CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204553Orig1s000

SUMMARY REVIEW

Signatory Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick, MD, MPH
Subject	Signatory Review
NDA #	204553
Applicant Name	Gator Pharmaceuticals, Inc.
Date of Submission	October 28, 2016
PDUFA Goal Date	December 27, 2016
Proprietary Name / Established (USAN) Name	ColPrep Kit (Sodium sulfate, potassium sulfate and magnesium sulfate) for oral solution
Dosage Forms / Strength	for oral solution/ Two bottles; Each bottle contains sodium sulfate 17.5 g, potassium sulfate 3.13 g, and magnesium sulfate 1.6 g.
Proposed Indication(s)	Cleansing of the colon as a preparation for colonoscopy in adults
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers:**
Medical Officer Review	NA this review cycle
OPQ Review	Hitesh Shroff
MOTL	Jessica Lee provided advice regarding clinical issues for labeling during this final labeling review in close consultation with this signatory. No additional MOTL review was written for this cycle.
OSE/DMEPA	Kellie Taylor, Sherly Abraham, Mishale Mistry
DMPP	Karen Dowdy
Previous Signatory Reviews	Donna Griebel

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OPQ = Office of Pharmaceutical Quality
DMPP=Division of Medical Policy Programs
MOTL= medical officer team leader

1. Introduction

On October 28, 2016, Gator Pharmaceuticals, Inc. submitted an amendment in response to the Tentative Approval sent from CDER on 10/04/2013. This application included the Court's proceedings in which they determined that "Breckenridge's motion for summary judgment of non-infringement is GRANTED." (Dated March 15, 2016). The Applicant requested final approval be granted. Gator confirms that the information submitted earlier for this application has no changes including labeling, chemistry, manufacturing and controls data.

2. Background

This 505(b)(2) NDA was originally submitted on August 2, 2012, but was withdrawn by the Applicant on September 27, 2012 due to CMC deficiencies identified during the preliminary review of the submission. The listed drug upon which this this NDA relies is Suprep® Bowel Prep Kit (Braintree Laboratories, Inc., NDA 22372). The Applicant notified FDA that the patent owner and/or approved application holder for the referenced drug has initiated a patent infringement suit against the Applicant with respect to patent 6946149, therefore, a Tentative Approval was granted on 10/04/2013.

This amendment requesting final approval is appropriate because the 30-month stay of approval has expired. Per 21 CFR 314.107 (b)(3): "... approval may be made effective 30 months after the date of receipt of the notice of certification by the patent owner or by the exclusive licensee (or their representatives) unless the court has extended or reduced the period because of a failure of either the plaintiff or defendant to cooperate reasonably in expediting the action."

The date of receipt of the notice of certification was 3/7/13 and the expiration of the 30-month stay of approval was 9/7/15. Therefore, their request for full approval is appropriate.

This 505(b)(2) NDA proposes a powder form of the referenced osmotic laxative product, COLPREP KIT (sodium sulfate, potassium sulfate, and magnesium sulfate) for oral solution, which is an oral solution that contains the same component electrolytes. In the Suprep product, the packaged oral solution is further diluted with water before oral consumption. In the proposed product, the patient will reconstitute the dry powder that contains the electrolytes with water before consuming it. The active ingredients and their amounts, the indications, and the split dose administration schedule are the same. The same volume of fluid is ingested with each product. Hence, the labels of the two products will be essentially identical, with the exception of details related to the dosage form (powder vs. oral solution) and the specific steps required to prepare each product for consumption. Because the proposed product is identical to the referenced product in its active ingredients and their amount, and there were only minor differences in inactive ingredients that would not be expected to impact safety and efficacy of the product, the Applicant was not required to conduct clinical trials to support this application.

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3. CMC/OPQ

ColPrep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) for solution is an osmotic laxative packaged in white 200 cc HDPE round bottles. Each drug product kit contains two bottles of powder (22.7 g) for reconstitution. Each bottle contains 17.5 g of sodium sulfate, 3.13 g of potassium sulfate, and 1.6 g of magnesium sulfate. Inactive ingredients include citric acid anhydrous USP, sucralose NF, and lemon flavor, and one 20-ounce polypropylene mixing container with a 16 ounce fill line.

At the time of the Tentative Approval the chemistry reviews found that the manufacturing of the drug product and drug substance were acceptable. Manufacturing site inspections were acceptable. Drug product stability data support an expiration dating period of 2 years when stored at 20° to 25°C (68° to 77°F).

During this final review cycle the OPQ review found the final revised package insert, carton and container labels acceptable. In addition; "On December 9, 2016 the Office of Process and Facilities has made an overall "Approve" recommendation for the facilities involved in this NDA."

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 2 years as previously noted. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

There are no outstanding issues since the previous review.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

There are no outstanding issues since the previous review.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical-Efficacy

No new clinical trials were submitted for this 505(b)(2) NDA. The Applicant was granted a waiver for the in vivo bioequivalence study requirement (see Biopharmaceutics section, review by Dr. Griebel, attachment).

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8. Safety

As noted in the previous review by Dr. Griebel, The safety evaluators in DPV/OSE provided FAERS data for Suprep Bowel Prep Kit to assess for new safety signals with the referenced product. They concluded the data do not reveal a new potential serious safety issue. Dr. Griebel reviewed the list of events and they all represent expected adverse reactions, including gastrointestinal events (vomiting, nausea, retching), electrolyte abnormalities, malaise, headache, dehydration, dizziness, falls, mental status changes.

Since the Tentative Approval, the Post Market Required (PMR) trials for Suprep have been completed and reviewed. Dr. Griebel notes that based upon those results the need to require additional PMRs for ColPrep will be considered.

The PMRs listed in the Suprep approval letter are as follows:

> **PMR 1580-7**: A randomized, active control, single-blind trial to evaluate renal and metabolic toxicity and sulfate levels in patients, including elderly patients, patients with renal impairment, and patients with hepatic impairment taking sodium sulfate, potassium sulfate, magnesium sulfate, powder for oral solution prior to colonoscopy.
>
> **PMR 1580-8:** A clinical trial to assess ECG changes to capture maximum effects of sulfate exposures in subjects taking sodium sulfate, potassium sulfate, magnesium sulfate, powder for oral solution.

The PMR studies for Suprep to address renal/metabolic toxicity and sulfate levels (PMR 1580-7 in Suprep approval letter) and ECG changes (PMR 1580-8 in Suprep approval letter) – both have been fulfilled by Braintree (PMR 1580-7 on 9/8/14 and PMR 1580-8 on 2/27/14). No new safety issues were found and no additional labeling was recommended.

In discussions with the MOTL, Dr. Jessica Lee, we have determined that there is no need to require these PMRs for ColPrep. I agree with this conclusion.

9. Advisory Committee Meeting

This 505(b)(2) product was not referred for review to an Advisory Committee.

10. Other Relevant Regulatory Issues

Pediatrics:

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to less than 1 year 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

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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.

We are deferring submission of the pediatric study for ages 1 year to 16 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

The following PREA studies will be required:

3144-1 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). This study will include PK assessments.

Final Protocol Submission:	September 2017
Study Completion:	March 2019
Final Report Submission:	September 2019

3144-2 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.

Final Protocol Submission:	September 2017
Study Completion:	March 2019
Final Report Submission:	September 2019

3144-3 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). This study will include PK assessments.

Final Protocol Submission:	June 2019
Study Completion:	December 2020
Final Report Submission:	June 2021

PeRC met to consider the pediatric plan on July 17, 2013, and agreed with the Division's recommendations and agreed with the studies outlined above. PREA PMRS were finalized as previously discussed in Dr. Griebel's review. The timelines were finalized during this review.

There was no financial disclosure review. No clinical studies were conducted to support this 505(b)(2) NDA. The application was granted a waiver.

"There are no other unresolved relevant regulatory issues"

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11. Labeling

The new proprietary name, ColPrep Kit, was found acceptable (letter: 11/01/2013; Kellie Taylor: Office of Medication Error Prevention and Risk Management). I concur with this recommendation.

Discussions regarding labeling were relatively mature at the time of the previous action for the Physician labeling, Carton and Container labels, Information for Use, and Medication Guide. During this review cycle, the review team worked with the Applicant to finalize the labeling. Issues discussed during this final review included representation of the non-proprietary name of the referenced drug, instructions for the administration, including mixing of the preparation, references to the mixing cup and final pictures of the cup as it is in the to be marketed package (especially, the fill line). These issues are reflected in each of the documents listed above and were addressed satisfactorily. A brief note for each is listed below.

The new name is determined to be ColPrep KIT (sodium sulfate, potassium sulfate, and magnesium sulfate) for oral solution.

The non-proprietary name of the Colprep and Suprep made it difficult to distinguish which product was used in the clinical trial section, since both products have the same non-proprietary name. This was addressed throughout the label in the following manner:

> "The safety of ColPrep Kit has been established from adequate and well-controlled trials **of another** oral formulation of sodium sulfate (17.5 g), potassium sulfate (3.13 g), and magnesium sulfate (1.6 g)."

During the last cycle there were concerns regarding potential medication errors due to the wording in the various sections of the labeling as well as the absence of a fill line on the mixing cup. During this cycle the review team received a ColPrep Kit which included the cup, and a red line on the cup was clearly marked was considered satisfactory.

In addition, the use of oz. vs ounce was confusing and not consistent in the labeling. This was resolved.

The final recommendations by DMEPA were as follows:

> "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 "(b) (4) (b) (4)" to "See enclosed patient booklet for complete dosage and administration instructions".
>
> **B. Carton Labeling:**

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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, "(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 "(b) (4) (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."

The mixing container to be included in the kit was found acceptable and it was noted that the markings were very clear.

The recommendations from the DMEPA or the DMEP reviews were considered in the final labeling discussions with the sponsor and these issues were resolved.

The final professional labels, including the Medication Guide, IFU, and Carton and Container have been agreed upon. I agree with the final editing recommendations, and there are no outstanding issues. See attachments in the Approval letter for final versions of these documents.

12. Decision/Action/Risk Benefit Assessment

- **Regulatory Action**: Approval

- **Risk Benefit Assessment:**

The Applicant has established an adequate bridge between the proposed product and the listed drug upon which this NDA relies, Suprep Bowel Prep Kit. No new safety issues have been identified. There is no reason to conclude the product proposed in this NDA will be less efficacious or less safe than the referenced product. This conclusion has not changed since the previous review cycle.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS):**

It was determined that a REMS was not needed for this product.

- **Recommendation for other Postmarketing Requirements and Commitments:**

Only PREA PMRs will be required of the sponsor. As stated above, the safety PMRs requested of the referenced drug are considered fulfilled, and did not result in additional safety findings. Finally, no new safety issues have arisen during the final review of this application.

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Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna J. Griebel, MD
Subject	Division Director Summary Review
NDA #	204553
Applicant Name	Gator Pharmaceuticals, Inc.
Date of Submission	August 2, 2012
PDUFA Goal Date	October 4, 2013
Proprietary Name / Established (USAN) Name	No Proprietary Name/ sodium sulfate, potassium sulfate, and magnesium sulfate powder for oral solution
Dosage Forms / Strength	Powder for oral solution/ Two bottles; Each bottle contains sodium sulfate 17.5 g, potassium sulfate 3.13 g, and magnesium sulfate 1.6 g.
Proposed Indication(s)	Cleansing of the colon as a preparation for colonoscopy in adults.
Action:	Tentative Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Pharmacology Toxicology Review	Tamal Chakraborti, PhD/Sushanta Chakder, PhD
CMC Review	Jane L Chang, PhD/Moo Jhong Rhee, PhD
Biopharmaceutics Review	Mark R. Seggel/Angelica Dorantes, PhD
Clinical Pharmacology Review	Insook Kim, PhD/Sue-Chih Lee, PhD
OSE/DMEPA	Lisa Khosla, PharmD, MHA/Lubna Merchant, MS, PharmD/Carol Holquist, RPh
DMPP	Karen Dowdy, RN, BSN/LaShawn Griffiths, MSHS-PH, BSN, RN/Barbara Fuller, RN,MSN, CWOCN
OPDP	Meeta Patel, PharmD

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Programs
OPDP=Office of Prescription Drug Promotion

Reference ID: 3084200

Division Director Review

1. Introduction

This 505(b)(2) NDA proposes a powder form of the referenced osmotic laxative product, Suprep Bowel Prep Kit, which is an oral solution that contains the same component electrolytes. In the Suprep product, the packaged oral solution is further diluted with water before oral consumption. In the proposed product, the patient will reconstitute the dry powder that contains the electrolytes with water before consuming it. The active ingredients and their amounts, the indications, and the split dose administration schedule are the same. The same volume of fluid is ingested with each product. Hence, the labels of the two products will be essentially identical, with the exception of details related to the dosage form (powder vs. oral solution) and the specific steps required to prepare each product for consumption. Because the proposed product is identical to the referenced product in its active ingredients and their amount, and there were only minor differences in inactive ingredients that would not be expected to impact safety and efficacy of the product, the applicant was not required to conduct clinical trials to support this application.

2. Background

This 505(b)(2) NDA was originally submitted on August 2, 2012, but was withdrawn by the applicant on September 27, 2012 due to CMC deficiencies identified during the preliminary review of the submission. The listed drug upon which this this NDA relies is Suprep® Bowel Prep Kit (Braintree Laboratories, Inc., NDA 22372). The applicant notified FDA that the patent owner and/or approved application holder for the referenced drug has initiated a patent infringement suit against the applicant with respect to patent 6946149, which means this application can only receive tentative approval.

3. CMC

Sodium sulfate, potassium sulfate, and magnesium sulfate powder for solution is an osmotic laxative packaged in white 200 cc HDPE round bottles. Each drug product kit contains two bottles of powder (22.7 g) for reconstitution. Each bottle contains 17.5 g of sodium sulfate, 3.13 g of potassium sulfate, and 1.6 g of magnesium sulfate. Inactive ingredients include citric acid anhydrous USP, sucralose NF, and lemon flavor.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Drug product stability data support an expiration dating period of 2 years when stored at 20° to 25°C (68° to 77°F).

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted in support of this 505(b)(2) NDA. The Pharmacology/Toxicology reviewer evaluated the application for novel excipients and

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impurities/degradants of concern. The excipients "were similar to the excipients present in the referenced drug product." The reviewer noted that the CMC team had the applicant set the limits of the elemental impurities as per the USP <232> and stated in his review, "All the elemental impurities are below the USP <232> limits." He specifically discussed the (b) (4) limits, which had a proposed specification of NMT (b) (4) ppm. The reviewer calculated the maximum exposure of (b) (4) per dose in the labeled split dose regimen (half administered the night before endoscopy and the second half the morning of endoscopy), and found that the maximum daily (per dose) (b) (4) would be (b) (4) micrograms/day, which is below the USP limit of 25 micrograms/day. This calculation supported the safety of the proposed (b) (4) specification of NMT (b) (4) ppm.

The Nonclinical reviewers found the relevant sections of labeling acceptable. They have recommended approval, and I concur.

5. Clinical Pharmacology/Biopharmaceutics

The proposed product is a powder form of the referenced osmotic laxative product, Suprep Bowel Prep Kit, which is an oral solution that contains the same component electrolytes. For Suprep Bowel Prep Kit, the packaged oral solution is further diluted with water before oral consumption. In the proposed product, the patient will reconstitute the dry powder that contains the electrolytes with water before consuming it.

No clinical trials were conducted to support this application, and no clinical pharmacology trials were submitted for review. The applicant requested a biowaiver, based on the following, as stated in the Clinical Pharmacology review, "Although the dosage forms are different, i.e., powder for the proposed product versus solution for the reference product, the two products will be administered as oral solution with the same final concentrations of each active ingredient after reconstitution to the final solution. Each ingredient can be completely dissolved from the (b) (4) prior to oral administration; therefore the difference in the dosage forms prior to reconstitution is not expected to affect the oral bioavailability." The Biopharmaceutics review stated that the applicant provided a quantitative comparison of the active components of the proposed product and the approved formulation in support of the biowaiver request.

The following table reproduced from the Clinical Pharmacology review summarizes the similarity between the proposed product and the listed product upon which this NDA relies.

Table 1. Formulation comparison between proposed product and SUPREP Bowel Prep

	Proposed Powder Product	SUPREP Bowel Prep Kit
Dosage form	two 22.7 g bottles of powder	two 6 oz. bottles of solution
Active ingredient	sodium sulfate 17.5 g potassium sulfate 3.13 g magnesium sulfate 1.6 g	sodium sulfate 17.5 g potassium sulfate 3.13 g magnesium sulfate 1.6 g

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Inactive ingredient	sucralose citric acid	sodium benzoate sucralose malic acid citric acid
Final volume after reconstitution	16 oz.	16 oz.

The Biopharmaceutics reviewer noted that although there were minor differences (b) (4) (b) (4) between the proposed product and the referenced product, "these would not be expected to impact the performance of the osmotic laxative." The Biopharmaceutics reviewer concluded, "the equivalence of the products is self-evident. A waiver of the in vivo bioequivalence study requirement is granted."

The Biopharmaceutics reviewers recommended approval. The Clinical Pharmacology reviewers found the application acceptable. I concur. Their labeling recommendations, which were primarily editorial in nature, were incorporated.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

There were no new clinical trials submitted for review in this 505(b)(2) NDA. See Section 5 of this review. The application was granted a biowaiver for the in vivo bioequivalence study requirement.

8. Safety

There were no new clinical trials submitted for review in this 505(b)(2) NDA. See Section 5 of this review. The application was granted a biowaiver for the in vivo bioequivalence study requirement.

The safety evaluators in DPV/OSE provided FAERS data for Suprep Bowel Prep Kit to assess for new safety signals with the referenced product. They concluded the data do not reveal a new potential serious safety issue. I reviewed the list of events and they all represent expected adverse reactions, including gastrointestinal events (vomiting, nausea, retching), electrolyte abnormalities, malaise, headache, dehydration, dizziness, falls, mental status changes.

Assessment for need to require postmarketing safety trials/studies under the Food and Drug Administration Amendments Act of 2007 (FDAAA). The approved osmotic colon cleansing product labels, carry very similar, if not identical, warnings regarding risks of dehydration and serious fluid and electrolyte adverse effects and their consequences (including seizures and cardiac arrhythmias), in addition to a Medication Guide. The label for the product proposed in this NDA will also include these warnings and a Medication Guide.

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A PMR study and two PMR trials were a condition of approval of the referenced approved osmotic colon cleansing product, Suprep Bowel Prep Kit, under 505(o). The Suprep Bowel Prep Kit approval letter stated "We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of ischemic colitis, renal failure or other serious renal disease, seizure disorders, new arrhythmias, or other uncommon but serious adverse events. Available data for other drugs in the same pharmacologic class indicate the potential for these serious risks. Analysis of spontaneous postmarketing adverse events also will not be sufficient to assess the signals of serious risks of aggravation of gout and serious outcomes associated with elevations of creatine kinase related to the use of the drug." In addition, other recently approved bowel prep products, Prepopik and Suclear, have had post marketing studies required as a condition of approval.

The PMR study for Prepopik was required "to assess a signal of a serious risk of renal insufficiency."

Suclear (sodium sulfate, potassium sulfate and magnesium sulfate oral solution and PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride powder for oral solution) contains a sulfate solution component that contains the same amount of the sulfate salts found in one of the two-dose total in Suprep Bowel Prep Kit and the product proposed in the current 505(b)(2) NDA. The January 2013 approval letter for Suclear contained requirements to conduct trials under 505(o)(3), based on "only clinical trials (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of fluid and serum chemistry abnormalities and the signal of a serious risk related to exposure to toxic impurities." The Suclear NDA approval letter required conduct of an adequate randomized, active control, single-blind trial to evaluate renal dysfunction and laboratory abnormalities in adult patients, including elderly patients, patients with renal impairment and patients with hepatic impairment taking Suclear prior to colonoscopy. Serial laboratory and clinical assessments will be performed at regular pre-specified intervals for at least 30 days post-treatment.

The Agency has not completed the review of all the PMR trials required under FDAAA as a condition of approval for Suprep. For this reason, the safety issues that triggered the required studies for the referenced product remain a concern for the proposed NDA product. The tentative approval letter for this 505(b)(2) will state the following:

> We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of dangerous fluid and electrolyte disturbances with the potential for cardiac sequelae or renal injury, when available data for other drugs in the same pharmacologic class indicate the potential for a serious risk.
>
> Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

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Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to identify unexpected serious risks of dangerous fluid and electrolyte disturbances or renal injury, when available data for other drugs in the same pharmacologic class indicate the potential for a serious risk.

Therefore, based on appropriate scientific data, FDA has determined that if this application is ultimately approved, you will be required to conduct the following:

1: A randomized, active control, single-blind trial to evaluate renal and metabolic toxicity and sulfate levels in patients, including elderly patients, patients with renal impairment, and patients with hepatic impairment taking sodium sulfate, potassium sulfate, magnesium sulfate, powder for oral solution prior to colonoscopy.

2: A clinical trial to assess ECG changes to capture maximum effects of sulfate exposures in subjects taking sodium sulfate, potassium sulfate, magnesium sulfate, powder for oral solution.

The review team determined that it was unnecessarily redundant to duplicate the epidemiologic PMR study (40, 000 patients in a data resource with access to electronic medical records) required in the Suprep Bowel Prep Kit approval letter. It should be noted that it is possible that data from the pending PMR trials for the listed drug upon which this NDA relies, Suprep Bowel Prep Kit, will have been reviewed and added to the label before final approval of this NDA is granted. The data from those PMR trials will be considered in determining whether to include the PMRs listed above in the final approval letter for this NDA. In addition, the data could provide new safety information that could prompt addition of a new PMR study or trial in the final approval letter.

9. Advisory Committee Meeting

There was no advisory committee meeting for this 505(b)(2) NDA. There were no decisional issues that required input from an Advisory Committee.

10. Pediatrics

PREA was triggered by this NDA because it is a new dosage form. PeRC met to consider the pediatric plan on July 17, 2013, and agreed with the Division's recommendations, as follows:

1) Waiver of studies birth to 1 year because the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested. In this age group (birth to 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.

2) Deferral of studies in children ages 1 year to 16 years.

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The applicant will conduct the following studies. Tentative approval letters do not include the PREA studies, so this list will be included in the future final approval letter, and the dates will be re-calculated at that time.

Study 1: A randomized, single-blind, multicenter dose-ranging study comparing the safety and efficacy of (b) (4) for Oral Solution to community standard of care in children (ages 11 years to 16 years). This study will include PK assessments.
Final Protocol Submission: April 2014
Study Completion: April 2017
Final Report Submission: October 2017

Study 2: A randomized, single-blind, multicenter dose-ranging study comparing the safety and efficacy of (b) (4) for Oral Solution to community standard of care in children (ages 2 years to <11 years). This study will include PK assessments.
Final Protocol Submission: April 2017
Study Completion: April 2020
Final Report Submission: October 2020

Study 3: A randomized, single-blind, multicenter dose-ranging study comparing the safety and efficacy of (b) (4) for Oral Solution to community standard of care in children (ages 12 months to <2 years). This study will include PK assessments.
Final Protocol Submission: April 2019
Study Completion: October 2020
Final Report Submission: April 2021

11. Other Relevant Regulatory Issues

There was no financial disclosure review. No clinical studies were conducted to support this 505(b)(2) NDA. The application was granted a biowaiver.

This 505(b)(2) application can only receive tentative approval at this time because the patent owner and/or approved application holder for the listed drug upon which this NDA relies (Suprep Bowel Prep Kit) has initiated a patent infringement suit against the applicant, with respect to patent 6946149.

12. Labeling

The applicant's proposed proprietary name, (b) (4), was found unacceptable by both DMEPA and OPDP, because the name (b) (4) At the time of approval of this product, the applicant had not proposed an alternative proprietary name for review. The name of the product at the time of this tentative approval was limited to its established name: sodium sulfate, potassium sulfate, and magnesium sulfate powder for oral solution.

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An additional issue related to the product name was [redacted]. The OPDP reviewer considered the applicant's name [redacted] in the label in sections that summarized clinical trial data [redacted] inappropriate. The Clinical team discussed with the CMC and DMEPA reviewers how best to distinguish the products in relevant sections of the label. The reviewers ultimately used "sodium sulfate, potassium sulfate, and magnesium sulfate powder in solution (Solution Product) [emphasis added]," to distinguish the products in those sections. [redacted]

The DMEPA reviewers further evaluated the label for "areas of vulnerability that could lead to medication errors." They conducted a FAERS database search for evidence of medication errors associated with use of the referenced product, Suprep Bowel Prep Kit, and did not identify cases of medication errors. They identified the following concerns with the proposed product labeling:

1) Instructions for use in the booklet packaged with the product and on the carton were missing the additional steps of preparation required for the powder formulation.
2) The instructions for timing of completion of the prep prior to colonoscopy were incorrect (the instructions stated [redacted]; however, the timing is more appropriately stated as "at least 2 hours before colonoscopy" due to the need to limit pre-sedation oral intake. This information is included in the instructions for Suprep Bowel Prep Kit.
3) The highlights subsection Dosage Forms and Strengths did not reflect each component of the formulation.
4) Presentation of the proprietary name used inappropriate font.

The cup that would be included in packaging was not submitted with the NDA. DMEPA requested its submission for examination, as fill line visibility has been identified as a potential source of medication errors in other bowel prep NDA reviews. However, the applicant had not yet received cups from their manufacturer at the completion of this review cycle. The cup will be evaluated during the future review for granting final approval.

The DMEPA reviewers' recommendations for labeling revisions were incorporated. The reviewers recommended some additional editorial changes in the instructions for use intended

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for the patient, which further clarified diet instructions, including the types of foods/liquids that can be consumed during the prep, and specific timing of the various steps.

The reviewers from DMPP were consulted to review the proposed Medication Guide and Instructions for Use. The referenced product and other bowel preps have Medication Guides. The applicant's Medication Guide was modeled after the referenced product's Medication Guide. The reviewers recommended some revisions to the Medication Guide and Instructions for Use, which were accepted by the applicant. The recommended revisions were aimed at simplifying wording, clarifying concepts, ensuring consistency with the prescribing information, and removing redundancy. Some changes in the Medication Guide were recommended in order to achieve consistency with more recently approved bowel preps (for example, the addition of "high blood pressure medication" to the list of things that increase the risk of fluid loss and changes in body salts with the product, and instructions to contact a healthcare provider "right away if you have severe stomach-area pain or rectal bleeding" added to the bullet ulcers of the bowel or ischemic colitis).

The DMPP reviewers rewrote the Instructions for Use, adding approximate times for doses to help guide patients determine when to start the prep the evening before colonoscopy and when to take the second dose the morning of colonoscopy.

The tentative review letter contains additional editorial changes that must be made to the labeling appended to the tentative approval letter. These changes align the instructions to patients regarding dietary restrictions on the day prior to colonoscopy (clear liquids after a light breakfast) among the various components of labeling, i.e., package insert, Medication Guide, carton, and Instructions for Use. In addition, the changes include removal of references (b) (4) in Section 8.5 Geriatric use, and replacing them with (b) (4).

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Tentative approval.

- Risk Benefit Assessment – The applicant has established an adequate bridge between the proposed product and the listed drug upon which this NDA relies, Suprep Bowel Prep Kit. No new safety issues have been identified. There is no reason to conclude the product proposed in this NDA will be less efficacious or less safe than the referenced product.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – None

- Recommendation for other Postmarketing Requirements and Commitments
  The NDA will only receive tentative approval at this time. Upon receipt of the future application amendment that includes the legal/regulatory basis for final approval, the applicant will be required to conduct studies under PREA, as outlined in Section 10 Pediatrics. In addition, the applicant will be required, under FDAAA, to conduct two clinical trials, as described in Section 8 Safety. The necessity to conduct those two

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trials will be re-evaluated at the time of final approval, as the applicant for the referenced product has been required to conduct the same two trials. If the results of those trials have been reviewed by the Agency for inclusion in product labeling, and the Agency has determined that these trials should no longer be required as a condition of final approval of this NDA (204553), the trials will no longer be required in the final approval letter. However, new safety concerns may be identified in the review of the data from the safety trials that are currently underway, and under those circumstances, different PMR trials or studies may be required as a condition of approval at the time of final approval of this product.

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/s/

DONNA J GRIEBEL
10/04/2013

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/s/

JOYCE A KORVICK
12/27/2016

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna J. Griebel, MD
Subject	Division Director Summary Review
NDA #	204553
Applicant Name	Gator Pharmaceuticals, Inc.
Date of Submission	August 2, 2012
PDUFA Goal Date	October 4, 2013
Proprietary Name / Established (USAN) Name	No Proprietary Name/ sodium sulfate, potassium sulfate, and magnesium sulfate powder for oral solution
Dosage Forms / Strength	Powder for oral solution/ Two bottles; Each bottle contains sodium sulfate 17.5 g, potassium sulfate 3.13 g, and magnesium sulfate 1.6 g.
Proposed Indication(s)	Cleansing of the colon as a preparation for colonoscopy in adults.
Action:	Tentative Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Pharmacology Toxicology Review	Tamal Chakraborti, PhD/Sushanta Chakder, PhD
CMC Review	Jane L Chang, PhD/Moo Jhong Rhee, PhD
Biopharmaceutics Review	Mark R. Seggel/Angelica Dorantes, PhD
Clinical Pharmacology Review	Insook Kim, PhD/Sue-Chih Lee, PhD
OSE/DMEPA	Lisa Khosla, PharmD, MHA/Lubna Merchant, MS, PharmD/Carol Holquist, RPh
DMPP	Karen Dowdy, RN, BSN/LaShawn Griffiths, MSHS-PH, BSN, RN/Barbara Fuller, RN,MSN, CWOCN
OPDP	Meeta Patel, PharmD

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Programs
OPDP=Office of Prescription Drug Promotion

Reference ID: 3384630

Division Director Review

1. Introduction

This 505(b)(2) NDA proposes a powder form of the referenced osmotic laxative product, Suprep Bowel Prep Kit, which is an oral solution that contains the same component electrolytes. In the Suprep product, the packaged oral solution is further diluted with water before oral consumption. In the proposed product, the patient will reconstitute the dry powder that contains the electrolytes with water before consuming it. The active ingredients and their amounts, the indications, and the split dose administration schedule are the same. The same volume of fluid is ingested with each product. Hence, the labels of the two products will be essentially identical, with the exception of details related to the dosage form (powder vs. oral solution) and the specific steps required to prepare each product for consumption. Because the proposed product is identical to the referenced product in its active ingredients and their amount, and there were only minor differences in inactive ingredients that would not be expected to impact safety and efficacy of the product, the applicant was not required to conduct clinical trials to support this application.

2. Background

This 505(b)(2) NDA was originally submitted on August 2, 2012, but was withdrawn by the applicant on September 27, 2012 due to CMC deficiencies identified during the preliminary review of the submission. The listed drug upon which this this NDA relies is Suprep® Bowel Prep Kit (Braintree Laboratories, Inc., NDA 22372). The applicant notified FDA that the patent owner and/or approved application holder for the referenced drug has initiated a patent infringement suit against the applicant with respect to patent 6946149, which means this application can only receive tentative approval.

3. CMC

Sodium sulfate, potassium sulfate, and magnesium sulfate powder for solution is an osmotic laxative packaged in white 200 cc HDPE round bottles. Each drug product kit contains two bottles of powder (22.7 g) for reconstitution. Each bottle contains 17.5 g of sodium sulfate, 3.13 g of potassium sulfate, and 1.6 g of magnesium sulfate. Inactive ingredients include citric acid anhydrous USP, sucralose NF, and lemon flavor.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Drug product stability data support an expiration dating period of 2 years when stored at 20° to 25°C (68° to 77°F).

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted in support of this 505(b)(2) NDA. The Pharmacology/Toxicology reviewer evaluated the application for novel excipients and

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impurities/degradants of concern. The excipients "were similar to the excipients present in the referenced drug product." The reviewer noted that the CMC team had the applicant set the limits of the elemental impurities as per the USP <232> and stated in his review, "All the elemental impurities are below the USP <232> limits." He specifically discussed the (b) (4) limits, which had a proposed specification of NMT (b) (4) ppm. The reviewer calculated the maximum exposure of (b) (4) per dose in the labeled split dose regimen (half administered the night before endoscopy and the second half the morning of endoscopy), and found that the maximum daily (per dose) (b) (4) would be (b) (4) micrograms/day, which is below the USP limit of 25 micrograms/day. This calculation supported the safety of the proposed (b) (4) specification of NMT (b) (4) ppm.

The Nonclinical reviewers found the relevant sections of labeling acceptable. They have recommended approval, and I concur.

5. Clinical Pharmacology/Biopharmaceutics

The proposed product is a powder form of the referenced osmotic laxative product, Suprep Bowel Prep Kit, which is an oral solution that contains the same component electrolytes. For Suprep Bowel Prep Kit, the packaged oral solution is further diluted with water before oral consumption. In the proposed product, the patient will reconstitute the dry powder that contains the electrolytes with water before consuming it.

No clinical trials were conducted to support this application, and no clinical pharmacology trials were submitted for review. The applicant requested a biowaiver, based on the following, as stated in the Clinical Pharmacology review, "Although the dosage forms are different, i.e., powder for the proposed product versus solution for the reference product, the two products will be administered as oral solution with the same final concentrations of each active ingredient after reconstitution to the final solution. Each ingredient can be completely dissolved from the (b) (4) prior to oral administration; therefore the difference in the dosage forms prior to reconstitution is not expected to affect the oral bioavailability." The Biopharmaceutics review stated that the applicant provided a quantitative comparison of the active components of the proposed product and the approved formulation in support of the biowaiver request.

The following table reproduced from the Clinical Pharmacology review summarizes the similarity between the proposed product and the listed product upon which this NDA relies.

Table 1. Formulation comparison between proposed product and SUPREP Bowel Prep

	Proposed Powder Product	SUPREP Bowel Prep Kit
Dosage form	two 22.7 g bottles of powder	two 6 oz. bottles of solution
Active ingredient	sodium sulfate 17.5 g potassium sulfate 3.13 g magnesium sulfate 1.6 g	sodium sulfate 17.5 g potassium sulfate 3.13 g magnesium sulfate 1.6 g

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Inactive ingredient	sucralose citric acid	sodium benzoate sucralose malic acid citric acid
Final volume after reconstitution	16 oz.	16 oz.

The Biopharmaceutics reviewer noted that although there were minor differences (b) (4) (b) (4) between the proposed product and the referenced product, "these would not be expected to impact the performance of the osmotic laxative." The Biopharmaceutics reviewer concluded, "the equivalence of the products is self-evident. A waiver of the in vivo bioequivalence study requirement is granted."

The Biopharmaceutics reviewers recommended approval. The Clinical Pharmacology reviewers found the application acceptable. I concur. Their labeling recommendations, which were primarily editorial in nature, were incorporated.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

There were no new clinical trials submitted for review in this 505(b)(2) NDA. See Section 5 of this review. The application was granted a biowaiver for the in vivo bioequivalence study requirement.

8. Safety

There were no new clinical trials submitted for review in this 505(b)(2) NDA. See Section 5 of this review. The application was granted a biowaiver for the in vivo bioequivalence study requirement.

The safety evaluators in DPV/OSE provided FAERS data for Suprep Bowel Prep Kit to assess for new safety signals with the referenced product. They concluded the data do not reveal a new potential serious safety issue. I reviewed the list of events and they all represent expected adverse reactions, including gastrointestinal events (vomiting, nausea, retching), electrolyte abnormalities, malaise, headache, dehydration, dizziness, falls, mental status changes.

Assessment for need to require postmarketing safety trials/studies under the Food and Drug Administration Amendments Act of 2007 (FDAAA). The approved osmotic colon cleansing product labels, carry very similar, if not identical, warnings regarding risks of dehydration and serious fluid and electrolyte adverse effects and their consequences (including seizures and cardiac arrhythmias), in addition to a Medication Guide. The label for the product proposed in this NDA will also include these warnings and a Medication Guide.

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A PMR study and two PMR trials were a condition of approval of the referenced approved osmotic colon cleansing product, Suprep Bowel Prep Kit, under 505(o). The Suprep Bowel Prep Kit approval letter stated "We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of ischemic colitis, renal failure or other serious renal disease, seizure disorders, new arrhythmias, or other uncommon but serious adverse events. Available data for other drugs in the same pharmacologic class indicate the potential for these serious risks. Analysis of spontaneous postmarketing adverse events also will not be sufficient to assess the signals of serious risks of aggravation of gout and serious outcomes associated with elevations of creatine kinase related to the use of the drug." In addition, other recently approved bowel prep products, Prepopik and Suclear, have had post marketing studies required as a condition of approval.

The PMR study for Prepopik was required "to assess a signal of a serious risk of renal insufficiency."

Suclear (sodium sulfate, potassium sulfate and magnesium sulfate oral solution and PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride powder for oral solution) contains a sulfate solution component that contains the same amount of the sulfate salts found in one of the two-dose total in Suprep Bowel Prep Kit and the product proposed in the current 505(b)(2) NDA. The January 2013 approval letter for Suclear contained requirements to conduct trials under 505(o)(3), based on "only clinical trials (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of fluid and serum chemistry abnormalities and the signal of a serious risk related to exposure to toxic impurities." The Suclear NDA approval letter required conduct of an adequate randomized, active control, single-blind trial to evaluate renal dysfunction and laboratory abnormalities in adult patients, including elderly patients, patients with renal impairment and patients with hepatic impairment taking Suclear prior to colonoscopy. Serial laboratory and clinical assessments will be performed at regular pre-specified intervals for at least 30 days post-treatment.

The Agency has not completed the review of all the PMR trials required under FDAAA as a condition of approval for Suprep. For this reason, the safety issues that triggered the required studies for the referenced product remain a concern for the proposed NDA product. The tentative approval letter for this 505(b)(2) will state the following:

> We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of dangerous fluid and electrolyte disturbances with the potential for cardiac sequelae or renal injury, when available data for other drugs in the same pharmacologic class indicate the potential for a serious risk.
>
> Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

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Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to identify unexpected serious risks of dangerous fluid and electrolyte disturbances or renal injury, when available data for other drugs in the same pharmacologic class indicate the potential for a serious risk.

Therefore, based on appropriate scientific data, FDA has determined that if this application is ultimately approved, you will be required to conduct the following:

1: A randomized, active control, single-blind trial to evaluate renal and metabolic toxicity and sulfate levels in patients, including elderly patients, patients with renal impairment, and patients with hepatic impairment taking sodium sulfate, potassium sulfate, magnesium sulfate, powder for oral solution prior to colonoscopy.

2: A clinical trial to assess ECG changes to capture maximum effects of sulfate exposures in subjects taking sodium sulfate, potassium sulfate, magnesium sulfate, powder for oral solution.

The review team determined that it was unnecessarily redundant to duplicate the epidemiologic PMR study (40, 000 patients in a data resource with access to electronic medical records) required in the Suprep Bowel Prep Kit approval letter. It should be noted that it is possible that data from the pending PMR trials for the listed drug upon which this NDA relies, Suprep Bowel Prep Kit, will have been reviewed and added to the label before final approval of this NDA is granted. The data from those PMR trials will be considered in determining whether to include the PMRs listed above in the final approval letter for this NDA. In addition, the data could provide new safety information that could prompt addition of a new PMR study or trial in the final approval letter.

9. Advisory Committee Meeting

There was no advisory committee meeting for this 505(b)(2) NDA. There were no decisional issues that required input from an Advisory Committee.

10. Pediatrics

PREA was triggered by this NDA because it is a new dosage form. PeRC met to consider the pediatric plan on July 17, 2013, and agreed with the Division's recommendations, as follows:

1) Waiver of studies birth to 1 year because the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested. In this age group (birth to 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.

2) Deferral of studies in children ages 1 year to 16 years.

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The applicant will conduct the following studies. Tentative approval letters do not include the PREA studies, so this list will be included in the future final approval letter, and the dates will be re-calculated at that time.

Study 1: A randomized, single-blind, multicenter dose-ranging study comparing the safety and efficacy of (b) (4) for Oral Solution to community standard of care in children (ages 11 years to 16 years). This study will include PK assessments.
Final Protocol Submission: April 2014
Study Completion: April 2017
Final Report Submission: October 2017

Study 2: A randomized, single-blind, multicenter dose-ranging study comparing the safety and efficacy of (b) (4) for Oral Solution to community standard of care in children (ages 2 years to <11 years). This study will include PK assessments.
Final Protocol Submission: April 2017
Study Completion: April 2020
Final Report Submission: October 2020

Study 3: A randomized, single-blind, multicenter dose-ranging study comparing the safety and efficacy of (b) (4) for Oral Solution to community standard of care in children (ages 12 months to <2 years). This study will include PK assessments.
Final Protocol Submission: April 2019
Study Completion: October 2020
Final Report Submission: April 2021

11. Other Relevant Regulatory Issues

There was no financial disclosure review. No clinical studies were conducted to support this 505(b)(2) NDA. The application was granted a biowaiver.

This 505(b)(2) application can only receive tentative approval at this time because the patent owner and/or approved application holder for the listed drug upon which this NDA relies (Suprep Bowel Prep Kit) has initiated a patent infringement suit against the applicant, with respect to patent 6946149.

12. Labeling

The applicant's proposed proprietary name, (b) (4), was found unacceptable by both DMEPA and OPDP, because (b) (4) At the time of approval of this product, the applicant had not proposed an alternative proprietary name for review. The name of the product at the time of this tentative approval was limited to its established name: sodium sulfate, potassium sulfate, and magnesium sulfate powder for oral solution.

An additional issue related to the product name was (b) (4) (b) (4) (b) (4). The OPDP reviewer considered the applicant's (b) (4) name (b) (4) (b) (4) inappropriate. The Clinical team discussed with the CMC and DMEPA reviewers how best to distinguish the products in relevant sections of the label. The reviewers ultimately used "sodium sulfate, potassium sulfate, and magnesium sulfate powder in solution (Solution Product) [emphasis added]," to distinguish the products in those sections. (b) (4) (b) (4)

The DMEPA reviewers further evaluated the label for "areas of vulnerability that could lead to medication errors." They conducted a FAERS database search for evidence of medication errors associated with use of the referenced product, Suprep Bowel Prep Kit, and did not identify cases of medication errors. They identified the following concerns with the proposed product labeling:

1) Instructions for use in the booklet packaged with the product and on the carton were missing the additional steps of preparation required for the powder formulation.
2) The instructions for timing of completion of the prep prior to colonoscopy were incorrect (the instructions stated (b) (4) however, the timing is more appropriately stated as "at least 2 hours before colonoscopy" due to the need to limit pre-sedation oral intake. This information is included in the instructions for Suprep Bowel Prep Kit.
3) The highlights subsection Dosage Forms and Strengths did not reflect each component of the formulation.
4) Presentation of the proprietary name used inappropriate font.

The cup that would be included in packaging was not submitted with the NDA. DMEPA requested its submission for examination, as fill line visibility has been identified as a potential source of medication errors in other bowel prep NDA reviews. However, the applicant had not yet received cups from their manufacturer at the completion of this review cycle. The cup will be evaluated during the future review for granting final approval.

The DMEPA reviewers' recommendations for labeling revisions were incorporated. The reviewers recommended some additional editorial changes in the instructions for use intended

for the patient, which further clarified diet instructions, including the types of foods/liquids that can be consumed during the prep, and specific timing of the various steps.

The reviewers from DMPP were consulted to review the proposed Medication Guide and Instructions for Use. The referenced product and other bowel preps have Medication Guides. The applicant's Medication Guide was modeled after the referenced product's Medication Guide. The reviewers recommended some revisions to the Medication Guide and Instructions for Use, which were accepted by the applicant. The recommended revisions were aimed at simplifying wording, clarifying concepts, ensuring consistency with the prescribing information, and removing redundancy. Some changes in the Medication Guide were recommended in order to achieve consistency with more recently approved bowel preps (for example, the addition of "high blood pressure medication" to the list of things that increase the risk of fluid loss and changes in body salts with the product, and instructions to contact a healthcare provider "right away if you have severe stomach-area pain or rectal bleeding" added to the bullet ulcers of the bowel or ischemic colitis).

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13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Tentative approval.

- Risk Benefit Assessment – The applicant has established an adequate bridge between the proposed product and the listed drug upon which this NDA relies, Suprep Bowel Prep Kit. No new safety issues have been identified. There is no reason to conclude the product proposed in this NDA will be less efficacious or less safe than the referenced product.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – None

- Recommendation for other Postmarketing Requirements and Commitments
  The NDA will only receive tentative approval at this time. Upon receipt of the future application amendment that includes the legal/regulatory basis for final approval, the applicant will be required to conduct studies under PREA, as outlined in Section 10 Pediatrics. In addition, the applicant will be required, under FDAAA, to conduct two clinical trials, as described in Section 8 Safety. The necessity to conduct those two

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trials will be re-evaluated at the time of final approval, as the applicant for the referenced product has been required to conduct the same two trials. If the results of those trials have been reviewed by the Agency for inclusion in product labeling, and the Agency has determined that these trials should no longer be required as a condition of final approval of this NDA (204553), the trials will no longer be required in the final approval letter. However, new safety concerns may be identified in the review of the data from the safety trials that are currently underway, and under those circumstances, different PMR trials or studies may be required as a condition of approval at the time of final approval of this product.

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/s/

DONNA J GRIEBEL
10/04/2013