

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204553Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA/BLA # NDA 204553
Product Name: ColPrep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) for oral solution

PMR/PMC Description: A randomized, single-blind, multicenter dose-ranging study comparing the safety and efficacy of ColPrep Kit (sodium sulfate, potassium sulfate and magnesium sulfate) for oral solution to an active control or community standard of care in children (ages 2 years to <11 years).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	09/2017
	Study/Trial Completion:	03/2019
	Final Report Submission:	09/2019

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Deferral of this pediatric study is granted because the product is ready for approval for use in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This is a required PREA study that is intended to inform labeling in pediatric patients 2 to less than 11 years of age. This product has not been studied in the pediatric population. This is not a FDAAA PMR.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, single-blind, multicenter dose-ranging study comparing the safety and efficacy of ColPrep Kit (sodium sulfate, potassium sulfate and magnesium sulfate) for oral solution to an active control or community standard of care in children (ages 2 years to <11 years). This study will include PK assessments.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☒ Other (provide explanation)
PREA PMR
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA/BLA # NDA 204553
Product Name: ColPrep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) for oral solution

PMR/PMC Description: A randomized, single-blind, multicenter dose-ranging study comparing the safety and efficacy of ColPrep Kit (sodium sulfate, potassium sulfate and magnesium sulfate) for oral solution to an active control or community standard of care in children (ages 12 months to <2 years).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	06/2019
	Study/Trial Completion:	12/2020
	Final Report Submission:	06/2021

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Deferral of this pediatric study is granted because the product is ready for approval for use in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This is a required PREA study that is intended to inform labeling in pediatric patients 12 months to less than 2 years of age. This product has not been studied in the pediatric population.

It should be noted that the pediatric study requirement for ages birth to less than 1 year is waived because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group. In this age group (birth to less than 1 year), bowel cleansing can be achieved with administration of clear liquids only for 24 hours with or without suppositories or enemas. Additionally, there are an insubstantial number of colonoscopies performed in pediatric patients under age 1 year.

This is not a FDAAA PMR.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

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- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
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- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

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4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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Required

- ☐ Observational pharmacoepidemiologic study
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Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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PREA PMR
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Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
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PMR/PMC Description: A randomized, single-blind, multicenter dose-ranging study comparing the safety and efficacy of ColPrep Kit (sodium sulfate, potassium sulfate and magnesium sulfate) for oral solution to an active control or community standard of care in children (ages 11 years to 16 years).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/2017</u>
	Study/Trial Completion:	<u>03/2019</u>
	Final Report Submission:	<u>09/2019</u>

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This is a required PREA study that is intended to inform labeling in pediatric patients 11 to 16 years of age. This product has not been studied in the pediatric population. This is not a FDAAA PMR.

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PREA PMR
-

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PMR/PMC Development Coordinator:

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(signature line for BLAs)

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/s/

JAMES B CARR
12/27/2016

JESSICA J LEE
12/27/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 19, 2016,
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 204553
Product Name and Strength:	ColPrep Kit (sodium sulfate, potassium sulfate, magnesium sulfate) for Oral Solution 17.5 g/3.13 g/1.6 g per bottle
Submission Date:	December 15, 2016
Applicant/Sponsor Name:	Gator Pharmaceuticals
OSE RCM #:	2016-2518-1
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMO

Division of Gastroenterology and Inborn Error Products (DGIEP) requested that we review the revised container label and carton labeling for ColPrep Kit (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container label and carton labeling is unacceptable from a medication error perspective. Although Gator Pharmaceuticals implemented our recommendations to the proposed labels and labeling per our previous review, we have additional recommendations and clarifications.

^aAbraham, S. Label and Labeling Review for ColPrep Kit (NDA 204553). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 12 12. 32 p. OSE RCM No.: 2016-2518

3 RECOMMENDATIONS FOR GATOR PHARMACEUTICALS

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels and Carton Labeling:

1. The established name is not at least half the size of the proprietary name. Thus, we request you revise the established name to be in accordance with 21 CFR 201.10(g) (2).
2. Replace the abbreviation “oz” with its intended meaning “ounce” to prevent misinterpretation and confusion.
3. Revise the statement [REDACTED] (b) (4) to “See enclosed patient booklet for complete dosage and administration instructions”.

B. Carton Labeling:

1. Revise the diagrams of mixing container in the instruction steps to ensure that the diagrams accurately reflect the actual product in terms of markings and cautionary statements.
2. Revise the statement, [REDACTED] (b) (4) to “This carton contains: 1 mixing container” to be consistent with the prescribing section and Instructions for use. Additionally, revise step 3 from [REDACTED] (b) (4) to “mixing container”. This will prevent any confusion between the 16 ounce fill line and the size of the mixing container.

C. Mixing Container:

1. Revise the abbreviation on the mixing container to its intended meaning to read “16 ounce fill line” to prevent misinterpretation and confusion.

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/s/

SHERLY ABRAHAM
12/20/2016

MISHALE P MISTRY
12/20/2016

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

PATIENT LABELING REVIEW

Date: December 12, 2016

To: Donna Griebel, MD
Director
**Division of Gastroenterology and Inborn Errors
Products (DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): ColPrep Kit (sodium sulfate, potassium sulfate and
magnesium sulfate)

Dosage Form and Route: for oral solution

Application Type/Number: NDA 204553

Applicant: Gator Pharmaceuticals, Inc.

1 INTRODUCTION

On October 28, 2016, Gator Pharmaceuticals, Inc. re-submitted for the Agency's review 505(b)(2) New Drug Application (NDA) 204553 for ColPrep Kit (sodium sulfate, potassium sulfate and magnesium sulfate) for oral solution. The Division of Gastroenterology and Inborn Errors Products (DGIEP) considers the Applicant's submission to be a complete, class 1 response to the Agency's action letter for Tentative Approval issued October 4, 2013. ColPrep Kit (sodium sulfate, potassium sulfate and magnesium sulfate) for oral solution is indicated for cleansing of the colon in preparation for colonoscopy in adults.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on October 31, 2016 for DMPP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for ColPrep Kit (sodium sulfate, potassium sulfate and magnesium sulfate) for oral solution.

2 MATERIAL REVIEWED

- Draft ColPrep Kit (sodium sulfate, potassium sulfate and magnesium sulfate) for oral solution MG and IFU received on October 28, 2016 and received by DMPP on October 31, 2016.
- Draft ColPrep Kit (sodium sulfate, potassium sulfate and magnesium sulfate) for oral solution Prescribing Information (PI) received on October 28, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on December 10, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU documents using the Arial font, size 10.

In our review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG and IFU is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

KAREN M DOWDY
12/12/2016

MARCIA B WILLIAMS
12/13/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 12, 2016
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 204553
Product Name and Strength:	ColPrep Kit (Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate) for Oral Solution 17.5 g/3.13 g/1.6 g per bottle
Product Type:	Multiple ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Gator Pharmaceuticals
Submission Dates:	October 28, 2016 (Prescribing information (PI), Container labels and Carton Labeling) November 1, 2016 (Instructions for Use)
OSE RCM #:	2016-2518
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

This review evaluates the labels and labeling for ColPrep Kit (NDA 204553), 505 b(2) NDA to Suprep Bowel Prep Kit (NDA 022372), submitted for a final approval after receiving Tentative Approval on October 4, 2013. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that DMEPA review the proposed Prescribing Information (PI), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C– N/A
ISMP Newsletters	D–N/A
FDA Adverse Event Reporting System (FAERS)*	E– N/A
Other	F– N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Gator Pharmaceuticals submitted a 505 b(2) NDA to Suprep Bowel Prep Kit (NDA 022372), for a final approval after receiving Tentative Approval on October 4, 2013. The reference listed drug (RLD), for this product is Suprep Bowel Prep Kit (NDA 22372), an oral solution available in strength of 17.5 g/3.13 g/1.6 g per 6 ounces, which requires dilution in water prior to ingestion. The proposed product is a powder for oral solution, available in strength of 17.5 g/3.13 g/1.6 g per bottle, which requires reconstitution and dilution in water prior to ingestion. We note that the Applicant is pursuing the same indication as the RLD, the dosing regimen is the same between the two products (i.e., split-dose [two-day]), and both products are supplied in kits with two bottles of the product and a mixing container.

DMEPA reviewed the labels and labeling for areas of concern relating to medication errors. We identified areas in the Prescribing Information that can be improved to increase clarity in the preparation and administration of the ColPrep Kit.^a Specifically, we note the use of multiple

units of measurement in Section 2 Dosage and Administration (e.g., milliliters, quarts, ounces) when referring to the volume of water to be added to the product. The mixing container packaged in the kit has a marking indicating the 16 ounce fill line, as referenced in the PI. Additionally, we note that as proposed by the Division, both terms “mixing container” and (b) (4) are used in Section 2 to refer to the container in the kit. However, we do not recommend the use of the term (b) (4) as the term may be mistaken as a household measurement (b) (4). We note that the Applicant proposes the statement “additional fluids must be consumed after each dose” in Section 2 of the Highlights and full PI. As currently stated, it is unclear whether the Applicant intends that patients should consume additional fluid along with the proposed 32 ounces of water or if the Applicant is referring to the 32 ounces of water. Finally, we recommend including in Section 17 Patient Counseling a statement regarding the dosing regimen for the product (i.e., one bottle is to be administered in the evening [10-12 hours prior to the second dose] before colonoscopy and the second bottle is administered in the morning of colonoscopy [at least 3 ½ hours before]).

DMEPA also identified areas in the container labels and carton labeling that can be improved to ensure that patients understand the dosing regimen and preparation/administration of the product. We provide letter-ready recommendations for the Division in Section 4.1 and for the Applicant in Section 4.2 to address these concerns.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed prescribing information, carton labeling, and container labels can be improved to increase the clarity of information to promote the safe use of the product. Please see recommendations to the Division in Section 4.1 and for the Applicant in Section 4.2 below:

4.1 RECOMMENDATIONS TO THE DIVISION

A. Section 2 Dosage and Administration

1. We recommend using a single unit of measurement for the volume of water used in the preparation and administration of the product, which is consistent with the markings on the mixing container (i.e., ounces).
2. We recommend revising the term (b) (4) to “mixing container” to ensure that end users do not inadvertently mistaken the term (b) (4) for the household measurement and for consistency with the RLD.
3. We recommend asking the Applicant for clarification on the following statement: “Additional fluids must be consumed after each dose.” As currently stated, it is unclear whether the Applicant intends that patients should consume additional fluid along with the proposed 32 ounces of water or if the Applicant is referring to the 32 ounces of water.

B. Section 3 Dosage Forms and Strengths

^a Recommendations provided in response to revisions proposed by the DGIEP review team.

1. We recommend revising the term (b) (4) to “mixing container” to ensure that end users do not inadvertently mistaken the term (b) (4) for the household measurement and for consistency with the RLD.
- C. Section 17 Patient Counseling
1. We recommend including a statement to instruct healthcare providers to counsel patients on the dosing regimen for the product (i.e., one bottle is to be administered in the evening [10-12 hours prior to the second dose] before colonoscopy and the second bottle is administered in the morning of colonoscopy [at least 3 ½ hours before].

4.2 RECOMMENDATIONS TO THE APPLICANT

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels and Carton Labeling:

1. Revise the established name from (sodium sulfate, potassium sulfate and magnesium sulfate) Powder for Oral Solution to the following per USP General Chapter 1121:
“(sodium sulfate, potassium sulfate and magnesium sulfate) for Oral Solution”
2. Revise the “Instructions for Use Start here” section of the container labeling and the “Directions” on the container labels for consistency with the Patient Instructions for Use.
3. The container label of one unit and the carton labeling of two units should have different NDC numbers. Revise the NDC numbers so that the carton labeling and vial label NDC numbers are different for these two package configurations.
4. Refer patients to read the Patients Instructions for Use. For example, revise the statement on the side panel of the carton labeling “(b) (4)”
“(b) (4)” to “Please read full prescribing information and Patient Instructions in this kit”. We recommend adding this statement to the container label.

B. Carton Labeling:

1. We note discrepancies in markings on the mixing containers in the two sample kits that were provided to FDA. Clarify which mixing container will be used in the to-be-marketed kit. Revise the diagrams of the instruction steps (steps 3 to 6) to accurately reflect the to-be-marketed mixing container.
2. To ensure that the patients understand the dosing regimen (i.e., both bottles constitute a complete dose, one bottle is to be used the evening before, and the other bottle to be used the morning of the colonoscopy), we recommend you revise the statement (b) (4)
“(b) (4)” to the following:
“Split-Dose (2-Day) – Both bottles are required for a complete prep”

C. Container Label:

1. Include the following statements to ensure that patients prepare and administer the product as instructed:

“Reconstitute and dilute with water prior to use.”

“Both bottles are required for a complete prep.”

“Read Patient Instructions prior to use.”

2. Consider re-locating the statement “This bottle contains...” on the PDP to the side panel to allocate space for the above recommendations.
3. The directions listed on the container label are incomplete as it does not include instructions for the patient to drink additional 32-ounces of water. We recommend revising the directions for consistency with the Prescribing Information and Instructions for Use.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for ColPrep Kit submitted by Gator Pharmaceuticals on October 28, 2016, and the reference listed drug (RLD).

Table 2. Relevant Product Information for ColPrep Kit and the RLD		
Product Name	Colprep Kit (NDA 204553)	Suprep Bowel Prep (NDA 22372)
Initial Approval Date	N/A	
Active Ingredients	Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate	Sodium Sulfate, Potassium Sulfate, and Magnesium Sulfate
Indication	Cleansing of the colon in preparation for colonoscopy in adults	cleansing of the colon in preparation for colonoscopy in adults
Route of Administration	Oral	Oral
Dosage Form	oral solution	Oral solution
Strength	17.5 g/3.13 g/1.6 g per bottle	17.5 grams of Sodium Sulfate, 3.13 grams of Potassium Sulfate, and 1.6 grams of Magnesium Sulfate per 6 ounce bottle
Dose and Frequency	Split-Dose (2 day) Regimen: First bottle containing 22.7 g the evening before the colonoscopy, then the second bottle containing 22.7 g on the morning of the procedure.	Split-Dose (2 day) Regimen: First dose evening before the colonoscopy, then the second bottle on the morning of the procedure.
How Supplied	Two bottles containing 22.7 g of powder for reconstitution and a mixing container with 16 ounce fill line	Two 6 ounce bottles of oral solution and one 19 ounce mixing container with a 16 ounce fill line
Storage	Storage: Store between 20° to 25°C (68° to 77°F). Excursions permitted between 15° to 30°C (59° to 86°F).	Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F). See USP controlled room temperature.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On December 9, 2016, we searched the L: drive and AIMS using the terms, ColPrep Kit, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review^b and we confirmed that our previous recommendations were implemented or considered.

^bKhoslo, L. Label and Labeling Review for ColPrep Kit (NDA 204553). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 09 05 p. 32 OSE RCM No.: 2013-805.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following ColPrep Kit and labeling submitted by Gator Pharmaceuticals on October 28, 2016 and November 1, 2016.

- Container label
- Carton labeling
- Prescribing information
- Instructions for use

G.2 Label and Labeling Images

Container Label



2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

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

/s/

SHERLY ABRAHAM
12/12/2016

MISHALE P MISTRY
12/12/2016

505(b)(2) ASSESSMENT

Application Information		
NDA # 204553	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: To be determined (referred to as (b) (4))		
Established/Proper Name: sodium sulfate, potassium sulfate and magnesium sulfate		
Dosage Form: Powder for Oral solution		
Strengths: sodium sulfate 17.5 g, potassium sulfate 3.13 g, magnesium sulfate 1.6 g		
Applicant: Gator Pharmaceuticals, Inc.		
Agent for Applicant (if applicable): KVK-Tech, Inc.		
Date of Receipt: 12-4-12		
PDUFA Goal Date: 10-4-13	Action Goal Date (if different): Target: 9-30-13	
RPM: Matthew Scherer		
Proposed Indication(s): for cleansing of the colon in preparation for colonoscopy in adults		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 022372 (SUPREP BOWEL PREP KIT)	FDA's previous finding of safety and effectiveness (clinical, nonclinical))

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The drug (name to be determined, referred to as (b) (4)) has the same active ingredients and quantities of those actives as the reference listed drug (SUPREP). Both drugs will be administered as oral solutions with identical concentrations of actives, the difference being that prior to administration, SUPREP (a solution) is diluted to volume while (b) (4) (a powder) is dissolved and then diluted to volume.

The scientific bridge is a listing of the active ingredients and the quantities of each. Since the actives are rapidly dissolving salts, DGIEP considers this bridge to be acceptable.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?
- YES ☒ NO ☐
If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
SUPREP BOWEL PREP KIT	022372	yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
- N/A ☒ YES ☐ NO ☐
If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".
If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒
If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒
If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

If “YES”, please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a new dosage form, Powder for Oral Solution. The innovator dosage form is Oral Solution.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; and **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☐ NO ☒

If “**NO**” to (a) proceed to question #11.
If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

If this application relies only on non product-specific published literature, answer “**N/A**”

If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES ☒ NO ☐

If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

If this application relies only on non product-specific published literature, answer “**N/A**”

If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS
--

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): Suprep/6946149

No patents listed ☐ proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

If “**NO**”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification*

was submitted, proceed to question #15.

- ☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- ☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.
- ☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 6946149

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

If “NO”, please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

If “NO”, please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date: March 7, 2013

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES ☒ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

MATTHEW C SCHERER
09/18/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date:	September 5, 2013
Reviewer:	Lisa V. Khosla, PharmD, M.H.A Division of Medication Error Prevention and Analysis
Team Leader:	Lubna Merchant, M.S., PharmD Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name(s) and Strength(s):	Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate Powder for Oral Solution 17.5 g/3.13 g/1.6 g per bottle
Application Type/Number:	NDA 204553
Applicant/Sponsor:	Gator Pharmaceuticals
OSE RCM #:	2013-805

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, carton labeling, medication guide, and professional labeling for Sodium Sulfate, Potassium Sulfate, and Magnesium Sulfate Powder for Oral Solution, NDA 204553, for areas of vulnerability that could lead to medication errors.

The Division of Gastroenterology and Inborn Errors Products (DGIEP) requested this review as part of their evaluation of the 505(b)(2) submission for NDA (b) (4). The reference listed drug, Suprep Bowel Prep Kit (NDA 022372), was approved in August 5, 2010.

1.1 PRODUCT INFORMATION

The proposed product differs from the reference listed drug (RLD) in that the proposed product is a powder for oral solution with a strength of 17.5 g/3.13 g/1.6 g per bottle whereas the reference listed drug (RLD) is an oral solution with a strength of 17.5 g/3.13 g/1.6 g per 6 ounces.

The following product information is provided in the June 28, 2013 submission.

- Active Ingredient: Sodium Sulfate, Potassium Sulfate, Magnesium Sulfate
- Indication of Use: Cleansing of the colon in preparation for colonoscopy in adults
- Route of Administration: Oral
- Dosage Form: Powder for oral solution
- Strength: 17.5 g/3.13 g/1.6 g
- Dose and Frequency: Split-Dose (2 day) Regimen: First bottle containing 22.7 g the evening before the colonoscopy, then the second bottle containing 22.7 g on the morning of the procedure.
- How Supplied: Two bottles containing 22.7 g of powder for reconstitution and a 16 ounce mixing container.
- Storage: Store between 20° to 25°C (68° to 77°F). Excursions permitted between 15° to 30°C (59° to 86°F).

2 METHODS AND MATERIALS REVIEWED

2.1 FAERS SEARCH

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1 for errors involving the RLD Suprep. The FAERS database search did not retrieve any cases of medication errors.

Table 1: FAERS Search Strategy	
Date	July 2, 2013
Drug Names	*Suprep* (verbatim)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

2.2 ISMP PUBLICATIONS SEARCH

We searched the ISMP publications on June 28, 2013 for additional cases and actions concerning Suprep Bowel Kit. There were no medication error cases found.

2.3 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 28, 2013 (Appendix B)
- Carton Labeling submitted June 28, 2013 (Appendix C)
- (b) (4) Dimensions submitted July 3, 2013 (Appendix D)
- Insert Labeling (included in the Patient Medication Guide) submitted June 28, 2013
- Patient Medication Guide submitted June 28, 2013

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The Applicant is proposing a powder for oral solution formulation of Sodium Sulfate, Potassium Sulfate, and Magnesium Sulfate.

We reviewed the instructions in the package insert labeling and note that the Split Dose (2-Day) Regimen was missing the additional steps of preparation required for this powder formulation. We also note that the time to complete preparation before colonoscopy is presented with the incorrect timeframe (b) (4). Moreover, the presentation of the contents of each bottle under the Dosage Forms and Strengths subsection under the heading “Highlights of Prescribing Information” does not reflect each individual component of the formulation.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Additionally, we reviewed the container label and carton labeling and note that the presentation of the proprietary name uses a different font from the established name and uses tall man lettering, which is inappropriately applied. Furthermore, similar to the professional labeling, we note that the carton labeling is missing the additional steps of preparation required for a powder formulation. We have made recommendations in Section 4 to address these deficiencies and to improve clarity in the labels and labeling.

Finally, we requested a sample kit of the product, but the (b) (4) was missing from the kit. We note that the (b) (4) was in the process of being made at the time of request, so only the dimensions (b) (4) was submitted by the Applicant. Hence, we are not able to assess the (b) (4).

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed container label, carton labeling, and professional labeling can be improved to increase clarity and to increase the readability and prominence of important information on the labels to promote the safe use of the product and to mitigate any confusion that can lead to medication errors.

We defer to the Division of Medical Policy and Programs (DMPP) for the evaluation of the language in the Medication Guide (MG). However, we worked collaboratively with DMPP to provide recommendations regarding Instructions For Use (IFU) on the carton labeling.

4.1 COMMENTS TO THE DIVISION

Based on this review, DMEPA has made revisions to the Package Insert Labeling for review and consideration by DGIEP. See Appendix F for details.

4.2 COMMENTS TO THE APPLICANT

DMEPA recommends the following be implemented prior to approval of this Application:

A. Container Label

1. Remove all references to the proprietary name “(b) (4)” as this name has been found unacceptable.
2. Relocate the statement “Dispense the enclosed Medication Guide to each patient” to appear beneath the presentation of the strength on the principal display panel.
3. Decrease the font size of the “Rx Only” statement.
4. Revise the “Directions” statement on the side panel as follows:
“DIRECTIONS: Reconstitute powder by adding water up to the neck of the bottle. Then further dilute the mixed solution by pouring it into the mixing container and adding water to the 16 oz. fill line prior to use.”

B. Carton Labeling

1. See comment A1 and A2 above.
2. Revise the instructions on the side panel that appear below the “Instructions for Use Start Here” as follows:

On the day before your colonoscopy:

- You may eat a light breakfast
- **Do not** eat solid foods or drink milk or alcohol while taking TRADENAME and until after your colonoscopy.
- **Do not** eat or drink anything colored red or purple.
- Drink only clear liquids until 2 hours before your colonoscopy:

You may eat or drink any of the following clear liquids:

- water
- clear fruit juices without pulp including apple, white grape, or white cranberry
- strained limeade or lemonade
- coffee or tea (Do not use any dairy or non-dairy creamer)
- clear broth
- clear soda
- gelatin desserts without added fruit or topping
- popsicles (without pieces of fruit or fruit pulp)

Do not eat or drink anything 2 hours before your colonoscopy.

3. Revise the (b) (4) statement on the back panel to “Split-dose (2-day) instructions” to improve patient understanding.
4. The box (on the back panel) containing the Split-dose (2-day) instructions should be revised as follows:
 - Both doses of TRADENAME are required for a complete bowel prep.
 - Dose 1 - Take this dose early in the evening before your colonoscopy, about 10 to 12 hours before you take Dose 2, or when your doctor tells you to take it. Complete steps 1 through 6 using 1 bottle of TRADENAME before you going to bed.
 - Dose 2 - Take this dose on the morning of your colonoscopy, at least 3 ½ hours before your colonoscopy. Repeat steps 1 through 6 using the remaining bottle of TRADENAME. Finish taking Dose 2 and all of the prescribed water **at least 2 hours** before your colonoscopy.
5. Revise the (b) (4) highlighted in the blue box on the back panel to read “NOTE: Each bottle of TRADENAME powder must be mixed with water and diluted with additional water according to instructions.” to highlight that there are two steps in the preparation of this product.

C. Instructions for Use on Carton Labeling

1. Revise Steps 1 through 6 of the instructions (that accompany each figure) as follows:
 - Step 1: Open 1 bottle of TRADENAME
 - Step 2: Add water up to the neck of the bottle. Replace cap and shake the bottle well to mix the powder solution.
 - Step 3: Pour the mixed powder solution from the bottle into the 16-ounce mixing container.
 - Step 4: Add water to the 16-oz. Fill Line on the mixing container.
 - Step 5: Drink **all** of the liquid in the container.
 - Step 6: Drink 2 more 16-ounce containers of water over the next 1 hour.

If you have further questions or need clarifications, please contact Phong Do, OSE Project Manager, at 301-796-4795.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/

LISA V KHOSLA
09/05/2013

LUBNA A MERCHANT
09/05/2013

CAROL A HOLQUIST
09/05/2013

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

PATIENT LABELING REVIEW

Date: September 3, 2013

To: Donna Griebel
Director
**Division of Gastroenterology and Inborn Errors
Products (DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Meeta Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): TRADENAME (sodium sulfate, potassium sulfate and
magnesium sulfate)

Dosage Form and Route: powder for oral solution

Application Type/Number: NDA 204-553

Applicant: Gator Pharmaceuticals, Inc.

1 INTRODUCTION

On November 30, 2012, Gator Pharmaceuticals, Inc. submitted for the Agency's review an original New Drug Application (NDA) 204-553 for TRADENAME (sodium sulfate, potassium sulfate and magnesium sulfate) powder for oral solution with the proposed indication for cleansing of the colon in preparation for colonoscopy in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on June 6, 2013, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for TRADENAME (sodium sulfate, potassium sulfate and magnesium sulfate) powder for oral solution.

2 MATERIAL REVIEWED

- Draft TRADENAME (sodium sulfate, potassium sulfate and magnesium sulfate) powder for oral solution MG received on April 1, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 20, 2013.
- Draft TRADENAME (sodium sulfate, potassium sulfate and magnesium sulfate) powder for oral solution IFU received on April 1, 2013, and received by DMPP and OPDP on August 20, 2013.
- Draft TRADENAME (sodium sulfate, potassium sulfate and magnesium sulfate) powder for oral solution Prescribing Information (PI) received on April 1, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 20, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Verdana font, size 11.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible

- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed IFU review comments are collaborative of DMPP and DMEPA.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG or IFU.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
09/03/2013

MEETA N PATEL
09/03/2013

BARBARA A FULLER
09/03/2013

LASHAWN M GRIFFITHS
09/03/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Application: 204553

Application Type: New NDA

Name of Drug: (b) (4) (sodium sulfate, potassium sulfate, magnesium sulfate)

Applicant: Gator Pharmaceuticals

Submission Date:

Receipt Date:

1.0 Regulatory History and Applicant's Main Proposals

On 8-3-12, DGIEP received NDA 204553 for (b) (4). This is an eCTD 505b2 NDA that references the FDA's previous findings of safety and efficacy for Suprep (NDA 22372). (b) (4) appears to have the same chemical composition as Suprep (a mixture of the sulfate salts), the only difference is that (b) (4) is a powder for reconstitution while Suprep comes as a concentrate for dilution. This NDA was withdrawn prior to filing on September 26, 2012 because of outstanding CMC and administrative deficiencies. The resubmission was received 12-4-12.

The proposed indication is: for cleansing of the colon in preparation for colonoscopy in adults.

This NDA appears to consist solely of administrative documents, labeling, CMC information and biopharmaceutics data.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted SPL of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format within 2 weeks of the date the advice letter is issued. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- NO** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.
- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).
- NO** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.
- NO** 4. White space must be present before each major heading in HL.
- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).
- NO** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment: Sponsor should remove (b) (4) before Highlights heading and insert placeholder for Initial US Approval

Selected Requirements of Prescribing Information (SRPI)

- NO** 7. A horizontal line must separate HL and Table of Contents (TOC).

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **“HIGHLIGHTS OF PRESCRIBING INFORMATION”**.

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: **“These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).”**

Comment: *Product name should be presented in UPPER CASE.*

Product Title

- YES** 10. Product title in HL must be **bolded**.

Initial U.S. Approval

- NO** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement **“Initial U.S. Approval:”** followed by the **4-digit year**.

Boxed Warning

- N/A** 12. All text must be **bolded**.

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word **“WARNING”** (even if more than one Warning, the term, **“WARNING”** and not **“WARNINGS”** should be used) and other words to identify the subject of the Warning (e.g., **“WARNING: SERIOUS INFECTIONS”**).

- N/A** 14. Must always have the verbatim statement **“See full prescribing information for complete boxed warning.”** centered immediately beneath the heading.

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement **“See full prescribing information for complete boxed warning.”**)

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, **“Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”**.

Selected Requirements of Prescribing Information (SRPI)

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.
- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Patient Counseling Information Statement

- NO** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment: The current statement is: “See 17 for PATIENT COUNSELING INFORMATION (b) (4) (b) (4) Sponsor should remove (b) (4) from PCI Statement.”

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Contents: Table of Contents (TOC)

GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.

Selected Requirements of Prescribing Information (SRPI)

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**.
- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
- NO** 33. All subsection headings must be indented, not bolded, and in title case.
***Comment:** Subsection headings are not indented. (b) (4) is bolded.*
- YES** 34. When a section or subsection is omitted, the numbering does not change.
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading **“FULL PRESCRIBING INFORMATION: CONTENTS”** must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: **“FULL PRESCRIBING INFORMATION”**.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE

Selected Requirements of Prescribing Information (SRPI)

11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

YES

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

YES

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

N/A

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A

42. All text is **bolded**.

N/A

43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

N/A

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Contraindications

N/A

45. If no Contraindications are known, this section must state “None”.

Adverse Reactions

YES

46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

N/A

47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information (SRPI)

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Patient Counseling Information

NO

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: Sponsor should modify current reference to read “See FDA-approved patient labeling (Medication Guide)”.

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/s/

MATTHEW C SCHERER
04/17/2013

RICHARD W ISHIHARA
04/17/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 204553 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: sodium sulfate, potassium sulfate and magnesium sulfate Dosage Form: Powder for Oral solution Strengths: sodium sulfate 17.5 g, potassium sulfate 3.13 g, magnesium sulfate 1.6 g		
Applicant: Gator Pharmaceuticals, Inc. Agent for Applicant (if applicable): KVK-Tech, Inc.		
Date of Application: 11-30-12 Date of Receipt: 12-4-12 Date clock started after UN: NA		
PDUFA Goal Date: 10-4-13	Action Goal Date (if different):	
Filing Date: 2-2-13	Date of Filing Meeting: 1-23-13	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3, new dosage form		
Proposed indication(s)/Proposed change(s): for cleansing of the colon in preparation for colonoscopy in adults		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☒		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): NA				
List referenced IND Number(s): 113084				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system?	x			
<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the proprietary, established/proper, and applicant names correct in tracking system?	x			
<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm	x			
<i>If no, ask the document room staff to make the appropriate entries.</i>				
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		x		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?		x		Small business waiver

<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application: ☐ Paid ☐ Exempt (orphan, government) ☒ Waived (e.g., small business, public health) ☐ Not required
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		This is not eligible for a 505(j) approval because it is a new dosage form.																
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		X																		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>		X																		
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below: <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <tr> <th style="width: 25%;">Application No.</th> <th style="width: 25%;">Drug Name</th> <th style="width: 25%;">Exclusivity Code</th> <th style="width: 25%;">Exclusivity Expiration</th> </tr> <tr> <td>NDA 22372</td> <td>Suprep</td> <td>NC</td> <td>8/5/13</td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	NDA 22372	Suprep	NC	8/5/13									X			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
NDA 22372	Suprep	NC	8/5/13																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product (same active moiety) have orphan		x																		

exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i>				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			x	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	x			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		x		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			x	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	x			
Index: Does the submission contain an accurate comprehensive index?	x			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2	x			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(BLAs/BLA efficacy supplements) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #			x	
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			X	
• If yes, were all of them submitted on time?			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			X	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			X	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included.</i> Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	x			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	x			No patents
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?		x		Not necessary because there are no applicable trials

<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	x			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	x			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	x			New dosage form
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	x			Full waiver requested
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			x	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	x			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		x		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		x		
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		x		
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☒ Instructions for Use (IFU)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	X			
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?			X	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?		x		Pending successful filing
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)		x		Pending successful filing
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?		x		Pending successful filing
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?				
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		x		to be determined
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		x		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): Pre-IND/pre-NDA meeting preliminary responses issued 11-16-11. Meeting canceled <i>If yes, distribute minutes before filing meeting</i>	x			Pre-IND/pre-NDA meeting preliminary responses issued 11-16-11.
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		x		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 204553

BLA/NDA/Supp #: 204553

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: sodium sulfate, potassium sulfate and magnesium sulfate

DOSAGE FORM/STRENGTH: Powder for Oral Solution/sodium sulfate 17.5 g, potassium sulfate 3.13 g, magnesium sulfate 1.6 g

APPLICANT: Gator Pharmaceuticals, Inc. (KVK-Tech is the agent)

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): for cleansing of the colon in preparation for colonoscopy in adults

BACKGROUND: On 8-3-12, DGIEP received NDA 204553 for (b) (4). This is an eCTD 505b2 NDA that references the FDA's previous findings of safety and efficacy for Suprep (NDA 22372). (b) (4) appears to have the same chemical composition as Suprep (a mixture of the sulfate salts), the only difference is that (b) (4) is a powder for reconstitution while Suprep comes as a concentrate for dilution. This NDA was withdrawn prior to filing because of outstanding CMC and administrative deficiencies. The resubmission was received 12-4-12.

The proposed indication is: for cleansing of the colon in preparation for colonoscopy in adults.

This NDA appears to consist solely of administrative documents, labeling, CMC information and biopharmaceutics data.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Matthew Scherer	y
	CPMS/TL:	Wes Ishihara	n
Cross-Discipline Team Leader (CDTL)	Rob Fiorentino		y
Clinical	Reviewer:	Zana Marks	n
	TL:	Rob Fiorentino	y

Clinical Pharmacology	Reviewer:	Insook Kim	y
	TL:	Sue Chih Lee	n
Biostatistics	Reviewer:	TBD	n
	TL:	Mike Welch	n
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tamal Chakraborti	y
	TL:	Sushanta Chakder	y
Product Quality (CMC)	Reviewer:	Jane Chang	y
	TL:	Marie Kowblansky	y
OSE/DMEPA (proprietary name)	Reviewer:	TBD	
	TL:		
Other reviewers			
Other attendees	Maria Walsh, Andrew Mulberg, Matt Brancazio		

FILING MEETING DISCUSSION:

GENERAL 505(b)(2) filing issues? If yes, list issues:		☐ Not Applicable ☐ YES ☒ NO
Per reviewers, are all parts in English or English translation? If no, explain:		☒ YES ☐ NO
Electronic Submission comments List comments: submission organization is minimally acceptable		☐ Not Applicable
CLINICAL Comments: No clinical data. PREA waiver requested, however, it is unlikely to be granted.		☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain: No clinical sites		☐ YES ☒ NO

- Advisory Committee Meeting needed? Comments: Not an NME <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL PHARMACOLOGY Comments: No clinical pharmacology data included in the submission	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments: Likely NAI from Biostatistics as there is no new efficacy data submitted	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: no new clinical pharmacology data	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> - Establishment(s) ready for inspection? - Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments: confirming with ONDQA	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>CMC Labeling Review</u> Comments: Not specifically addressed at filing meeting. This will be handled over the course of the CMC review.	☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Division level, signatory to be determined. Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): TBD, not a program NDA 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): To be established Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing.

	<u>Review Issues:</u> ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☒	Other: Labeling review consults to OPDP, DRISK, DMEPA. Consult PMHS if necessary. Remind sponsor to submit tradename request.

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

MATTHEW C SCHERER
02/01/2013

RICHARD W ISHIHARA
02/01/2013