Product Name / Strength: Sodium picosulfate, magnesium oxide, and citric acid oral solution

Route of Administration: Oral

Indication: bowel preparation prior to colonoscopy

Applicant Name: Ferring Pharmaceuticals

Review Recommendation: Adequate

Review Summary: The proposed drug product is a low-volume, pre-mixed, oral solution referencing NDA 202535 Prepopik (the listed drug), which was approved on July 16, 2012. The composition of the proposed drug product is shown in Table 1.

Table 1. Composition of the proposed drug product

Component	Amount per 160 mL	Function	Quality standard
Sodium picosulfate	10 mg	Active ingredient	USP-NF curr. ed.
Magnesium oxide (b) (4)	3.5 g	Active ingredient	USP-NF curr. ed.
Anhydrous citric acid	12 g	Active ingredient	USP-NF curr. ed.
Edetate disodium	(b) (4)		USP-NF curr. ed.
Sodium benzoate			USP-NF curr. ed.
Malic acid			USP-NF curr. ed.
Sucralose			USP-NF curr. ed.
Acesulfame potassium			USP-NF curr. ed.
Sodium hydroxide			USP-NF curr. ed.
Sodium metabisulfite			USP-NF curr. ed.
Cranberry flavouring, (b) (4)	(b) (4)	Flavouring agent	In-house specification
(b) (4) water		(b) (4)	USP-NF curr. ed.

Compared to the listed drug PREPOPIK oral solution, the proposed drug product contains the same amount of active drug ingredient sourced from the same supplies. However, there are differences in the inactive ingredients between the proposed drug product and the listed drug product PREPOPIK (Table 2).

Table 2. Comparative Composition of PREPOPIK and Sodium Picosulfate, Magnesium Oxide, and Anhydrous Citric Acid Oral Solution

PREPOPIK® Powder for Oral Solution (approved under NDA 202535)		Sodium Picosulfate, Magnesium Oxide, and Anhydrous Citric Acid Oral Solution	
Component	**Amount per Unit Dose**	**Component**	**Amount per Unit Dose**
Active Ingredients			
Sodium picosulfate	10 mg	Sodium picosulfate	10 mg
Magnesium oxide	3.5 mg	Magnesium oxide	3.5 mg
Anhydrous citric acid	12 g	Anhydrous citric acid	12 g
Inactive Ingredients			
Saccharin sodium	(b) (4)	Sodium benzoate	(b) (4)
Potassium hydrogen carbonate		Acesulfame potassium	
		Sucralose	
		Edetate disodium	
		Sodium metabisulfite	
		Sodium hydroxide	
		Malic acid	
		(b) (4) water	
Flavoring Agent			
(b) (4)		Cranberry flavor	

Regardless of the difference in the formulation, the Applicant requested for a waiver of in vivo bioavailability (BA) and bioequivalence (BE) studies pursuant to 21 CFR 320.22 (b) (3) :

(i) is an oral solution; and

(ii) contains the same active drug ingredient(s) in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application; and

(iii) contains no inactive ingredient or other change in formulation from the drug product that is the subject of an approved full new drug application that may significantly affect absorption or systemic or local availability.

Biopharmaceutics review focus on the evaluation of request for waiving the BA/BE studies and the impact of the difference in inactive ingredients on drug absorption.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: ***{Adequate/Inadequate}N/A***

{Assess method development, method robustness, and criteria; modeling approach}

The proposed drug product is a pre-mixed oral solution. Therefore, there is no dissolution review.

Biowaiver Request

Reviewer's Assessment: ***{Adequate/Inadequate}Adequate***

The Applicant submitted a request for waiver of BA/BE based on 21 CFR 320.22 (b) (3). The proposed drug product is a pre-mixed oral solution and contains the same amount of active ingredients as shown in Table 2. Therefore, the proposed drug product met the requirement (i) and (ii) in 21 CFR 320.22 (b) (3).

Based on Table 2, there is difference in inactive ingredients in formulation compared to the listed drug. Therefore, the questions remained are that whether the different inactive ingredients in the formulation of the proposed drug product would significantly affect absorption or systemic or local availability as stated in requirement (iii) in 21 CFR 320.22 (b) (3). To support that the difference in formulation would not affect absorption or systemic or local availability, in pre-NDA meeting dated May 17, 2016, the Applicant proposed the following studies:

- *comparative solubility study under relevant physiological pH* (b) (4)
- *comparative permeability study (magnesium, picosulfate)*
- *in vivo rat study to measure formation of the metabolite and the laxative effect for both formulations*
- *comparative osmolality study*
- *comparative sodium study*

In the meeting minutes dated May 17, 2016, the Agency stated that the above approach seems reasonable, and the acceptability of these studies would be a review issue.

In the current NDA submission, the Applicant submitted the following studies for review.

1. Comparative permeability study

Based on the results from tolerability of Caco-2 cell to the proposed drug product, it was found that the integrity of Caco-2 cell monolayers were compromised in the presence of 30% diluted, 50% diluted, and 100% (undiluted) of the proposed pre-mixed oral solution. Further Caco-2 tolerability and permeability studies showed that, the Caco-2 cells monolayer integrity was maintained in the presence of up to 25% dilution of the proposed drug product (b) (4)

Therefore, the Applicant evaluated the in vitro permeability of three active ingredients as well as bisacodyl related compound BHPM in validated Caco-2 cell monolayer model in series dilutions (10%, 15%, and 20%) of the test drug product and reference PREPOPIK drug product (b) (4) as well as unformulated individual active ingredients (without excipient) (Table 3). Based on the validation study of the Caco-2 cells model, the Applicant considered the permeability would not change if the difference of Papp values from two compounds were within 2-fold.

Table 3 A-to-B Permeability of Magnesium and Co-dosed Reference Compounds

Nominal MgO Dosing Conc. (mM)			54.3	81.4	108
Strength			10%	15%	20%
Formulation	**Analyte**	**Parameter**			
Unformulated	Magnesium	P_{app} (10^{-6} cm/s)	2.8 ± 0.2	1.7 ± 0.1	1.8 ± 0.1
		Recovery (%)	149 ± 14	117 ± 3	130 ± 12
		% Permeated	9.3 ± 0.2	6.7 ± 0.8	5.1 ± 0.1
	Minoxidil	P_{app} (10^{-6} cm/s)	5.1 ± 0.2	5.1 ± 0.2	4.8 ± 0.1
		Recovery (%)	94 ± 2	93 ± 3	92 ± 2
	Atenolol	P_{app} (10^{-6} cm/s)	0.21 ± 0.03	0.32 ± 0.09	1.5 ± 0.1[a]
		Recovery (%)	99 ± 3	98 ± 4	98 ± 6
PREPOPIK®	Magnesium	P_{app} (10^{-6} cm/s)	1.8 ± 0.7	2.4 ± 0.2	2.3 ± 0.2
		Recovery (%)	115 ± 6	132 ± 20	104 ± 8
		% Permeated	5.1 ± 0.8	6.8 ± 0.2	7.6 ± 0.7
	Minoxidil	P_{app} (10^{-6} cm/s)	4.7 ± 0.3	5.0 ± 0.3	5.1 ± 0.1
		Recovery (%)	79 ± 2	90 ± 2	88 ± 1
	Atenolol	P_{app} (10^{-6} cm/s)	1.5 ± 0.1[a]	0.52 ± 0.05	0.38 ± 0.03
		Recovery (%)	80 ± 2	89 ± 4	84 ± 3
CLENPIQ™	Magnesium	P_{app} (10^{-6} cm/s)	2.42 ± 0.11	1.7 ± 0.1	1.1 ± 0.1
		Recovery (%)	119 ± 5	100 ± 16	89 ± 3
		% Permeated	8.2 ± 0.1	5.4 ± 0.0	3.3 ± 0.0
	Minoxidil	P_{app} (10^{-6} cm/s)	4.9 ± 0.2	4.7 ± 0.2	3.5 ± 0.2
		Recovery (%)	92 ± 3	92 ± 3	92 ± 2
	Atenolol	P_{app} (10^{-6} cm/s)	0.13 ± 0.02	0.16 ± 0.03	0.27 ± 0.02
		Recovery (%)	89± 4	93 ± 3	93 ± 3

* All results are from the initial permeability experiment in which atenolol and minoxidil were co-dosed with the test articles to monitor cell monolayer integrity.

[a] All six replicates failed the monolayer integrity test based on the P_{app} of co-dosed atenolol, but the results are reported to enable comparison with other treatments.

The data in Table 3 indicate that the Papp for magnesium was similar at each MgO dosing concentration across formulations (going down each column) and at different dosing concentrations within a given formulation (across each row).

Table 4. A-to-B Permeability of Citric Acid

Nominal Citric Acid Dosing Conc. (mM)			39.0	58.6	78.1
Strength			10%	15%	20%
Unformulated	Citric Acid	P_{app} (10^{-6} cm/s)	0.18 ± 0.01[a]	0.18 ± 0.05	0.16 ± 0.03
		Recovery (%)	93 ± 4[a]	97 ± 8	91 ± 9
		% Permeated	0.28 ± 0.05[a]	0.30 ± 0.10	0.23 ± 0.04
	Minoxidil*	P_{app} (10^{-6} cm/s)	3.0 ± 0.3	2.5 ± 0.3	4.3 ± 0.3
	Atenolol*	P_{app} (10^{-6} cm/s)	0.54 ± 0.09	0.45 ± 0.10	0.40 ± 0.04
PREPOPIK®	Citric Acid	P_{app} (10^{-6} cm/s)	0.24 ± 0.02[a]	0.26 ± 0.01	0.29 ± 0.05[a]
		Recovery (%)	100 ± 8[a]	90 ± 4[b]	71 ± 8[a]
		% Permeated	0.33 ± 0.03[a]	0.38 ± 0.03	0.39 ± 0.06[a]
	Minoxidil*	P_{app} (10^{-6} cm/s)	4.1 ± 0.4	2.8 ± 0.2	3.1 ± 0.2
	Atenolol*	P_{app} (10^{-6} cm/s)	0.77 ± 0.11	0.90 ± 0.05	1.28 ± 0.02
CLENPIQ™	Citric Acid	P_{app} (10^{-6} cm/s)	0.12 ± 0.02	0.15 ± 0.02	0.18 ± 0.04
		Recovery (%)	86 ± 6	93 ± 11	82 ± 12
		% Permeated	0.19 ± 0.02	0.22 ± 0.03	0.30 ± 0.04
	Minoxidil*	P_{app} (10^{-6} cm/s)	2.3 ± 0.0	2.3 ± 0.5	4.5 ± 0.3
	Atenolol*	P_{app} (10^{-6} cm/s)	0.26 ± 0.03	0.33 ± 0.05	0.52 ± 0.03

* All results are from the repeat permeability experiment in which atenolol and minoxidil were not co-dosed and cell monolayer integrity was monitored by a post experimental test.

[a] One replicate was excluded from calculation of mean and SD; n=5.

Papp for citric acid was low and similar to that of the low-permeability reference compound atenolol. The data in Table 4 show that the Papp for citric acid was similar at each dosing concentration across formulations (going down each column) and at different dosing concentrations within a given formulation (across each row).

Table 5. A-to-B Permeability of Sodium Picosulfate

Nominal Sodium Picosulfate Dosing Conc. (µM)			13.0*	19.5#	26.0*
Strength			10%	15%	20%
Unformulated	Picosulfate	P_{app} (10^{-6} cm/s)	0.24 ± 0.06[a,b]	0.20 ± 0.02[b]	0.18 ± 0.04[b]
		Recovery (%)	99 ± 10[b]	85 ± 10[b]	104 ± 7[b]
		% Permeated	0.33 ± 0.08[b]	0.19 ± 0.02[b]	0.28 ± 0.07
	Minoxidil	P_{app} (10^{-6} cm/s)	3.0 ± 0.3	5.1 ± 0.2	4.3 ± 0.3
	Atenolol	P_{app} (10^{-6} cm/s)	0.54 ± 0.09	0.32 ± 0.09	0.40 ± 0.04
PREPOPIK®	Picosulfate	P_{app} (10^{-6} cm/s)	0.25 ± 0.07[b]	0.51 ± 0.04[b]	0.33 ± 0.06
		Recovery (%)	81 ± 6[b]	80 ± 8[b]	73 ± 5[b]
		% Permeated	0.39 ± 0.07[b]	0.44 ± 0.08	0.45 ± 0.10[b]
	Minoxidil	P_{app} (10^{-6} cm/s)	4.1 ± 0.4	5.0 ± 0.3	3.2 ± 0.2
	Atenolol	P_{app} (10^{-6} cm/s)	0.77 ± 0.11	0.52 ± 0.05	1.3 ± 0.0
CLENPIQ™	Picosulfate	P_{app} (10^{-6} cm/s)	0.19 ± 0.02	0.15 ± 0.04	0.17 ± 0.02
		Recovery (%)	93 ± 4	100 ± 10	86 ± 2
		% Permeated	0.26 ± 0.03	0.15 ± 0.05	0.28 ± 0.02
	Minoxidil	P_{app} (10^{-6} cm/s)	2.3 ± 0.05	4.7 ± 0.2	4.5 ± 0.3
	Atenolol	P_{app} (10^{-6} cm/s)	0.26 ± 0.03	0.16 ± 0.03	0.52 ± 0.03

* The reported results are from the repeat permeability experiment in which atenolol and minoxidil were not co-dosed and cell monolayer integrity was monitored by a post experimental test.

The reported results are from the initial permeability experiment in which atenolol and minoxidil were co-dosed with the test articles to monitor cell monolayer integrity.

As the data shown in Table 5, at two of the three dosing concentrations the Papp for sodium picosulfate was very similar across formulations and that in all cases picosulfate shows very low permeability similar to that for the low-permeability reference compound atenolol. At 19.5 µM, Papp for picosulfate was higher for PREPOPIK® than

the unformulated test solutions and CLENPIQT. However, the relative Papp of picosulfate compared to low permeability compound (referenced to atenolol) is similar across three formulations (0.20/0.32 vs. 0.51/0.52 vs. 0.15/0.16). The difference in Papp at 19.5 µM is unlikely to translate into difference in in vivo absorption.

Table 6. A-to-B Permeability of BHPM

Nominal BHPM Dosing Conc. (µM)			1.30	2.60	13.0
Strength			1%	2%	10%
Unformulated	BHPM	P_{app} (10^{-6} cm/s)	28 ± 4	29 ± 2	31± 2
		Recovery (%)	108 ± 8	83 ± 4	101 ± 5
		% Permeated	40 ± 5	42 ± 4	47± 4
	Minoxidil*	P_{app} (10^{-6} cm/s)	3.1 ± 0.4	2.5 ± 0.2	2.4 ± 0.2
	Atenolol*	P_{app} (10^{-6} cm/s)	0.38 ± 0.09	0.37 ± 0.05	0.19 ± 0.04
PREPOPIK®	BHPM	P_{app} (10^{-6} cm/s)	55 ± 3[a]	39 ± 4	30 ± 2
		Recovery (%)	144 ± 10	85 ± 7	104 ± 6
		% Permeated	87 ± 4	55 ± 5	49 ± 2
	Minoxidil*	P_{app} (10^{-6} cm/s)	3.9 ± 0.6	5.4 ± 0.3	4.7 ± 1.3
	Atenolol*	P_{app} (10^{-6} cm/s)	0.8 ± 0.2	2.1 ± 0.2	2 ± 1
CLENPIQ™	BHPM	P_{app} (10^{-6} cm/s)	49 ± 6	34 ± 2	29 ± 2
		Recovery (%)	131 ± 14	112 ± 9	103 ± 4
		% Permeated	77 ± 11	52 ± 4	46 ± 2
	Minoxidil*	P_{app} (10^{-6} cm/s)	1.5 ± 0.2	1.5 ± 0.2	2.7 ± 0.1
	Atenolol*	P_{app} (10^{-6} cm/s)	0.16 ± 0.03	0.27 ± 0.02	0.39 ± 0.01

* All results are from the repeat permeability experiment, in which atenolol and minoxidil were not co-dosed and cell monolayer integrity was monitored by a post experimental test.

As shown in Table 6 in all cases the Papp of BHPM was similar (within a factor of 2) at each dosing concentration across formulations (going down each column).

Overall, the existence of excipients in the proposed drug product didn't affect the permeability of active ingredients. The proposed drug product (CLENPIQ) and the reference drug (PREPOPIK) have comparable permeability in the tested Caco-2 cell systems, regardless of the difference in excipients composition between them. Furthermore, the test drug product is unlikely administrated with other drugs at the same time; therefore, the potential impact of the excipients in the test drug product on other drug products would be minimal.

The final acceptability of Caco-2 permeability study would be determined by Clinical Pharmacology reviewer. Based on clinical pharmacology reviewer Dr. Xinyuan Zhang, in vitro Caco-2 permeability studies are acceptable.

2. Comparative solubility study under relevant physiological pHs.

As requested by the Agency at pre-NDA meeting dated May 17, 2016, the Applicant conducted a study to assess whether precipitation would occur with the proposed and referenced pre-mixed oral solutions, CLENPIQ vs. PREPOPIK over a pH range of (b) (4) (b) (4) These pHs represent the physiological pH range that the oral solution will encounter from the stomach to the large intestine at fasted condition.

The content of sodium picosulfate, magnesium oxide, and citric acid was measured for both neat solution (CLENPIQ and PREPOPIK) and all diluted samples. The sample

preparations for solubility study were shown in Table 7. Note: It is not clearly indicated that the following in vitro studies were conducted at 37°C.

Table 7. Sample preparation for pH 1.3, pH 6.5, pH 7.4, and pH 7.0 buffers

Samples	Sample preparation	Interval to second sampling
pH 1.3	160 mL of CLENPIQ or 150 mL of PREPOPIK+ 50 mL of 0.1 N HCl	20 min
pH 6.5	30 mL of pH 1.3 + 15 mL of pH 6.5	30 min
pH 6.8 immediate dilution	30.0 mL of pH 6.5 solution + 15.0 mL of pH 6.8 buffer	2 hours
pH 7.4 immediate dilution	30.0 mL of pH 6.8 solution + 15.0 mL of pH 7.4 buffer	2 hours
pH 7.0 immediate dilution	30.0 mL of pH 7.4 solution + 15.0 mL of pH 7.0 buffer	14 hours

The Applicant referenced the two literatures for their design of solubility study (Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging. Schiller. et al. 2005. 22:971-979. Aliment. Pharmacol. Ther.; Designing a Dynamic Dissolution Method: A Review of Instrumental Options and Corresponding Physiology of Stomach and Small Intestine; Culen et al. J Pharm Sci. 2013. 2995). Based on these two literatures, the mean fluid volume of stomach at fasting condition is 45 mL (+/-18), while the mean volume in small intestine and large intestine is 105 mL (+/-72) and 13 mL (+/- 12 mL), respectively. Therefore, the sample dilution shown in Table 7 is acceptable, and represents the physiological conditions of GI track. Gastric empty time at fasting conditions is ~10 to15 min. The transit of dosage forms through the whole small intestine (SI) lasts approximately 3-4 hrs. Therefore, the interval to second sampling shown in Table 7 mimics the approximate physiological conditions, and is acceptable.

Based on solubility study, the recovery of sodium picosulfate in all samples ranges (b) (4)% for the listed drug PREPOPIK, and ranges (b) (4)% for the test drug CLENPIQ, respectively. The recovery of magnesium oxide ranges (b) (4)% for the listed drug PREPOPIK, and ranges (b) (4)% for the test drug CLENPIQ, respectively. The recovery of citric acid ranges (b) (4)% for the listed drug PREPOPIK, and ranges (b) (4)% for the test drug CLENPIQ, respectively. There was no reduction in any of the measured values. Furthermore, the visual check for precipitation at each step of the experiment didn't observe any precipitation for both PREPOPIK and CLENPIQ. Therefore, the solubility study indicated that solubility of the test drug product was maintained over the physiological pH range.

Electrolyte comparison with PREPOPIK powder for oral solution

As shown in Table 8A and 8B, (b) (4) As a result, there is significant large amount of (b) (4)g sodium in the formulation of CLENPIQ, compared to (b) (4)g of sodium in PREPOPIK. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

2). Although the sodium content in CLENPIQ is significantly higher than that in PREPOPIK, the sodium content is substantially less than the amounts present in common bowel cleansing preparations in the markets (e.g. MoviPrep (sodium (b) (4) g/ per unit), SUPREP ((b) (4) g / per unit), GoLYTELY ((b) (4) g/ per unit).

3). The sodium content in CLENPIQ is slightly higher than FDA recommended daily

intake of (b) (6) g; however, it is within (b) (4) % of the average American daily consumption of (b) (6) of sodium, and therefore within the dietary expectations of the average American diet (Gillespie et al. 2015; 101: 344-53. Am J Clin Nutr.).

4). Both CLENPIQ and PREPOPIK are taken at most two doses once every year, instead of chronically. Therefore, the existence of higher sodium content will be transient, especially as recommended in Medication Guide, CLENPIQ would be diluted by ingesting of clear liquids.

Overall, the difference in electrolyte (e.g. sodium and potassium) between CLENPIQ and PREPOPIK would not be a concern.

Comparison of osmolality in PREPOPIK and CLENPIQ

As comparison of osmolality between two formulations shown in Table 9, the proposed oral solution formulation has approximately a 3-fold higher osmolality.

Table 9. Osmolality of Neat Formulations

Solution		**Osmolality (mOsm)**
PREPOPIK® (b) (4) (Commercial) after reconstitution	Rep 1	442
	Rep 2	440
	Rep 3	441
	Mean	**441**
Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid Oral Solution	Rep 1	1266
	Rep 2	1271
	Rep 3	1269
	Mean	**1269**

As described in medication guide, after drinking the CLENIPIQ or PREPOPIK, the patient needs to drink (b) (4) five 8-ounce cups of clear liquids, which will further dilute the formulations after their initial dilution with gastric fluid and intestinal fluid. Examples of clear liquids include water, clear broth, Jell-O etc.

Therefore, the Applicant evaluated the osmolality of PREPOPIK and CLENPIQ after dilution with various clear liquids (Table 10). As shown in Table 10, although the initial difference in osmolality between two formulations is more than 3 fold, the osmolality difference is substantially narrowed after dilution with three cups of clear liquids.

After drinking 5 cups of clear liquids (except tap water with low osmolality), the osmolality of two formulations is very close. Therefore, the higher osmolality in neat formulation of CLENPIQ would be close to that in PREPOPKIQ after administration

into human body and drinking (b) (4) 5 cups of 8-oz clear liquids as suggested in medication guide.

Furthermore, the osmolality in CLENPIQ (~ 1269 mOsm/kg) is not unusual higher as it is within the range of commonly ingested beverages (e.g. cranberry juice (907 mOsm/kg), prune juice (1174 mOsm/kg), white wine (2577 mOsm/kg) (Feldman 1995. Gastroenterology. 108: 125-131); hence would not pose any safety risks.

The principle active osmotic agents, magnesium and magnesium citrate, remained primarily associated with fecal material in the gut accounting for the osmotically-mediate increase of water retained in the gut contributing to the laxative effect. The transient differences in the osmolality of these two formulations would not be expected to alter the laxative effect, particularly in the colon, which was shown in in vivo animal study.

Table 10. Osmolality (mOsm/kg) of PREPOPIK® and CLENPIQ™ after Sequential Dilution of SGF/SIF and Clear Liquids of Low and High Osmolalities

Solution	Osmolality (mOsm) N=3							
	Neat	50 mL SGF	100mL SIF	8 ounce glasses				
				1	2	3	4	5
Low Osmolality Liquids								
Jell-O (82 mOsm)								
PREPOPIK®	441	385	300	176	146	134	125	122
CLENPIQ™	1269	1014	730	376	289	274	249	190
Gatorade (139 mOsm)								
PREPOPIK®	441	385	300	213	185	174	164	160
CLENPIQ™	1269	1014	730	389	302	256	230	215
Tap Water (18 mOsm)								
PREPOPIK®	441	385	300	139	88	71	59	51
CLENPIQ™	1269	1014	730	316	205	154	126	110
High Osmolalty Liquids								
White Grape Juice (1082 mOsm)								
PREPOPIK®	441	385	300	765	876	939	968	1015
CLENPIQ™	1269	1014	730	950	1000	1024	1044	1049
Cranberry Juice (563 mOsm)								
PREPOPIK®	441	385	300	478	513	532	541	551
CLENPIQ™	1269	1014	730	654	626	613	603	601
Apple Juice (765 mOsm)								
PREPOPIK®	441	385	300	574	644	682	700	714
CLENPIQ™	1269	1014	730	764	774	776	779	779
Beef Broth (mOsm)								
PREPOPIK®	441	385	300	344	353	356	360	365
CLENPIQ™	1269	1014	730	522	458	431	413	406

SGF = Simulated Gastric Fluid without pepsin (2% w/v sodium chloride in 0.7% v/v hydrochloric acid
SIF = Simulated Intestinal Fluid without pancreatin (potassium dihydrogen phosphate, sodium hydroxide)
Jell-O (Lemon lime Jell-O sugar free), Gatorade (G2 Glacier Freeze), White grape juice (Welch's 100% crisp), Apple juice (Welch's pourable concentrate – diluted), White cranberry juice (Ocean Spray).

Comparison of malic acid

The CLENPIQ formulation contains (b) (4) g of malic acid, while it is not present in the formulation of PREPOPIK. Malic acid is a dicarboxylic acid existing in all living organisms, and is commonly used as food additive. In the formulation of CLENPIQ, malic acid is functioning as (b) (4) Based on the Dr. Tamal from Pharm & Tox, the higher amount of malic acid would not have any safety concern, since the safety of malic acid is well established.

(b) (4)

(b) (4) the existence of malic acid in CLENPIQ would not affect the laxative effect of the proposed drug product:

(b) (4)

(b) (4)

[redacted]

Overall, the existence of high amount of malic acid would not affect laxative function of the proposed drug product, and would not pose any safety concern.

Comparison of edetate disodium (EDTA)

There is (b) (4) mg (b) (4) of edetate disodium (EDTA) in CLENPIQ, which is not present in PREPOPIK formulation. The existence of (b) (4) mg of EDTA in (b) (4) g of Clenpiq is out of the ILL limit for the approved oral solution drug products. Thus, an IR was sent to the Applicant on April 19, 2017 as the following:

> *FDA Request:*
> *Justify the existence of (b) (4) mg edetate disodium (EDTA) in the formulation of Clenpiq oral solution would not affect drug absorption and that the daily exposure of (b) (4) mg disodium EDTA from the recommended dose of Clenpiq would not pose any safety concern.*

On May 19, 2017, the Applicant justified the EDTA in their formulation:

1) . Salts of EDTA (e.g. disodium EDTA), are poorly absorbed in GI tract (<5% in humans), and are not acutely toxic. EDTA is absorbed and eliminated intact in kidney, with low potential for skin sensitization.

2). Based on study from WHO/FAO JECFA, the ADI of EDTA established based on rat study was (b) (4) mg/kg/day. The two doses of (b) (4) mg disodium EDTA in CLENPIQ oral solution is equivalent to (b) (4) mg / kg for a 50 kg individual. Although, (b) (4) mg/kg is higher than the ADI of (b) (4) mg/kg/day, the Applicant concluded that due to low toxicity (acute and chronic) of disodium EDTA and given 6 hours apart between the two doses of CLENPIQ, the amount of EDTA in oral solution is considered to be of no safety concern.

The acceptance of above justifications regarding the safety of disodium EDTA in CLENPIQ oral solution would be reviewed and determined by Pharma/Tox reviewer.

The Applicant also submitted justifications on that EDTA in solution would not affect drug absorption.

1) The in vitro study evaluating Papp in Caco-2 cells (Caco 2 permeability) of the proposed oral solution and the reference drug indicated that the permeability and local

availability of the active ingredients were similar and were not affected by the difference in inactive ingredients (including EDTA) between CLENPIQ and PREPOPK solutions.

2). The results of studying the laxative effect in rats as described in the following section showed that there was no difference in measures of the laxative effect between the proposed CLENPIQ oral solution and the reference PREPOPK oral solution.

The above two studies indicated that the different in inactive ingredients including EDTA in CLENPIQ would have comparable permeability and laxative effect to the reference drug PREPOPK oral solution. However, as reported by the literature, EDTA is a paracellular permeability enhancer; therefore, the existence of EDTA in CLENPIQ oral solution might be expected to have a higher Caco-2 permeability, which was not observed in the Applicant's studies. Regarding this inconsistence, the Applicant provided the following explanation:

(b) (4)

4)

Overall, the Applicant's justification on the presence of EDTA is acceptable.

Existence of sucralose in CLENPIQ

There is (b) (4) mg of sucralose in the formulation of CLENPIQ, which is not present in the formulation of PREPOPIK. According to Pharm & Toxicology reviewer, there is no safety concern on the existence of sucralose. Sucralose (b) (4) and

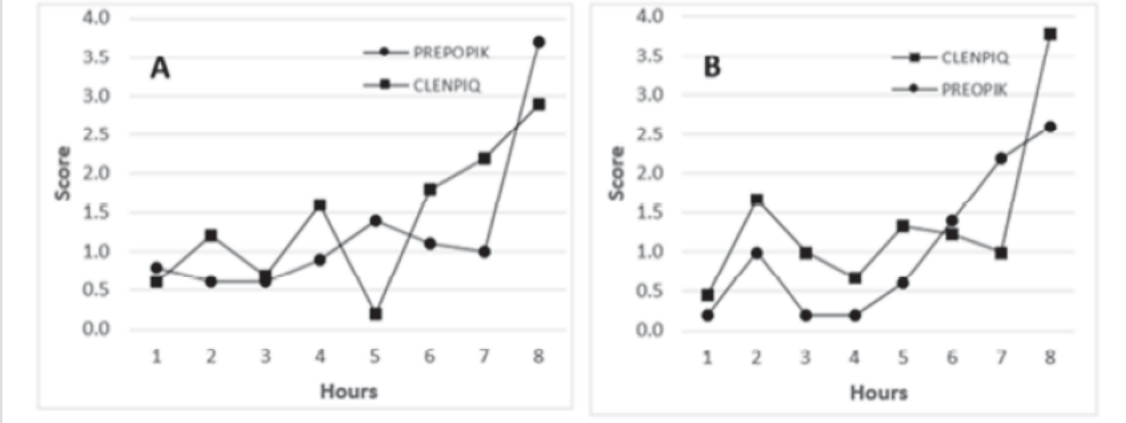
sucralose was reported to might be able to affect drug absorption in rat through P-glycoprotein (P-gp) and CYP3A4/CYP2D6 in the intestine. However, none of the active ingredients in CLENPIQ was reported to be substrate of either P-gp or CYP3A4/CYP2D6 based on University of Washington Drug Interaction Database (DiDB database). Furthermore, the in vitro Caco-2 permeability study and laxative demonstrated similar in vitro permeability and laxative effect of the proposed drug product and RLD despite the existence of sucralose. Therefore, the possibility that sucralose in CLENPIQ might affect drug absorption would be low.

Comparison of the laxative effect of CLENPIQ and PREPOPIK in a rat model
As requested by the Agency in Pre-NDA meeting dated May 17, 2016, the Applicant conducted a study in rats (study 77647) to provide an assessment of the laxative pharmacodynamic effect of CLENPIQ compared to PREPOPIK, as one of evidence that the difference in inactive ingredients in CLENPIQ will not affect the metabolism of sodium picosulfate to its active metabolite BHPM, and efficacy of the product.

The rat model used by the Applicant was based on previous similar studies in rat in the submission of PREPOPIK. Accordingly, the laxative effect of CLENPIQTM and PREPOPIK® was examined following administration by oral gavage twice (~ 8 hr between doses) in one day to rats using a cross-over study design. Rats received 2 oral doses of 2000 mg/kg CLENPIQTM or PREPOPIK® on day 1 with each dose separated by 8 hours and after seven days were crossed over to receive the same treatment with the other formulation and followed until normal fecal output was achieved.

The data presented in the following Figure 1 show that the onset and time to maximal effect (8 hours) was equivalent for the two formulations. The onset and time to maximal effect of two formulations were overlapped with each other depends on the treatment sequence (Figure 1A and Figure 1B).

Figure 1A. Onset of Purgative Effect: CLENPIQ vs PREPOPIK®

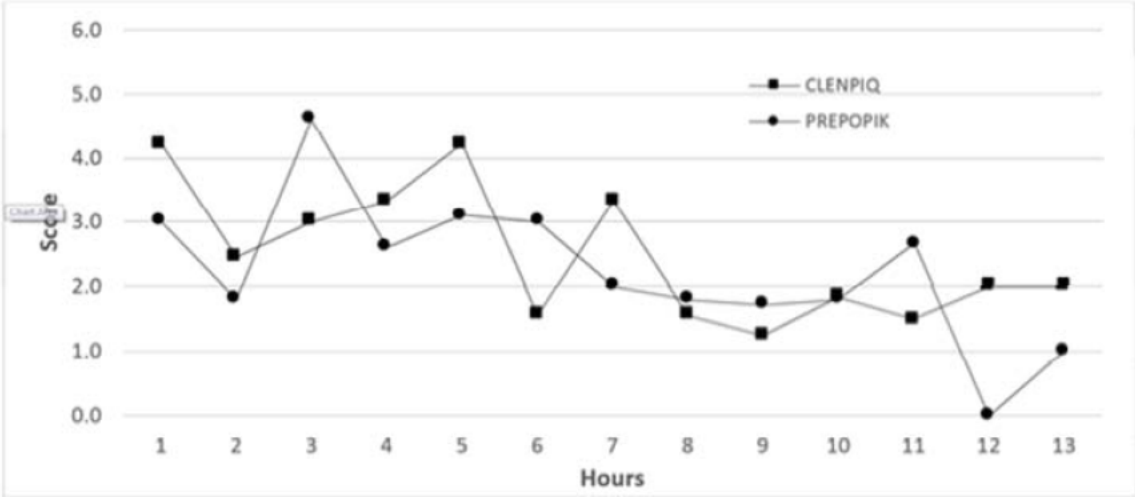


On Day 1 (Panel A) rats were administered 2000 mg/kg CLENPIQTM (squares) or PREPOPIK® (circles) by oral lavage and the average feces score was determined (N = 10 rats/group) hourly for 8 hours. On Day 8 (Panel B) rats were crossed over to the other test formulation and were administered 2000 mg/kg of

either CLENPIQTM (squares) or PREPOPIK® (circles) by oral lavage and the average feces score was determined (N = 10 rats/group) hourly for 8 hours.

Furthermore, as the data for the time to normalization of fecal output shown in Figure 1B, there was no significant difference between the two formulations as well. This animal study would be reviewed by Pharm & Tox reviewer, and according to the reviewer, this study is acceptable.

Figure 1B. Normalization of Fecal Output: CLENPIQTM vs PREPOPIK®



On Day 8 rats that were crossed over to the other test formulation and were administered two 2000 mg/kg doses of either CLENPIQTM (squares) or PREPOPIK® (circles) by oral lavage and the average feces score was determined (N = 9 or 10 rats/group) hourly for 13 hours following the second dose to determine the time to normalization of fecal output

Although the active metabolite from picosulfate, BHPM, was not measured directly, these data indicate that the inactive ingredients in CLENPIQTM did not significantly alter the production of BHPM or interfere with its activity as the pharmacodynamic effect of CLENPIQTM was indistinguishable from that of PREPOPIK®.

The Applicant evaluated the difference in inactive ingredients between CLENPIQ and PREPOPIK in solubility, Caco-2 permeability, and laxative effect in rat, osmolality, and electrolyte. And the Applicant also demonstrated justifications on the existence of malic acid, EDTA, and sucralose in CLENPIQ formulation would unlikely pose any safety issue and affect drug absorption.

Therefore, the Applicant justifications on the requirement of *(iii) contains no inactive ingredient or other change in formulation from the drug product that is the subject of the an approved full new drug application that may significantly affect absorption or systemic or local availability* for Biowaiver request based on 21 CFR 320.22 (b) (3), are overall acceptable.

Finally, the bridge (bioavailability/bioequivalence) between the proposed drug product and the listed drug product is considered to be established. The submitted biowaiver

request is therefore acceptable.

From Biopharmaceutics perspective, NDA 209589 is recommended for approval. However, the final conclusion of Biopharm decision will depend on the ClinPharm and Pharm/Tox final reviews and conclusions.

List of Deficiencies: N/A

Primary Biopharmaceutics Reviewer Name and Date: Vincent (Peng) Duan, Ph.D. 9/18/2017

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

Tien-Mien Chen, Ph.D. 10/06/17
Acting Biopharm. Lead
DBBII/ONDP/OPQ

Peng Duan

Digitally signed by Peng Duan
Date: 10/06/2017 03:46:02PM
GUID: 54579633000330547a76e69866efb4b3

Tien Mien Chen

Digitally signed by Tien Mien Chen
Date: 10/06/2017 03:50:17PM
GUID: 508da7240002a26723d38018ce005126

MICROBIOLOGY

Product Background: -

NDA: 209589

Drug Product Name / Strength: Sodium picosulfate, Magnesium oxide, and anhydrous Citric acid Oral Solution / 10 mg NaPicosulfate; 3.5 g MgO; 12 g Citric acid

Route of Administration: Oral

Applicant Name: Ferring Pharmaceuticals Inc.

Manufacturing Site:

ASM Aerosol-Service AG, Industriestrasse 11
CH-4313 Möhlin
Switzerland

Method of Sterilization: This non-sterile drug product is manufactured by (b) (4)

(b) (

Review Summary:

The submission is **recommended** for approval. No outstanding microbiology deficiencies remain. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

List Submissions being reviewed: Only list the received date.

Submit	Received	Review Request	Assigned to Reviewer
01/31/2017	01/31/2017	N/A	02/16/2017
05/19/2017	05/19/2017	N/A	05/26/2017
06/29/2017	06/29/2017	N/A	06/29/2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: No outstanding issues remaining.

Supporting/Related Documents: None

Remarks Section:

This is an electronic submission.
No CP was included in the application.
The GDUFA goal date is 07/31/2017.

The deficiencies issued in the 04/19/2017 microbiology information request were responded to in the 05/19/2017 and 06/29/2017 submissions.

P.1 Description of the Composition of the Drug Product

Description of drug product –

(section 3.2.P.1).

Sodium Picosulfate, Magnesium Oxide, and Anhydrous Citric Acid Oral Solution are colorless to slightly yellow, clear solution.

Drug product composition –

(section 3.2.P.1.2).

Component	Amount per 160 mL
Sodium picosulfate	10 mg
Magnesium oxide, (b) (4)	3.5 g
Anhydrous citric acid	12 g
Edetate disodium	(b) (4)
Sodium benzoate	
Malic acid	
Sucralose	
Acesulfame potassium	
Sodium hydroxide	
Sodium metabisulfite	
Cranberry flavoring, (b) (4)	
(b) (4) water	

Description of container closure system –

(b) (4)

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain the microbiological quality of the product.

Acceptable

P.2.5 Microbiological Attributes

(b) (4)

Reviewer's Assessment:

(section 3.2.P.2).

(b) (4)

(b) (4)

Results

Study/Report # not provided and date: 01/17/2017
Preservative: (b) (4)
Lot #: not identified
Preservative content or % label claim: (b) (4) %

(b) (4)

(b) (4)

The following deficiency was issued in the 04/19/2017 microbiology information request and responded to in the 06/29/2017 submission:

(b) (4)

(b) (4)

All of the applicant's acceptance criteria were met.

Acceptable USP [redacted] (b) (4) test result was provided to justify its [redacted] (b) (4)

Acceptable

P.3 Manufacture

P.3.1 Manufacturers

ASM Aerosol-Service AG, Industriestrasse 11
CH-4313 Möhlin
Switzerland

P. 3.3 Description of the Manufacturing Process and Process Controls

Overall Manufacturing Operation

Reviewer's Assessment:

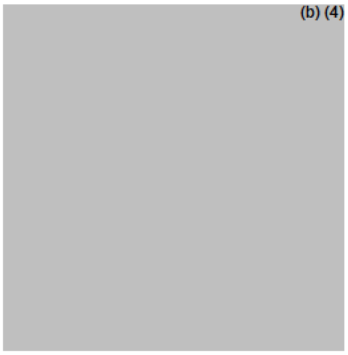
[redacted] (b) (4)

Acceptable

[redacted] (b) (4)

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

(b) (4)



Executed batch records for lots were included in the submission.

Acceptable

Comparability Protocols

Reviewer's Assessment:

No CP was included in the application.

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

2.A. Package Insert

Reviewer's Assessment:

(section 1.14.1.3).

The drug product is stored at 25 °C (77 °F). Excursions permitted at 15 – 30 °C (59 – 86 °F). Do not refrigerate or freeze.

Acceptable

Primary Microbiology Reviewer Name and Date:

Eric Adeeku, 06/29/2017

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

"I concur" should be sufficient

Erika Pfeiler

Digitally signed by Erika Pfeiler
Date: 7/11/2017 11:41:03AM
GUID: 502d1da500002b6a73a00c0e0dff6e1d

Eric Adeeku

Digitally signed by Eric Adeeku
Date: 7/11/2017 11:22:18AM
GUID: 508da70b00028e3db199467cfbd47cb0