CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022372Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	August 5, 2010
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA#	022372
Applicant Name	Braintree Laboratories, Inc
Date of Submission	July 1, 2008
PDUFA Goal Date	August 2, 2009 (initially May 2, 2009; however, clock was extended 3 months due to submission of major amendment)
Proprietary Name / Established (USAN) Name	SUPREP Bowel Prep Kit/ (sodium sulfate, potassium sulfate, magnesium sulfate) Oral solution
Dosage Forms / Strength	Liquid concentrate of sodium sulfate, USP (17.51g), potassium sulfate, FCC (3.13g), magnesium sulfate anhydrous, USP (1.6g) in 170.41 g water per 6 oz bottle
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	Jasmine Gatti, MD
Statistical Review	Milton Fan, PhD/Mike Welch, PhD Benjamin B. Neustifter, PhD/Antonio Paredes, MA, MS/ Aloka Chakravarty, PhD
Pharmacology Toxicology Review	Tamal Chakraborti, PhD/Sushanta Chakder, PharmD
CMC Review/OBP Review	Tarun Mehta, PhD/Marie Kowblansky, PhD
Clinical Pharmacology Review	Jane Bai, PhD/Sue-Chih Lee, PhD
DDMAC	Shefali Doshi
DSI	Khairy Malek, MD Constance Lewin, M.D, MPH
CDTL Review	John Hyde, PhD, MD
OSE/DMEPA	Anne Crandall, PharmD
OSE/DRISK	Melissa Hulett, MSBA, BSN, RN Shawna Hutchins, MPH, BSN, RN Barbara Fuller, RN, MSN
Division of Cardiovascular and Renal Products	Melanie Blank, MD/Norman L Stockbridge, MD, PhD
Office of Pharmaceutical Science	Vinayak. B. Pawar, Ph.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK= Division of Risk Management
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

1. Introduction

The applicant proposes Suprep Bowel Prep Kit for use as a bowel cleanser prior to colonoscopy. It consists of a carton that contains two equal doses (6 oz) of 17.5 g sodium sulfate, 3.13 g potassium sulfate and 1.6 g magnesium sulfate in each of the 6 oz bottles. The bottled solutions are further diluted before the patient drinks them. The applicant proposes (b) (4) dose schedules. (b) (4) studied in phase 3 clinical trials. In the "Split dose" regimen the patient dilutes the contents of one of the 6 oz bottles to 16 oz, drinks the diluted solution (b) (4) and follows with two additional 16 oz "cups" of water (b) (4). The sequence is then repeated with the second 6 oz bottle, 12 hours after the first dose. (b) (4)

The proposed product is a cathartic agent that produces its effect by exposure of the bowel lumen to a hyperosmolar solution. There are other approved hyperosmolar solution products available, including oral sodium phosphate products. (See summary in Section 2 Background below.) In addition there are combination products of salts combined with polyethylene glycol (PEG). Suprep is unique in that it contains no phosphate salts. The osmotic ions in Suprep are all in sulfate form. The phosphate salt products have been the subject of class labeling for renal impairment. Recently the Division has required that the manufacturers of phosphate salt products conduct a safety study to evaluate the risk of developing acute kidney injury in patients undergoing bowel cleansing. (See Background Section below.) The applicant proposes that Suprep will be a safer bowel prep product because it doesn't contain phosphate salts. There are other currently marketed bowel prep products that contain sulfate salts, but the amount in Suprep is higher. The applicant proposes that sulfate salts will be safer, even at the higher doses present in Suprep, because the total amount present will not crystallize in the body.

The major review issue for this NDA is the adequacy of the data to support the safety of this new product. The review disciplines have recommended approval, but the CDTL has voiced concerns that the safety of Suprep has not been adequately studied to determine its full safety profile. He has recommended against its approval to allow for further large safety studies to be conducted. I have evaluated his concerns in the context of the reviews of the other FDA reviewers and his supporting arguments. These concerns were also discussed at a regulatory briefing. I do not agree that approval of the application should be delayed until further safety studies have been conducted. There might be a safety advantage for this product over the phosphate salt bowel prep products, but the submitted data cannot support such a comparative claim. I did not find a safety signal in the head to head comparison of Suprep administered in the "Split dose" regimen to a marketed bowel prep that should preclude approval of Suprep at this time. However, I have concerns about the tolerability of the "Same day/evening only" regimen and have concluded that that regimen should not be approved. In my discussions

with the CDTL, I have concluded that he expects to utilize the additional safety data being sought from the premarketing studies he recommended to enhance labeling. I have determined that those additional safety studies should be conducted as post marketing required studies under FDAAA and that the labeling can be changed to reflect the findings in the studies when the data are submitted and reviewed. I agree with the CDTL's recommendations that the Suprep labeling should include similar Warnings and Precautions to those of the phosphate salt cathartics, because osmotic catharsis can cause fluid and electrolyte shifts that may result in severe dehydration, seizures, renal injury and cardiac adverse events. In light of those risks, I have recommended a Medication Guide to clearly inform patients of the risks of fluid and electrolyte disturbances that can lead to serious adverse events, including cardiac arrhythmias, seizures and renal impairment. The Medication Guide will inform patients of signs and symptoms of severe volume contraction and potential electrolyte abnormalities that should prompt them contacting their health care provider. In addition the Medication Guide will reinforce the importance of ingesting plenty of fluids during the bowel preparation process, and will educate patients that they should inform the prescriber if they are taking specific medications that could increase the risk of severe volume contraction and/or electrolyte abnormalities.

2. Background

There are a number of osmolar cathartic agents marketed for bowel prep before colonoscopy and/or surgery. The contents of those agents are summarized in the table below to facilitate a comparison of the specific salt content between Suprep and the approved products. The total sulfate exposure with Suprep exceeds that of the other approved products that contain sulfate, double that of the other products. Suprep does not contain phosphate salts. Suprep is unique in that it contains magnesium (3.2 grams of magnesium sulfate is equivalent to 27 mmoles of magnesium per total dose/treatment). A course of treatment with Suprep is also associated with a higher dose of potassium than the other products that contain potassium salts. The other products contain potassium in the chloride salt form, whereas Suprep contains potassium sulfate. The mEquivalent (mEqu) dose of potassium in the Suprep product for the entire treatment (72 mEqu of potassium) is nearly twice that of the highest potassium dose in approved products, Colyte and Golytely, which provide potassium 40 mEqu. The potassium content of the active comparator in the phase 3 trials that support this application, Moviprep, is 27 mEquivalents. Moviprep contains no magnesium salts.

Table 1: Summary of Approved Products and Ion Content

Drug Name	Content	Indication
Suprep *treatment consists of ingestion of 2- 6 oz bottles*	*Per total 12 oz dose* **Sodium Sulfate, 35.02g** Potassium **Sulfate** 6.26 g (2.8g or 72 mEqu K) Magnesium **Sulfate** 3.2 g (2.66 mMoles) Sodium Benzoate, (b) (4) ***sulfate = 312 mmol/ 12 oz dose***	colonoscopy
Oral Sodium Phosphate Preps		
Visicol *treatment consists of*	*Per tablet* Sodium Phosphate	Colonoscopy

Drug Name	Content	Indication
ingestion of 40 tablets	monobasic monohydrate 0.398 g dibasic anhydrous, 1.5 g	(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	
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 (40 mEqu K) PEG-3350, 240g ***sulfate = 320 mEq/4L dose (labeled)*** ***160 mmol/4L dose***	Colonoscopy, Barium enema
GoLytely *Treatment consists of ingestion of a 4 liter solution*	*Per total 4 liter dose, jug/packet* **Sodium Sulfate, 22.74 g/21.5g** Sodium Chloride, 5.86 g/5.53 g Sodium Bicarbonate, 6.74 g/6.36 g Potassium Chloride, 2.97g/2.82 g (40 mEqu K) PEG-3350, 236g/227.1 g ***sulfate = 160 mmol/ 4 L dose in a jug***	Colonoscopy, Barium enema 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 (20 mEqu K) 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 (27 mEq K) PEG-3350, 200g Sodium Ascorbate, 11.8 g Ascorbic Acid, 9.4 g ***sulfate = 105.6 mmol/ 2 L dose***	Colonoscopy Last lab day of colonoscopy

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 oral sodium phosphate 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 FDA had issued a Science Paper in 2006 and a Healthcare Professional sheet describing the risks associated with use of oral sodium phosphate products for bowel cleansing. Since May 2006, the FDA received reports of 20 unique cases of kidney injury associated with the use of Osmoprep, of which 3 were biopsy-proven cases of acute phosphate nephropathy. The onset of kidney injury in the cases varied from within several hours of use to up to 21 days after use. In addition, observational retrospective cohort studies were published that reported an increased risk of acute kidney injury in patients undergoing bowel cleansing using oral sodium phosphate products, as defined by changes in serum creatinine.[1,2,3,4]

The development plan and preparation for the Suprep NDA included an end-of-phase 2 (EOP2) meeting on March 26, 2007 and two Special Protocol Assessments (SPAs) submitted April 10, 2007. The original phase 3 trial designs discussed at the EOP2 meeting included a (b) (4) active control arm. The Division of Gastroenterology Products' (DGP) recommendations at the meeting included:

1) Follow-up at 1, 3 and 6 months to assess for acute phosphate nephropathy associated with the active control arm.
2) Inclusion of subpopulation studies of geriatric and high risk patients with cardiac disease in the phase 3 trials.
3) Pharmacokinetic studies to evaluate electrolytes and sulfate in patients with hepatic and renal disease.

In light of the recommendation for prolonged follow-up to assess acute phosphate nephropathy, the applicant proposed changing the active control arm to Moviprep, which does not contain sodium phosphate. The design of the studies submitted for SPA review compared Suprep to MoviPrep. The FDA stated that follow-up limited to 30 days post procedure was "acceptable".

[1] Hurst, F, et al. Association of oral sodium phosphate purgative use with acute kidney injury. J Am Soc Nephrol 18: 3192-3198; 2007.
[2] Brunelli SM, et al. Risk of kidney injury following oral phosphosoda bowel preparations. J Am Soc Nephrol 18:3199-3205; 2007
[3] Markowitz GS, e al. Towards the incidence of acute phosphate nephropathy. J Am Soc Nephrol 18: 3020-3022; 2007
[4] Russmann, S, et al. Risk of impaired renal function after colonoscopy; a cohort study in patients receiving either oral sodium phosphate or polyethylene glycol. Am J Gastroenterol 102: 2655-2663, 2007.

Timing of follow-up in the clinical trials that supported approval of marketed cathartics is discussed later in this review. Only one NDA was identified that evaluated patients after the day of colonoscopy, and in that NDA the follow-up was limited to 2-3 days after colonoscopy. The trials submitted to support Suprep do not include a 24-48 hour post colonoscopy interim laboratory evaluation between the day of colonoscopy and the Day 30 visit. The Day 30 visit does provide an opportunity to evaluate whether abnormalities detected on the day of colonoscopy have resolved.

Sulfate is an anion present in abundance in human serum. Its concentration ranges 0.3-0.5 mM. (Krick W, Schnedler N, et al. Am J Physiol Renal Physiol 297: F145-F154, 2009). The Veterans Administration Normative Aging Study found that study participants' serum sulfate levels ranged from 0.21 mM to 0.51 mM over a course of 33 years of follow-up. The mean and median sulfate levels rose with age.[5] Sulfate's biological functions include biotransformation and detoxification of xenobiotics and conjugation of bile acids for excretion. It is absorbed in the small intestine, filtered through the glomerulus, and in light of its physiological importance, is actively reabsorbed in the kidney's proximal tubule. Dramatic increases in serum sulfate levels have been documented in humans after ingestion of a high protein meal.[6]

A component of magnesium sulfate, there is substantial clinical experience with intravenous doses of sulfate (as MgSO4) in prevention and control of seizures in patients with preeclampsia or eclampsia with pregnancy. Doses used historically have varied, but recommended doses include a loading dose of 4-6 g of MgSO4 infused over 20 minutes followed by continuous infusion of 2g/hour. The product label for magnesium sulfate (heptahydrate, $MgSO4 \cdot 7H2O$; molecular weight 246.48) states that the IV injection should "generally not exceed 150 mg/minute, except in severe eclampsia with seizures." In eclampsia the "total initial dose is 10 to 14 g….Intravenously, a dose of 4-5g…may be infused. Simultaneously, intramuscular doses of up to 10 g …are given. Alternatively, the initial intravenous dose of 4 g may be given….injected intravenously over a period of 3 to 4 minutes. Subsequently 4 to 5 g …. are injected intramuscularly into alternate buttocks every 4 hours, depending on the continuing presence of the patellar reflex and adequate respiratory function. Alternatively, after the initial IV dose, some clinicians administer 1 to 2 g/hour by constant IV infusion. ….A total daily dose of 30 to 40 g should not be exceeded. In the presence of severe renal insufficiency, the maximum dosage of magnesium sulfate is 40 g/48 hours."

Based on the molecular weight of MgSO4 heptahydrate, the 14 g loading dose for eclampsia is equal to 57 mmol of SO4; the 5 g dose is 21 mmol; the 2 g dose is 8 mmol. (If the molecular weight of MgS04 only is utilized, i.e., without the 7 water molecules, the mmol MgS04 per dose doubles.) A 14 g loading dose followed by 2g/hour would equal 241 mMol over 24 hours of the heptahydrate molecular weight product. This exposure can be compared to the

[5] Blinn CM, Dibbs ER, et al. Fasting Serum Sulfate Levels Before and After Development of Osteoarthritis in Participants of the Veterans Administration Normative Aging Longitudinal Study Do Not Differ From Levels in Participants in Whom Osteoarthritis Did Not Develop. Arthritis and Rheumatism. Vol 52, No. 9, 2005: 2808-2813.

[6] Tallgren LG. Inorganic sulphates in relation to the serum thyroxine level and in renal failure. Acta Med Scand 1980;S640:34-44.

312 mmol of sulfate exposure in a full dose of Suprep; however, Suprep is not 100% absorbed. Magnesium sulfate infusions in the setting of eclampsia/preeclampsia are titrated to keep serum magnesium concentrations in the range of 4-8 mg/dL[7]. Elevated baseline sulfate levels have been reported in patients with preeclampsia (0.85 mM), and serum levels were documented to rise further to 1.4 mEq/L or 2.8 mM/l after administration of intravenous magnesium sulfate for eclampsia.[8]

Magnesium sulfate infusions have been studied as a therapeutic intervention for subarachnoid hemorrhage. Doses in this setting include a bolus of 16 mmol, followed by a continuous infusion of 8 mmol/hour. Infusions were adjusted to maintain serum magnesium levels of 2.0-2.5 mmol/L. If the level fell below 2.0 mmol/L, the infusion rate was increased by 1 mmol/hour. Infusions continued over 10 days, followed by a taper over 12 days. Authors have concluded that this regimen is safe. [9] Magnesium sulfate infusions have also been studied in treatment of patients with tetanus. In one publication patients were administered 70 mg/kg MgSO4 intravenously over 30 minutes followed by an infusion of 2 g/hour, which was increased by 0.5 g/hour every 6 hours until spasms ceased. [10] Mean duration of therapy in 33 patients was 19.5 days. Conduction disturbance and hypocalcemia reported in this trial were attributed to known effects of magnesium infusions.

3. CMC

I concur with the conclusions reached by the chemistry reviewers and the microbiology reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

The chemistry, DMEPA and clinical reviewers discussed the nomenclature of the dosage form of the product. USP monograph examples suggested that the product dosage form should be referred to as "oral solution". However, because the product requires further dilution for use there was concern that the nomenclature should include the word (b) (4), which is not consistent with USP nomenclature. The chemistry reviewers asked the clinical reviewers for their opinion regarding use of (b) (4) and the clinical reviewers did not feel there would be a safety issues associated with use of the USP conforming "solution" instead of the applicant's proposal to use the word (b) (4) The applicant was asked to change the nomenclature to "solution" to conform with USP.

[7] McCoy S and Baldwin K. Pharmacotherapeutic options for the treatment of preeclampsia. Am J Health-Syst Pharm. 2009; 66:337-44.
[8] Ricci J, Oster JR et al. Influence of magnesium sulfate-induced hypermagnesemia on the anion gap: role of hypersulfatemia. Am J Nephrol. 1990; 10(5):409-411.
[9] Westermaier T, Stetter C, et al. Prophylactic intravenous magnesium sulfate for treatment of aneurismal subarachnoid hemorrhage: A randomized, placebo-controlled, clinical study. Crit Care Med 2010 Vol. 38, No. 5:
[10] Mathew PJ, Samra T,, Wig J. Magnesium sulphate for treatment of tetanus in adults. Anaesth Intensive Care 2010; 38:185-189.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. I concur with the reviewers' recommendations for product labeling.

Dr. Chakraborti points out in his review that the pharmacodynamic action of Suprep relies on retention of water in the intestine, which is accomplished by the osmotic components of the product. He notes that sulfate and magnesium are the principal osmotic components of the product and that both are poorly absorbed, leading to water retention within the intestinal lumen.

Salient nonclinical findings that impacted the clinical safety discussion of the adequacy of the submitted clinical safety data included the electrolyte and renal findings in rats and dogs. Suprep was administered to rats and dogs in 28 day daily oral administration studies. (The clinical dose in humans will be administered at a maximum of 2 doses over 24 hours.) The maximum dose of Suprep studied in both rats and dogs in the 28 day studies was 5.0 g/kg, which was the maximum dose that could be delivered based on the ability to dissolve the product in a volume of water that the animals could ingest orally. The amount of Suprep administered in each daily dose in rats was 0.9 times the human dose and the daily dose in dogs was 3 times the human dose. The animals experienced diarrhea, vomiting (dogs), and excessive water drinking (dogs). In both rats and dogs electrolyte abnormalities included hypochloremia, hypokalemia, hyponatremia, reduction in serum osmolality, increases in urine sodium and potassium, alkalinization of the urine and increases in serum bicarbonate.

The 28 day rat study was designed with a oral sodium phosphate (OSP) control arm. The oral sodium phosphate control dose was 5.13 g/kg. All animals administered Suprep survived to Day 28; however 15/20 OSP treated animals died, nearly evenly divided between males and females. One died in the first seven days of the study (Day 6), 7 in the second week, 5 in the third week, and 2 in the last week. Deaths were attributed to renal insufficiency. Tubular degeneration was observed in the kidneys of all rats treated with OSP, and was severe in 2/10 males and 4/10 females. It was graded moderate in 8/10 males and 5/10 females. Mineralization of the kidney was noted in all OSP treated rats. It was graded as severe in 5/10 males and 4/5 females, and moderate in 5/10 males and 5/10 females. Mineralization was also observed in the stomach and aorta from rats treated with OSP. Two of 10 males had mineralization in the aorta and 1/10 females. Myocardial degeneration was observed in OSP treated rats, 7/10 males and 9/10 females. It was graded severe and moderate in 0 and 4 male rats, respectively, and 2 and 1 female rats, respectively. In contrast, there was no tubular or myocardial degeneration observed in any of the rats administered Suprep. However, histological examination revealed mild mineralization in the kidney of one female rat who received vehicle, and minimal mineralization in one female rat treated in each of the 2.5 g/kg and 5.0 g/kg Suprep groups.

The serum and urine chemistry results on Day 28 for each dose arm of this rat study, including the oral sodium phosphate control arm, are summarized in tabular form in Dr. Chakraborti's review. It should be noted that many of the animals treated on the OSP arm died before Day

28, so the values presented in the table for the OSP group represent a small minority of the OSP treated animals. Differences were observed between the Suprep and OSP treated animals, and between males and females treated with Suprep. Serum phosphate levels were nearly 3 times higher in OSP treated males than the Suprep animals, however, OSP treated females had levels similar to the Suprep animals. Serum calcium levels in OSP treated males were markedly lower than Suprep treated animals (males and females) (7.2 vs. 10.9-11.3). OSP treated females also had lower serum calcium, but not as numerically low as the males (9.9). There appeared to be a dose response trend in reduction in chloride and potassium with increasing doses of Suprep, with the levels in the 5.0 g/kg animals reaching the levels observed in the OSP treated animals. There was a trend for increasing serum bicarbonate levels with increasing doses of Suprep. Serum osmolality was higher in OSP treated males than Suprep males, but the levels in females were similar between groups.

The Cardiorenal consultant evaluated these data in her review and stated that "Suprep caused diarrhea, electrolyte and metabolic changes, including hypochloremia, hypokalemia, hyponatremia and lower serum osmolality, higher urine sodium and potassium, alkaline urine and high serum bicarbonate indicative of metabolic alkalosis."

The BUN in males treated with OSP was nearly double that of Suprep treated males and vehicle control. The BUN in OSP treated females that survived to Day 28 did not differ from the vehicle control treated females. No increase in serum creatinine was observed in the study, except for males treated with OSP who survived to Day 28.

Urine sodium levels on Day 28 increased in what appears to be a dose related trend with increasing doses of Suprep. Urine pH increased only in the highest Suprep dose evaluated, in both males and females. The urine pH was not elevated relative to vehicle control in the OSP animals that survived to Day 28.

Urine creatine levels dropped in a dose related fashion with increasing Suprep doses in both males and females, starting with the 2.5 g/kg dose level in both sexes. Creatinine clearance also appeared to drop off in a dose related fashion with increasing dose, starting at the 2.5 g/kg dose level of Suprep in males and at the 5 g/kg dose level in females. "Sodium clearance" increased in a dose related fashion across all Suprep treated animals, starting at the lowest dose studied. The fractional excretion of sodium, which incorporates the urine and serum creatinine levels in the calculation, also showed a dose response in both males and females treated with Suprep. The fractional excretion of sodium is summarized in the table below, which is a modification of Text Table 6 from Dr. Chakraborti's review.

Table 2: Fractional Excretion of Sodium in Rats Administered Sulfate Cathartic

	Males				Females			
Dose/day	0 g/kg	1.25 g/kg	2.5 g/kg	5.0 g/kg	0 g/kg	1.25 g/kg	2.5 g/kg	5.0 g/kg
	0.04	0.25	0.64	1.56	0.16	0.47	1.24	2.80

In OSP treated animals that survived to Day 28, the fraction excretion of sodium was 7.61 in males and 2.52 in females.

In humans, fractional excretion of sodium (FENa) can be utilized to evaluate patients with oliguria (urine output <500 cc/24 hours) to determine the differential diagnosis for the underlying etiology of oliguria. Patients with prerenal azotemia (e.g., dehydration, congestive heart failure, sepsis) generally have low FENa (<1%). Conversely, in patients with acute tubular injury, the FENa is higher (>1%). However, it should be noted that in patients with hepatorenal syndrome or acute glomerulonephritis, the FENa may also be low (<1%). Therefore, use of FENa should not be used to distinguish between acute renal injury and prerenal azotemia when these conditions are suspected.[11]

Dogs demonstrated increased urine pH and increase in "sodium clearance rate". The Day 28 sodium clearance values in vehicle treated males and females dog were 0.009 and 0.006, respectively. For male and female dogs administered 1.25 g, 2.5 g and 5.0 g/kg of the sulfate solution product, an increase in "sodium clearance" was observed, but there was no clear dose response. Sodium clearance in the vehicle treated dogs increased from pre-study treatment to Day 28, tripling in males and doubling in females. See table below which is a modified reproduction of Text Table 3 in Dr. Chakraborti's review:

Table 3: Sodium Clearance on Day 28 in Dogs Administered Sulfate Cathartic

	Males				Females			
Dose	0 g/kg	1.25 g/kg	2.5 g/kg	5.0 g/kg	0 g/kg	1.25 g/kg	2.5 g/kg	5.0 g/kg
Day 28	0.009	0.017	0.010	0.022	0.006	0.021	0.024	0.019

There were no significant organ toxicities detected in dogs.

5. Clinical Pharmacology

The Clinical Pharmacology review found the application acceptable for marketing approval as long as labeling recommendations were adequately addressed.

There were two clinical pharmacology studies submitted for review:

Study BLI800-101 – compared an experimental Suprep formulation to Fleet Phosphosoda as a positive control to compare the effects on fecal parameters, blood electrolytes and symptoms in 18 healthy male volunteers. Cathartic doses were separated by 12 hours, and at each of the two administration time points, the product dose was split into 3 doses and ingested by the subjects every 15 minutes.

Study BLI800-202 – a safety and PK study of a "Split dose" of Suprep administered in doses separated by 12 hours to healthy volunteers and patients with mild-moderate hepatic impairment.

The pharmacokinetics of the "Evening Only, One-day Regimen" (b) (4) studied in efficacy trial Study 301, was not evaluated with the to be marketed formulation. The

[11] http://www-users.med.cornell.edu/~spon/picu/calc/fenacalc.htm. Steven Pon, MD. Weill Medical College of Cornell University. Pediatric Critical Care. Medical Calculators. FENa Calculator.

Clinical Pharmacology reviewer considered the second study, BLI300-202, the most important of the two studies. I will briefly present the data from Study BLI800-101.

BLI300-101

Study BLI300-101 was conducted to compare the effects of an earlier Suprep formulation (BLI800-1, OSS in table below) with commercial Fleet Phosphosoda. The Suprep formulation studied differs from the to-be-marketed Suprep product in the relative distribution of the cation content, but Dr. Bai notes in her review that the total amount of sulfate present is identical between the formulation studied in this clinical pharmacology study and the to be marketed formulation. The sodium and potassium content is somewhat higher in the to-be-marketed formulation, and the magnesium content is lower. See summary comparison below, reproduced from Dr. Bai's review:

Comparison of the Total Sulfate Salts Content
Experimental BLI800-101 and the To-Be-marketed Product

	Amount (G)	
Sulfate	BLI800-101 (OSS) (b) (4)	To-be marketed Product
Na_2SO_4		35.02
$MgSO_4$		3.2
K_2SO_4		6.26

The mean age of the healthy male subjects in Study BLI300-101 was 22-27 years; median age was 22-24 years.

The product administration schedule in the oral sulfate solution Group 2 (OSS Group 2) was "split" by 11 hours, which approximates the **"Split-Dose (Two-Day) Regimen"** (b) (4) and studied in the efficacy trial Study 302). The first dose in OSS Group 2 was administered at 7 PM and the second dose administered at 6 AM. The sulfate solution Group 3 (OSS Group 3) received all doses of the sulfate solution in the evening, starting at 7 PM and finished with last dose at 8:15 PM. Water consumption was allowed ad lib in the study arms until approximately 6 hours after the second scheduled administration period.

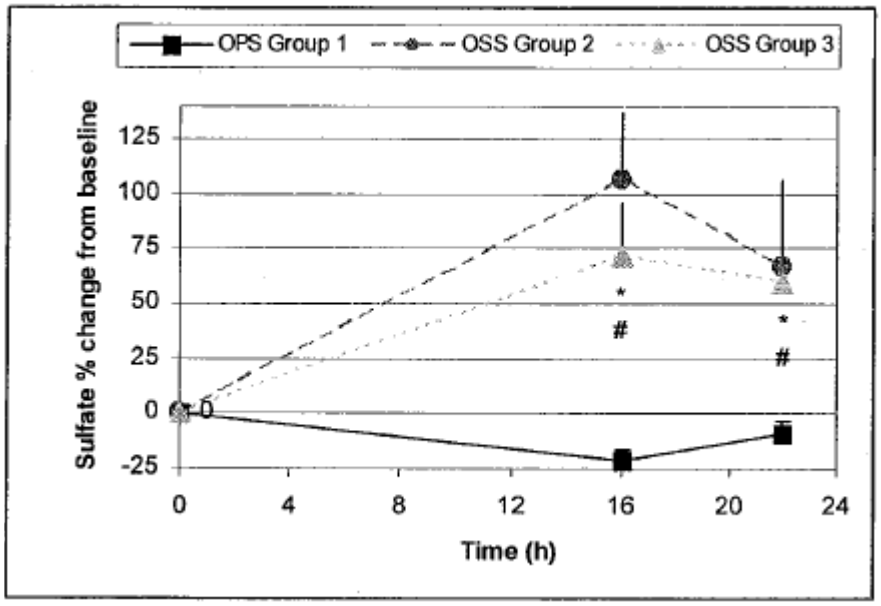
The blood samples were drawn at fixed times, which were the same for all groups, despite the variation in dosing regimen – 16 hours post the first dose and 22 hours post the first dose. For this reason, the 16 hour laboratory draw for OSS Group 2 ("Split dose" regimen) was obtained approximately 5 hours after starting the second half of the regimen, and for the OSS Group 3 ("Evening only/same day" regimen) the 16 hour blood sample was drawn **approximately 15 hours** after the last dose taken the evening before. Likewise, the 22 hour blood sample represents serum chemistry 11 hours after starting the second half of dosing in the split dose Group 2, and it reflects chemistry approximately **21 hours after the last dose in the** PM only sulfate solution group 3. This is summarized in the Table below.

Table 4: Correlation of Scheduled Blood Sampling Times with Time after Last Dose

	Split dose Regimen	Single Dose Regimen (Evening only)
Scheduled Blood Sample	Time after Second Dose	Time after Completing PM Dose
16 h after start of 1st dose	5 hours	15 hours
22 h after start of 1st dose	11 hours	21 hours

The percent change in serum sulfate at the assessment time points is presented in the figure below, which is reproduced from the Clinical Pharmacology review (OPS Group 1 = oral sodium phosphate, OSS Group 2 = "Split dose", OSS Group 3 = "Same day/evening only" regimen).

Figure 1: Post Initiation of Dosing Mean % Change in Serum Sulfate



Time to first bowel movement was 1.5-1.7 hours in the sulfate solution formulation arms. Change from baseline of serum electrolytes at 16 hours and 22 hours after the first dose was evaluated and the data are summarized in the table below. (OPS is the control arm, oral sodium phosphate product.)

Table 5: Percentage Change from Baseline in Selected Electrolytes By Time from Initiation of Dosing

	Mean changes from baseline for serum electrolyte concentrations (%)						p < 0.05	
	OPS Group 1		OSS Group 2		OSS Group 3			
	T = 16 hr	T = 22 hr	T = 16 hr	T = 22 hr	T = 16 hr	T = 22 hr	16 hr	22 hr
Ca (mmol/L)	-2.85	-1.86	0.78	-1.15	1.83	-1.60	* #	-
Ca x P (mg^2*dl^2)	25.0	18.3	-7.93	4.88	-5.72	5.84	* #	-
Cl (mmol/L)	-1.75	-0.44	-1.28	-0.96	-0.97	-0.15	-	-
HCO_3 (mmol/L)	-8.90	-1.44	-5.53	-3.97	-5.50	-0.86	-	-
K (mmol/L)	-5.12	-6.91	0.82	1.22	4.77	3.95	# $	#
Mg (mmol/L)	-6.28	1.41	-0.75	3.28	-0.63	5.28	* #	-
Na (mmol/L)	0.84	0.25	0.97	-0.72	-0.35	-0.24	-	-
PO_4 (mmol/L)	28.7	20.4	-8.76	5.96	-7.38	7.64	* #	-
SO_4 (mg/dL)	-21.0	-8.60	106	66.6	71.5	59.7	* #	* #

In light of the variation in time from completion of last dose to the time of obtaining blood samples between the two dosing regimens, changes over time in the impact of sulfate solution on other electrolytes were explored by examining relationships with time from last dose of Suprep in each regime. This is presented in the table below.

Table 6: Percentage Change from Baseline Over Time From Last Dose Across Sulfate Treatment regimens

Time of Blood Sample Relative to Ingestion of Last Suprep Dose	5 h	11 h	15h	21h
Regimen	(Split dose)	(Split dose)	(Same day)	(Same day)
Calcium	+0.78 %	-1.15 %	+1.83 %	-1.60 %
Magnesium	-0.75 %	+3.28 %	-0.63 %	+5.28 %
Chloride	-1.28 %	-0.96 %	-0.97 %	-0.15 %
Bicarbonate	-5.53 %	-3.97 %	-5.50 %	-0.86 %
Potassium	+0.82 %	+1.22 %	+4.77 %	+3.95 %
Sulfate	+106 %	+66.6 %	+71.5 %	+59.7 %

These data are interesting because, as shown in the graphic of the sulfate concentrations over time above (Figure 1), the percentage increase over baseline in sulfate levels in the "Split dose" and "Same day/evening only" regimens are not that dissimilar, despite the fact that the first assessment point corresponds to the approximate Cmax for the "Split dose" subjects (see description of study BLI800-202 below) and 15 hours out from the last dose in the "Same day/evening only" regimen subjects. Similarly, the second assessment point, subjects in the "Same day/evening only" regimen group had nearly the same level of increase at 21 hours after their last dose as the subjects in the "Split dose" regimen subjects who were only 11 hours out from their last dose. The application lacks a complete pharmacokinetic evaluation of the "Same day/evening only" regimen, but that dosing regimen would be expected to give a higher Cmax of sulfate. It also appears in this pharmacodynamic study to be associated with higher sulfate exposures over a similar time period, relative to the "Split dose" regimen.

If the data for the other electrolytes are reordered to correspond to the level of percentage increase of sulfate (instead of the timing of sample), a pattern of correlation with the sulfate level appears for chloride and bicarbonate. Sulfate is an acidic ion and can impact acid base balance. The impact seems to have nearly resolved in this dataset when the percentage increase in sulfate declines to 59%. The increases in serum calcium correlate with decreases in magnesium. The decline in serum magnesium tracks with the changes in the two highest incremental increases in sulfate, 106% and 71.5% (which track with serum bicarb and chloride). Causes of hypomagnesemia include gastrointestinal losses and metabolic acidosis. The calcium increases are noted at the two highest serum sulfate levels, which are from the earliest time points of assessment in each treatment regimen, 5 hours (split) and 15 hours (same day), and then flip at the lower incremental levels of sulfate. In the safety dataset from the phase 3 trials, hypercalcemia was seem most commonly in the patients treated with "Split dose" Suprep. The median time to serum chemistry assessment in the phase 3 trials was 5.7 hours in the "Split dose" trial and 13.75 hours in the "Same day" regimen trial, which is similar to the first lab assessment timing for the two regimens in Study BLI300-101.

Table 7: Percentage Change from Baseline in Electrolytes Orderd by Decreasing Sulfate Documented Increments of Sulfate Levels at 4 time points in Study BLI300-101

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

Dr. Bai notes in her review that although serum bicarbonate levels decreased in all treatment groups, none fell below the lower limit of normal. Likewise, none of the potassium or sodium levels fell outside the range of normal. Calcium levels increased slightly, followed by a decline. The only electrolyte documented outside the range of normal in any subject treated with the sulfate prep was phosphate (1 high phosphate in the "Split dose" group and 2 high phosphates in the "Same day/evening only" group), all observed at 22 hour blood sample.

Serum, urine and fecal sulfate levels were analyzed. Fecal sulfate in the oral sulfate solution groups ranged from 314 to 509 mEq. The applicant calculated that approximately 70% (67.7 ± 8.6 % in Group 2 "split dose" and 71.6 ± 11.2% in Group 3 single administration) of administered sulfate was recovered in the feces within 17 hours after initiation of dosing. It is estimated that about a third of the sulfate load in this product is absorbed. There are sulfate ion transporters present in the intestinal tract, liver sinusoids, and kidney.

Study BLI800-202

Six healthy subjects (2 males, 4 females) completed this study, which evaluated the to-be-marketed Suprep product administered in the "Split dose" regimen schedule. There were also

five study participants with Child Pugh A hepatic impairment, one with Child Pugh B hepatic impairment, and 6 with renal impairment. Predose sulfate levels are summarized below.

Table 8: Predose Sulfate Levels Study BLI800-202

	Healthy Subjects	Renal Impairment	Hepatic impairment
Serum level µmol/L (CV%)	335 (34%)	607 (32%)	407 (13%)

The sulfate pharmacokinetic parameters, corrected for baseline sulfate levels, are summarized in the table below, which is reproduced from Dr. Bai's Clinical Pharmacology review. The highest AUC and Cmax occurred in patients with renal impairment. Patients with hepatic impairment had higher AUC and Cmax than healthy subjects, but shorter half-life.

Table 9:

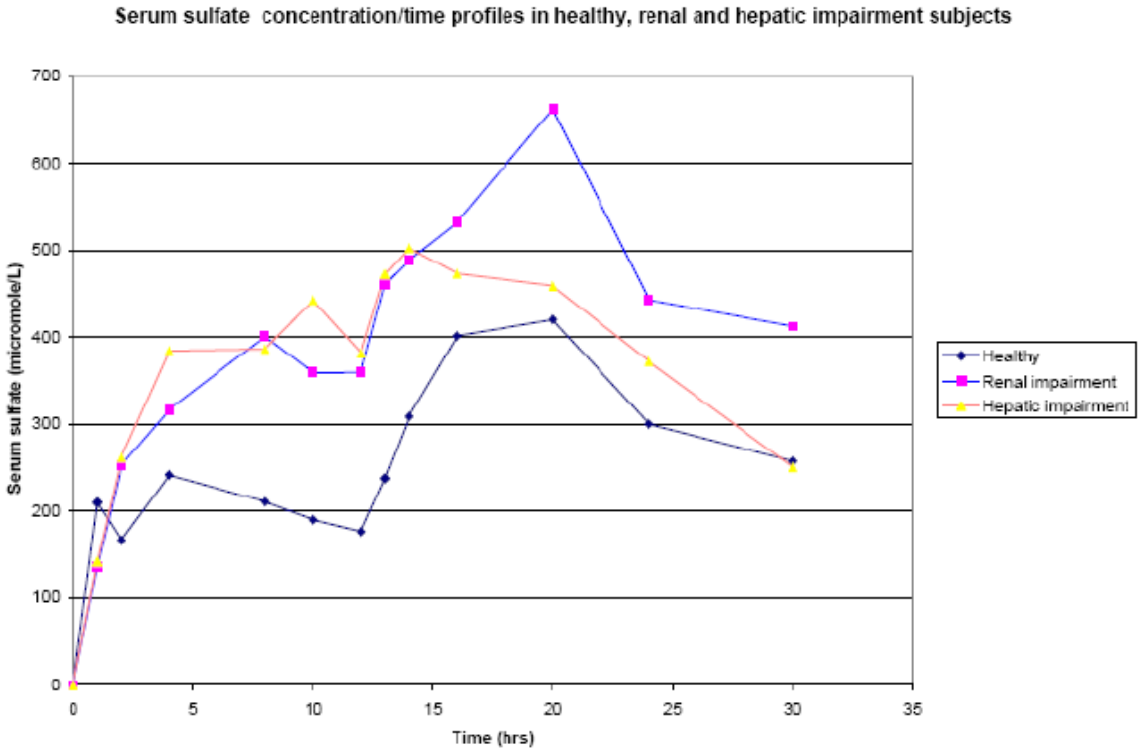
Mean (CV%) sulfate PK parameters (corrected for pre-dose sulfate level)

	Mild/moderate hepatic impairment	Healthy subjects	Moderate renal impairment
Cmax (µmol/L)	560.2 (27.27%)	499.50 (33.03%)	717.0 (37.77%)
AUC(0-tau) (µmol*hr/L)	10751.75 (26.77%)	8,029.88 (42.65%)	12,332.95 (34%)
Tmax (hr)	14.2 (35.27%)	16.80 (48.47%)	17.5 (16.85%)
T1/2 (hr)	5.58 (41.36%)	8.51 (53.76%)	10.16 (91.76%)

Note: N=6 for each group; AUC(0-tau): AUC over the 24-hr post dose.

Higher exposure in patients with renal impairment was anticipated since sulfate is primarily cleared via the kidneys. The sulfate pharmacokinetic parameters were highly variable. The following graphic (from Dr. Bai's review) shows that 30 hours after initiating dosing, which corresponds to18 hours after starting the second half of the Suprep dose, sulfate levels in healthy volunteers have not returned to baseline, but have dropped approximately 40% from the Cmax. The graphic also demonstrates that at the time of administration of the second half of the dose, at hour 12, the sulfate level had dropped approximately 30% from the peak level after the first dose. (Note that the graphic below presents sulfate levels corrected for pre-dose sulfate levels so that the baseline level appears to be zero.)

Figure 2:



Serum sulfate levels declined to predose levels by Day 6 in all 3 groups. The coefficient of variation was high relative to baseline. Serum sulfate levels over time are summarized in the table below:

Table 10: Serum Sulfate Concentrations (µmol/L) in Study BLI800-202 with Coefficient of Variation (%)

	Healthy Subjects	Renal Impairment	Hepatic impairment
Baseline	335 (34%)	607 (32%)	407 (13%)
Day 3	366 (103%)	617 (138%)	391 (52%)
Day 6	349 (90%)	575 (101%)	406 (51%)

Mean urine sulfate concentrations on Day 3 and 6 varied little from baseline levels in all 3 groups, as shown in the table below (reproduced from the Clinical Pharmacology review):

Table 11:

Urinary sulfate excretion

Mean (CV%) urine sulfate concentrations (mg/dL)

	M/MHD	Healthy volunteers	MRD
Predose 1	86.92 (57.63%)	131.2 (35.81%)	607.0 (31.66%)
Day 3	89.83 (75.49%)	145.62 (76.24%)	617.8 (22.37%)
Day 6	70.82 (118.11%)	134.65 (55.49%)	574.7 (17.60%)

M/MHD: mild or moderate hepatic impairment; MRD: moderate renal impairment.

The cumulative amount of sulfate excreted in urine over the 30 hours from the time of the first dose was calculated, assuming that all the sulfate detected was from the Suprep dose. The applicant estimated approximately 20% of the dose is renally excreted over 30 hours in healthy volunteers and patients with hepatic impairment. A lower proportion was excreted in the patients with renal impairment, 16%. This is summarized in the table below, which is reproduced from the Clinical Pharmacology review.

Table 12

Mean (CV%) urine sulfate excretion

	M/MHD	Healthy volunteers	MRD
Cum Ae $_{(0\text{-}30)}$ mg	6499.45 (21.37%)	6037.98 (61.93%)	5101.88 (30.67%)
Cum % dose (0-30hrs) mg	21.90 (21.40%)	20.35 (61.85%)	16.18 (30.66%)
Excretion rate (mg/hr)	216.63 (21.37%)	201.27 (61.93%)	170.05 (30.68%)

M/MHD: mild or moderate hepatic impairment; MRD: moderate renal impairment.

ECGs were performed at baseline (screening and pre-dose) and on Days 2, 3 and 6. No clinically significant ECG changes were reported.

Two of the healthy volunteers developed increases in serum creatinine, but only one exceeded the 1.3 mg/dL upper limit of normal: 1.4 mg/dL, at 30 hours. The creatinines returned to baseline by Days 3 and 6. One of the hepatic impairment patients developed a creatinine of 1.4 mg/dL on Day 6, but it returned to normal on the following day.

I concur with the clinical pharmacology reviewers that the pharmacokinetic and pharmacodynamic data presented in this NDA are sufficient to label the product, at least for the "Split dose" regimen. The NDA lacks information on sulfate Cmax for the "Same day" regimen.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The applicant submitted two adequate and well controlled trials to support the efficacy of Suprep. Both studies compared Suprep to Moviprep, which is an approved PEG plus

electrolyte osmotic laxative. The trials differed only by dosing regimen. In Study 301, the two doses of each product were administered the evening before colonoscopy ("Same day regimen"). In Study 302, one dose was taken the night before colonoscopy and second was administered the following morning, on the day of colonoscopy ("Split dose regimen"). The reviewers noted that the dietary instructions for each product differed. Patients randomized to Moviprep were allowed to have a normal breakfast, light lunch and a supper of clear soup or plain yogurt the day before colonoscopy. Supper had to have been eaten at least one hour prior to starting Moviprep dosing. In contrast, patients randomized to Suprep were only allowed a light breakfast followed by clear liquids on the day prior to colonoscopy. The Moviprep label Dosage and Administration section doesn't describe the diet prior to the bowel prep; however, Section 14 Clinical Studies states that for both "Split-dose" and "Same day/Evening only" regimens, 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. These diet instructions are identical that used in the Moviprep arms of the Suprep NDA trials.

The primary endpoint in both trials was quality of bowel preparation. Success was defined by a colonoscopy score equal to 3 or 4, where 3= "good" (small amount of feces or fluid not interfering with exam) and 4 = "excellent" (not more than small bits of adherent feces, fluid). The primary analysis was a noninferiority analysis, with a margin of 15%.

The statistical reviewer noted that although the applicant did not adequately justify their 15% noninferiority margin, the observed lower confidence limits in each of the trials were "sufficiently above the -15% threshold to support noninferiority with respect to colonic purgation." The statistical reviewer proposed that a prespecified noninferiority margin of 7% would have been more appropriate in Study 301, based on a relative difference of 10% between the arms, but noted that the observed margin in both the trials fell within that margin (lower bound -5.8% in Study 301 and -2.2% in Study 302). In Study 302, the reviewer concluded that the relative difference between arms for calculating noninferiority margin should be 5%, due to the higher proportion of successes observed in this trial. With a relative difference of 5%, the statistical reviewer considered a lower bound of -4% the most appropriate margin. The observed outcome in Study 302 fell within the -4% margin proposed by statistical reviewer. The efficacy results from the 2 trials, using the applicant's ITT analyses, are summarized in the tables below, which are reproduced from the Statistical Review. The definition of the ITT population, patients who took any of the drug, wasn't included in the study protocols and wasn't prespecified in the Statistical Analysis Plans.

Number and Percent of Adequate Preparations
Protocol BLI800-301
Sponsor's ITT Analysis

Treatment	Rate	Diff (BLI800 – MoviPrep)	95% C.I.
BLI800	178/190 (93.7%)	-1.1%	(-5.8%, 3.6%)
MoviPrep	182/192 (94.8%)		

Copied from sponsor Table 301-7

Number and Percent of Successful Preparations
Protocol BLI800-302
Sponsor's ITT Analysis

Treatment	Rate	Diff (BLI800 – MoviPrep)	95% C.I.
BLI800	175/180 (97.2%)	1.6%	(-2.2%, 5.4%)
MoviPrep	175/183 (95.6%)		

Copied from sponsor Table 302-5

The Statistical Reviewer repeated the analyses utilizing an ITT definition that included all randomized patients. Those ITT analyses, referred to by the statistical reviewer as the "True ITT Analysis", are presented in the tables below, which are reproduced from the Statistical Review. The applicant's ITT definition excluded 21 patients (10 patients randomized to Suprep and 11 randomized to Moviprep) in Study 301 and 16 patients (10 patients randomized to Suprep and 6 randomized to Moviprep) in Study 302. The Statistical Reviewer's ITT analyses included those patients as "failed."

Number and Percent of Successful Preparations
Protocol BLI800-301
True ITT Analysis

Treatment	Rate	Diff (BLI800 – MoviPrep)	95% C.I.
BLI800	159/204 (77.9%)	1.9%	(-6.2%, 10.1%)
MoviPrep	155/204 (76.0%)		

Compiled by this reviewer.

Number and Percent of Successful Preparations
Protocol BLI800-302
True ITT Analysis

Treatment	Rate	Diff (BLI800 – MoviPrep)	95% C.I.
BLI800	175/190 (92.1%)	-0.5%	(-5.8%, 4.9%)
MoviPrep	175/189 (92.6%)		

Compiled by this reviewer.

With this revised ITT analysis, the observed lower bounds of the confidence intervals in the Study 301 fell within the 7% margin that the statistical reviewer proposed as the most appropriate noninferiority margin for Study 301, based on a relative difference of 10%. While the patients treated with Suprep had comparable results to Moviprep in Study 301 in the revised ITT analysis, the proportion of successes dropped substantially in both arms, relative to the applicant's ITT analysis. In Study 302, the lower bound of the confidence interval for the FDA statistical reviewer's defined ITT analysis fell outside (slightly) the -4% margin that

he proposed as most appropriate, based on a relative difference of 5%. The proportions of successes were very similar between arms, and in contrast to the results of the "True ITT analysis" of Study 301, the success rate in Study 302 remained comparable to that observed in the applicant's ITT analysis, >90%.

In light of the outcome of the FDA's statistical analysis of Study 302 (with the FDA definition of ITT and the FDA statistical reviewer's calculated lower margin of the confidence interval), the statistical reviewer further explored the observed outcome to determine whether Suprep could be considered better than placebo. He computed a 95% confidence interval for the success rate of Suprep in the FDA defined "True ITT" population. The lower limit of the two-sided 95% confidence interval for the success rate of Suprep in Study 302 was 87.3%. The clinical reviewers considered this rate of success higher than that expected with placebo.

The Clinical Reviewers concurred with the Statistical Reviewer that both Studies 301 and 302 established the efficacy of Suprep. The Clinical Reviewer did not think that an absolute claim on noninferiority between the two preparations could be supported, in light of the difference in dietary restrictions between the two product regimens (more restrictive for Suprep). The Clinical Studies Section of the product label will report that Suprep was compared to a "marketed polyethylene glycol (PEG) bowel prep," and that "In the study, no clinically or statistically significant differences were seen between the group treated with SUPREP Bowel Prep Kit and the group treated with the PEG bowel prep."

I concur with the conclusions of the Clinical and Statistical reviewers and agree with their labeling recommendations. The Statistical reviewer agreed with including the applicant's ITT analysis in labeling.

8. Safety

The two major phase 3 trials that support this NDA (Studies 301 and 302) included 375 patients exposed to Suprep and 376 exposed to Moviprep. Supplemental safety information is available from phase 1 and 2 studies and from the PK study 202, which included more intensive safety monitoring, but utilized varying doses of Suprep and varying populations (young healthy volunteers and patients with hepatic impairment or renal impairment). History of renal or hepatic insufficiency and CHF were exclusion criteria for Studies 301 and 302. The electrolyte content of each product is summarized below:

Table 13: Summary of Ion Components of Suprep and Moviprep

Suprep	Moviprep
Per <u>total</u> 12 oz dose **Sodium Sulfate, 35.02g** Potassium **Sulfate** 6.26 g (2.8g or 72 mEqu K) Magnesium **Sulfate** 3.2 g (2.66 mMoles) Sodium Benzoate, (b) (4) ***Sulfate = 312 mmol/ 12 oz dose***	*Per <u>total</u> 2 liter dose* **Sodium Sulfate, 15 g** Sodium Chloride, 5.38 g Potassium Chloride, 2.03 g (27 mEq K) PEG-3350, 200g Sodium Ascorbate, 11.8 g Ascorbic Acid, 9.4 g ***Sulfate = 105.6 mmol/ 2 L dose***

Patients in Study 301 ("Same day/evening only" regimen) were instructed to take their first dose of Suprep or Moviprep at 6 PM the night before colonoscopy. The second Suprep dose was to be taken at about 7 PM, but no later than 9 PM. Patients randomized to Moviprep took their first liter of solution as divided doses over an hour (starting at 6 PM), and then started the second liter, again in divided doses, at 7:30 PM. One additional liter of clear fluid was to be taken during the evening. Concomitant medications weren't restricted.

Patients in Study 302 ("Split dose" regimen) were instructed to take their first dose of Suprep or Moviprep at 6 PM the night before colonoscopy. The second dose was to be taken at approximately 6 AM the following morning. Post-dose water intake was to be completed by one hour prior to colonoscopy.

Serious Adverse Events

There was one death reported, in a Moviprep arm patient who died two months after colonoscopy from complications (repiratory arrest and acute renal failure) of colonic resection. There were two serious adverse events (SAEs), both in Moviprep patients - one hospitalization for atypical chest pain and one colonic perforation.

The Clinical Reviewer identified two other adverse events that did not technically meet the criteria of SAE, but which the reviewers considered significant. One occurred in an 83 year old male treated with Suprep ("Split dose" regimen). He presented on the day of colonoscopy with third degree heart block. He had a history of gout and hypertension, and concomitant medications included allopurinol, fosinopril (ACE inhibitor) and aspirin. His screening/baseline vital signs and serum chemistry were unremarkable, except for an elevated potassium, BUN, creatinine, and uric acid. His chemistry was unremarkable at the time he presented with heart block, except for sustained elevation in creatinine and uric acid. The event was considered unrelated to Suprep by the investigator. The results of his serum chemistry at baseline and at the time of presentation with heart block are summarized graphically below:

Sodium	Chloride	BUN
Potassium	Bicarbonate	Creatinine

Screening:

141	108	29
5.2	29	1.6

Ca = 9.6 Mg = 1.6 Uric Acid = 7.4

Visit 2 (day of colonoscopy):

142	106	17
4.8	26	1.4

Ca = 9.6 Mg= 1.6 Uric Acid = 7.4

The second event of significance, a mild ischemic colitis noted during colonoscopy, occurred in a Moviprep treated patient.

Common Adverse Events

Adverse events collection procedures in Studies 301 and 302 included the usual investigator ascertainment and reporting procedures [a CRF page for reporting adverse event description, onset and stop dates, along with severity (mild, moderate, severe, life threatening, fatal), treatment, outcome and whether it was considered related and whether it qualified as serious]. In addition, the studies captured patient reports of events in a Symptoms Scale questionnaire, which targeted expected reactions associated with bowel preparations (cramping, stomach bloating, nausea, vomiting and overall discomfort). The questionnaire was returned on Visit 2 when the patient presented for colonoscopy. The rating scale for this instrument ranged 1-5 (none, mild, bothersome, distressing, severely distressing), and the applicant incorporated these symptom data in the NDA adverse events tables as adverse events if a patient rated a symptom as at least "bothersome". During the course of their review, the Clinical Reviewers requested that the applicant submit adverse event analyses that also included the targeted questionnaire symptom events for which patients had rated the severity "mild".

The most common adverse events that occurred at a rate of ≥ 1% are summarized in the table below, which is reproduced from the CDTL review. The most common adverse event was overall discomfort, followed by abdominal distension. The proportion of patients with overall discomfort was similar between Suprep and Moviprep, except in the "Split day regimen" in which a higher proportion of patients in the Moviprep arm reported general discomfort.

Table 14: Studies 301 & 302: Common Adverse Events (Incidence > 1%)

	Same (One) Day Regimen		Split Day Regimen	
Symptom	Suprep (n=194)	MoviPrep (n=193)	Suprep (n=181)	MoviPrep (n=183)
Discomfort	63%	60%	56%	69%
Abdominal Distension	57%	55%	43%	54%
Abdominal Pain	37%	35%	38%	44%
Nausea	46%	39%	38%	34%
Vomiting	13%	4%	9%	4%
Headache	2%	2%	1%	<1%

Adapted from Clinical Review, Section 7.1.5.4, Table 21.

Nausea was similar between Suprep and Moviprep, with the exception of the "Same Day/Evening Only" regimen, in which a higher number of the Suprep patients experienced nausea. Vomiting was more common with Suprep than Moviprep in both regimens, and the difference between the treatments was greatest in the "Same Day/Evening Only" regimen (Study 301): Suprep 13% vs. Moviprep 4%. The proportion of Suprep patients who vomited was still double that of the Moviprep arm in the "Split dose" trial, Study 302 – 9% vs. 4%. For Suprep, the "Same day" regimen seemed to cause more vomiting than the "Split dose" regimen - 13% vs. 9% - although this is a cross study comparison. The Statistical reviewer noted that a higher proportion of patients treated with Suprep reported mild to severe symptoms associated with vomiting than in the patients treated with MoviPrep. Vomiting was more common in the elderly (defined as >65 years of age) treated with Suprep than with

MoviPrep. In Study 301 the rate of vomiting in the elderly was 13% in the Suprep arm vs. 4% in the Moviprep arm, p=0.017. The difference in vomiting between arms in the elderly in Study 302 "Split dose" regimen, was reported by the Statistical reviewer as "slightly higher" but "failed to reach statistical significance."

Evaluation of weight loss/gain in the studies to assess for volume contraction/expansion revealed that for the combined trials, Suprep patients experienced a mean weight loss of 2.8 pounds (documented on the day of colonoscopy, visit 2) and Moviprep patients had a mean weight loss of 2.2 pounds. Examination of the individual studies, suggests weight loss was greatest for Suprep treated patients in Study 301 (the "Same day/Evening only" regimen), both by mean and median. In Study 302, the mean weight loss associated with Suprep appears slightly less than in 301, but is quite similar. The median weight loss is the same between arms within Study 302. See Table below.

Table 15: Summary and Mean/Median Weight Change and Change in Vital Signs Between Baseline and Day of Colonoscopy

	Study 301			Study 302		
	Suprep	Moviprep		Suprep	Moviprep	
Mean Change in Weight (lbs)	-2.85	-2.18	P=0.04	-2.77	-2.16	P=0.07
Median Change in Weight (lbs)	-3.00	-2.00		-2.00	-2.00	
Range (weight change)	-19 to 8	-16 to 6		-15 to 8	-14 to 12	
Change in Pulse	+2.1	+1.5		-0.04	-0.31	
Change in Systolic BP	-2.23	-0.40		+2.74	+3.74	

The difference in weight loss between arms in Study 301was nominally statistically significant, p = 0.04, with no adjustment for multiplicity. The median change in weight for Suprep in Study 301 was higher than the mean change in that arm, while the median for the Moviprep arm was slightly lower than its mean change. In Study 302, the means were higher than the medians in both arms. The increase in pulse rate and decrease in systolic pressure observed in Study 301 support the evidence of volume contraction from the weight loss data. The pulse and systolic pressure change data don't support a clinically meaningful change in weight related to volume contraction in Study 302.

In additional cross study comparisons to evaluate tolerability of the Suprep regimen in a "Same Day/Evening only" regimen vs. the "Split Dose" regimen, nausea, discomfort, and abdominal distension all appeared to be more common in the "Same day" regimen than with the "Split dose" regimen. This was not the case for Moviprep, in which there was a higher rate of discomfort and abdominal pain in the "Split Dose" regimen than in the "Same Day" regimen, and a similar rate of the other events between the two Moviprep dosing regimens.

Table 16: Studies 301 & 302: Common Adverse Events (Incidence > 1%)

	Same (One) Day Regimen		Split Day Regimen	
Symptom	Suprep (n=194)	MoviPrep (n=193)	Suprep (n=181)	MoviPrep (n=183)
Discomfort	63%	60%	56%	69%
Abdominal Distension	57%	55%	43%	54%
Abdominal Pain	37%	35%	38%	44%
Nausea	46%	39%	38%	34%
Vomiting	13%	4%	9%	4%
Headache	2%	2%	1%	<1%

Adapted from Clinical Review, Section 7.1.5.4, Table 21.

Were the Moviprep adverse event rates in Studies 301 and 302 comparable to those in the trials that supported Moviprep's approval? The rates in Study 302 appear to be higher than those observed and reported in the Moviprep label for the Split Dose study (a study conducted in Germany). The table "Most Common Drug-Related Adverse Reactions" for this study suggests a lower rate of these reactions, with the exception of vomiting (8%): (Malaise 19%, Nausea 14%, Abdominal Pain 13%, Vomiting 8%, and Upper Abdominal Pain 6%.) In contrast, the adverse events in the Moviprep label for the single day regimen study (a French study) of Moviprep are comparable to those reported in the "Same day/Evening only" Study 301. The apparent discrepancy for Moviprep "Split dose" adverse event data in the Moviprep label may be due to the fact that the labeled "Split dose" trial did not utilize a specific symptom questionnaire like that used in the single dose Moviprep study in the same label (and in the Suprep NDA). For this reason, the Moviprep single dose study data are the relevant data for comparison to the Moviprep data in this Suprep NDA, and the adverse events rates appear comparable.

Adverse events by subgroup were explored. The Statistical Reviewer notes in his review that in Study 301 ("Same day/Evening only" regimen), the overall adverse event rate was statistically significantly higher in patients ages greater than 65 treated with Suprep compared to Moviprep. This did not hold true for the "Split dose" regimen in Study 302, in which the adverse event rate in this same age group was slightly lower in the Suprep arm than Moviprep. For patients defined as "high risk" based on the applicant's definition (patients with a history of cardiac, renal, vascular disease/hypertension or diabetes), the Statistical reviewer found that there was a statistically significantly higher rate of adverse events on the Suprep arm of Study 301, the "Same day" regimen. In Study 302, the findings reversed, and there was a statistically significantly higher risk of adverse event in the high risk group treated with Moviprep. The distribution of high risk patients by study and by study arm in the safety dataset evaluated by the Statistical reviewer is summarized in the table below. In the safety dataset of Study 301 there was a higher proportion of patients who met the applicant's definition of high risk in the Moviprep arm. The proportions were similar between arms in Study 302.

Table 17: Summary Distribution of High Risk Patients in the Safety Datasets of Studies 301 and 302

	Proportion of Safety Dataset Considered High Risk	
Study	**Suprep**	**Moviprep**
301	87/201 (43%)	102/197 (52%)
302	86/187 (46%)	87/185 (47%)

Fluid and Electrolytes

In light of the cathartic effects of these regimens and the fact that bowel preps (including Moviprep) carry labeled warnings of electrolyte abnormalities and adverse reactions related to fluid and electrolyte disturbances, the reviewers were particularly attentive to the impact of Suprep on fluid and electrolyte disturbances. The currently marketed osmotic bowel preps, including the OSP products, carry Warnings and Precautions stating that they should be used with caution in patients with impaired renal function, patients with a history of acute phosphate nephropathy, severe renal insufficiency (creatinine clearance less than 30 mL/minute), and known or suspected electrolyte disturbances (e.g., dehydration).

The OSP labels state that patients with electrolyte abnormalities such as hypernatremia, hyperphosphatemia, hypokalemia, or hypocalcemia should have their electrolytes corrected before treatment. The labels warn that clinicians should be aware of and consider a patient's medical history of seizures, electrolyte abnormalities such as a hypocalcemia, hypokalemia, hypernatremia, hyperphosphatemia, uncontrolled arrhythmias, recent myocardial infarction, cardiomyopathy, prolonged QT, congestive heart failure, ascites, low salt diet, and unstable angina.

The Visicol (an OSP) label states that sodium phosphate products prior to colonoscopy have resulted in fatalities due to significant fluid shifts, severe electrolyte abnormalities, and cardiac arrhythmias, and that "Considerable caution should be advised before Visicol® Tablets are used in patients with the following illnesses: severe renal insufficiency (creatinine clearance less than 30 mL/minute), congestive heart failure, ascites, unstable angina, …." The label further states that the prescriber should "Consider performing baseline and post-colonoscopy labs (phosphate, calcium, potassium, sodium, creatinine, and BUN) in patients who may be at increased risk for serious adverse events, including those with history of renal insufficiency, history of ─ or at greater risk of ─ acute phosphate nephropathy, known or suspected electrolyte disorders, seizures, arrhythmias, cardiomyopathy, prolonged QT, recent history of a MI and those with known or suspected hyperphosphatemia, hypocalcemia, hypokalemia, and hypernatremia. Also if patients develop vomiting and/or signs of dehydration then measure post-colonoscopy labs (phosphate, calcium, potassium, sodium, creatinine, and BUN)."

The Visicol label states that there have been reports of renal failure and acute phosphate nepropathy in OSP products and that patients with increased risk include patients with hypovolemia, baseline kidney disease, increased age, and patients using medications that affect renal perfusion or function [such as diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and possibly nonsteroidal anti-inflammatory drugs (NSAIDs). Patients with electrolyte abnormalities such as hypernatremia, hyperphosphatemia, hypokalemia, or hypocalcemia should have them corrected before treatment. In addition there is a specific subsection in the OSP labels to address risk of seizures. In the Visicol label this subsection states that seizure cases were associated with electrolyte abnormalities (e.g., hyponatremia, hypokalemia, hypocalcemia, and hypomagnesemia) and low serum osmolality.

In Studies 301 and 302, serum chemistry (including electrolytes, BUN, creatinine, osmolality, transaminases, total bilirubin and direct bilirubin) and CBC were evaluated on the day of colonoscopy, when the patient had completed the bowel prep. The Division VII Safety

Statistical review group from the Office of Biostatistics was consulted to assist in exploratory analyses of the safety dataset of subjects with normal baseline laboratory values who developed abnormal values in subsequent laboratory evaluations. The specific abnormalities of interest included low serum bicarbonate, high BUN, high creatinine, high uric acid, high magnesium, and high/low chloride, sodium, potassium, phosphate and osmolality. The Statistical Safety reviewers were asked to explore whether any demographic correlates with identified abnormalities exist and whether correlations between laboratory abnormalities and adverse events exist.

The CDTL notes in his review that mean changes in serum chemistries were "generally mild" in the two studies. He stated the following contrasts in mean changes in serum chemistries between Suprep and Moviprep "deserve mention". Electrolytes for which shifts were greater on Suprep than Moviprep were uric acid (increase), serum osmolality (decrease), total serum protein (increase), serum albumin, and serum chloride.

1) Mean bicarbonate fell by <1.0 mEq/L in the Suprep arm in each study, but the mean decrease in the Moviprep arm was greater – 1.6 mEq and 1.7 mEq.

2) Uric acid rose by 0.45 to 0.55 mg/dL in the Suprep arms, but only by a mean of 0.0 to 0.02 mg/dL in the Moviprep arms. (Reported as a nominally statistically significantly difference between arms, $p<0.001$, in both studies.)

3) Mean Serum osmolality decreased by 1.8 and 2.6 mOsm/kg in the Suprep arms, but fell by 1.0 or less in the Moviprep arms.

4) Total serum protein increased by 0.12 to 0.18 g/dL for Suprep, but rose by 0 to 0.07 g/dL on the Moviprep arms.

5) Total serum albumin increased in both Suprep and Moviprep arms. It rose by 0.07 to 0.12 g/dL for Suprep and 0.01 to 0.07 g/dL for Moviprep.

6) Serum chloride decreased by 0.71 mEq/L and 0.75 mEq/Lin the Suprep arms. It rose by 1.61mEq/L and 0.89 mEq/L in the Moviprep arms of Study 301 and 302, respectively. (This was reported as nominally statistically significant, $p<0.001$, in both studies.)

The Clinical Reviewer, Dr. Gatti, and the Cardiorenal consultant noted that neither Suprep or Moviprep resulted in mean changes in serum creatinine from baseline at either the Day of colonoscopy (Visit 2) or 30 days post colonoscopy. This was also true for each study, with the exception of a small increase in mean creatinine, by 0.03 mg/dL, in the Suprep arm of Study 301. Reductions in mean BUN were noted in both arms in both studies at Visit 2 (approximately 3 mg/dL less than the mean baseline level), but returned to near baseline by the last visit on study. Dehydration may have been expected to cause an increase in BUN. The changes in weight and vital signs in Study 301 provide some evidence of volume contraction (see Table 15 above).

The CDTL review also presented frequencies of serum chemistry results that fell outside the range of normal in the combined study populations. His summary table is reproduced below:

Table 18: Combined Studies 301 & 302: Prevalence of Selected Abnormal Chemistry Results on Day of Colonoscopy

	Na ↓	Na ↑	K ↓	K ↑	Bicarb ↓	Bicarb ↑
Suprep (n=352)	2.8%	1.4%	0.9%	3.4%	11%	0.3%
MoviPrep (n=364)	2.2%	2.2%	1.9%	2.7%	16%	0.3%
	Ca ↓	Ca ↑	Phos ↓	Phos ↑	BUN ↑	Creat ↑
Suprep (n=352)	0.9%	9.1%	4.3%	2.6%	7.1%	8.2%
MoviPrep (n=364)	0.0%	3.8%	3.6%	1.4%	8.8%	9.6%

Derived from Applicant's Table 14.3.6.1, p. 137-139 in vol. 8.1 of Module 5.

Because some of these abnormalities occurred in patients whose baseline levels were also abnormal, the CDTL also presented the following summary table for the combined study population of the frequencies of interval newly developed abnormal chemistry values at Visit 2 (day of colonoscopy):

Table 19: Combined Studies 301 & 302: Incidence of Abnormal Chemistry Results in Patients with Normal Values at Screening Visit (Only Events with Proportion ≥ 5% for Suprep)

	Bicarb ↓	Ca ↑	Gluc ↑	bili ↑	T. prot ↑	Uric Acid ↑
Suprep	11%	7.2%	9.6%	9.1%	5.1%	26%
MoviPrep	15%	2.7%	11.1%	13.2%	1.1%	12%

Derived from Applicant's Table 14.3.6.1, p. 137-139 in vol. 8.1 of Module 5.

As suggested by the mean shifts, there was a greater proportion of Suprep treated patients in the overall combined safety database who developed incremental new high uric acid and total serum protein levels. These changes could reflect dehydration. In addition, this analysis identified a higher proportion with a new high serum calcium level in Suprep treated patients. In contrast, the mean changes of serum calcium in both studies and in both arms were decreases, -0.06 in both Suprep arms and -0.13 to -0.16 mg/dL in the Study 301 and 302 Moviprep arms, respectively. The serum calcium levels were not ionized. As noted above, the mean changes in serum albumin in both Suprep and Moviprep arms of both studies were increases.

Bicarbonate: The incremental mean decrease in serum bicarbonate in the Suprep arms in both studies was less than the mean decline with Moviprep. The incremental change in bicarbonate was similar between the dosing regimens. A higher proportion of patients in the Moviprep arms developed decreases in the serum bicarbonate. When the Statistical reviewers analyzed the relative rates of development of low bicarbonates in patients with normal baseline bicarbonate level, they found the proportion was higher in the Moviprep arm in Study 301 ("Same day" regimen), and similar between arms in Study 302. This is summarized in the table below, which is reproduced from their consult review:

Table 20:

Table 4: Frequency of subjects Flagged for Bicarbonate

N (% of cell) Flagged for Bicarbonate		Study 301		Study 302	
		SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Total Flagged		23 (11.86)	35 (18.13)	27 (14.92)	27 (14.75)
Sex	Female	15 (13.64)	21 (20.39)	14 (14.29)	19 (19.39)
	Male	8 (9.52)	14 (15.56)	13 (15.66)	8 (9.4)

Three patients were identified by the statistical reviewers as particular outliers – two treated with Moviprep and one treated with Suprep. All were female. The lower limit of normal was 22 for the central laboratory. The two Moviprep patients dropped to a serum bicarbonate of 15 each on Visit 2 (morning of colonoscopy) and had returned to normal by Day 30. The single Suprep outlier dropped to a serum bicarbonate of 11 and had recovered to 21 (still just below the lower limit of normal) on Day 30.

Development of low serum bicarbonate on study reflects metabolic acidosis. The sulfate in both bowel preps is an acid and could produce a gap acidosis. Although the sulfate content is lower in Moviprep than Suprep, there was a higher rate of interval development of low serum bicarbonate in the Moviprep arm of 301, and an almost identical rate to Suprep in Study 302 ("Split dose" trial). This reviewer asked the applicant to present the calculated anion gap data for these studies, and evaluated the proportion of patients in each arm that developed evidence of new gap acidosis in the trials, using a gap defined as ≥ 13. In addition, this reviewer also examined how many patients had their newly diagnosed acidosis on the last visit (which was Day 30/Visit 3 for patients who completed the study, and the Day of colonoscopy/Visit 2, for those who did not). Those data are summarized in the table below. The majority were gap acidosis.

Table 21: Summary of New Onset Acidosis by Study Visit and Presence/Absence of Gap

	Study 301		Study 302	
	Suprep	Moviprep	Suprep	Moviprep
New Low HCO3 Visit 2 or 3	22 (11%)	34 (18%)	27 (15%)	27 (15%)
Low HCO3 Visit 2 only	12 (6%)	25 (13%)	20 (11%) (Gap = 16/20)	23 (13%) (Gap = 14/23)
Low HCO3 Visit 3 Only	7 (4%)	6 (3%)	7 (4%) (Gap =4/7)	3 (2%) (Gap = 2/3)
Low HCO3 Visit 2 and 3	3 (2%) (Gap = 3/3)	2 (1%) (Gap = 1/2)	0	1 (1%) (Gap = 1/1)
Low HCO3 Visit* 3 or last Visit	11 (6%) Gap = 8/11	12 (6%) Gap = 5/12	8 (4%) (Gap = 4/8)	7 (4%) (Gap = 4/7)

* Includes patients who might also have Visit 2 as well

The table shows that most new acidosis events were confined to day of colonoscopy, Visit 2. In both of the Suprep and Moviprep "Split dose" regimens (Study 302), most of the low serum bicarbonate events occurred on Visit 2, the day of colonoscopy, and the majority of those Visit 2 events were associated with an anion gap. For Suprep, a higher proportion of patients in the

"Split dose" regimen had a low Visit 2 serum bicarbonate than in the "Same day/Evening Only" regimen. If the low serum bicarbonate is related to the sulfate ingested, this relative difference between the two Suprep regimens might reflect the closer proximity to the last dose of Suprep (sulfate) in the "Split dose" regimen to the Visit 2 serum chemistry sample than the "Same day" dose schedule. However, this difference was not observed in the exploratory analysis of the Study BLI300-101 serum bicarbonate by time data by dose regimen presented in Tables 6 and 7 (reproduced below) in Section 5 Clinical Pharmacology of this review. That study suggests that the serum bicarbonate changes observed at the time Visit 2 serum chemistry was drawn in Studies 301 and 302 (median 13.75 hours and 5.7 hours after the last dose in each trial, respectively) should be similar between Suprep regimens. There was a higher rate of vomiting in the Suprep arm of Study 301 (13%) compared to Study 302 (9%), and vomiting can result in alkalosis from loss of chloride.

Table 22: Percentage Change from Baseline in Electrolytes Ordered by Decreasing Sulfate Increments at 4 Time Points

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

There were patients who had new acidosis documented on Visit 2, who sustained it through Visit 3 (one month visit), but these were confined primarily to the "Same Day/Evening Only" regimen study. In the "Split dose" trial, the only patient with acidosis on both days was in the Moviprep arm. A new low bicarbonate on both Visit 2 AND 3 might represent a renal injury with the bowel prep. A new low serum bicarbonate event observed only on Visit 3could be related to intercurrent events, including other medical conditions, surgical procedures or new medications. There were a similar number of acidosis events limited to Day 30 across the studies and arms, with the exception of the lower number in the Moviprep arm of 302. Within Study 302, a higher number of Suprep patients had new low serum bicarbonate at the follow-up visit than Moviprep.

Overall, comparing Suprep regimen ("Same day" vs. "Split dose") impact on acidosis, only the analysis of new onset acidosis at Visit 2 sustained through Visit 3 suggests a trend favoring the "Split dose" regimen.

This reviewer also explored the dataset for hyperchloremic acidosis (normal anion gap), for which the differential diagnosis is renal failure, renal tubular acidosis, GI loss with diarrhea. In Study 301 there were 2 Suprep patients and 7 Moviprep patients who met these criteria. Both of the Suprep patients had this documented on Day 30 only, in which one had a rising creatinine that was greater than the upper limits of normal. Only 1/7 Moviprep patients had

this documented on Day 30. That patient had a high creatinine documented on Day 30 visit. In the "Split dose" regimen, Study 302, only 1 patient in each treatment arm appeared to meet the criteria for hyperchloremic acidosis and both occurred on Visit 2. Both had normal creatinines. The mean chloride change in Study 301 (summarized in the Clinical Reviewer's Table 33) at Visit 2 in the Moviprep arm was a gain of 1.61 mEq/L, while on the Suprep arm it was a mean loss of -0.71 mEq/L. In both arms the mean change at the last visit (Day 30) relative to baseline was a small gain of approximately 0.74 mEq/L.

The Cardiorenal consultant noted in her review that the decrease in serum bicarbonate levels were "statistically significantly greater in the MoviPrep group than in the [Suprep] group in both studies." She stated that these changes "may not be of great clinical significance", but she noted that consumption of pure sulfur has been reported to cause metabolic acidosis, citing Blum and Coe, Metabolic acidosis after sulfur ingestion. NEJM 297:869-870, 1977. She also cited Acid-Base Physiology, 3.2, http://www.anaesthesiamcq.com/AcidBaseBook/ab3_2.php to support that sulfate is known to cause an increased anion gap metabolic acidosis. She noted that acidosis "will tend to decrease uric acid excretion", and can decrease calcium and magnesium reabsorption (increasing their clearance). She also noted that metabolic acidosis increases sulfate excretion, citing Pelis R, et.al, Amer J Phys Renal Physiology 205; 289(1):F208-16. For this reason, one might expect patients with mild renal insufficiency and acidosis to clear sulfate more rapidly than patients with normal renal function. She recommended that patients with severe kidney disease should be studied to ensure that Suprep does not worsen their baseline metabolic acidosis. The applicant provided summary data on the number of patients in each regimen who had a low serum bicarbonate at baseline who subsequently developed worsening of their apparent acidosis on study (based on a further decrease in serum bicarbonate). The shifts observed in the study in this patient subset were limited to Visit 2 only and were similar across studies and treatment arms. Those data are presented in the table below:

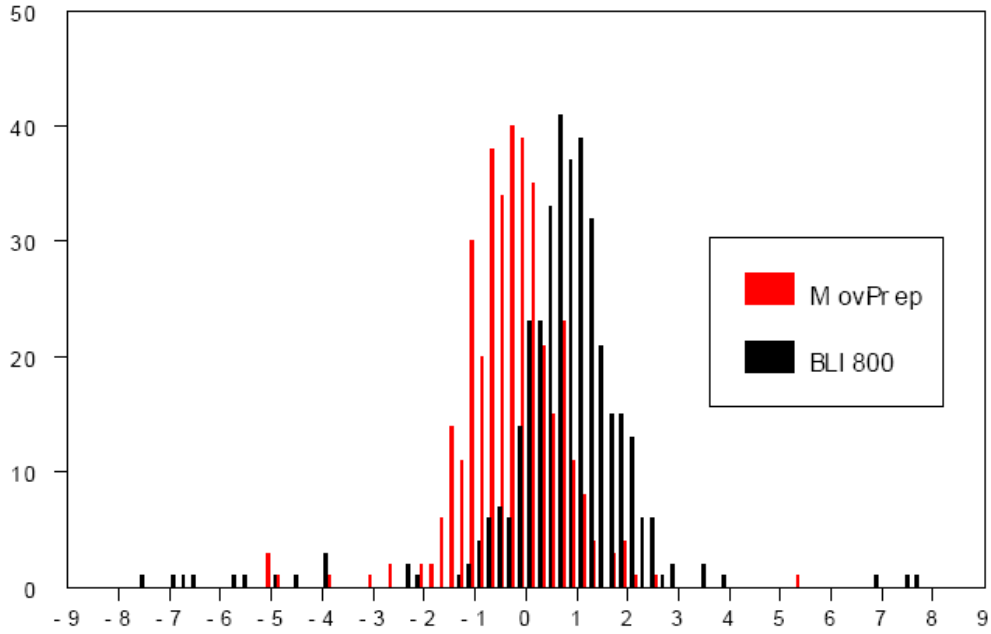
Table 23: Shifts in Bicarbonate in Patients Whose Baseline Bicarbonate Was Low

	Study 301		Study 302	
	Suprep	Moviprep	Suprep	Moviprep
Proportion of Overall Population with Low Baseline Bicarbonate	8 (4.1%)	5 (2.6%)	10 (5.5%)	11 (6.0%)
Bicarbonate Decreased Further at Visit 2 Only	1 (0.5%)	1 (0.5%)	1 (0.6%)	1 (0.5%)
Bicarbonate Decreased Further at Visit 3 Only	0	0	0	0
Bicarbonate Decreased Further at Visit 2 AND Visit 3	0	0	0	0

Uric Acid: The mean increases in uric acid were higher in the Suprep arms than in the Moviprep arms. The Cardiorenal consultant noted that the mean increase in uric acid observed in the Suprep treated patients was greatest in the patients treated in the "Same day" regimen, but that the administration regimen did not seem to impact the degree of incremental increase in uric acid observed in patients treated with Moviprep. The difference between Suprep and Moviprep was nominally statistically significant, without adjustment for multiplicity, and she

found the difference "impressive". She noted a "much greater variance" existed in the Suprep treated patients – "while there are greater increases, there are also greater decreases." This is shown in the histogram below, which is reproduced from her review.

Figure 3: Distribution in Change of Uric Acid Levels from Baseline to Visit 2 (Colonoscopy visit) in the Combined Studies 301 and 302.



The Cardiorenal consultant discussed the physiological basis for this observation in her review. She pointed out the complexity of the potential acid/base and fluid/electrolyte status of patients treated with an osmotic cathartic. She noted that the nonclinical studies indicated animals treated with Suprep had alkalinized urine, and that alkalinized urine would be expected to be uricosuric, leading to a fall in serum uric acid (instead of what was observed in the clinical trial dataset). She noted that volume contraction leads to increased serum uric acid and that there may have been greater volume contraction in the Suprep group due to vomiting. The other potential etiology suggested by the Cardiorenal consultant was that sulfate might be interfering with uric acid secretion; however, she could not find evidence for this mechanism in the literature. The kidneys do have sulfate transporters to scavenge sulfate, but the ions that are exchanged in this transport are bicarbonate and oxalate ions. Sulfate is filtered through the glomerulus and undergoes net reabsorption. Sulfate uptake takes place in the proximal tubule cells. Uptake across the luminal membrane occurs through cotransport with sodium via transmembrane sodium gradient, and in the basolateral membrane it occurs via sulfate-anion exchanger Sat-1[12]. Krick, et al found that chloride may also play a role in sulfate exchange, and they have found in their experiments that the transporter demonstrates competitive inhibition of sulfate uptake by oxalate. Oxalate uptake increased with intracellular injection of sulfate in their experimental model. They found that bicarbonate competitively inhibited sulfate uptake; sulfate efflux increased with increase of bicarbonate.

[12] Krick W, Schnedler N, et al. Am J Physiol Renal Physiol 297: F145-F154, 2009.

Further review of the literature for etiologies of elevated serum uric acid identified starvation and high dietary intake of fructose as causes that may be relevant to these studies. Starvation causes metabolism of body's own tissues for energy, releasing purines. In addition, ketones compete for transport of uric acid in the kidneys. Patients using bowel preps stop eating once the bowel prep is initiated. High fructose diets have been studied and there is evidence that ingestion of fructose increases serum uric acid.[13] Soft drinks sweetened with high fructose corn syrup may have been ingested by patients in the study who were told only to consume clear liquids after initiating the bowel prep.

The Cardiorenal consultant recommended that since it is not clear whether the increase in uric acid observed in these studies was related to increased formation or decreased excretion, the fractional excretion of uric acid and the urine pH should be evaluated in a future safety study to better understand the mechanism. She recommended the label state that the product should be used with caution in patients with a history of gout.

The CDTL reviewer stated that the proportion of patients whose baseline serum uric acid was normal and developed a high uric acid on study was higher in the Suprep population of the combined study populations – 26% vs. 12% for Moviprep. The Statistical reviewers noted that this difference was consistent in both of the individual studies, as summarized in the table below, although there was a lower rate of elevated serum uric acid in the Suprep arm of Study 302 ("Split dose") than in the Suprep arm of Study 301. The lower proportion of uric acid elevation observed in 302 was closer to the range observed for Moviprep. The rate of uric acid elevation for Moviprep was similar between the two administration schedules.

Table 24:

Table 23: Frequency of subjects Flagged for Uric Acid

N (% of cell) Flagged for Uric Acid		Study 301		Study 302	
		SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Total Flagged		47 (24.23)	29 (15.03)	33 (18.23)	26 (14.21)
Sex	Female	21 (19.09)	15 (14.56)	17 (17.35)	12 (12.24)
	Male	26 (30.95)	14 (15.56)	16 (19.28)	14 (14.29)

Interestingly, the delta between arms in proportion of patients with "flagged uric acid" in each study matches the delta between arms in proportion of patients with vomiting. [In Study 301 the proportions of patients were 13% and 4% for Suprep and Moviprep, respectively (delta=9%). In Study 302, the proportions were 9% and 4% (delta = 5%).] Vomiting could lead to volume contraction, an etiology of uric acid elevation. Examination of new onset acidosis does not show the same pattern. However, one might expect concomitant new elevation of BUN in the setting of volume contraction. This reviewer examined the patients with new elevations of uric acid in Study 301 and only identified 8 patients who had both new onset of elevated uric acid and elevated BUN on Visit 2 (3073, 4010, 4100, 5033, 7011, 9053, 10028 and 21003). In 302, only 3 such patients were identified (11001, 15063 and 15064).

[13] Choi, JWJ, Ford ES, et al. Arthritis and Rheumatism. Vol 59, No. 1 : 109-116, 2008

Four patients were identified by the statistical reviewers as particular outliers – one treated with Moviprep and three treated with Suprep. All but one were female. The upper limit of normal for uric acid was 5.7 for females and 7 for males at the central laboratory. The Moviprep patient, a female, had a uric acid of 8.1 on Visit 2 (the morning of colonoscopy) that decreased to 6.2 (still high) by Day 30. The two female Suprep outliers had uric acids of 9 and 7.4. One recovered to normal and the other to 7.2 at Day 30. The male Suprep treated patient had a serum uric acid of 9.6 on Day 30 only.

Chloride: The mean change in chloride went in opposite directions for the Suprep and Moviprep arms. The mean change was greater in the Moviprep arms and reflected an increase, whereas the change in the Suprep arms was a reduction. In the Statistical reviewers' analyses of proportions of patients with new onset of any abnormal chloride level, in both studies the Moviprep arm had a higher proportion (double) of patients "flagged" (high or low) than the Suprep arms. For Moviprep, the proportion flagged with abnormal serum chloride was similar in each study to the proportion with decreased serum bicarbonate (18% in 301 and 14.75% in 302). In contrast the proportion of patients with decreased serum bicarbonate in the Suprep arms (12% in 301 and 14.9% in 302) was double that of the proportion with a flagged chloride.

Table 25:

Table 10: Frequency of subjects Flagged for Chloride

N (% of cell) Flagged for Chloride		Study 301		Study 302	
		SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Total Flagged		12 (6.19)	29 (15.03)	12 (6.63)	27 (14.75)
Sex	Female	7 (6.36)	17 (16.50)	6 (6.12)	20 (20.41)
	Male	5 (5.95)	12 (13.33)	6 (7.23)	7 (8.24)

Calcium: A higher proportion of Suprep treated patients with normal baseline serum calcium developed hypercalcemia in the combined population (301 and 302) compared to Moviprep – 7% vs. 3%. The calciums in the data set were not ionized calciums. Group mean changes in albumin from baseline in this dataset were small gains at Visit 2, and slightly larger in the Suprep arm. At Visit 3 the albumin group means relative to baseline were reductions in both groups in both studies.

The CDTL reported in his review that on Visit 2, regardless of baseline calcium level, 9% of patients in the database treated with Suprep had a high serum calcium vs. 4% on the Moviprep arms. A low calcium on Visit 2 (regardless of baseline normal value) was reported in 1% of patients treated with Suprep and no patient treated with Moviprep in the overall dataset.

The statistical reviewers evaluated differences between arms in patients flagged as change to abnormal, ***both*** high and low serum calciums, in the two studies. They noted that the proportion of any abnormal calcium (high or low) after baseline was higher in the Suprep arms than in Moviprep, but the difference was most marked in Study 302, in which the proportion in the Suprep arm was double that observed in Study 301.

Table 26: Shifts from Normal at Baseline - Flagged for High or Low Calcium

Table 8: Frequency of subjects Flagged for Calcium

N (% of cell) Flagged for Calcium		Study 301		Study 302	
		SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Total Flagged		15 (7.73)	11 (5.70)	30 (16.57)	16 (8.74)
Sex	Female	9 (8.18)	5 (4.85)	15 (15.31)	10 (10.20)
	Male	6 (7.14)	6 (6.67)	15 (18.07)	6 (7.06)

The outliers selected for presentation by the statistical reviewers all had hypocalcemia documented on Visit 2, and all had returned to normal on Day 30. All were female. The lower limit of normal for serum calcium in the central laboratory was 8.4. The Visit 2 serum calcium levels for these 3 patients were: 7.8, 7.9 and 5.5.

This reviewer examined the patients in each study who "were flagged" in the dataset for having newly documented hypercalcemia after the baseline screening visit. The distribution of these events by study and by visit (Visit 2 day of colonoscopy vs. Visit 3, Day 30) is summarized below:

Table 27: New High Serum Calcium - By Study and By Study Visit

	Study 301		Study 302	
	Suprep	Moviprep	Suprep	Moviprep
Visit 2	7 (4%)	3 (2%)	16 (9%)	6 (3%)
Visit 3 Only	4 (2%)	7 (4%)	6 (3%)	4 (2%)

The hypercalcemia seems most evident and limited to Visit 2 in the Suprep arm of Study 302. This difference between the studies may be related to the proximity of the ingestion of the last dose of Suprep before obtaining the Visit 2 blood sample. However, this difference between regimens was not observed in the exploratory analysis of the Study BLI300-101 serum calcium data, which was presented in Section 5 Clinical Pharmacology of this review. (See Table 5 above.) It is notable that the group mean total serum albumin and total serum protein levels increased to the greatest degree in the Suprep arms of these studies, and that the greatest incremental increases occurred in the Suprep arm of Study 302.

The upper limit of normal for calcium in the central laboratory was 10.2 mg/dl. When this reviewer examined the degree of elevation of serum calcium documented in the two studies on the day of colonoscopy in those patients who had normal baseline serum calcium, across the two studies the highest serum calcium in the Suprep arms was 10.7 mg/dl (in a single patient) and the median was 10.5 mg/dl. A similar evaluation in the same group of Moviprep patients (normal at baseline but elevated on the day of colonoscopy), revealed the highest serum calcium was 10.8 mg/dl (in a single patient) and the median was 10.3 mg/dl.

Creatinine; Visit 2 elevations in creatinine, regardless of whether the creatinine was normal at baseline, were reported in 8.2% of patients treated with Suprep and 9.6% of patients treated with Moviprep. The statistical reviewers found that the proportions of patients who developed new onset of creatinine elevation (baseline normal) were similar between arms, but the

proportions were higher in Study 301's "Same day" administration schedule than in Study 302.

Table 28:

Table 12: Frequency of subjects Flagged for Creatinine

N (% of cell) Flagged for Creatinine		Study 301		Study 302	
		SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Total Flagged		16 (8.25)	13 (6.74)	9 (4.97)	9 (4.92)
Sex	Female	5 (4.55)	3 (2.91)	3 (3.06)	2 (2.04)
	Male	11 (13.10)	10 (11.11)	6 (7.23)	7 (8.24)
Race	Asian	0 (0)	—	0 (0)	0 (0)
	Black or African-American	2 (9.52)	2 (8.70)	3 (18.75)	1 (6.25)
	White	13 (7.69)	11 (6.51)	6 (3.90)	8 (5.00)
	Other	0 (0)	—	0 (0)	0 (0)

These events occurred predominantly in males. Overall 3% of females in the studies were flagged for high creatinines compared to 9.9% of males. This contrasts with the higher proportion of women that reported vomiting with Suprep.

The Statistical reviewers described one outlier, a male treated with Suprep, whose Visit 2 serum creatinine increased to 1.9 mg/dL (upper limit of normal was 1.2 mg/dL) and then dropped to 1.2 mg/dL on Day 30. His baseline was 1.1 mg/dL.

Data for interval development of newly elevated creatinines by study visit day are summarized below:

Table 29: New High Creatinine By Study and By Study Visit

	Study 301		Study 302	
	Suprep	Moviprep	Suprep	Moviprep
Visit 2 Only	6 (3%)	4 (2%)	4 (2%)	1 (0.6%)
Visit 3 Only	7 (3.6%)	7 (3.6%)	5 (2.8%)	7 (3.8%)
Visit 2 and 3	2 (1%)	1 (0.5%)	0	1 (0.6%)

Few patients had an elevation of creatinine on both Visit 2 and Visit 3. The treatment arms looked similar within and across studies. Elevations limited to Visit 3 could reflect a residual impact of the bowel prep, not captured on the day of colonoscopy, or the impact of an intercurrent event unrelated to the bowel prep, including surgery, other medical event, or a new medication. (Please note that discrepancies between the numbers in this table and the product label reflect the reviewer's exploratory analysis methodology, which included imputation of abnormal value if a data point was missing and followed by an abnormal value, and use of a single upper limit of normal for baseline creatinine.)

Upper limit of normal for creatinine in these trials was 1.1 or 1.2 mg/dL. The most common elevated creatinine value in Study 301 was 1.3 mg/dL (Moviprep = 8; Suprep = 6). Creatinine of 1.4 mg/dL was observed in 1 Moviprep patient and 5 Suprep patients, and a creatinine of

1.2 mg/dL was observed in 1 Moviprep patient and 4 Suprep patients. A single Suprep patient had a creatinine of 1.5 mg/dL on Visit 2 and a single Moviprep patient had a creatinine of 1.9 mg/dL on Visit 2 (ULN = 1.1 or 1.2 mg/dL). Half of the creatinines of 1.4 mg/dL were documented on Visit 2. The single Moviprep patient with an elevation at both Visit 2 and 3 had a creatinine of 1.3 mg/dL (ULN=1.2 mg/dL). Two Study 301 Suprep patients had elevated creatinines at both Visit 2 and 3; one had a creatinine of 1.5 mg/dL on Visit 2 and a creatinine of 1.2 mg/dL on Visit 3 (ULN=1.1 mg/dL), and the other had a creatinine of 1.3 mg/dL on both Visit 2 and 3 (ULN=1.2 mg/dL)

The most common elevated creatinine level in Study 302 was 1.3 mg/dL (Moviprep = 7; Suprep = 4), followed by 1.4 mg/dL (Moviprep=1; Suprep = 4), and 1.2 mg/dL (one each arm). Upper limit of normal was 1.1 or 1.2 mg/dL. All creatinines of 1.4 mg/dL were documented at the Day 30 visit. The single Moviprep patient with elevated creatinines at both Visits 2 and 3 had a creatinine of 1.3 mg/dL.

The applicant provided analyses of the patients whose baseline creatinine was elevated and who developed further incremental increases of creatinine on study, summarized below.

Table 30: Shifts in Creatinine in Patients Whose Baseline Creatinine Was High

	Study 301		Study 302	
	Suprep	Moviprep	Suprep	Moviprep
Proportion with **High Baseline Creatinine** [Range]	20 (10.3%) [1.2-1.6]	5 (11.9%) [1.2-2.1]	14 (7.7%) [1.3-1.6]	15 (8.2%) [1.2-2.8]
Creatinine Increased Further at Visit 2 Only [Range]	2 (1.0%) [1.4-1.5]	0	2 (1.1%) [1.4-1.5]	0
Creatinine Increased Further at Visit 3 Only [Range]	1 (0.5%) [1.4]	4 (2.1%) [1.3-1.6]	1 (0.6%) [1.7]	3 (1.6%) [1.6-2.3]
Creatinine Increased Further at Visit 2 AND Visit 3 [Range]	1 (0.5%) [1.4]	4 (2.1%) [1.3-2.0]	1 (0.6%) [1.4]	0

These data show that there were more patients in the Moviprep arm of the "Same day/evening only" regimen Study 301 that developed further incremental increase in creatinine than in the Suprep arm. Those events were limited to elevations at both Visit 2 and 3, or Visit 3 only. Only the Suprep arm of Study 301 had patients who experienced an incremental increase on the Day of Colonoscopy that resolved by Day 30. There were fewer overall events of incremental increase of creatinine in patients with elevated baseline creatinines treated with the "Split dose" regimen in Study 302. The events in the Moviprep arm were limited to Day 30. The Suprep arm in Study 302 had the only event limited to Visit 2 (similar to Study 301). There was only one patient who had incremental elevation at both Visit 2 and 3 in Study 302, a patient treated with Suprep.

The Cardiorenal Reviewer recommended that patients who develop elevation in creatinine after Suprep exposure should be treated with volume resuscitation, discontinuation of medications that could contribute, such as diuretics, NSAIDs, ACE inhibitors, and Angiotensin II Receptor Blockers, and other standard management. She suggested that additional PK data should be collected to evaluate serum pH, urine pH, anion gap, serum calcium, serum magnesium, and uric acid measured at several intervals post-ingestion, in order to better understand the metabolic effects of Suprep.

Creatine Kinase – The Clinical Reviewer observed CK elevations in both Suprep (N=6) and Moviprep (N=4) arms in both studies. Isoenzymes were not available. In the majority, the elevation was most pronounced at the one-month follow-up visit (4/4 in Moviprep and 4/6 in the Suprep arm). A number of the patients had elevated CK at baseline. None of these CK elevations was associated with cardiac symptoms or other clinical sequelae. The Applicant proposed exercise or medications as the etiology because a number of the patients were taking concomitant "statins". No other clinical correlates were identified by the Clinical Reviewer.

Statistical Reviewers' Overall Summary of Safety

The Safety Statistical consult reviewers' summary comments included the following:

1) Evidence suggests a relationship between Suprep and the number of subjects for whom calcium falls outside the range of normal (high/low) and for whom uric acid is elevated. There was no interaction with a demographic category for these abnormalities.
2) Evidence suggests that for both Suprep and Moviprep the "Split dose" regimen is related to more subjects with abnormal calcium values (high/low). No interaction with a demographic variable was identified.
3) Evidence suggests a lower rate of abnormal chloride (high/low) with Suprep relative to Moviprep. No demographic interaction was identified.
4) Across treatments and administration regimens, there appears to be a relationship between gender and developing an abnormally high creatinine.

The Statistical reviewers explored the data for a relationship between serum chemistry abnormalities and development of specific adverse events. Their observations included:

1) For Suprep, the "Same day" regimen was more strongly related with abdominal distension adverse events than the "Split dose" regimen - 57% vs. 43%.
2) For both Suprep and Moviprep, patients whose serum osmolality became abnormal (high/low) had a greater likelihood of experiencing abdominal pain adverse events.
3) For both Suprep and Moviprep, patients whose serum sodium became abnormal were more likely to have experienced vomiting adverse events.
4) Females in all treatment arms and administration schedules were at higher risk for reporting abdominal distension, abdominal pain, discomfort, nausea and vomiting.

Historical Record: Safety Evaluations in Previously Approved Osmotic Bowel Preps

The Clinical reviewers expressed concern that laboratory and vital signs evaluations in the Suprep NDA were limited to the day of colonoscopy (Visit 2) and one month later. (The

median time from last dose of Suprep to the Visit 2 blood sample was 5.7 hours in Study 302 and 13.75 hours in Study 301.) The NDA reviews for previously approved osmotic bowel prep products were examined to determine the extent of follow-up evaluations performed in the trials supporting those applications.

Moviprep NDA: Electrolytes were evaluated on the day of colonoscopy in the two major trials that supported product labeling. The labeled electrolyte adverse event data are limited to the same day regimen comparison of Moviprep to OSP. The clinical review was examined to identify any additional electrolyte information that was not included in the product label. The Moviprep clinical review included the following electrolyte shift summary:

Table 31: Summary of Changes in Electrolytes Observed in Moviprep Trials

	German Study (Split Dose)		French (Same Day Regimen)	
	Moviprep %	GoLytely %	Moviprep %	OSP %
Sodium				
Hypernatremia	1%	1%	2%	5%
Hyponatremia	2%	2%	0	2%
Potassium				
Hyperkalemia	0	0	1%	1%
Hypokalemia	5%	8%	8%	31%
Creatinine Increased	2%	1%	1%	2%
BUN Increased	0	0	1%	2%
Increased AST/ALT	7%/3%	5%/3%	NA	NA

The most common electrolyte abnormality (aside from hyperphosphatemia) was hypokalemia. Creatinine increases were observed in the range of 1-2%, similar to the Suprep NDA.

The Moviprep NDA Clinical reviewer considered the laboratory evaluation schedule inadequate because the last evaluation was before the colonoscopy procedure, i.e., no more than 2 hours pre-procedure. He pointed out that previous Visicol NDA registration studies included laboratory evaluation 2-3 days after colonoscopy. The Suprep NDA also lacks that 2-3 day follow-up, but did perform an evaluation not previously incorporated in bowel prep development plans, a Day 30 follow-up visit.

Visicol NDA (2-3 day post colonoscopy follow-up): The Visicol NDA (21-097, approved in 2000) is relevant because it included a Day 2-3 post colonoscopy evaluation, the comparator product was a PEG based product (Nulytely) administered in a split dose regimen similar to the regimen in Study 302 (one dose the evening prior to colonoscopy and one dose the morning of colonoscopy, 3-5 hours before), and Visicol is in the OSP class of products that was subject to the recent FDAAA action due to acute phosphate nephropathy (Black Box, Medication Guide, Required Safety Trial). It is the only NDA identified with a post colonoscopy assessment. The Day 2-3 post colonoscopy serum chemistry evaluation should permit exploration for serum chemistry changes that could have been missed in the Suprep

NDA (with its lack of an interval evaluation between the day of colonoscopy and one month follow-up).

The summary of group mean electrolyte changes by assessment day, reproduced below from the NDA review, shows that the day of colonoscopy (Visit 1) changes had resolved or nearly resolved by Day 2-3 (Visit 2). The differences between Visicol and the PEG product Nulytely were most marked for sodium, phosphorus, and bicarbonate. NuLytely contains PEG 3340 [420g], sodium chloride [11.2 g], sodium bicarbonate [5.72 g] and potassium chloride [1.48g].

Table 32: Mean Changes in Electrolytes Across Study Visits (including 1-2 Days post Colonoscopy Visit 2 in the Visicol NDA Trials

Table 26. Mean Changes in Electrolyte Values from Baseline - Combined Data Studies 301 and 302

	Diacol (n=427)			NuLYTELY (n=432)		
Analyte (normal range)	Screening	Visit 1	Visit 2	Screening	Visit 1	Visit 2
Sodium (138-148 mEq/L)	138.4	2.3	0.3	138.3	0.7	0.0
Potassium (3.5-5.1 mEq/L)	4.2	-0.6	-0.1	4.2	-0.1	-0.1
Calcium (8.6-10.4 mg/dL)	9.1	-0.5	-0.1	9.1	-0.1	-0.1
Phosphorus (2.4-4.7 mg/dL)	3.3	3.7	-0.7	3.3	0.0	0.0
Bicarbonate (22-30 mEq/L)	27.3	-1.7	-0.5	27.1	-0.9	-0.4
Magnesium (1.3-2.5 mg/dL)	1.9	0.0	0.0	1.9	0.0	-0.1

Source: ISS Table 26

In an exploratory cross study comparison, the mean changes on the day of colonoscopy for Moviprep in Study 302 of the Suprep NDA were compared to the mean changes in the table above. The Moviprep mean change for sodium (+0.57, SD 2.6), potassium (-0.02, SD 0.48), phosphorus (-0.04, SD 0.52), magnesium (-0.01, SD 0.13) and calcium (-0.16, SD 0.41) are similar to the mean change for Nulytely above. The Moviprep mean change for bicarbonate in Study 302 (-1.68, SD 2.7), however, was less similar to the change noted for Nulytely (-0.9), and appears more comparable to the result for Visicol, -1.7.

The summary table of treatment emergent chemistry adverse events from the Visicol NDA clinical review is reproduced below. Unfortunately, this table doesn't discern between events documented on the day of colonoscopy and those 2-3 days later. The differences between Visicol and Nulytely in mean changes of potassium, phosphorus, calcium are reflected in differences of proportions of patients with hypokalemia, hyperphosphatemia, hypocalcemia, and hypophosphatemia between arms that were nominally significant; however, although there appeared to be a difference between Visicol and Nulytely in mean change in bicarbonate levels, the proportions of patients with acidosis appeared similar. The proportion with acidosis was similar to that observed on the day of colonoscopy in Suprep Study 302.

Table 33: Treatment Emergent Adverse Events in the Visicol NDA Trials:

Table 23. Treatment emergent adverse events in serum chemistry- number (%) of All Treated Patients (adverse events occurring in ≥1% of patients in the All Diacol group)

Body System & COSTART term	Diacol			NuLYTELY Studies 301 & 302 (n=432)	Diacol 60 g (301/302) vs NuLYTELY p-value
	All Patients (n=548)	60 g Studies 101, 201, 301 & 302 (n=481)	60 g Studies 301 & 302 (n=427)		
Any adverse events	526 (96.0)	459 (95.4)	405 (94.8)	407 (94.2)	
Metabolic/Nutritional	475 (86.7)	408 (84.8)	357 (83.6)	291 (67.4)	<0.0001
Hypochloremia	194 (35.4)	173 (36.0)	166 (38.9)	172 (39.8)	
Hypokalemia	176 (32.1)	171 (35.6)	156 (36.5)	38 (8.8)	<0.0001
Hyperphosphatemia	173 (31.6)	107 (22.2)	73 (17.1)	0 (0.0)	<0.0001
Alkalosis (increased bicarbonate)	131 (23.9)	114 (23.7)	87 (20.4)	81 (18.8)	
Hypocalcemia	101 (18.4)	70 (14.6)	54 (12.6)	2 (0.5)	<0.0001
Hypophosphatemia	84 (15.3)	75 (15.6)	62 (14.5)	4 (0.9)	<0.0001
Acidosis (decreased bicarbonate)	83 (15.1)	80 (16.6)	79 (18.5)	62 (14.4)	
Hyponatremia	75 (13.7)	63 (13.1)	40 (9.4)	53 (12.3)	
Hypervolemia (decreased BUN, creatinine)	56 (10.2)	55 (11.4)	54 (12.6)	51 (11.8)	
Hyperglycemia	16 (2.9)	2 (0.4)	0 (0.0)	0 (0.0)	
BUN increase	13 (2.4)	11 (2.3)	10 (2.3)	12 (2.8)	
Hyperkalemia	11 (2.0)	9 (1.9)	7 (1.6)	24 (5.6)	0.0028
Creatinine increase	9 (1.6)	6 (1.2)	5 (1.2)	11 (2.5)	

Elevated creatinine was reported in 1.2% of Visicol patients vs. 2.5% in the NuLytely control arm. The rate for NuLytely appears somewhat higher than the treatment emergent pre-colonoscopy rate in the Moviprep arm of Study 302 (0.6%). The Visit 3 (one month follow-up) rate of treatment emergent creatinine elevation in the Suprep NDA was 4% for Moviprep. The rate of treatment emergent high serum creatinine in the Suprep arm of Study 302 was 2% pre-colonoscopy and 2.8% at the follow-up visit. These cross study comparisons are at best exploratory, but suggest the Day 30 evaluation in the Suprep studies was effective at detecting additional events. However, the additional elevations could have been secondary to intervening medical conditions, such as new medications, surgery or new medical conditions.

Nulytely - The reviewer of the Nulytely NDA expressed concern that there was no interval evaluation of electrolyte shifts between the time of administration of the prep and the time that the patient presented for colonoscopy (and blood sample). Although there was no post-colonoscopy serum chemistry evaluated either, the deficiency identified by the reviewer was

the lack of capture of electrolyte data between pre-ingestion of Nulytely and the pre-colonoscopy serum chemistry sample.

Despite the lack of post colonoscopy laboratory evaluations, the description of the safety outcome from Protocol 7 of the NuLytely NDA is of interest since that trial was a comparison of pre-prep and post-prep mean values of NuLytely and a "standard prep". The "standard prep" was a combination of diet restriction, "cathartic" and enemas. The data from the standard prep from this trial are of interest since it shows the electrolyte changes that one can expect from the bowel preparation utilized prior to availability of approved and marketed osmotic bowel preps. These data were presented in tabular form (reproduced below). Although the timing of the post-prep evaluation is not contained in the review, it appears to have been pre-colonoscopy. Serum creatinines were not provided. The laboratory evaluation includes urine specific gravity, which decreases in both groups. The group mean serum bicarbonate decreased in both groups, equally, and is comparable to the mean drop in bicarbonate observed in the arms of the studies submitted for review in this Suprep NDA, in which bicarbonate fell by <1.0 mEq/L in the Suprep arm in each study, but the mean decrease in the Moviprep arm was greater – 1.6 mEq and 1.7 mEq. BUN and urine specific gravity decreased in both groups. In the Suprep NDA, BUN also declined. An elevation could be expected with volume contraction.

Table 34: Changes in Specific Laboratory Measures Associated with NuLytely and a "Standard Prep" that included diet restriction, enemas and cathartic.

Table 3
LABORATORY MEASUREMENTS SUMMARY
Surgery
(Braintree Protocol #7)

Measurement	Pre(SD)	Post(SD)	Post - Pre (SD)	ta (Pooled SD)	p
Hemoglobin (g/dl)					
NuLytely	12.6(2.2)	12.5(1.8)	-0.1 (1.3)	-0.54b	.58
Std Prep	13.1(1.9)	13.1(2.0)	0.0 (1.3)	(1.3)	
Hematocrit (%)					
NuLytely	38.0(6.0)	37.3(4.9)	-0.7 (3.4)	-1.15	.25
Std Prep	38.9(5.4)	39.3(5.7)	0.4 (4.0)	(3.7)	
Specific Gr.					
NuLytely	1.019(.007)	1.015(.007)	-0.004(.009)	-1.43	.16
Std Prep	1.018(.008)	1.017(.008)	-0.001(.010)	(0.009)	
Sodium (mEq/l)					
NuLytely	141.4(3.4)	139.2(3.2)	-2.2(4.1)	0.02	.98
Std Prep	140.5(3.0)	138.4(4.3)	-2.1(5.0)	(4.6)	
Potassium (mEq/l)					
NuLytely	4.13(0.6)	4.10(0.5)	-0.03(0.5)	0.04	.97
Std Prep	4.23(0.4)	4.21(0.5)	-0.02(0.7)	(0.6)	
Chloride (mEq/l)					
NuLytely	103.4(3.2)	105.0(3.8)	1.6(4.0)	1.8	.07
Std Prep	103.9(4.2)	103.3(5.4)	-0.4(5.1)	(4.6)	
CO2 (mEq/l)					
NuLytely	26.3(3.9)	25.6(4.1)	-0.9(3.7)	0.19	.85
Std Prep	26.7(3.6)	25.7(3.8)	-1.0(4.3)	(4.0)	
BUN (mg/dl)					
NuLytely	15.4(16.0)	14.0(14.8)	-1.4(3.9)	0.60	.55
Std Prep	11.5(5.2)	10.5(5.6)	-1.0(5.4)	(4.7)	

Summary Comments

The Clinical Reviewers of the Suprep NDA have raised concerns about the lack of an interval serum chemistry evaluation between the Day of colonoscopy and the one month follow-up visit. The reviewers of other bowel prep product NDAs have expressed concern about the adequacy of safety evaluations included in the major trials supporting those applications. In the NuLytely NDA, the Clinical reviewer expressed concern about the lack of interval serum electrolyte evaluation between the last administered dose of the product and the time of presentation for colonoscopy. The reviewer of the Moviprep NDA voiced concern that there had been no follow-up blood sampling after the colonoscopy visit, pointing to the Visicol NDA in which there had been a laboratory evaluation 2-3 days after colonoscopy that documented serum chemistries returning to normal.

The current NDA performed the follow-up laboratory evaluation on Day 30. The longer interval period after colonoscopy had been viewed as an advantage in the negotiations of the development plan because the original control arm for the development program was an OSP product, and the Division wanted to see laboratory evaluations at a greater time interval after colonoscopy in light of concerns raised in the literature about delayed recognition of phosphate nephropathy after exposure to sodium phosphate products. This NDA is unusual, relative to currently marketed bowel preps, in that the development plan included this delayed one month follow-up evaluation in the registration trial design. The Visicol NDA is the only NDA identified that incorporated post colonoscopy evaluations of electrolytes in a registration trial (2-3 days after colonoscopy). As described above, the information available on resolution of electrolyte shifts from that NDA are limited, but for the electrolytes presented in a summary table reproduced from that NDA, there was near complete resolution of shifts by the Day 2-3 follow-up. The resolution of shifts within 2-3 days post colonoscopy suggests that an interval check between the day of colonoscopy and Day 30 would not have identified additional relevant safety signals in the two major trials submitted in support of the Suprep NDA.

The Clinical Reviewer recommended approval with postmarketing requirements to obtain additional safety data. The CDTL concluded the safety evaluation in this NDA were inadequate and recommended a Complete Response action, stating that additional safety information should be obtained pre-approval. Please refer to the Risk/Benefit discussion at the end of my review for a detailed presentation of the important issues raised in the CDTL review. I have determined that the product cannot be approved with labeling that includes the "Same day/evening only" regimen, because the risk/benefit ratio does not support approval of that regimen. The "Split dose" regimen is approvable with appropriate labeling that describes the potential adverse events that can occur with an osmotic bowel prep product. The product label will contain Warnings and Precautions similar to those found in the other osmotic bowel prep agents, including the oral sodium phosphate products, with the exception of the warning regarding acute phosphate nephropathy and nephrocalcinosis. The product will also be required to have a Medication Guide, as described below:

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution to ensure that the benefits of the drug outweigh the risks of fluid and electrolyte disturbances that can lead to serious adverse events, including cardiac arrhythmias, seizures and renal impairment. In reaching this determination, we considered the following:

A. An estimate of the size of the population likely to use SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution is difficult and is influenced by the number of colonoscopies performed and the fact that alternative preparations available for bowel cleansing in the US. Between 4 and 15 million Americans have the potential to be exposed to SUPREP Bowel Prep Kit(sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution, based on estimates in the literature of annual screening and diagnostic colonoscopy rates in the US in 2000.[i,ii]

B. SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution is used as part of a bowel cleansing regimen to prepare the patient for colonoscopy. Screening colonoscopy is a procedure recommended by the American Cancer Society[iii]. Screening colonoscopy can lead to early detection of colon cancer and adenomatous colon polyps, which if not removed could lead to colon cancer.

C. SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution has been shown to be effective in cleansing the colon prior to colonoscopy. A poor preparation can lead to missed lesions. The current recommendation for colonoscopy for individuals of average risk for colon cancer begins at age 50 with follow-up every 10 years thereafter if the procedure does not detect lesions. The potential benefits of these products are adequate preparation prior to a colonoscopy permitting better visualization of polyps or cancers in the colon. Early detection of colon cancer can result in more effective treatment and survival advantage. Detection and removal of adenomatous polyps can interrupt their progression to cancer.

D. SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution is administered for one course prior to colonoscopy. The whole course, including liquid intake and bowel cleansing, is finished within 24 hours.

E. Osmotic bowel preps can cause fluid and electrolyte disturbances. There have been reports of serious adverse events including cardiac arrhythmias, seizures and renal impairment associated with osmotic bowel preps. Risk factors for adverse events associated with fluid and electrolyte disturbances include hypovolemia, baseline kidney disease, and use of medicines that affect renal perfusion or function (such as diuretics, angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and possibly nonsteroidal anti-inflammatory drugs [NSAIDs]).

F. SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution. FDA has determined that SUPREP Bowel Prep Kit poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution. FDA has determined that SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution is a product for which patient labeling could help prevent serious adverse effects.

The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

In addition, as a condition of approval the Applicant will be required under Section 505(o) of the Federal Food, Drug, and Cosmetic Act to conduct the following PMR study and trials:

1580-6: A prospective, descriptive epidemiologic study to identify adverse events associated with SUPREP administration in 20,000 patients undergoing screening colonoscopy and 20,000 patients in an appropriate control group. This study should be conducted in a data resource with access to electronic medical records (EMR); a claims-only database is insufficient. The eligible population will be all patients prescribed SUPREP. Outcomes of interest are those that occur within three months of SUPREP administration.

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 SUPREP prior to colonoscopy.

1580-8: A clinical trial to assess ECG changes to capture maximum effects of sulfate exposures in subjects taking SUPREP.

9. Advisory Committee Meeting

There was no Advisory Committee convened to discuss this application. The application, however, was presented at a Regulatory Briefing on August 28, 2009. The Division presented

to the briefing panel that while Suprep is a sulfate-based bowel preparation and the oral sodium phosphate products are phosphate based, they are all osmotic laxatives. The Division of Gastroenterology Products (DGP) presented its concerns that Suprep may have risks that are present with other osmotic laxatives, including renal impairment, cardiac arrhythmias, colonic mucosal ulcers, and ischemic colitis. The DGP sought advice of the Regulatory Briefing Panel whether an additional safety study should be conducted pre-approval to provide a more intensive safety evaluation of Suprep or if a required postmarketing safety study would be a more appropriate means to acquire additional safety information. The following questions were presented for discussion:

1. Should safety investigations be required pre-approval to provide additional safety data for Suprep?

   If yes, should these investigations include:
   a. Repeat of active-controlled Phase 3 trials with additional safety monitoring?
   b. Large, uncontrolled safety study?

2. If no further investigations are required pre-approval, should there be Post-Marketing Requirements (PMRs) for additional safety data?

   If yes, should these PMRs include:
   a. Repeat of active-controlled Phase 3 trials with additional safety monitoring?
   b. Large, uncontrolled safety study?

3. If repeated Phase 3 trials are required (either pre- or post-marketing), what study design elements should be required:
   a. ECGs?
   b. U/A?
   c. Orthostatic vital signs?
   d. More intensive safety evaluation between the day of colonoscopy and Day 30? If so, what testing and when?
   e. Baseline blood tests closer to the beginning of the prep?
   f. Monitoring beyond 30 days?
   g. Other?

4. If a large safety study is required (either pre- or post-marketing), what should be specified regarding:
   a. Size?
   b. Duration?
   c. Type and intensity of safety monitoring?

5. If Suprep is approved without additional pre-market studies, how should this new osmotic laxative be labeled regarding safety?

In the discussion that followed the presentations, members of the panel noted that in order for DGP to require additional safety data pre-approval, the division would have to explain why the

Special Protocol Assessment agreement is no longer valid and should carefully consider whether science has changed in the time since the agreement was made. A member of the panel recommended studying approximately 2000 patients to better characterize safety, and that a control group would be critical. Some members of the panel recommended that the safety be further characterized prior to approval, while others recommended that the safety be further characterized in a PMR trial.

10. Pediatrics

The application was presented to the Pediatric Research Committee (PeRC) on April 29, 2009, and the PeRC recommended that studies in pediatric patients should be required because Suprep represents a new therapeutic option. The Committee recommended that studies should be required down to the age of 6 months. A PEG product, NuLytely, is approved for use down to the age of 6 months.

The applicant's pediatric study plan, which was submitted on March 30, 2009, contained the following:

1) A retrospective survey of colonoscopy rates in the pediatric population
2) An open-label tolerability and effectiveness study in 20 patients ages 12 years to 16 years.
3) A randomized dose-ranging study of 3 different doses of Suprep compared to NuLytely in patients ages 12 years to 16 years.
4) A randomized dose-ranging study of 3 doses of Suprep compared to NuLtyely in patients 3 years to 11 years, if supported by the study in bullet 3 above.
5) A randomized dose-ranging study of 3 different doses of Suprep compared to NuLytely in patients birth to 2 years, if supported by the study in bullet 4 above.

The approval letter will state that we are deferring submission of pediatric studies for ages birth to 16 years because pediatric studies should be delayed until additional safety or effectiveness data have been collected. The deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies and are listed below:

1580-1: Conduct a retrospective study of colonoscopy rates in the pediatric population (birth through 16 years). This data review will determine the number of colonoscopies being performed in the pediatric population. The need to develop an age appropriate formulation will be based on the results of this study.

1580-2: Conduct an open-label pilot study assessing the efficacy and tolerability of Suprep in adolescents (12 to 16 years). The adult formulation (and any age appropriate reformulations) will be evaluated for tolerability and efficacy in this pilot study.

1580-3: Conduct a randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of SUPREP to NuLytely in adolescents (12 to 16 years).

1580-4: Conduct a randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of SUPREP to NuLytely in children (3 years to 11 years).

1580-5: Conduct a randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of SUPREP to NuLytely in children (birth to 2 years).

11. Other Relevant Regulatory Issues

Four clinical sites were inspected by DSI. All 4 received a final classification of VAI (deviations from regulations), but the DSI reviewer determined that the violations would not affect the validity of the data. He concluded that the data from all 4 sites appeared valid 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.

I concur with the CDTL reviewer that the Combination Policy has been adequately addressed in this NDA based on scientific principles. All the ions present in the product contribute to the osmotic effects of the product.

12. Labeling

DMEPA conducted name reviews and had no objections to the proposed proprietary name of Suprep Bowel Prep Kit. DMEPA recommended improvements to sections of the carton and container labels to improve comprehension of instructions for use.

DDMAC made recommendations to improve clarity and formatting. DDMAC's recommendations for labeling revisions to avoid statements in the label that could be promotional were incorporated in the label review and negotiations.

Division of Risk Management (DRISK) provided recommendations for improving the patient instructions for use.

The Cardiorenal consultant recommended that the Division consider including in the label a recommendation against Suprep use in patients with ulcerative colitis.

Additional labeling issues are discussed in the CDTL review. I will summarize those that are related to safety here:

1) The Applicant proposed dosing instructions that were different from the way the drug was used in the clinical studies, (b) (4) I concur with the CDTL that the labeling should provide instructions for use that match the way the product was evaluated in clinical trials. Since the "Same day/evening only" regimen appeared to have lower efficacy

and a higher frequency of adverse reactions than the "Split-dose" regimen, the CDTL recommended that labeling should describe those differences and encourage use of the "Split-dose" regimen when possible. After considering the safety issues associated with the "Same day" dosing regimen, including higher adverse event rates in the elderly and in high risk populations, the increased rate of vomiting, and higher proportion of patients with elevated uric acids, (b) (4)

2) The proposed labeling only included a warning for serious pre-existing GI conditions and a warning not to drink the solution undiluted. Currently approved osmotic laxatives have more complete descriptions in Warnings of the adverse reactions that may arise from the complex electrolyte abnormalities associated with osmotic catharsis. The CDTL recommended that the Warnings text from these related products should be adapted as applicable for Suprep. He recommended that the labeling should have warnings regarding fluid and chemistry abnormalities, cardiac arrhythmias, seizures, and risk when used in patients with renal impairment. He recommended including information regarding the risk of uric acid elevation, which could precipitate a flair in patients with gout. I concur with all these recommendations and they were incorporated in product labeling. He also recommended that because aphthous ulcerations and ischemic colitis have been reported with some bowel preps and there are no studies that eliminate those concerns for this product, a warning with information regarding those risks should be included. This was done.

3) The CDTL recommended that more detailed information on the effects on electrolytes observed in the dataset should be included in labeling. I concur with this recommendation. Section 6 Adverse Reactions of the product label was revised to include a table showing the percentages of patients in the "Split dose" regimen trial who developed new specific serum chemistry changes on the day of colonoscopy. In addition, there is a text description of chemistry abnormalities that developed in the "Same day" regimen trial, with a statement that "Administration of Suprep in an evening-only (1-day) dosing regimen is *not* recommended." Not all numbers in the labeled summary table for chemistry match the numbers found in my review or the Safety Stats Consult review. I have evaluated the patient lists generated by the applicant to create this table and have identified that the differences can be explained by differences in the approach to these analyses. The differences in results were minor and the applicant's summary numbers were accepted, with the exception of anion gap. The applicant was asked to reanalyze anion gap using 13 as the cut-off for normal, (b) (4) and those data were utilized for the labeled table.

4) The CDTL noted that the Warnings for approved osmotic laxatives make reference to drugs that may increase the likelihood of fluid and electrolyte abnormalities or that may increase the risks of complications that result from these fluid and electrolyte abnormalities. He recommended inclusion of a subsection in Section 7 (Drug

Interactions) to call attention to the possibility of this type of drug interaction. I agree that this information should be incorporated in labeling.

5) Section 12.3 (Pharmacokinetics) was revised to include additional information about sulfate kinetics.

6) Section 13 (Nonclinical Toxicology) was revised to provide more complete information about the toxicities seen in the nonclinical studies and to remove statements (b) (4)

7) The Applicant was asked to provide FDA-Approved Patient Labeling (b) (4) that provided more complete information about how to prepare and use the product.

8) As described above, at the end of Section 8 Safety, we determined that a Medication Guide is necessary for patients' safe and effective use of SUPREP Bowel Prep Kit.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval of the "Split dose" regimen with labeling revisions as described above.

- Risk Benefit Assessment – Although all review disciplines have recommended approval, the CDTL has recommended a CR action and that the applicant be required to submit additional safety studies preapproval. Because the "Same day/evening only" regimen appeared to have lower efficacy and a higher frequency of adverse reactions than the "Split dose" regimen, including higher adverse event rates in the elderly and in high risk populations, increased rate of vomiting, higher proportion of patients with elevated uric acids, and higher median decrease in weight associated with increased pulse rate and decreased systolic pressure (suggesting volume contraction), I have concluded that the risk/benefit of the "Same day" dosing regimen does not support its approval. However, I do not agree with the CDTL that the safety data submitted to support the "Split dose" regimen of Suprep for bowel cleansing prior to colonoscopy is inadequate to support the approval of that regimen at this time. In his review, the CDTL has thoughtfully evaluated the adequacy of the safety dataset and provided a clear explanation of the basis for his conclusion. I will address each of his points here.

  1) Lack of ECG data – Although the CDTL notes this as a deficiency, he does not identify this as an issue that should preclude approval. The CDTL states that the few ECGs obtained were in studies of early formulations of the product administered to healthy young adults. He notes that ECGs appear not to have been part of drug development programs for bowel prep applications subsequent to the Visicol NDA in 2000, due to close similarities of these products. In the Visicol NDA, QT prolongation was noted and the QT changes were correlated with hypokalemia and hypocalcemia, which were expected physiologically to have an effect on QT. He acknowledged that the reviewers of the HalfLytely and

MoviPrep NDA's identified absence of ECG data as deficiencies, but he concludes that he accepts that the prior approval of bowel preps without these data provides an adequate argument for not requiring ECGs in the current application. He also concluded that a thorough QT study should not be a requirement for this product, since the components of Suprep have been present in other approved products. I agree with these conclusions. I do think that it is reasonable to ask the applicant to obtain ECG data as part of their PMR post-marketing safety study.

2) Inadequate evaluation of blood chemistry – The CDTL acknowledged that an effect on certain blood chemistries is an expected event with bowel preps. He expressed concern that although the applicant evaluated blood chemistry on the day of colonoscopy, a time when the effect of the prep would be anticipated to be greatest, another short-term follow-up test subsequent to the day of colonoscopy and more proximal than the 1 month follow-up sample, would have helped to determine the persistence of the changes identified on the day of colonoscopy. This additional evaluation after the colonoscopy might also identify delayed, but transient effects. He also noted that sulfate data in the larger clinical trials were not provided and that CKs were not fractionated.

   The Suprep healthy volunteer PK study of the "Split dose" regimen, which is described above in Section 5 Clinical Pharmacology, found that the Tmax of sulfate was 16.8 hours from start of treatment, which occurred 4.8 hours after the second dose of Suprep. The median time from last dose of Suprep to the Visit 2 blood sample was 5.7 hours in the "Split dose" study, Study 302, and 13.75 hours in the "Same day/evening only" study, Study 301. Based on the Tmax from the PK study and the median time from last dose on study to Visit 2 blood sample, it appears that these two studies document the electrolyte effects at or near sulfate Tmax. When patients present for colonoscopy, catharsis has completed, and an IV access is obtained for administration of sedation/IV fluids. I believe that the Visit 2 blood sample obtained when the patient presented for colonoscopy could be reasonably expected to capture electrolytes in the peak period of fluid and electrolyte shifts secondary to the osmotic catharsis.

   The oral sodium phosphate bowel prep Visicol NDA study included a 2-3 day post colonoscopy evaluation, which showed near normalization of major (sodium, potassium, calcium, bicarbonate, magnesium, phosphorus) electrolyte shifts had occurred at that time point, albeit, the comprehensive chemistry data analysis is not available in that NDA review.

   The Suprep PK study in healthy volunteers showed that sulfate levels returned to baseline by Day 6. While it is conceivable that there may have been a new finding detected in the period between the Day 2 visit and the Visit 3 (one month follow-up visit), I do not think that "new finding" would have impacted approvability, in light of the generally unremarkable safety evaluation at Day 30.

While I agree that additional laboratory evaluations in the days between the colonoscopy and the one month follow-up visit in the Suprep NDA could have detected transient interval changes and may have provided an exact time course of resolution of Visit 2 shifts and/or the time of onset of the changes first detected at the one month follow-up visit, it is unknown how many evaluations and when those evaluations should have occurred over the course of a month to assure that the goal of clearly describing the time course of potential meaningful changes was accomplished. Currently, it is unknown how best to monitor serum chemistries in patients who are undergoing bowel preps, i.e., specific timing, frequency, and which patients. The OSP labeled warnings state that health care providers should "Consider performing baseline and post-colonoscopy labs…..in patients who may be at increased risk for serious adverse events…….Also if patients develop vomiting and/or signs of dehydration then measure post-colonoscopy labs"; however, a specific time interval and number of laboratory evaluations is not recommended, because the appropriate specific recommendation is not known.

The last follow-up evaluation (one month) on the Suprep trials provided an opportunity for identifying progressive worsening or non-recovery from changes identified on the day of colonoscopy, in addition to identifying new and persistent changes not documented on the day of colonoscopy that may have been related to the prep. I do not think that the absence of interval information between the day of colonoscopy and one month after colonoscopy is a deficiency that should preclude approval of the product. I think this additional information should be obtained in a required postmarketing trial.

3) Urinalysis was not done in either of the pivotal studies – I agree with the CDTL that a urinalysis is a reasonable component of the safety evaluation of bowel preps since these products have an impact on fluid and electrolytes. While I agree that the existence of urine pH and urine electrolytes would have permitted a clearer understanding of the serum chemistry data for the acid/base and fluid/electrolyte in each patient, and could help identify whether there were any underlying renal tubular effects, it is clear from the submitted safety dataset that bowel preps have a very large, complex and variable impact on human metabolic/volume/electrolyte status and should be expected to have the potential for a detrimental impact on the kidney. The labeling of the currently approved products carry multiple warnings about these risks and Suprep was compared to an approved product in the clinical trials that support this application.

These products are designed to administer an electrolyte load that causes diarrhea. They are partially absorbed, can cause vomiting, and may cause volume contraction. The sulfate in some of osmotic cathartics, including Suprep, is itself an acidic ion that can impact the acid/base balance in the body. 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.

The submitted dataset shows a range of serum chemistry responses to Suprep and Moviprep. Obtaining additional descriptive information could help provide a better understanding of the spectrum of physiological responses to bowel preps in individual patients and may help identify those patients who are more at risk for having one or the other response, including any potential subclinical renal tubular effects. I do not think that this is unique to the Suprep bowel product and that approval of this product should be withheld until more granular information is obtained. However, I do think that these additional assessments should be incorporated in a post marketing trial (PMR). Such information may help identify ways to more effectively provide supportive care during and after bowel preps.

4) Failure to obtain orthostatic vital signs – The CDTL noted that orthostatic vital sign data could have helped elucidate volume status. He only found evidence that orthostatic vital sign data were collected in the Osmoprep NDA. I agree with him that orthostatic vital signs could optimize the ability to detect the product's impact on volume status. Although orthostatic vital sign measures would have been ideal, the applicant did measure weight. Mean changes in weight in the overall safety dataset NDA did show a drop in weight equivalent to a 1 liter decrement in volume related to bowel prep, which could have been anticipated in light of the intended cathartic effect of these product, and the nausea and vomiting reported by patients. However, when median and mean weight changes were examined by treatment regimen ("Same day" vs. "Split dose"), differential effects were observed, and these were supported by changes in pulse and blood pressure. I believe the weight and vital sign measures that were performed in these studies support that patients treated with the "Same day" regimen of Suprep have a higher risk of volume contraction.

5) Lack of coagulation testing – The CDTL expressed concern that the effects of Suprep on coagulation were not evaluated at any phase of this development program. He acknowledges that there are "no special concerns… for this pharmacologic class regarding an effect on coagulation, and there is no a priori expectation of a safety issue based on the composition of Suprep", but stated it should have been performed because testing is readily available and "a reasonably applicable test to incorporate into new drug development." I don't agree that the lack of coagulation testing is a deficiency in this application. Incorporation of laboratory tests in safety evaluation of drug development should not be based on ready availability, but on reasonable expectation that the product might have an impact on the physiologic function that the test evaluates.

6) Lack of systematic collection of endoscopic findings other than cleansing – The CDTL expressed concern that there appeared to have been no systematic collection of adverse events related to endoscopic findings, i.e. aphthous ulceration or ischemic colitis. He was concerned the CRF did not include specific questions

regarding the presence or absence of these observations during the conduct of the colonoscopy. He noted that the studies for the Visicol NDA identified an increased frequency of aphthous ulceration associated with the Visicol prep compared to a PEG-based product. He acknowledged that the study reports in the Suprep NDA did identify a case of ischemic colitis in one MoviPrep patient, but noted that since it did not appear that these types of events were methodically collected, he could not conclude that there were not other events that went unreported.

I agree that the trial conduct would have been improved if these events had been specifically queried for in the CRF; however, it is not clear that the CRF in the Visicol studies specifically collected this information for this product, which was approved despite the imbalance for presence of apthous ulcers compared to the PEG product. It is also not clear that endoscopists who observed aphthous ulcers would not have voluntarily reported them as adverse events, as they routinely report adverse events in clinical trials that are not always specifically queried on CRFs. Review of the CRF reveals that there was a place for investigators to report "colonoscopy findings", separate from the page on which the bowel prep efficacy assessments were collected. Review of the JMP dataset "CL" reveals that investigators did record descriptions of what "pathology" they observed in the procedure, e.g. "moderate sigmoid diverticulosis, severe small, non-bleeding proximal colonic angiodysplasia." I am not concerned that significant pathology that might be attributed to the bowel prep was not captured in these trials. I agree that specific queries for these data can be incorporated into the required postmarketing safety trial and that product labeling should include in Warnings and Precautions the potential risk for ulcerations and ischemic colitis that has been observed with osmotic laxative bowel preps.

7) Inadequate body of safety experience – The CDTL states that "Because Suprep is not directly therapeutic, but is in a sense an adjunct to prophylaxis, there is a large number needed to treat to obtain the benefits of routine endoscopic cancer screening." Based on the premise that bowel preps are used as part of a screening procedure in which most patients will not have need for a therapeutic intervention, the CDTL states that the large number to treat to achieve therapeutic benefit requires setting a low threshold for safety. The CDTL concludes that this justifies and necessitates requiring a much larger safety database for bowel preps than for the "general minimum expectation for a new therapeutic drug." He notes that the rate for serious complications of colonoscopy without biopsy is cited at around 0.1%.[14] Based on this reported rate of colonoscopic complications, the CDTL concludes that it would be appropriate to expect that a new bowel prep for colonoscopy should not substantially contribute to that risk. He calculated that to establish this, an experience in at least 3,000 patients would be needed (to be 95% confident of a risk < 0.1% if no event is seen). This number exceeds the size of the safety database submitted in this NDA. The CDTL states that for this reason the safety database "cannot provide confidence that the incidence of serious reactions

[14] Nelson DB, McQuaid KR, et al. Procedural success and complications of large-scale screening colonoscopy. Gastrointestinal Endoscopy. 2002; 55(3): 307-314.

is much less than 1%." He states that for "a product such as this" a safety database large enough to provide this degree of confidence should be required.

While I agree the Division should reconsider the size and content of the safety datasets it requires for bowel prep marketing applications, I do not entirely agree with the CDTL's recommendations and the foundation for his recommendations. An adequate bowel prep is key to a successful screening colonoscopy as well as surveillance colonoscopy post resection of colon carcinoma and diagnostic colonoscopy. If the colon is not adequately visualized, the patient has undergone a procedure under sedation and taken on all the risk of the procedure without any benefit. Without successful visualization, the prep and procedure have to be repeated, exposing the patient to additional risk. If the visualization is inadequate, a high risk adenoma might be missed and result in the development of an intercurrent carcinoma between screening examinations.

The literature report by Nelson, et. al., cited by the CDTL, states that colon cancer is the second leading cause of cancer mortality in the United States and that screening reduces the mortality from colorectal cancer in average risk, asymptomatic individuals. Studies have reported that removal of polyps reduces subsequent colorectal cancer by 76-90%. The U.S. Preventive Services Task Force recommendations for colorectal cancer screening, last updated in 2008, state that screening should be performed using fecal occult blood testing, sigmoidoscopy, or colonoscopy, in adults beginning at age 50 years and continuing until age 75 years. The American Cancer Society and the U.S. Multi-Society Task Force on Colorectal Cancer state the screening tests that provide full structural examination of the colon are the preferred modality for screening. The authors point out that there has been a shift in screening modalities for the average risk population from a combination of fecal occult blood test + sigmoidoscopy to colonoscopy. The recent increase in screening rates has been driven by increased utilization of colonoscopy since Medicare began reimbursing for its use in 2001. According to the NIH State of the Science Conference Final Panel Statement from February 2010 (http://consensus.nih.gov/2010/colorectalstatement.htm), colonoscopy is the most commonly used screening procedure today. The risks of colonoscopy cited in the panel statement are sedation and perforation.

The study cited by the CDTL to support the size of the safety database needed to evaluate bowel preps (Nelson, et. al.) was a large multicenter trial (VA system) that enrolled 3196 patients to evaluate the efficacy and safety of colonoscopy as a screening modality for asymptomatic individuals at average risk for colorectal neoplasia. Patients were told to contact their center if a complication occurred, and the study coordinator also contacted each patient 24 hours and 1 week after the procedure to solicit reports of adverse events. The bowel prep was a PEG-based electrolyte solution. Only one procedure characteristic was found on adjusted analysis to statistically significantly impact whether the procedure failed, and that was having a poor quality prep. Procedural failure rates ranged from 0.7% to 6.7%

among centers. Approximately 54% of patients had at least 1 polyp removed during the procedure.

The authors reported the proportion of patients who had "major complications" definitely or possibly related to the procedure and "minor complications." Major complications were defined as events that required blood transfusion, hospitalization, surgery or resulted in death. Among the patients who did not have a polypectomy (N=1435), the rate of overall major complications was reportedly 0.1% (2 events in 1435 subjects); however, it is not clear whether this figure was confined to those events considered "definitely related", excluding those that were "possibly related." For the overall group, the rate of major complications was 0.56%. For the overall population, these major complications included GI bleeding (N=7), new onset atrial fibrillation (N=1), MI/CVA (N=4), death within 30 days (N=1), and other (N=4). The "other" category included a thrombosed carotid-subclavian bypass (N=1) attributed to stopping aspirin for the procedure, Fournier's gangrene of the perineum (N=1), thrombophlebitis at the IV site (n=1), and abdominal pain (N=1).

Among the MI/CVA events there were two of some concern to this reviewer from a bowel prep perspective, although the authors did not attribute the events to bowel prep. One was a CVA immediately after the colonoscopy and the other was an MI associated with a vasovagal event immediately after the procedure. In light of sedation administered during the procedure and the procedure itself, it is unknown whether hypovolemia from the bowel prep could have contributed to these events. In addition to the death considered possibly related to the procedure due to its temporal relationship to the endoscopy (witnessed cardiac arrest in the physician's office 2 days after the procedure), there were 2 deaths within 30 days of colonoscopy not considered related by the investigators (one at Day 9 and one at Day 21). One was attributed to "natural causes" and the other was attributed to "electrolyte imbalance/dehydration from alcohol abuse." Delayed recovery from a bowel prep could conceivably have contributed to these deaths. Those 3 deaths (3/3196) represent a 0.1% risk of death in the total population studied (not just limited to those who did not undergo polypectomy). It is likely that in the 3000 patient safety database proposed by the CDTL, a similar rate of death would have been observed, and would have to be weighed in the risk/benefit assessment for approval decisions.

Most of the events considered "definitely related" were confined to the patients who had an intervention, i.e. polypectomy. The authors specifically state that 2 "definitely related" complications occurred in the 1435 subset of patients who did not undergo polypectomy, yielding a "major complication" rate of 0.1% in that population. However, it is unclear from the publication whether the authors reported the major complication rate for the combined "possibly" and "definitely" in this population. The CDTL proposes that the size of the population that should be studied should be based on the event rate in the patients who do not undergo intervention (i.e. polypectomy) since he identifies this subgroup as a population

who did not benefit from the procedure; however, not all polyps removed in this study were adenomatous polyps, and not all adenomatous polyps contain malignant cells or will become malignant. By his definition, the population would have to be extended to those patients who had intervention for a lesion that was not considered pre-malignant or malignant. The authors found the major complication rate for the overall population in this study, 0.5% acceptable, but considered it an overestimation. The total number in a population to exclude an event rate of 0.5% is 600, which is similar in size to the total combined dataset (for both bowel preps) in the Suprep NDA.

Nelson, et. al, also describe "minor complication" rates that did not result in hospitalization and were not broken out based on whether the patient had had a polypectomy or not. Hypotension or vasovagal event occurred in 0.5% (N=15). These "required intervention" but did not have "adverse sequelae." There were 173 (5.4%) additional subjects who had vasovagal events that did not require intervention.

Interestingly, when the authors critically evaluated whether ascertainment of adverse events by patient contact on 1 day and 7 days after colonoscopy was adequate, they cited a publication by Zubarik R, et al. who contacted patients 30 days post colonoscopy to obtain an adverse event history, as evidence that pushing the follow-up out further may have been more ideal. (The 30 day evaluation was utilized in the Suprep NDA trials.) In that published study, 7/1196 reported complications that necessitated hospitalization (0.59%; abdominal discomfort, rectal bleeding, genitourinary problems) and 20 additional patients were seen in the ER (1.7%; abdominal discomfort, rectal bleeding, altered bowel habits, oversedation/fatigue, gas, nausea/vomiting, musculoskeletal pain, genitourinary problems, syncope [n=1], rash, shortness of breath). One hundred eighty-eight patients reported complications (15.7%) at the 30 day follow-up contact, among which 6 were dizziness/syncope and 17 were nausea/vomiting. Most of the overall complications reportedly occurred within 48 hours of the procedure. The most common events were abdominal discomfort and rectal bleeding.[15] In this smaller dataset, 5 patients (0.4%) died before the end of the 30-day follow-up period, but the deaths were not considered procedure related.

Zubarik, et. al, noted that there are no standard definitions for "complications" post procedure. They also noted that surgical specialties use a standard period of 30 days as the recommended period for assessing for procedure-related complications. No such recommended period exists for endoscopy. The authors conclude that more events are recognized if patients are contacted, that these results should not limit the use of colonoscopy, and that clinicians should first recognize the effects of colonoscopy on patients. The exact time that patients should be contacted for assessment was not clear to the authors, and they recommended that this should be studied. I believe this conclusion identifies/supports the need for future studies to

[15] Zubarik R, Fleisher DE, et. al. Prospective analysis of complications 30 days after outpatient colonoscopy. Gastrointestinal Endoscopy. 50(3):322-328, 1999.

define the optimal monitoring and follow-up of patients after endoscopy, including monitoring the effects of post-osmotic catharsis.

8) Role of a SPA in the context of the FD&C Act – I agree with the CDTL that a SPA is specific to a protocol and not an entire development program. I disagree with the CDTL regarding his conclusions about the adequacy of the overall safety database to support the approval of this NDA. He has pointed to the "past decade's experience with bowel preps" as evidence that "a simplified safety screen" is not acceptable to support approval of bowel cleansing products. Presumably the CDTL is referring to the FDAAA-related action in December 2008 for the OSPs, in which the safety issue was acute phosphate nephropathy. At that time, the Agency was unable to make specific recommendations in the OSP product labels about the specific timing of laboratory evaluation, but did not require that the products be removed from the prescription market. A postmarketing trial required under FDAAA for the OSP products will assess renal function and electrolytes at pre-determined intervals following bowel cleansing, which will refine our understanding of the time course of abnormalities in serum chemistry associated with colon cleansing. I believe these assessments should be required as postmarketing trials under FDAAA as a condition for approval of Suprep.

9) Food Drug and Cosmetics Act 505 (d)(1) – this section of the Act is cited by the CDTL as the benchmark for safety that must be met to support approval. "(d) Grounds for refusing application; approval of application; "substantial evidence" defined. If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof."

The CDTL states that while he recognizes that the lack of coagulation testing and orthostatic vital signs may not meet criteria for inadequate testing, he finds it difficult to justify lack of urinalysis and short-term follow-up blood chemistry in the drug development of an osmotic bowel prep. In addition, he has concluded that the overall size of the safety database is inadequate. He further supports his concerns about these short-comings by what is known about the adverse events that have been associated with the available bowel prep products. The ingestion of the large amount of fluid and electrolytes in these products have resulted in class labeling warning of ECG changes, seizures, risks of use in patients with renal impairment or who are taking certain drugs that impact fluid/electrolytes and renal function (though not removal from the market). Nephrocalcinosis has been associated with the oral sodium phosphate products and aphthous ulcerations were observed in the Visicol NDA safety data. He expressed that this historical record of the adverse events associated with these products have established that new bowel preps should be subjected to more thorough evaluation, including targeted

evaluations for safety issues known to be associated with the class. He concludes that in light of the issues in the Suprep NDA safety database that he has identified as inadequacies, the conditions set forth in the Act have not been met.

I do not agree with the CDTL's conclusions. The safety issues cited above resulted in labeling changes, including class labeling, but not removal of prescription bowel prep products from the market. Post-marketing trials were deemed appropriate to further assess safety concerns raised by the OSP class issue that prompted the recent FDAAA action. The CDTL has acknowledged that the statement from the Act that substantial evidence of safety hinges on submission of "adequate tests by all methods reasonably applicable to show whether or not such drug is safe" should not necessarily be interpreted as requiring that applicants submit the results of every known test available to evaluate a drug's impact on physiological systems. While he is willing to set aside the need for coagulation tests and orthostatic vital signs, he is most concerned about the lack of an interval serum chemistry between the time of presentation for colonoscopy and the 1 month follow-up visit and the lack of urinalysis. I have already presented my conclusions regarding whether the lack of the interval serum chemistry is a substantial issue that should preclude approval earlier. They include:

a. The chemistry evaluation on the day of colonoscopy was performed at a time that maximum fluid shift and catharsis should have occurred.

b. I believe that the one month follow-up laboratory evaluation data in this NDA are valuable. There was no clear evidence of irreversible toxicity and Suprep was comparable to the approved bowel prep comparator in terms of safety. We will require postmarketing safety trials as a condition of approval to investigate the time interval between endoscopy and 30 days, and beyond 30 days. These trials will include evaluation of urine chemistries. The goal of the trials is not to establish whether the product is safe, but to better understand the complexities of the volume/acid/base chemistry in individuals. The more intensive evaluation may help define future recommendations for post endoscopy monitoring and supportive care measures.

c) I think the number of patients in the database is adequate to support approval of the product. There were a total of 751 patients in the randomized trials that supported this application, of which 194 were treated with Suprep in the more intensive "Same day" regimen, which was associated with more adverse events, and 181 were treated with the "Split dose" regimen. A total of 375 patients were treated with Suprep in a setting of a concurrent control of an approved and marketed PEG based product. This number falls far short of the 3000 patients that the CDTL proposes should be studied for new osmotic cathartic products, a number based on excluding with confidence an event that occurs at a rate of 0.1%.

The 0.1% event rate was selected by the CDTL because it is the rate of serious complications (leading to transfusion or hospitalization) that were considered definitely related to endoscopy in a subset of patients who underwent screening colonoscopy and did not have a polypectomy, as reported by investigators in the large VA multicenter study (Nelson, et. al.) of screening colonoscopy discussed above. (It is not clear from the publication whether there were additional major complications in this subgroup that were not considered "definitely related", i.e. "possibly related.") However, the overall screened population in the study, including those who had polypectomy, had a rate of serious complication (transfusion or hospitalization) considered definitely or possibly related to the procedure equal to 0.5%, which was considered acceptable by the authors. There were 3 deaths in the study within 30 days of the procedure (0.1%) and there were "vasovagal events" in 5.9%, of which 0.5% required supportive intervention. In comparison, there were 3 SAEs reported in the Suprep NDA, all in the Moviprep arm (3/751=0.4% for the entire randomized trial dataset of patients endoscoped; 3/376 = 0.8% for the Moviprep arm).

I don't agree with the CDTL's foundation for targeting a 0.1% rate for a bowel prep NDA, i.e. using the event rate for the subgroup of patients without polypectomy, based on the conclusion that those patients did not benefit from colonoscopy. In the trial cited by the CDTL, not all patients who underwent polypectomy had a high risk polyp or even an adenoma, so one could argue that not all of the patients who had a polypectomy "benefited" from the procedure. One could argue that all patients who utilize an effective bowel prep that provides adequate visualization of the colonic mucosa experiences benefit from the prep. An adequate prep optimizes the chance that a lesion is not missed, avoiding intercurrent development of a carcinoma between scheduled screening examinations, and assures that the patient does not have to repeat the endoscopy with sedation (with attendant risks) because the initial prep failed.

If the 0.5% event rate observed in the entire endoscoped population in the cited study is used as the foundation to calculate the size of the safety database for drug development of bowel preps, the population to be studied is much lower, 600, and the Suprep NDA still falls short. The Suprep NDA studies and previous NDAs for osmotic cathartic agents have documented vomiting, abdominal pain and electrolyte abnormalities at a higher rate than 0.5%. It is a physiological and clinical fact that fluid and electrolyte shifts can have serious and even life threatening impact, including arrhythmias, seizures and renal insufficiency/failure. The product labels reflect this. There is no reason to believe that Suprep does not carry the same risk. Pushing patient

enrollment numbers to capture and document 0.1-0.5% event rates of the known potential serious consequences of fluid and electrolyte shifts seems unnecessary. If they were documented, they would be expected and the product would still be approved. The serum chemistry data submitted in this NDA has demonstrated that this risk also exists with this Suprep and these data support including in its label the Warnings and Precautions that appear in the other osmotic bowel preps.

Although I don't think that documenting the actual percentage of adverse events predictably related to these products is a worthwhile goal preapproval in this NDA, I do think that a postmarketing required trial (PMR) should be conducted. The ultimate goals of the large safety trial that will be required include developing a better understanding of the impact of Suprep on serum chemistry and the time course of these effects, defining which patients may be more at risk for particular events, and identifying the monitoring and supportive care measures/schedule that should be incorporated to minimize risk of adverse events. If there is a "standard shift" that should occur with this NDA, it makes most sense that it should be to require manufacturers of osmotic bowel preps to answer the important clinical question of specifically who, what and with what evaluation schedule patients who undergo bowel preps should be monitored to optimize the safety of administration of bowel preps for colon cleansing.

Based on the articles cited above that suggest that standard post colonoscopy monitoring of patients is minimal, the fact that patients are generally not endoscoped (and prescribed the bowel prep) by their primary care giver, and the inherent risks of serious fluid and electrolyte shifts that can cause serious adverse events, I have determined that Suprep should be approved with a Medication Guide Only REMS. The Medication Guide will help patients to identify medical conditions and/or medications that may increase their risk for adverse events with the bowel prep and will help them identify symptoms that should prompt them to seek attention from their physician after taking the bowel prep.

In summary, I have concluded that the data in this NDA demonstrate that Suprep administered in the "Split dose" regimen is comparable in safety and efficacy to the approved and marketed product, Moviprep. The major differences identified in the Suprep safety profile relative to Moviprep, for the "Split dose" regimen, was a higher proportion of patients with elevation of uric acid and serum calcium. The difference in uric acid may be related to the higher sulfate content in Suprep, which is an acidic ion and might be expected to decrease uric acid clearance. Although volume contraction could play a role in this, the body weights, vital signs and changes in BUN in the two treatment arms were similar, which does not suggest

that there was greater degree of volume contraction with Suprep administered according to this dose regimen.

The "Same day/evening only" Suprep regimen was associated with an increased rate of vomiting compared to Moviprep. There was also evidence to suggest that there was greater volume contraction associated with this Suprep regimen. There was a higher rate of adverse events in the elderly treated with the "Same day/evening only" regimen and a higher risk of adverse events in "high risk" patients treated with this regimen. The absolute efficacy of this regimen compared to the "Split dose" regimen, in cross-study comparisons, is numerically lower. In the face of unfavorable comparability to the approved product Moviprep for these important safety parameters and weaker evidence of efficacy, I have determined that the "Same day" dosing regimen should not be approved due to an unfavorable risk/benefit profile.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

This NDA will be approved with a Medication Guide only REMS. Please see the approval letter and product label for details. See Section 8 Safety of this review, under Summary Comments, for further discussion.

- 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 the following:

1580-6: A prospective, descriptive epidemiologic study to identify adverse events associated with SUPREP administration in 20,000 patients undergoing screening colonoscopy and 20,000 patients in an appropriate control group. This study should be conducted in a data resource with access to electronic medical records (EMR); a claims-only database is insufficient. The eligible population will be all patients prescribed SUPREP. Outcomes of interest are those that occur within three months of SUPREP administration.

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 SUPREP prior to colonoscopy.

1580-8: A clinical trial to assess ECG changes to capture maximum effects of sulfate exposures in subjects taking SUPREP.

The product will be approved with the following required deferred studies under PREA:

1580-1: Conduct a retrospective study of colonoscopy rates in the pediatric population (birth through 16 years). This data review will determine the number of colonoscopies being

performed in the pediatric population. The need to develop an age appropriate formulation will be based on the results of this study.

1580-2: Conduct an open-label pilot study assessing the efficacy and tolerability of SUPREP in adolescents (12 to 16 years). The adult formulation (and any age appropriate reformulations) will be evaluated for tolerability and efficacy in this pilot study.

1580-3: Conduct a randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of SUPREP to NuLytely in adolescents (12 to 16 years).

1580-4: Conduct a randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of SUPREP to NuLytely in children (3 years to 11 years).

1580-5: Conduct a randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of SUPREP to NuLytely in children (birth to 2 years).

---

[i] Brown ML, Klabunde CN, Mysliwiec P. Current capacity for endoscopic colorectal cancer screening in the United States: data from the National Cancer Institute Survey of Colorectal Cancer Screening Practices. *Am J Med* 115(2):129-133; 2003.

[ii] Laura C. Seeff, Thomas B. Richards, Jean A. Shapiro, et al. How many endoscopies are performed for colorectal cancer screening? Results from CDC's survey of endoscopic capacity. *Gastro* 127: 1670-1677; 2004.

[iii] Levin B, Lieberman DA, McFarland, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: A joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Published online March 5, 2008. *CA Cancer J Clin*. 2008; 58.

Donna Griebel, M.D.
Director, Division Gastroenterology Products
Office of Drugs Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22372	ORIG-1	BRAINTREE LABORATORIES INC	SUPREP BOWEL PREP KIT

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
08/05/2010