CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203595Orig1s000

SUMMARY REVIEW

Division Director Review

Date	January 18, 2013
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA#	203595
Applicant Name	Braintree Laboratories, Inc.
Date of Submission	December 16, 2011
PDUFA Goal Date	October 19, 2012 Extension: January 19, 2013
Proprietary Name / Established (USAN) Name	Suclear/ (Sodium sulfate, potassium sulfate and magnesium sulfate oral solution; PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution)
Dosage Forms / Strength	Oral solution and powder for oral solution.
Proposed Indication(s)	Colon cleansing in preparation for colonoscopy in adults
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Jessica Lee, MD
Statistical Review	Wen Jen Chen, PhD/Mike Welch, PhD
Pharmacology Toxicology Review	Yuk-Chow Ng, PhD/David Joseph, PhD
CMC Review/OBP Review	Gene Holbert PhD/M. Kowblansky, PhD
Clinical Pharmacology Review	Sandhya Apparaju, PhD/Sue-Chih Lee, PhD
OSI	Khairy Malek, MD/Susan Leibenhaut, M.D
CDTL Review	Robert Fiorentino, MD, MPH
OSE/DMEPA	Teresa McMillan, PharmD/Lubna Merchant, PharmD, MS/Carol Holquist, RPh
OB/DB7	Bradley McEvoy, MS, DrPH/LaReeTracy, MA,PhD/ Aloka Chakravarty, PhD
DMPP (Patient labeling)	Karen Dowdy, RN, BSN/
OMP/OPDP (DCDP and DPDP)	Kathleen Klemm, PharmD/Kendra Jones/Eunice Chung-Davies PharmD
PMHS	Erica Radden, MD/Hari Cheryl Sachs, MD/Lynne Yao, MD
DMPP	Karen Dowdy, RN, BSN/Lashawn Griffiths, MSHS-PH, BSN, RN
SEALD	Jeanne Delasko/Laurie Burke, RPh, MPH

OND=Office of New Drugs
DEPI = Division of Epidemiology
DMPP=Division of Medical Policy Programs

OSE= Office of Surveillance and Epidemiology
DB7= Division of Biometrics 7
DMEPA=Division of Medication Errors Prevention and Analysis
DPV = Division of Pharmacovigilance
OSI=Office of Scientific Investigations
DRISK= Division of Risk Management
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader
OMP= Office of Medical Policy
OPDP=Office of Prescription Drug Promotion
PMHS=Pediatric and Maternal Health Staff
SEALD=Study Endpoints and Label Development

1. Introduction

The applicant proposed Suclear for colon cleansing as a preparation for colonoscopy in adults. Suclear is a combination product consisting of two major components: 1) a sulfate salt solution and 2) a polyethylene glycol (PEG) plus electrolyte solution. Two dosing regimens were proposed: 1) a "Split Dose (2-Day)" regimen (in which the sulfate salt solution is consumed the night before colonoscopy and the PEG plus electrolyte solution is consumed the following morning before colonoscopy) and 2) a (b) (4) (1-Day)" regimen (in which both components are consumed the night before colonoscopy). The results of two adequate and well controlled clinical trials were submitted to support approval. In each trial, the control arm was an approved product for the indication, and the applicant concluded that the trial results established that Suclear is noninferior to each active control.

The reviewers and CDTL have recommended approval. I concur. The major efficacy review issues included: 1) whether the applicant provided sufficient information to establish that the combination rule had been fulfilled, 2) whether the approved label should include the (b) (4) (1-Day)" (entire regimen administered the day prior to colonoscopy), and 3) whether the applicant had established that Suclear was noninferior to the active control in each of the two major randomized, controlled trials submitted for review. The major safety issues included: 1) whether the eGFR, creatinine and other laboratory data available from the two assessments (baseline and day of colonoscopy) in the trials raised sufficient safety concerns to justify requiring a post marketing safety trial, and 2) considerations regarding potential adverse safety impact of the PEG process impurities, (b) (4)

2. Background

There are a number of osmolar cathartic agents marketed for colon cleansing for colonoscopy and/or surgery. The contents of those agents are summarized in the table below to facilitate a comparison of the specific salt content of Suclear and marketed products. Suclear contains two separate components, each of which is a component of two approved colon cleansing products listed in the table below (rows highlighted with shading), i.e., Suprep and Half-lytely.

The two components of Suclear are:

> (1) **sodium sulfate (17.51g), potassium sulfate (3.13g) and magnesium sulfate (1.6g)** oral solution that must be diluted prior to ingestion [half of the dose in Suprep; there is ***one*** 6-oz bottle in Suclear compared to ***<u>two</u>*** 6-oz bottles in Suprep], and
>
> (2) **PEG-3350 (210 g),** sodium chloride (5.6g), sodium bicarbonate (2.86 g) and potassium chloride (0.74g) powder that must be constituted into an oral solution prior to ingestion [the PEG and electrolytes component of HalfLytely].

Table 1: Summary of Approved Products and Ion Content

Drug Name	Content	Indication
Oral Sulfate Prep		
Suprep *treatment consists of ingestion of* ***2- 6 oz bottles***	*Per total 12 oz dose* Sodium Sulfate, **35.02g** Potassium Sulfate **6.26 g** Magnesium Sulfate **3.2 g** Sodium Benzoate, (b) (4) (b) (4)	colonoscopy
Oral Sodium Phosphate Preps		
Visicol *treatment consists of ingestion of 40 tablets*	*Per tablet* Sodium Phosphate monobasic monohydrate (b) (4) dibasic anhydrous, (b) (4)	Colonoscopy *(F/u Day 2-3)
Osmoprep *treatment consists of ingestion of 32 tablets*	*Per tablet* Sodium Phosphate monobasic monohydrate 1.102 g dibasic anhydrous, 0.398 g	Colonoscopy *(Day of colonoscopy=last lab) NDA includes comparison to Visicol)
Fleets	Sodium Phosphate	
Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid		
Prepopik *Treatment consists of ingestion of 2 packets, each reconstituted in 5 oz of water; first packet followed by five 8oz clear liquid drinks and second dose followed by at least three 8-oz clear liquid drinks.*	*Per packet* Sodium picosulfate 10 mg Magnesium oxide 3.5 g Anhydrous citric acid 12 g	Colonoscopy *(F/u in clinical trials was: day of colonoscopy, 24-48 hours, Day 7 and Day 30)
PEG + Electrolytes		
Colyte *Treatment consists of ingestion of a 4 liter solution*	*Per total 4 liter dose* Sodium Sulfate, 22.72 g (anhydrous) Sodium Chloride, 5.84 g Sodium Bicarbonate, 6.72 g Potassium Chloride, 2.98 g (b) (4) PEG-3350, 240g	Colonoscopy, Barium enema
GoLytely *Treatment consists of ingestion of a 4 liter*	*Per total 4 liter dose, jug/packet* Sodium Sulfate, 22.74 g/21.5g Sodium Chloride, 5.86 g/5.53 g	Colonoscopy, Barium enema

Drug Name	Content	Indication
solution	Sodium Bicarbonate, 6.74 g/6.36 g Potassium Chloride, 2.97g/2.82 g (b) (4) PEG-3350, 236g/227.1 g	*(Data in the Moviprep NDA: no f/u post colonoscopy)
Nulytely *Treatment consists of ingestion of a 4 liter solution*	*Per total 4 liter dose* Sodium Chloride, 11.2 g Sodium Bicarbonate, 5.72 g Potassium Chloride, 1.48 g (b) (4) PEG-3350, 420g	Colonoscopy *(F/u Day 2-3 in comparison to Visicol)
Moviprep *Treatment consists of ingestion of a 2 liter solution (comparator arm in the phase 3 trials for Suprep)*	*Per <u>total</u> 2 liter dose* Sodium **Sulfate, 15 g** Sodium Chloride, 5.38 g Potassium Chloride, 2.03 g (b) (4) **PEG-3350, 200g** Sodium Ascorbate, 11.8 g Ascorbic Acid, 9.4	Colonoscopy *(Last lab: day of colonoscopy)
HalfLytely: PEG + Electrolytes + Bisacodyl *Treatment consists of ingestion of a 2 liter solution*	One 5 mg bisacodyl delayed-release tablet + *Per 2 liter bottle (total dose; 2000cc water reconstitution*) Sodium chloride 5.6 g Sodium bicarbonate 2.86 g Potassium chloride 0.74 g **PEG 3350, 210 grams** Flavoring 1 g	Colonoscopy *(No laboratory assessment in recent supplement. [Reviews not clear how assessments performed in original application])

*(NDA registration trial schedule of followup laboratory evaluations in 3rd column.)

FDA issued a Supplement Request Letter on December 10, 2008 under Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) to manufacturers of <u>oral sodium phosphate</u> products requiring that the labels be revised to include a Boxed Warning to warn of the risk of acute phosphate nephropathy and directing the manufacturers to develop a risk evaluation and mitigation strategy (REMS) that included a Medication guide to alert patients to the risk of acute kidney injury associated with the use of these products and a communication plan to inform healthcare providers likely to prescribe or dispense oral sodium phosphate products, and to conduct a postmarketing clinical trial to further assess the risk of acute kidney injury with the use of these products. The required clinical trial under section 505(o)(3) of the FDCA was "A prospective, randomized, active-controlled trial comparing the risk of developing acute kidney injury in patients undergoing bowel cleansing using (the oral phosphate product) as compared to patients undergoing bowel cleansing using polyethylene glycol (PEG) containing products."

The approved osmotic colon cleansing product labels (not just the oral sodium phosphate products) 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). Postmarketing safety studies were a condition of approval of recently approved osmotic colon cleansing products Suprep and Prepopik. With regard to the PMR, the Suprep approval letter states, "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." The Prepopik 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 assess a signal of a serious risk of renal insufficiency associated with the use of Prepopik (sodium picosulfate, magnesium oxide and citric acid) for Oral Solution, 10 mg sodium picosulfate/sachet."

Regulatory History of Current NDA: Key points in the regulatory history were summarized in the CDTL review. They related to selection and justification of the noninferiority margin, the preferred analysis population, and addressing missing data in analyses. In an advice letter dated January 30, 2009, the Division recommended selection of a noninferiority margin based on historical evidence of the efficacy of the active control. The letter also recommended that the noninferiority analysis should be conducted on both ITT and per protocol (PP) populations. In a subsequent advice letter regarding the statistical analysis plans for the two major efficacy trials (June 9, 2009), the Division recommended use of a noninferiority margin of 9%, instead of 15%, and performance of the primary efficacy analysis using the PP population.

No regulatory record of the Division notifying the applicant that they must provide evidence the product under development meets the combination rule was identified. The applicant did not request an end of phase 2 meeting or a pre-NDA meeting, the settings in which this advice is generally documented. The applicant did not specifically address the combination rule in the NDA, as submitted. The reviewers sent an information request to the applicant during the review cycle requesting that the applicant submit information to establish that this important requirement (21 CFR 300.50) had been met. The information submitted for review and the reviewers' conclusions can be found in both the Clinical review and in the CDTL review

At the time the phase 3 trials were designed, the active comparator arm in one of the trials (Study 301), HalfLytely with 10 mg bisacodyl was an approved and marketed product. In the interim since the trials' initiation, the comparator product was removed from the market for reasons of safety, as stated above, and a Halflytely product with a lower dose of bisacodyl replaced that product. Use of the previously marketed Halflytely product as the control arm in the trials that support the NDA under review is acceptable since the basis of removal of the product from the market was not efficacy, and the safety issue (ischemic colitis) could be assessed within the context of the controlled clinical trials submitted for review.

3. CMC

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Labeling issues that were approval issues have been adequately addressed by the applicant. The CMC reviewers have recommended approval.

The CDTL has summarized the major CMC review issues in his review. During the review, the CMC reviewers identified that there was inadequate specification for assuring the purity of the PEG 3350 drug substance. As proposed, (b) (4) This was an approvability issue. Ultimately, the CMC, Pharmacology/Toxicology and Clinical reviewers concurred that a combined limit of (b) (4) would be acceptable from a safety standpoint. (See Section 4 Nonclinical Pharmacology/Toxicology below.) The applicant was asked to provide information that the two sources of PEG drug substance fell within that limit, in addition to a method validation summary for the assay for these impurities. This information was submitted January 8, 2013. The reviewers found that the assay appeared adequate; however, the PEG from one of the suppliers does not meet the final specification (b) (4) . The applicant withdrew that supplier from the NDA.

During the course of the NDA review, the applicant replaced the cup for mixing the product, which will be included in product packaging. This was in response to concerns raised by the DMEPA reviewer regarding the potential for medication errors related to poor visibility of the original cup's fill line. The CMC reviewer reviewed the new cup specification and found it acceptable.

4. Nonclinical Pharmacology/Toxicology

I concur with the reviewers' conclusions that there are no outstanding nonclinical issues that preclude approval. No new nonclinical studies were submitted to support the current NDA, as the two components of Suclear are components of approved products (marketed by the applicant).

The Pharmacology/Toxicology reviewers worked with the CMC and Clinical reviewers to assess the process impurity limits for (b) (4) the PEG-3350 component of Suclear. The Nonclinical reviewers initially recommended a (b) (4) limit for the combined total amount (b) (4), based on the ICH Permitted Daily Exposure (PDE) level and an intake of 210 g of PEG. The applicant responded that although they could reduce the limit for the combination (b) (4) they could not reduce it to (b) (4) The applicant proposed a (b) (4) limit, which the nonclinical reviewers evaluated, and ultimately found acceptable based on reasons listed in their review and in the CDTL review. I have considered the bases for their conclusion and concur with their decision. Although I did not find the justification based on lifetime exposure vs. one time exposure related to PDE and ICH Q3C persuasive, I did find the justifications based on the Agency for Toxic Substances and Disease Registry MRL (minimal

risk level) and the EPA [redacted] reference dose and safe limit in [redacted] for children sufficient to justify the safety of this limit for Suclear. The latter limits exceed those proposed for Suclear.

5. Clinical Pharmacology

The Clinical Pharmacology review found the application acceptable for marketing approval as long as labeling recommendations were adequately addressed and as long as the Clinical team found the information submitted by the applicant to address the Combination Rule (21 CFR 300.50) adequate to meet this regulatory requirement. The Clinical Pharmacology reviewers' labeling recommendations were addressed in labeling negotiations.

The Clinical Pharmacology reviewers expressed concern about the absence of a full factorial study to address the Combination Rule; however, they recognized that there are ethical issues associated with conducting a full factorial study if the individual components of the combination are expected to have inadequate efficacy. The applicant submitted pharmacodynamic stool weight and "scatocrit" (percentage of stool solids, determined by taking a 5 g stool sample from the final bowel movement, centrifuging it, decanting the fluid, and weighing the pellet: % stool solid=(pellet weight/5g) x 100) data as a key component of the evidence to support that the Combination Rule was met. The Clinical Pharmacology reviewers evaluated the strength of the evidence that these PD data correlated with or predicted efficacy. They concluded these data "for various approved and unsuccessful bowel cleansing preparations suggest a relationship between the PD endpoint and efficacy." The Clinical Pharmacology review states that the information submitted by the applicant "suggest likely correlation between the PD endpoint and the clinical efficacy outcomes" based on the following (reproduced here from their review):

> *1) the observed trend for association between PD parameters and clinical efficacy noted for the single components of approved HalfLytely or half-doses of approved NuLYTELY 4L,*
> *2) the observed association between the PD parameter and clinical efficacy noted for the full dose of approved Suprep, along with higher scatocrit (PD) noted for ½ dose of Suprep, and*
> *3) the comparable efficacy of full doses of Suprep and BLI850 in randomized clinical trials (93.5% vs. 97.2%).*

The submitted PD data for each component of the combination suggest each would be inadequate as a stand alone colon cleansing prep and make it ethically difficult to justify conduct of a full factorial study. The applicant did provide efficacy data from a clinical trial conducted in support of a previous NDA that established that the PEG plus electrolytes component of Suclear is ineffective as a stand alone bowel cleansing prep for colonoscopy. The Clinical and CDTL reviews include a detailed analysis of the information submitted to address the Combination Rule, and I concur with them that the scientific standards of the Combination Rule have been met.

I concur with the Clinical Pharmacology reviewers that a trial to investigate a drug/drug interaction between the two components of Suclear is unnecessary. The basis for their conclusions is documented in their review.

A pharmacokinetic study was not conducted with the Suclear product. A pharmacokinetic evaluation of the sulfate solution component was submitted in the Suprep NDA (double the sulfate solution dose of the sulfate solution component of Suclear). In that study, Suprep was administered in a split dose, with 12 hours between doses. Because the sulfate solution administered in Suclear is merely one of the two doses administered in this PK study of Suprep, the PK data associated with the first dose in this study were relevant for inclusion in the Suclear product label. (Blood samples were obtained pre-dose, and at 1, 2, 4, 8, and 10 hours after the first dose.) Given the availability of these relevant data, a new pharmacokinetic evaluation of serum sulfate levels was not considered necessary for this new NDA. A summary of these sulfate data (in healthy subjects, subjects with renal impairment and subjects with hepatic impairment) can be found in the Clinical Pharmacology and CDTL reviews.

The reviewers noted that PEG3350 pharmacokinetic data are lacking and that the applicant had pointed to literature to support their contention that PEG is not absorbed. The reviewers agreed that the submitted literature suggests that PEG absorption is minimal; however, these studies did show PEG is absorbed and renal excretion was documented. The reviewers initially recommended a pharmacokinetic evaluation of PEG3350 as a post marketing commitment; however, the clinical team noted that since (b) (4) exposures are of interest from a safety standpoint, that the pharmacokinetic study should also include measurement of these potential impurities. As this would constitute important safety information, the clinical team recommended this evaluation should be required as a PMR under FDAAA. When the (b) (4) impurity limits were evaluated and finalized, the Clinical Pharmacology reviewers argued that these low limits made it difficult to justify requiring this pharmacokinetic trial for safety reasons. The Clinical team disagreed because they had questions about whether the levels of (b) (4) changed when PEG it is exposed to gut flora post ingestion. In light of the clinical team's concerns regarding the lack of exposure data for (b) (4) the Clinical Pharmacology reviewers ultimately agreed that the PEG pharmacokinetic study would be conducted as a PMR under FDAAA. I concur with this decision. Refer to Section 8 Safety of this review for a description of this trial.

I concur with the CDTL and Clinical Pharmacology reviewers' determination that a thorough QT study was not necessary to support approval of this NDA and that a thorough QT study will not be required as a postmarketing safety evaluation. The electrolyte shifts that may occur when taking bowel cleansing products are known to have a potential impact on cardiac conduction.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The applicant submitted two randomized, controlled trials (unblinded for the subject and site study coordinator) to support the efficacy of Suclear.

In one study (Study 301) Suclear was compared to HalfLytely and 10-mg Bisacodyl Tablets Bowel prep Kit, an approved PEG plus electrolyte osmotic laxative at the time of trial was conducted. It has subsequently been withdrawn from the market and replaced by a Halflytely product that contains a lower (5 mg) dose of bisacodyl. Suclear was administered as a "Day-Before (1-Day)" regimen (administered entirely the day prior to colonoscopy) in this trial. This schedule is consistent with the Dosage and Administration section of the HalfLytely product label. In Study 301, the dietary component of the prep was the same for both arms, i.e., consumption of clear liquids only on the day prior to colonoscopy, which appears consistent with the HalfLytely product label. The HalfLytely (10 mg bisacodyl) label described the dietary component of the clinical trials in Section 14 Clinical Studies as follows, "Patients were instructed to refrain from solid food and to have clear liquids on the day before colonoscopy. In addition, patients were instructed to consume nothing by mouth, except clear liquids, from the time the preparation was completed (b) (4) until after the colonoscopy was completed." The label also stated in Section (b) (4) FDA-Approved Patient Labeling, "No solid food or milk (clear liquids only) should be consumed on the day of the preparation."

In the second study (Study 302), Suclear, administered as a "Split Dose (2-Day)" regimen, was compared to Moviprep administered as a split dose (2-day). The product label for Moviprep includes both ""Evening only (full dose)" and "Split-dose" administration instructions. In this trial, the dietary component of the prep differed between arms. For the Suclear arm, patients consumed only clear liquids the day prior to colonoscopy. In the Moviprep arm, patients were permitted to eat a normal breakfast, a "light lunch", and clear soup and/or plain yogurt for dinner the day prior to start of the prep. Once the prep was initiated, only clear liquids could be consumed. The prep in the Moviprep arm appears consistent with the diet described in the Moviprep product label. The Moviprep label states in Section 14 Clinical Studies that the dietary component of the prep in the clinical trial was "Patients were allowed to have a morning breakfast, a light lunch, clear soup and/or plain yogurt for dinner. Dinner had to be completed at least one hour prior to initiation of the colon preparation administration." Moviprep label Section 17 Patient Counseling Information states, "Patients may have clear soup and/or plain yogurt for dinner, finishing the evening meal at least one hour prior to the start of MoviPrep treatment. No solid food should be taken from the start of MoviPrep treatment until after the colonoscopy." The Medication Guide states, "Do not eat solid foods while taking MoviPrep. Only clear liquids are allowed while taking and after taking MoviPrep until your colonoscopy."

The primary efficacy analyses in both trials were noninferiority evaluations based on proportion of patients with a bowel cleansing outcome of "success," which was defined as a bowel cleansing grade of "excellent" or "good" on a 4 point rating scale called the Colonoscopist Colon Cleansing score, which is shown in the table below.

Table 2 (Applicant's) Colonoscopist Colon Cleansing Assessment Scores

Score	Grade	Description
1	**Poor**	**Large amounts of fecal residue, additional cleansing required**
2	**Fair**	**Enough feces or fluid to prevent a completely reliable exam**
3	**Good**	**Small amounts of feces or fluid not interfering with exam**
4	**Excellent**	**No more than small bits of adherent feces/fluid**

Secondary endpoints included: 1) adequacy of colon cleaning, defined as cleansing adequate for evaluation, and need for re-preparation, 2) number of excellent preparations, and 3) number of colonoscopic examinations in which the cecum was reached. There was no prespecified plan for adjusting for multiplicity for analysis of the secondary endpoints.

As noted earlier in this review, the regulatory record includes a 2009 letter from FDA stating the noninferiority margin should be based on the historical evidence of efficacy of the active control. A subsequent letter, also in 2009, recommended use of a 9% margin, instead of 15%. The applicant utilized a 15% margin to analyze the trials and did not adequately justify that margin. They did not identify placebo controlled trials of the active controls (Moviprep and HalfLytely) that established the treatment effect of the active controls. The applicant also did not accept the margin suggested by the FDA correspondence. It should be noted that no placebo controlled trials were identified by the reviewers that supported the 9% margin recommended in the FDA correspondence. (Examination of the statistical review of the statistical analysis plan, dated March 31, 2009, suggests that that margin was selected based on what might be considered an acceptable relative decrease in efficacy, "For protocol BLI850-301, choosing δ=15% implies that as much as a 17.2% relative decrease of assumed expect event rate of 87% for HalfLytely might occur in patients prepared with BLI-850. This may occur with small probability but may not be acceptable. If at most a 10% relative decrease is considered acceptable, then the delta would be 9%.....For protocol BLI850-302, choosing δ=15% implies that as much as a 16.8% relative decrease of assumed expect event rate of 89% for MoviPrep might occur in patients prepared with BLI-850. This also may not be acceptable. If a 10% relative decrease is acceptable, then the delta would be 9%.") In light of the absence of placebo controlled trials to establish the treatment effect of the active control arms, as set forth by ICH E10, and other concerns described below, the Statistical Reviewer did not conduct exploratory analyses of noninferiority based on the 9% margin suggested by FDA.

The lower bound for the confidence interval for the difference between the two arms in the two trials, as reported by the applicant for the mITT population, were greater than -9% : -0.8% in Study 301 and -5.0% in Study 302. Both fell within the margin that the FDA had suggested in correspondence, a margin that was also ***not*** based on the necessary evidence as required by ICH guidelines. However, had there been adequate evidence to support the 9% margin, the statistical reviewers had other concerns about the adequacy of the trial designs for establishing noninferiority, which negatively impact the interpretability of the observed differences

between arms. They pointed out that the "breakpoint" for success, based on the scoring system utilized in the clinical trials conducted to support this NDA, was subjectively assigned by the colonoscopist (without objective visual documentation) and was vague enough that it leant itself to a clinical trial outcome of finding "noninferiority," even when the endoscopist was blinded. (The descriptions for "Good" and "Fair" appear relatively indistinct, and the Statistical reviewer noted that it would be easy for a blinded investigator to assign all marginal exams, regardless of treatment of assignment, one score in order to achieve the desired "noninferior" results.) In light of the absence of the appropriate trials to establish the noninferiority margin, the Statistical reviewers determined that efficacy could not be established based on (b) (4)

Acknowledging the ethical challenges of conducting a placebo controlled trial for bowel cleansing products to establish the treatment effect of the active controls, the Statistical reviewers stated that the trial data could establish that the product is effective by examining the lower bound of the confidence interval of the success rate in the Suclear arms to see if it exceeded any expectation of the placebo response rate. The clinical team stated that the placebo response expected for colon cleansing for colonoscopy would be exceedingly low, approaching 0%. Those data for each of the two trials are summarized in the tables below. It should be noted that the ITT population referred to in the Statistical Review is the mITT population in the clinical reviews (and the mITT population defined by the applicant). The mITT population was defined as patients who took any amount of the prep and did not withdraw prior to colonoscopy for reasons unrelated to safety or efficacy.

Table 3 Study 301: Statistical Reviewer's 95% two-sided confidence intervals for Success Rate of Suclear

	Suclear		95% Confidence Interval on
Patient Population	No. Success	Success Rate (n/N)	P_{BLI850}
Per-Protocol Population	158	0.90 (158/175)	(0.85, 0.94)
Intent-to-Treat Population	158	0.90 (158/176)	(0.84, 0.94)

Table 4 Study 302: Statistical Reviewer's 95% two-sided confidence intervals for Success Rate of BLI850 (Suclear)

	Suclear		95% Confidence Interval on
Patient Population	No. Success	Success Rate (n/N)	$\mathbf{P_{PLI850}}$
Per-Protocol Population	173	0.940 (173/185)	(0.890, 0.970)
Intent-to-Treat Population	173	0.940 (173/185)	(0.890, 0.970)

I concur with the Statistical reviewers' recommendations regarding the limited validity of the noninferiority analyses (b) (4)
However, in the recent approval of the Prepopik NDA (in the absence of placebo controlled data to establish the treatment effect of HalfLytely), (b) (4)

(b) (4)

Statistical reviewers have advocated setting a conservative NI margin (b) (4) and if not met, the clinical reviewers have examined the lower bound of the confidence interval for the observed success rate observed to determine if that rate exceeds what would be reasonably expected with a placebo in this setting. In the current application, the Statistical reviewer was not only satisfied with the observed outcome of the noninferiority analysis, but the split dose regimen of Prepopik was also found to be superior to the HalfLytely 10 mg product (administered entirely the day prior to colonoscopy)."

The Statistical reviewer for this Suclear NDA was also the reviewer of the Moviprep NDA. His Moviprep review raises similar concerns, and he recommended approval of Moviprep, not on the basis of noninferiority, but on a clinical team decision that the lower bound of the confidence interval associated with the rate of success in the Moviprep arms exceeded what would be expected with placebo. The lowest lower bound of the confidence interval for Moviprep success observed in the two major trials in that NDA was 0.64, which was observed in the "Same Day/Day Before" regimen trial (data shown below):

Table 5 (Reviewer's) 95% two-sided confidence intervals on $P_{moviprep}$

Patient Population	Moviprep No. Success	Success Rate (n/N)	$P_{moviprep}$	95% Confidence Interval on
Per-Protocol Population	100	0.73	(100/137)	(0.65, 0.80)
Intent-to-Treat Population	101	0.73	(101/137)	(0.64, 0.80)

The lower bound of the 95% confidence interval for the rate of success in the Moviprep NDA "Split Dose" trial was in the 0.82 range. The data are shown in the table below.

Table 6 (Reviewer's) Moviprep 95% two-sided confidence intervals on $P_{moviprep}$

Patient Population	Moviprep No. Success	Success Rate (n/N)	95% Confidence Interval on $P_{moviprep}$
Per-Protocol Population	136	0.87	(136/153)	(0.83, 0.94)
Intent-to-Treat Population	140	0.88	(140/153)	(0.82, 0.93)

In light of the Statistical reviewers' concerns about the impact of the rating scale on the interpretability of efficacy, i.e., concern that the distinction between "fair" and "good" is vague and allows inflation of the success score, it is worth exploring the secondary endpoint results. However, it must be noted that there are limitations associated with the secondary endpoints, which include: 1) the descriptions of "excellent" and "good" preps are similar in this clinical trial's scale, 2) reaching the cecum can be related to issues that have nothing to do with quality of bowel prep, and 3) cleansing adequate for evaluation and not needing re-preparation is a low standard for an examination in which it is critical to not miss lesions. In recent reviews, we have placed particular emphasis on examining relative proportions of excellent preps, since an excellent prep might be expected to result in the lowest miss rate, if other factors known to impact detection (such as colonoscope withdrawal rate) are optimized. The proportions of excellent preps in the two trials are summarized in the tables below. The rates are numerically similar between arms, with the rate in the Suclear arm of Study 301 exceeding that of HalfLytely. These data, though exploratory, provide some support of the efficacy of Suclear.

Table 7: Number of patients in Study 301 with "Excellent" colon cleaning score (reproduced from Clinical review)

	Treatment Group	
	Suclear	**HalfLytely**
Colon cleansing graded as "excellent"	84/176 (47.7%)	76/188 (35.6%)

Source: The Applicant's Clinical Study Report for Protocol BLI850-301, Table 301-4.

Table 8: Number of patients in Study 302 with "Excellent" colon cleaning score

	Treatment Group	
	Suclear	**MoviPrep**
Colon cleansing graded as "excellent"	96/185 (51.9%)	95/185 (51.4%)

Source: The Applicant's Clinical Study Report for Protocol BLI850-302, Table 302-4.

The scoring systems utilized in the clinical trials that supported recent product approvals were not used in the Suclear clinical trials. The scale used for this NDA's trials was developed by the applicant (and used in the HalfLytely and Suprep NDAs). In the Prepopik NDA, the scale used was the Aronchick scale, shown below. The description associated with each score appears more precise than the description used in the Suclear registration trials.

Aronchick Scale Grade	Description
Excellent	>90% of mucosa seen, mostly liquid stool, minimal suctioning needed for adequate visualization
Good	>90% of mucosa seen, mostly liquid stool, significant suctioning needed for adequate visualization
Fair	>90% of mucosa seen, mixture of liquid and semisolid stool, could be suctioned and/or washed
Inadequate	<90% of mucosa seen, mixture of semisolid and solid stool which could not be suctioned or washed

The Clinical Reviewer of the Prepopik NDA stated the following regarding the Aronchick scale in her review, "The Aronchick Scale is universally accepted and has been used in other pivotal trials…."

Review of the Moviprep product label indicates that additional scoring systems were utilized in the registration trials for that product:

Scoring system for Moviprep Study 1 (Split Dose):

*****A: colon empty and clean or presence of clear liquid, but easily removed by suction
†B: brown liquid or semisolid remaining amounts of stool, fully removable by suction or displaceable, thus allowing a complete visualization of the gut mucosa
‡C: semisolid amounts of stool, only partially removable with a risk of incomplete visualization of the gut mucosa
§D: semisolid or solid amounts of stool; consequently colonoscopy incomplete or needed to be terminated.

Scoring system for Moviprep Study 2 (Same day/Day Before regimen):

*****A: empty and clean or clear liquid (transparent, yellow, or green)
†B: brown liquid or semisolid remaining small amounts of stool, fully removable by suction or displaceable allowing a complete visualization of the underlying mucosa
‡C: semi solid only partially removable/displaceable stools; risk of incomplete examination of the underlying mucosa
§D: heavy and hard stool making the segment examination uninterpretable and, consequently, the colonoscopy needed to be terminated

The Ottawa Scale (shown below) was utilized to assess a secondary endpoint in the Prepopik registration trials, cleansing score of the ascending colon. This scale's intended use is to provide a total score and overall colon cleansing assessment based on subscoring the quality of cleansing of each colon segment.

Ottawa Scale Grade	Description
0	Excellent: Mucosal detail clearly visible. If fluid is present, it is clear. Almost no stool residue.
1	Good: Some turbid fluid or stool residue but mucosal detail visible. Washing and suctioning not necessary.
2	Fair: Turbid fluid or stool residue obscuring mucosal detail. However, mucosal detail becomes visible with suctioning. Washing not necessary.
3	Poor: Presence of stool obscuring mucosal detail and contour. However, with suctioning and washing, a reasonable view is obtained.
4	Inadequate: Solid stool obscuring mucosal detail and contour despite aggressive washing and suctioning.

It is of interest to compare the Aronchick scale-derived HalfLytely success rate data from the two Prepopik registration trials, 74.4% and 79.7%, to the HalfLytely success rate observed

with the applicant's scale used in Study 301 (Day-Before/1-Day) , 83.5%. The success rate was fairly similar, though numerically higher, in Study 301; however, this is an exploratory cross study comparison. Exploration of the relative proportion of "excellent" preps when Aronchick is utilized versus the scoring system in Study 301 reveals that the rates of excellent preps in the HalfLytely arms of Prepopik trials (Aronchick scores), 34 and 40%, are similar to the rate of Excellent preps, 36%, observed for the Halflytely arm of Suclear Study 301.

Similar comparisons can be explored, using the Split Dose regimen Moviprep data from its product label and the Moviprep data from the Split dose Study 302 in the Suclear NDA. The success rate for Split Dose Moviprep in its label is 88.9%, using the success definition: [Moviprep NDA success = (A: colon empty and clean or presence of clear liquid, but easily removed by suction) + (B: brown liquid or semisolid remaining amounts of stool, fully removable by suction or displaceable, thus allowing a complete visualization of the gut mucosa)]. The Moviprep success rate in the Split Dose Suclear trial is numerically higher, 93.6%. As with the HalfLytely cross study comparison exploration, the rates are similar, despite use of the different scales.

The Moviprep Clinical review posted on the web at the Drugs@FDA website contains the following breakdown of the scores observed in the split dose Moviprep trial, which suggests that although the "success" rates are similar when using the different scales, the distribution between excellent vs. good (in the current NDA) compared to Grade A vs. B in the scale used in the Moviprep NDA (split dose trial) is quite different. They are nearly evenly split between excellent/good with the scale used in the current NDA, and much more predominantly Grade B in the Moviprep NDA.

Table 9: The number(%) of PP* patients with effective colon cleansing rated by the expert

Treatment Group	Responder (A or B) n (%)	A n (%)	B n (%)	Non-Responder (C or D) n (%)	C n (%)	
MOVIPREP N=153	**136 (88.9)**	22 (14.4)	114 (74.5)	17 (11.1)	15 (9.8)	
GoLYTELY N=155	**147 (94.8)**	18 (11.6)	129 (83.2)	8 (5.1)		
	(-5.9)**	(2.6)	(-8.7)	(6.0)		

There are a number of factors that could contribute to the differences in distribution of the scores contributing to the overall responder definition in the Moviprep and Suclear applications. Although the trial methodology may have contributed to apparent differences [(1) the Moviprep trial utilized expert panels who scored videotapes, while the current NDA trials relied on the investigator giving an overall score at the time of actual endoscopy, and (2) the independent panel in the Moviprep trial scored both the appearance of colonic mucosa at ingress and egress and the default score was the worst of the two, whereas the Suclear trial just recorded the overall impression of the endoscopist at completion of endoscopy], it appears the

actual scoring system could contribute substantially to the differences in distribution of the scores. The Moviprep score Grade A is not well correlated with "Excellent" as it does not allow for the presence of any amount of solid stool (only clear liquid). The two scoring system definitions for each component considered a success are summarized in the table below to facilitate comparisons:

"Excellent" (Suclear NDA)	Grade A (Moviprep NDA		"Good" (Suclear NDA)	Grade B (Moviprep NDA)
No more than small bits of adherent feces/fluid	: colon empty and clean or presence of clear liquid, but easily removed by suction		**Small amounts of feces or fluid not interfering with exam**	brown liquid or semisolid remaining amounts of stool, fully removable by suction or displaceable, thus allowing a complete visualization of the gut mucosa

Summary. I concur with the clinical reviewer and CDTL that the two major trials submitted in this NDA establish the efficacy of Suclear and support its approval. I agree that the efficacy results observed in the Suclear arms of the trials far exceed the success rate that would be expected with use of a placebo for bowel cleansing. I agree with the Statistical reviewers that there is inadequate information to perform a valid noninferiority analysis (b) (4) This approach is consistent with other recent approvals, i.e., HalfLytely and Suprep NDAs. The most recent HalfLytely (5mg bisacodyl) label presents confidence intervals around the difference between the 5 mg and 10 mg product and states that the proportion of successful colon cleansing "was similar" between groups; (b) (4)

Finally, I agree with inclusion of the Day-Before (1-Day) dosing regimen in product labeling. Use of Split Dosing regimens is recommended by professional societies because this method is associated with superior cleansing. The Division did not approve "Day Before" dosing of Suprep in light of the professional society recommendations, coupled with safety concerns associated with Suprep when it was administered with this schedule. However, the Division allowed inclusion of the "Day before" regimen in the recently approved Prepopik label. That label refers to split dosing as the "preferred method" and states the "Day before" regimen should be reserved for use when the "Split Dose" regimen is "inappropriate." My review of the Prepopik NDA states that this decision was based on "…..The applicant argued that there are reasonable circumstances in which it is not optimal for a patient to take a split dose regimen, e.g., patients who have a long distance to travel to endoscopy, and that it would be remiss to leave out those instructions from the product label, due to the needs of these patients…..I concur with these labeling recommendations, as the safety review of the Day Before regimen did not identify significant safety issues relative to the Split Dose regimen that alter the risk/benefit decision."

The proportion of excellent preps in the Suclear arm was numerically somewhat lower in the "Same Day/Day Before" trial compared to the Suclear arm in the "Split dose" trial; however, the rates were relatively similar, as summarized in the table below.

Table 10: Number of patients with "Excellent" colon cleaning score (reproduced from Clinical review) in the Suclear arms of the Same Day (Study 301) and Split Dose (Study 302) Trials

	Suclear	
	Same Day Trial	**Split Dose Trial**
Colon cleansing graded as "excellent"	84/176 (47.7%)	96/185 (51.9%)

Source: Combined data from Applicant's Clinical Study Report for Protocol BLI850-301, Table 301-4 and Clinical Study Report for Protocol BLI850-302, Table 302-4.

In Study 301 ("Day Before/1-Day" trial), the success rate (excellent plus good) was numerically higher than HalfLytely, which is an approved regimen that is administered entirely the day before colonoscopy: 89.8% vs. 83.5%.

In light of these efficacy data and the absence of a safety issue for the "Day Before (1-Day)" regimen relative to the "Split Dose" regimen, I concur with the review team's decision to include the "Day Before (1-Day)" dosing regimen in the product labeling, with language that indicates that the "Split dose" regimen is the preferred dosing regimen (similar to the Prepopik label). The efficacy data that will be presented in the product label will include the primary endpoint efficacy data for both arms of both trials (Study 301 and 302). The Statistical Team leader concurred with including the 95% confidence intervals for the difference between treatment arms in each trial, (b) (4) He pointed to the precedents for this approach in other colon cleansing product labels.

8. Safety

Separate safety reviews were conducted of the two major phase 3 trials that support this NDA (Studies 301 and 302) because each trial studied a different Suclear dosing regimen.

The protocol specified safety evaluations were limited to a physical examination, vital signs, and laboratory testing at baseline and on the day of colonoscopy (Visit 2, prior to the procedure). Orthostatic vitals were not evaluated. Laboratory testing did not extend beyond the colonoscopy day. There was a follow-up phone contact 2 weeks after Visit 2 for patients that had ongoing adverse events. A follow-up blood sample was to be obtained if a laboratory result at Visit 2 was deemed "clinically significant" by the site investigator. There was no definition of "clinically significant" in the protocol, and only one patient in Study 301 (HalfLytely) and 5 subjects in Study 302 (3 in the BLI850 arm and 2 in the MoviPrep arm) had labs redrawn after Visit 2 to follow up abnormal chemistry laboratory results.

At Visit 2, the trials captured spontaneously reported adverse events, in addition to specifically solicited adverse reactions that are expected as part of bowel cleansing preparations. These specific reactions (stomach cramping, bloating, nausea, and overall discomfort) were included in a symptom scale that patients completed. An adverse reaction obtained in this questionnaire was included as an adverse reaction in the adverse event dataset score only if it was rated a 5 ("severely distressing") by the patient. Vomiting was also specifically captured in a questionnaire and was included as an adverse event, regardless of severity. The Clinical reviewer combined both types of adverse reactions (spontaneously reported and solicited) in the safety analysis as long as it was counted only once for each subject. (All specifically solicited symptoms, regardless of severity, were included in the AE dataset.)

There were no deaths reported up until 30 days after the colonoscopy in both trials. There was one non-fatal SAE, which occurred in Study 302. The patient, a 59-year old male, was in the Suclear arm of the trial and was admitted to the hospital the evening of the colonoscopy with severe abdominal pain. The patient's "febrile symptoms," resolved the same day with antibiotic treatment. The abdominal pain did not resolve completely until 2 days after discharge from the hospital. The colonoscopy report was reviewed by the Clinical reviewer and she noted that a 0.2 cm polyp was cold biopsied during the procedure. No diverticulosis or ulceration was noted. The investigator concluded the SAE was not related to Suclear. The Clinical reviewer determined that the presence of febrile symptoms and improvement on antibiotics suggested the event was not related to study drug. I concur. The lack of rectal bleeding and the colonoscopy report content do not support that this was a case of ischemic colitis.

A single patient in the Suclear arm of each trial discontinued study participation due to an adverse event. In the Day Before/1-Day trial (Study 301), a 71 year old male developed new onset atrial fibrillation which was detected the day of colonoscopy. In the Split Dose (2-Day) trial, a 52 year old female discontinued due to nausea.

The most common adverse reactions observed in the two trials are summarized in the table below, which is reproduced from the Clinical Review. Nearly all the events were the specifically solicited events, as set forth by the protocol (described above).

Table 11: Adverse reactions observed in at least 1% of patients in Studies 301 and 302

Symptom	Study 301: Day-Before Regimen		Study 302: Split-Dose Regimen	
	Suclear N=176 n (%)	HalfLytely N=190 n (%)	Suclear N=186 n (%)	MoviPrep N=185 n (%)
Overall discomfort	122 (69.3)	108 (56.8)	116 (62.4)	121 (65.4)
Abdominal distension	92 (52.3)	85 (44.7)	96 (51.6)	112 (60.5)
Abdominal pain	71 (40.3)	78 (41.1)	70 (37.6)	79 (42.7)
Nausea	74 (42.0)	75 (39.5)	86 (46.2)	72 (38.9)
Vomiting	19 (10.8)	15 (7.9)	26 (14.0)	13 (7.0)
Retching	2 (1.1)	1 (0.5)	0	2 (1.1)
Headache	1 (0.6)	3 (1.6)	3 (1.6)	2 (1.1)

Abdominal distension was numerically higher in the Suclear arm than the HalfLytely arm in the "Day Before (1-Day)" trial only. Nausea and vomiting were numerically higher in the Suclear arms than the control arms of both dosing regimen trials; however, the difference between arms appeared greater in the "Split Dose" regimen than the "Day Before" regimen. When certain demographic features were examined to investigate a risk relationship with vomiting (see Table 12 below), among elderly patients, a numerically higher rate of vomiting occurred in the HalfLytely arm of the "Day Before" trial (Study 301) than in the Suclear arm of that study, which is opposite of the trend in the overall age population. In the "Split Dose" trial (Study 302), the higher rate of vomiting observed in the Suclear arm in the overall age population was also observed in the subgroup of elderly patients.

Table 12: Demographic and clinical characteristics of patients who experienced vomiting during Studies 301 and 302 (Table reproduced and modified from Clinical Review, Table 49)

	Study 301: Day-Before Regimen		Study 302: Split-Dose Regimen	
	Suclear N=19 n (%)	HalfLytely N=15 n (%)	Suclear N=26 n (%)	MoviPrep N=13 n (%)
Elderly (≥65 years old)	1 (5.3)	2 (13.3)	3 (11.5)	1 (7.7)
High risk[2]	9 (47.7)	7 (46.7)	10 (38.5)	7 (53.8)

[2]High risk was defined as patients with reported medical history of cardiac, renal or vascular problems (hypertension), or diabetes.
Source: Clinical reviewer's analysis using the Applicant's AESY and AESY2 (adverse event plus symptoms) datasets for Studies 301 and 302, respectively, submitted in response to Information Request dated July 18, 2012.

There was a numerically higher number of subjects in the Suclear arm than in the control arm in each of the two trials who rated their specifically solicited adverse reactions as severe (only one of which was an SAE, i.e., the hospitalization for abdominal pain described above). The following summary of these "severe" events is taken from the Clinical Review.

Study 301 (5 Suclear, 1 Halflytely):
- Patient 1004 (Suclear) – abdominal distension, nausea
- Patient 1005 (Suclear) – headache
- Patient 3059 (Suclear) – abdominal distension
- Patient 5007 (HalfLytely) – abdominal distension
- Patient 9050 (Suclear) – abdominal pain, nausea, vomiting
- Patient 12001 (Suclear) – nausea

Study 302 (2 Suclear, 2 Moviprep):
- Patient 25002 (Suclear) –nausea, vomiting
- Patient 25014 (MoviPrep) – nausea
- Patient 25029 (Suclear) – abdominal pain (SAE)
- Patient 27023 (MoviPrep) – abdominal pain

Laboratory assessments
In her review of the laboratory testing data from the trials, the Clinical reviewer noted that there were numerically higher rates of new-onset elevated anion gap, elevated alanine aminotransferase (ALT), elevated creatine kinase (CK), and decreased estimated creatinine clearance (eC_{Cr}) in the Suclear treated patients than in the control arms. One patient treated with Suclear in Study 302, experienced a decline in eC_{Cr} (calculated using the Cockcroft-Gault method) from a baseline of 90 mL/min to 49 mL/min at Visit 2 (day of colonoscopy). The absence of laboratory testing beyond the day of colonoscopy in most patients made it impossible to determine whether laboratory abnormalities resolved.

Changes in electrolytes, renal function and transaminases/bilirubin, the time course of changes, degree of reversibility, and contributing factors such as concomitant medications or conditions (such as hypotension peri-procedure) are of particular interest and have been difficult to

evaluate in previous NDA's for colon cleansing products due to limitations in amount of data collected and the timing of assessments. The Division of Biometrics 7 was consulted to assist in evaluating the safety laboratory data for shifts from normal to abnormal. However, due to the lack of follow-up laboratory evaluations, comprehensive analyses of recovery cannot be performed. The Clinical Reviewer noted in her review that the protocol stated that if the investigator determined that a laboratory value was clinically significant that the value should be rechecked; however, there was no definition "clinically significant," and a follow-up value was not checked in all patients with laboratory values that fell outside normal range on Visit 2. She found that there were patients with laboratory values considered clinically significant by individual investigators that did not trigger reassessment by other investigators.

Electroloytes. The shift table created by the DB7 reviewer showing proportions of patients who shifted from normal baseline to abnormal at Visit 2 in specific electrolytes is presented below (reproduced from the CDTL review). Rows of particular interest and discussed in individual reviews are bolded. Imbalances between arms were not consistent between the two trials, which might be expected given the differences in control arms and administration schedules in the two trials.

Table 13: Proportion of subjects with normal baseline who developed abnormal electrolyte values at Visit 2 in Studies 301 and 302

Laboratory Parameter	Study 301		Study 302	
	Suclear n/N (%)	HalfLytely n/N (%)	Suclear n/N (%)	MoviPrep n/N (%)
Anion Gap (high)	**5/155 (3.2)**	**8/170 (4.7)**	**17/166 (10.2)**	**12/155 (7.7)**
Bicarbonate (low)	**4/156 (2.6)**	**5/167 (3.0)**	**6/170 (3.5)**	**20/161 (12.4)**
Calcium (high)	**12/139 (8.6)**	**5/139 (3.6)**	**6/141 (4.3)**	**7/144 (4.9)**
Chloride (low)	1/157 (0.6)	0/171 (0.0)	1/173 (0.6)	0/163 (0.0)
Magnesium (low)	1/158 (0.6)	1/169 (0.6)	0/169 (0.0)	1/163 (0.6)
Magnesium (high)	0/158 (0.0)	0/169 (0.0)	0/169 (0.0)	1/163 (0.6)
Osmolality (high)	3/139 (2.2)	8/153 (5.2)	6/151 (4.0)	12/145 (8.3)
Phosphate (low)	0/155 (0.0)	0/168 (0.0)	5/171 (2.9)	2/160 (1.3)
Phosphate (high)	2/155 (1.3)	2/168 (1.2)	1/171 (0.6)	2/160 (1.3)
Potassium (low)	5/144 (3.5)	4/160 (2.5)	6/162 (3.7)	7/159 (4.4)
Glucose (low)	0/146 (0.0)	1/156 (0.6)	3/160 (1.9)	3/150 (2.0)
Glucose (high)	**10/146 (6.8)**	**4/156 (2.6)**	**3/160 (1.9)**	**5/150 (3.3)**
Sodium (low)	0/157 (0.0)	0/169 (0.0)	1/169 (0.6)	1/163 (0.6)
Sodium (high)	1/157 (0.6)	0/169 (0.0)	0/169 (0.0)	0/163 (0.0)

Source: Adapted from Dr. Bradley McEvoy's Safety Statistical review dated September 12, 2012, Tables 28 and 33.

In general, when means and ranges for changes and absolute values for those patients who shifted to abnormal were examined, the CDTL and clinical reviewer concurred that these abnormal values were not of a magnitude that caused concern on an individual patient basis. The difference between arms in high glucose levels observed in Study 301 was reported as "statistically significant." This difference was not observed in the "Split dose" trial. The reviewers could not identify an explanation for this observation in Study 301. The observation

of a "statistically significant difference" may only reflect chance, in the context of these multiple comparisons.

There was particular interest in examining the dataset for low serum bicarbonate and high anion gap in light of the presence of sulfate in Suclear (sulfate can function as an organic acid) and concerns raised regarding the potential for presence of (b) (4) impurities in PEG solutions. Both may be expected to produce a high anion gap metabolic acidosis. Suclear and both the active comparators contain PEG, and the PEG amounts are similar. Suclear and Moviprep both contain sulfate salts. The sulfate content in Suclear is somewhat higher than Moviprep. (See Section 2 Background above for summary comparisons of product content.)

There was a numerically higher rate of high anion gap in both arms of "Split Dose" Study 302, compared to the arms in the "Day Before" Study 301, despite similar amounts of PEG administered in all arms of these trials. These differences may not be real and could merely be due to the fact that these are cross study comparisons. If real, they could be related to closer proximity of the laboratory evaluation of the last administered dose of drug in the "Split dose" trial. The proportion of Suclear treated patients with high anion gap appears higher in Study 302 than in Study 301.

With regard to low serum bicarbonate levels, the rates are similar between arms in the "Day Before" Study 301. The proportion of Suclear treated patients who shifted to low serum bicarbonate is similar between the two trials. There was a higher proportion of patients with low serum bicarbonate in the Moviprep arm than the Suclear arm of the "Split Dose" Study 302, despite the similar PEG content in the two products and the somewhat lower sulfate level in the Moviprep product. The percentage of low serum bicarbonate in Study 302 is similar to that observed in the Split Dose study conducted to support the Suprep NDA approval, in which 13% of Moviprep arm patients developed low serum bicarbonate on the day of colonoscopy (14/23 had high anion gap) and 11% of the Suprep arm had low serum bicarbonate (16/20 had high anion gap). In Study 302, there was a higher proportion of patients in the Suclear arm that had a high anion gap than had a low serum bicarbonate. The Clinical reviewer has explained that this was secondary to contributions of sodium and chloride shifts.

Pharmacokinetic and electrolyte data from Study BLI300-101 allowed exploration of serum bicarbonate levels by time of laboratory assessment relative to administration of a Suprep dose in my review of the Suprep NDA (table reproduced below). That exploration suggested the greatest shifts downward in serum bicarbonate occurred when serum sulfate levels were highest. In light of this, shifts in serum bicarbonate on the day of colonoscopy related to sulfate exposure would be expected to be consistent in the Suclear arm between Study 301 and Study 302, since the sulfate solution component of Suclear is administered the day prior to colonoscopy in both regimens. However, for Moviprep in the Split Dose Study 302, the sulfate ion exposure occurs again with a dose of Moviprep the morning of the procedure. This difference between timing of sulfate administration relative to laboratory assessment might have contributed to observed differences in serum bicarbonate between Suclear and Moviprep in Study 302.

Table 14: Exploratory Analysis of Change in Electrolytes with degree of change in Serum Sulfate levels post Suprep in Study BLI300-101: Percentage Change from Baseline in Electrolytes Ordered by Decreasing Sulfate Increments at 4 Time Points (Table Reproduced from Division Director Review of NDA 022372 Suprep, Table 22)

Sulfate	+106 %	+71.5 %	+66.6 %	+59.7 %
Calcium	+0.78 %	+1.83 %	-1.15 %	-1.60 %
Magnesium	-0.75 %	-0.63 %	+3.28 %	+5.28 %
Chloride	-1.28 %	-0.97 %	-0.96 %	-0.15 %
Bicarbonate	-5.53 %	-5.50 %	-3.97 %	-0.86 %
Potassium	+0.82 %	+4.77 %	+1.22 %	+3.95 %
Reference time point after last dose and regimen	5h split dose	15 h same day	11 hour split dose	21 hour same day

Creatinine and eGFR. Shift tables were also created for renal function, based on measured creatinine and eGFR (calculated with various formulae). These tables are presented and discussed in the CDTL, Clinical and DB7 reviews. As in recent NDA reviews for other bowel cleansing products, shifts to abnormal range were observed in both the Suclear arms and the control arms. Numerically higher proportions of shifts to abnormal were observed in eGFR than in creatinine (which was also observed in the Prepopik NDA).

The reviewer's recommended that the Suclear label include only the Cockcroft-Gault eGFR values. As summarized in the table below (reproduced from the Clinical review), in the "Day Before" regimen (Study 301), there is a higher proportion of patients in the Suclear arm who shift to low eGFR; however, with other eGFR calculation methods, this difference is not observed.

Table 15: Proportion of patients with normal baseline who developed abnormal renal function at Visit 2 in Studies 301 and 302

Laboratory Parameter	Study 301		Study 302	
	Suclear n/N (%)	HalfLytely n/N (%)	Suclear n/N (%)	MoviPrep n/N (%)
Creatinine (high)	3/145 (2.1)	4/155 (2.6)	2/167 (1.2)	1/153 (0.7)
eC_{Cr} CG (low)	21/84 (25.0)	12/88 (13.6)	9/101 (8.9)	9/85 (10.6)
eGFR MDRD (low)	12/45 (26.7)	21/63 (33.3)	20/59 (33.9)	17/54 (31.5)
eGFR CKD-EPI (low)	14/46 (30.4)	28/67 (41.8)	20/61 (32.8)	15/56 (26.8)

eC_{cr}, estimated creatinine clearance; CG, Cockcroft-Gault; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
Source: Adapted from Dr. Bradley McEvoy's Safety Statistical review dated September 12, 2012, Tables 14 and 22.

It was difficult to justify not including the "Day Before/1-Day" regimen in the product label as an option, if needed for specific patients. The higher proportion of patients with shift to low eGFR was not consistent among the various methods for calculating eGFR.

Serum transaminases and bilirubin. Shifts of transaminases and bilirubin from normal to high are summarized in the table below, which is reproduced from the CDTL review. The rows of particular interest are highlighted in bold. There were no patients with laboratory values that met Hy's law in these datasets. Transaminase elevations have been observed in other bowel cleansing product NDAs. Elevations of bilirubin noted in NDA reviews for other bowel cleansing preparations have been attributed to dehydration and Gilbert's syndrome. In the Picoprep NDA safety dataset, which included a check of serum electrolytes 24-48 hours after colonoscopy, these elevations were generally observed to resolve by that first follow-up evaluation. The Clinical reviewers for the current NDA carefully evaluated the number of patients in each arm with shifts to abnormal and the magnitude of the shifts in their reviews. I agree with their conclusions that the distribution of these elevations and the magnitude of the elevations do not raise safety concerns that preclude approval of Suclear.

Table 16: Proportion of subjects with normal baseline who developed abnormal liver and biliary enzyme values at Visit 2 in Studies 301 and 302

Laboratory Parameter	Study 301		Study 302	
	Suclear n/N (%)	HalfLytely n/N (%)	Suclear n/N (%)	MoviPrep n/N (%)
Albumin (high)	**7/152 (4.6)**	**9/164 (5.5)**	**12/164 (7.3)**	**6/159 (3.8)**
AST (high)	9/151 (6.0)	7/161 (4.3)	13/161 (8.1)	14/154 (9.1)
ALT (high)	**8/148 (5.4)**	**5/161 (3.1)**	**10/162 (6.2)**	**5/150 (3.3)**
Gamma GT (high)	2/126 (1.6)	5/140 (3.6)	4/149 (2.7)	3/134 (2.2)
Total bilirubin (high)	**12/157 (7.6)**	**17/170 (10.0)**	**19/170 (11.2)**	**6/162 (3.7)**
Direct bilirubin (high)	14/157 (8.9)	18/167 (10.8)	16/169 (9.5)	10/163 (6.1)

Source: Adapted from Dr. Bradley McEvoy's Safety Statistical review dated September 12, 2012, Tables 28 and 33.

Creatinine kinase. The following table summarizes the shift data for creatine kinase. A numerically higher rate of shift to high creatine kinase was noted in the Suclear arm of both trials. Elevations in CK have been observed in other colon cleansing trials, including the registration trials in the Suprep NDA. The underlying etiology is not clear.

Table 17: Proportion of subjects with normal baseline who developed abnormal creatine kinase (CK) levels at Visit 2 in Studies 301 and 302

Laboratory Parameter	Study 301		Study 302	
	Suclear n/N (%)	HalfLytely n/N (%)	Suclear n/N (%)	MoviPrep n/N (%)
Creatine kinase (high)	10/138 (7.2)	6/151 (4.0)	10/147 (6.8)	7/143 (4.9)

Source: Adapted from Dr. Bradley McEvoy's Safety Statistical review dated September 12, 2012, Tables 28 and 33.

Summary. I concur with the CDTL and Clinical reviewer that no significant safety signals have been identified that preclude approval of this product. Fluid and electrolyte shifts, as well as shifts in renal function, which are known to be associated with colon cleansing products, were observed in this NDA. Class labeling has been developed to address these known adverse reactions and I concur with the reviewers of this NDA that the Suclear label should also carry these warnings. As noted earlier, this NDA did not incorporate safety laboratory evaluations beyond the day of colonoscopy, which is not historically unusual for clinical development programs for bowel cleansing products for colonoscopy. The recently reviewed NDA for Prepopik included trials that incorporated additional monitoring, which documented that in some patients there are even greater shifts in creatinine and eGFR that occur beyond the day of colonoscopy (including new shifts in patients who had not shifted to abnormal on the day of colonoscopy). The active control agents in the Prepopik registration trials were the same active controls for the Suclear trials. The presumed etiology of the creatinine and eGFR changes is volume contraction, perhaps compounded by resuming hypertension medications and/or other medications such as NSAIDs. The contribution of the effects of sedation during colonoscopy can't be excluded. In the absence of follow-up testing in the registration trials for Suclear, it must be assumed that had follow-up examinations been performed, a similar continued deterioration would have been observed in a subset of patients.

Bowel cleansing products are designed to cause diarrhea. They can cause vomiting and volume contraction. A thorough knowledge of each patient's physiological response to a bowel prep could be expected to reveal a variable impact, depending on whether a patient becomes nauseated, vomits, cannot or does not adequately hydrate, has co-existing medical conditions that cause altered renal perfusion or renal function, or takes medications that alter renal perfusion/renal function. There are multiple factors that could influence how an individual patient responds to osmotic catharsis. Sedation for colonoscopy may also cause hypotension, which could negatively impact renal function. Obtaining additional information for further analysis may help identify those patients who are more at risk for having adverse effects associated with colon cleansing. Such information may help identify ways to more effectively provide supportive care during and after bowel preps. The reviewers discussed and agreed that a PMR safety trial should be required to better assess the effects of Suclear on fluid status and serum chemistry (including renal function), as well as to more thoroughly assess the contributing risk factors for these changes. The approval letter will state the following (to address both the fluid and electrolyte issues raised by the clinical trial review, as well as the safety issues related to PEG impurities):

"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 assess a known serious risk of fluid and serum chemistry abnormalities, and the signal of a serious risk related to exposure to toxic impurities (b) (4) associated with the use of Suclear (sodium sulfate, potassium sulfate, and magnesium sulfate oral solution and PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride powder for oral solution)…..Finally, we have determined that 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 following postmarketing requirements under 505(o) will be included in the letter:

1998-6: An adequate randomized, active control, single-blind trial to evaluate renal dysfunction and laboratory abnormalities in patients, including elderly patients, patients with renal impairment, and patients with hepatic impairment taking SUCLEAR prior to colonoscopy. Serial laboratory and clinical assessments should be done at regular pre-specified intervals for at least 30 days post-treatment.

- Final Protocol submission: 06/14
- Trial Completion: 06/16
- Final Report Submission: 12/16

1998-7: Assess the systemic exposure and pharmacokinetics of PEG3350, (b) (4) following oral administration of SUCLEAR to adult subjects. These assessments may be conducted as part of 1998-6 (above).

- Final Protocol Submission: 06/14
- Trial Completion: 06/16
- Final Report Submission: 12/16

9. Advisory Committee Meeting

There was no Advisory Committee convened to discuss this application because::

A) this drug is not the first in its class

B) the safety profile is similar to that of other drugs approved for this indication

C) the clinical study design is similar to previously approved products in the class

D) evaluation of the safety data did not raise significant safety or efficacy issues that were unexpected for a drug of this class

E) the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease

F) outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

The applicant requested a waiver of PREA studies for (b) (4) pediatric ages because it believes that Suclear fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients, specifically NuLYTELY, and is unlikely to be used in a substantial number of (b) (4) pediatric age group(b) (4) The Division consulted PMHS for their assessment of this waiver request and asked that PMHS consider the safety questions that have been raised in recent years regarding use of PEG in children, i.e., consumer reports of neuropsychiatric changes in children after use of PEG as a laxative and metabolic acidosis.

The PMHS reviewers summarized the regulatory record regarding the safety issues that have been evaluated regarding neuropsychiatric changes and metabolic acidosis in their consult. They noted that these issues had been presented to the Drug Safety Oversight Board (DSB) on June 18, 2009, and the presentation included a description of the adverse events, a safety review of the published literature (which didn't identify clinically significant electrolyte or neurologic issues in children exposed to PEG), a summary of practice guidelines [North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition and two clinical references (the Harriet Lane Handbook and Up-to Date) all recommend pediatric use of PEG for constipation], and a review of PEG pharmacokinetic data. The PMHS reviewers summarized the DSB discussion, as follows (quoted from their consult review):

> Metabolic acidosis appears to be associated with lower molecular weight PEGs such as (b) (4) and (b) (4) (b) (4) and (b) (4) are more readily absorbed than higher molecular weight PEG (b) (4)
>
> A wide variability in systemic absorption of PEG was also noted in adults and children.
>
> There are gaps in the knowledge of the molecular weight distribution of PEG products, long term stability of PEG-3350, and systemic exposure of PEG in patients with GI lesions or children with constipation

The PMHS reviewers went on to state, "The Board was split as to whether the 25 reports of neuropsychiatric events represented a safety signal as all the reports were classified as consumer reports and none were verified by health care professionals; several board members advised caution with interpreting any potential safety signal from consumer reports of adverse events when healthcare professionals had not also reported the adverse event. Furthermore, these reports were mostly noted in patients taking MiraLax (14/25) primarily for constipation with the majority of reports (16/25) noting use for over a month. Four adverse events involving metabolic acidosis were reported. The minutes did not mention any use of PEG products for bowel preparation. There was no consensus on recommended labeling changes in the absence of additional data, however, areas warranting further study were proposed, such as safety of one-time vs. chronic use, assessment of associated metabolic or neuropsychiatric safety signals, characterization of the molecular weights comprising PEG products, and evaluation of the 20-40 fold variability in absorption seen between patients….However, three cases noted use of larger volume PEG solutions (2400mL per NG tube, 1 gallon orally and 20mL/kg/hr per NG tube) over 24 hours or less that were associated with metabolic acidosis. Thus, studies are needed to evaluate the safety of larger dose administration of PEG in one-time bowel cleaning regimens, as well as smaller doses of OTC PEG-3350 which are often used chronically to treat constipation."

PMHS concluded that the request for (b) (4) pediatric waiver should be denied; however, they concurred with a partial waiver for patients less than one year of age. They recommended staggered enrollment of the pediatric cohorts, with enrollment of adolescents first. They recommended that systemic exposure of sulfate, PEG, (b) (4) and electrolytes should be assessed in the pediatric studies. Fluid status, vital signs and neuropsychiatric adverse events should be monitored.

The Applicant will be required to conduct pediatric studies under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b)). The deferred pediatric studies will be conducted step-wise, with trials conducted in older cohorts first. Consistent with Divisional decisions regarding the Prepopik NDA pediatric development plan, pediatric trials will be waived in children younger than 1 year of age. The PMHS reviewers were consulted and contributed to development of the pediatric plan that was presented at the Pediatric Review Committee (PeRC) on August 1, 2012. These assessments will be included in the protocols that will be developed for the pediatric studies listed below.

The following pediatric studies will be included in the approval letter as requirements under PREA. The PeRC Committee members concurred with this plan.

1998-1: An open-label pilot study assessing the efficacy and tolerability of Suclear in pediatric patients12-16 years of age, inclusive. This study will include PK assessments.

- Protocol submission: 06/14
- Study completion: 03/15
- Study report submission: 06/15

1998-2: A randomized, single-blind, multicenter, dose-ranging study comparing the safety and efficacy of Suclear (up to 3 doses) versus community standard of care in pediatric patients 12-16 years of age, inclusive.

- Protocol submission: 09/15
- Study completion: 09/16
- Study report submission: 12/16

1998-3: A randomized, single-blind, multicenter, dose-ranging study comparing the safety and efficacy of Suclear (up to 3 doses) versus community standard of care in pediatric patients 3-11 years of age, inclusive.

- Protocol submission: 03/17
- Study completion: 03/18
- Study report submission: 06/18

1998-4: A randomized, single-blind, multicenter, dose-ranging study comparing the safety and efficacy of Suclear (up to 3 doses) versus community standard of care in pediatric patients 1-2 years of age, inclusive.

- Protocol submission: 09/18
- Study completion: 09/19
- Study report submission: 12/19

1998-5: Assess the systemic exposure and pharmacokinetics of PEG-3350, (b) (4) following administration of Suclear in an adequate number of pediatric patients, encompassing all relevant age groups. These assessments may be conducted as part of the PREA required studies listed above.

- Protocol submission: 09/18

- Study completion: 09/19
- Study report submission: 12/19

11. Other Relevant Regulatory Issues

Four clinical sites were inspected by DSI (two from each of the two major trials submitted to support this NDA). The DSI reviewers concluded that the data from the sites appeared reliable and could be used in support of the NDA.

The Applicant provided a signed 3454 form for Certification of Financial Interests and Arrangements of Clinical Investigators denying any financial arrangements with the clinical investigators from the sites that performed the clinical trials Study 301 and Study 302, as defined in 21 CFR 54.2(a).

I concur with the Clinical reviewer and the CDTL that the Combination Policy has been adequately addressed in this NDA. It was determined that a full factorial study could not be required to address the combination rule due to serious ethical concerns because review of the information submitted by the applicant in response to an information request during the review cycle (including a clinical trial of the PEG component of Suclear and a pharmacodynamic study of the PEG component, the sulfate solution component, and a combination of the two) indicated that each component as a stand alone would result in inadequate colon cleansing for colonoscopy. The details of the review that formed the basis for this decision can be found in the Clinical and CDTL reviews. Additional information regarding the PD assessment can be found in the Clinical Pharmacology review.

12. Labeling

DMEPA conducted name reviews and determined that the name, Suclear, was acceptable.

The Clinical Reviewers worked with the reviewers from DMEPA and OMP to assure that the product label, patient instructions for use and the Medication Guide provided adequate clarity to assure that patients understood how to correctly administer Suclear. In addition, the reviewers worked to assure that information regarding the dietary component of the colon cleansing preparation in the information provided to patients in product labeling is appropriate and clear. This review and resulting labeling revisions were guided by the framework of the clinical trial protocols; however, the reviewers noted as they worked to develop clarity in the labeling instructions that consistent handwritten instructions for patients were not part of the protocol documents. This may have contributed to some of the protocol deviations related to food restriction and timing of taking doses described in the Clinical review, which are summarized in the table below. The Clinical reviewer found that most of the food restrictions reported in Study 302 were related to eating solid food.

Table 18: Food Restriction and Preparation Dose Timing Protocol violation summary for Study 301 and Study 302

Protocol violation category Study 301	Suclear n	HalfLytely n	Total n
Patient violated food restriction	19	21	40
Preparation dose time not followed as instructed	3	8	11
Study 302	**Suclear**	**Moviprep**	
Patient violated food restriction	30	10	40
Preparation dose time not followed as instructed	10	11	21

The reviewers also revised product labeling (including patient instructions for use) to clarify that patients should be NPO for two hours prior to colonoscopy.

During the review, the DMEPA Reviewer expressed concern about the cup proposed for inclusion in the packaging. She noted that the fill line may be difficult to see for some patients. The schematic of the cup provided in the instructions for use for patients also lacked clarity. The applicant was contacted about modifying the cup to enhance the external markings to make it easier to see the fill line. Ultimately the applicant submitted information on an alternative cup, which both the CMC reviewers and the patient labeling team found acceptable. The applicant also modified the patient instructions for use to improve the clarity of the schematic.

See other sections of this review and the CDTL review for additional labeling review issues and recommendations.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval
- Risk Benefit Assessment – All review disciplines have recommended approval. Two adequate and well controlled trials have established the efficacy of Suclear for the proposed indication. I agree with the reviewers' recommendation that the product labeling should clearly state that the "Split-Dose (2-Day) regimen is the preferred regimen, since "split dose" regimens are recommended by professional societies for their superior colon cleansing results relative to "day before" regimens. There were no substantive differences in safety between the two dosing regimens that would justify not including the "Day-Before (1-Day)" dosing in labeling for use, if necessary, in patients for whom the "Split Dose (2-Day)" regimen is not considered appropriate.

  The safety profile and serum chemistry changes observed in this application appeared comparable to what has been observed with other marketed bowel cleansing products, and the labeling for Suclear will carry the same warnings as other marketed products.

The changes in creatinine and eGFR observed in the two clinical trials submitted in this application (in both treatment arms) have also been observed in other studies of bowel cleansing products. The trials submitted in this application did not include laboratory assessments beyond the day of colonoscopy. The applicant will be required to conduct a PMR trial to assess fluid and serum chemistry abnormalities associated with use of Suclear, with assessments conducted at pre-specified intervals for at least 30 day post-treatment, as described above in Section 8 Safety. To assess a signal of risk related to presence of toxic impurities (b) (4) associated with the use of Suclear the applicant will be required to conduct a PMR trial to assess systemic exposure and pharmacokinetics of PEG3350, (b) (4) as described above in Section 8 Safety. Consistent with other colon cleansing products intended for use as preparation for colonoscopy, Suclear will be approved with a Medication Guide.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

The reviewers have not recommended a REMS and I concur that there is no reason to require a REMS.

- Recommendation for other Postmarketing Requirements and Commitments

As a condition of approval the Applicant will be required under Section 505(o) of the Federal Food, Drug, and Cosmetic Act to conduct two trials, which can be found in the approval letter and in Section 8 Safety of this review. In addition, the applicant will be required to conduct the pediatric studies under PREA described in Section 10 Pediatrics of this review.

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

/s/

DONNA J GRIEBEL
01/18/2013