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June 25, 2003

**VIA FEDERAL EXPRESS**

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852



**Re: Citizen Petition Requesting That FDA Modify the Tentative Final Monograph on Laxative Drug Products for Over-the-Counter Human Use to Include Professional Labeling for 2 x 30 mL to 2 x 45 mL Dosing of Sodium Phosphates Oral Solution, Administered 10-12 Hours Apart**
**Docket No. 78N-036L**

Dear Sir or Madam:

On behalf of C.B. Fleet Company, Incorporated ("Fleet") of Lynchburg, Virginia, which markets an Over-the-Counter ("OTC") Sodium Phosphates Oral Solution under the brand name Fleet® Phospho-soda®, we submit this Citizen Petition requesting that the Food and Drug Administration ("FDA" or "the Agency") modify the Tentative Final Monograph on Laxative Drug Products for OTC Human Use ("TFM") to include professional labeling for 2 x 30 mL to 2 x 45 mL dosing of Sodium Phosphates Oral Solution, administered 10-12 hours apart. The proposed professional labeling will enable physicians to safely and effectively use Sodium Phosphates Oral Solution at a dosing regimen of 2 x 30 mL to 2 x 45 mL administered 10-12 hours apart for bowel cleansing purposes, prior to diagnostic procedures such as colonoscopy or x-ray, or prior to surgery.

## I. ACTION REQUESTED

Pursuant to 21 C.F.R. § 10.30, this Citizen Petition requests that the Commissioner of Food and Drugs (the "Commissioner") issue a proposed rule to modify the TFM for Laxative Drug Products for OTC Human Use to include the following professional labeling:

**§ 334.80 Professional labeling**

(a) Indications:

(1) "For use as part of a bowel cleansing regimen in preparing the colon for surgery, x-ray or endoscopic examination."

(b) Warnings:

(2) For products containing dibasic sodium phosphate or monobasic sodium phosphate identified in § 334.16(d), (e), or (f)

(i) Oral liquid dosage forms

(A) "Do not use" [these three words in bold print] "in patients with megacolon, gastrointestinal obstruction, ascites, congestive heart failure, kidney disease or in children under 5 years of age."

(B) "Use with Caution" [these three words in bold print] "in patients with impaired renal function, heart disease, acute myocardial infarction, unstable angina, pre-existing electrolyte disturbances, increased risk for electrolyte disturbances (e.g., dehydration, gastric retention, bowel perforation, colitis, ileus, inability to take adequate oral fluid, concomitant use of diuretics or other medications that affect electrolytes), with debilitated or elderly patients or with patients who are taking medications known to prolong the QT interval."

(C) "In at-risk patients, including elderly patients, consider obtaining baseline and post-treatment sodium, potassium, calcium, chloride, bicarbonate, phosphate, blood urea nitrogen, and creatinine values, and consider using the lower end of the dosage range. [this sentence in bold print]. There is a risk of elevated serum levels of sodium and phosphate and decreased levels of calcium and potassium; consequently hypocalcemia, hypokalemia, hyperphosphatemia, hypernatremia, and acidosis may occur."

(D) "Additional fluids by mouth are recommended with all bowel cleansing dosages." [This statement in bold print].

(E) "No other sodium phosphate preparations should be given concomitantly."

(F) "OVERDOSAGE" [this word in bold type] "Overdosage or retention may lead to severe electrolyte disturbances, including hyperphosphatemia, hypernatremia, hypocalcemia, and hypokalemia, as well as dehydration and hypovolemia, with attendant signs and symptoms of these disturbances (such as metabolic acidosis, renal failure, and tetany). Certain severe electrolyte disturbances may lead to cardiac arrhythmia and death. The patient who has taken an overdose should be monitored carefully. Treatment of electrolyte imbalance may require immediate medical intervention with appropriate electrolyte and fluid replacement." [The last sentence in bold print].

(G) PRESCRIBE BY VOLUME. DO NOT PRESCRIBE BY THE BOTTLE AS SERIOUS SIDE EFFECTS FROM OVERDOSAGE MAY OCCUR.

(c) Directions:

(1) For products containing oral sodium phosphates solution

(A) Dosage: Adults and children 12 years of age and over: two doses of sodium phosphate 4.99 to 7.56 grams and sodium biphosphate 13.33 to 20.2 grams taken 10 to 12 hours apart. Children 5 to under 12 years of age: ask a physician. Children under 5 years of age: do not use.

(B) In at-risk patients see "Warnings". Consider using the lower end of the dosage range.

(C) Remain on a clear liquid diet once the first dose is started and drink as much clear liquid as possible, but at least 48 fluid ounces in total as part of and following use of the solution.

## II. Statement of Grounds

Fleet® Phospho-soda® (Sodium Phosphates Oral Solution, USP) is marketed as an OTC laxative product, indicated for use in treatment of occasional constipation. It is also used extensively, under professional labeling and pursuant to a physician's instructions, as a purgative prior to surgery, colonoscopies, and other endoscopic and x-ray examinations. Fleet believes, based on the evidence it has submitted with this Petition, that the 2 x 30 mL to 2 x 45 mL dosing of Fleet® Phospho-soda® administered 10-12 hours apart has been shown safe for bowel cleansing purposes. Specifically, Fleet performed a clinical trial to determine the safety (and efficacy) of Fleet® Phospho-soda® for preparation of the bowel prior to colonoscopy, when two 30- or 45 mL doses are administered within a 10-12 hour period. That final study report is attached as Exhibit A. In addition, Fleet performed a pharmacokinetic study of the product. That final study report is attached as Exhibit B. Therefore, Fleet requests that the Commissioner

modify the TFM for Laxative Drug Products for OTC Human Use to include the professional labeling proposed above.

## A. REGULATORY HISTORY OF DOSING 10-12 HOURS APART

Professional labeling for use of Sodium Phosphates Oral Solution as a bowel cleansing preparation was included in the Proposed Monograph on Laxative Drug Products for OTC Human Use as far back as 1975. See proposed 21 C.F.R. §334.16(a), 40 Fed. Reg. 12940 (March 21, 1975) and proposed 21 C.F.R. §334.80(a), 40 Fed. Reg. 12942. See, also, 40 Fed. Reg. 12911. Professional labeling for the use of Sodium Phosphates Oral Solution as a bowel cleanser was also included in the TFM on Laxative Drug Products for OTC Human Use. See proposed 21 C.F.R. §§334.80(a)(2) and (b)(2), and (c), 50 Fed. Reg. 2157 (January 15, 1985). At about that time, the product began to be extensively used by gastroenterologists, colon and rectal surgeons and other physicians as a bowel cleansing preparation given in 2 x 45 mL, doses usually administered 10-12 hours apart. This practice has continued through the present and is in fact used by a majority of physicians when bowel cleansing is required prior to examination or surgery of the colon. The safety and efficacy of this regimen (and other dosing regimens) is widely reported in medical journals, reference texts and is generally recognized as safe and effective by experts in the appropriate disciplines.

In addition, since 1985, due to improper overdosing or other misuse of Fleet® Phospho-soda® in patients in whom it should not have been used, FDA has reduced package sizes for Sodium Phosphates Oral Solution and has issued labeling requirements relevant to directions for use. See 21 C.F.R. §201.37, as promulgated at 61 Fed. Reg. 27483 (May 21, 1998). Fleet has complied with all of these requirements in marketing Fleet® Phospho-soda®.

Because the product was primarily being dosed for bowel cleansing at 2 x 45 mL given 10-12 hours apart, on March 23, 1993, Fleet filed a Citizen Petition (CP14, Docket 78N-036L) with the Agency requesting that the TFM for OTC Laxative Drug Products for Human Use be amended to include two 45 mL doses of dibasic sodium phosphate/monobasic sodium phosphate solution (hereinafter, "Sodium Phosphates Oral Solution" or "Fleet® Phospho-soda®") in sequential administration 10-12 hours apart as a bowel cleansing system for use prior to surgery or diagnostic procedures of the colon. Fleet provided a number of studies and abstracts demonstrating that the two-dose monobasic and dibasic sodium phosphate bowel preparation administered 10-12 hours apart had been found safe and well tolerated, with equal or better colonic cleansing results and better patient compliance and tolerability than polyethylene glycol (PEG) lavage products also used for bowel cleansing and preparation. This was followed by supplemental submissions by Fleet on December 22, 1993, June 13, 1994, and January 18, 1995, in which Fleet provided the Agency with final published versions of some of the studies relied upon in the original Petition that had been previously submitted in abstract form.[1]

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[1] Vanner, S. J., et al., "A Randomized Prospective Trial Comparing Oral Sodium Phosphate with Standard Polyethylene Glycol-Based Lavage Solution (GoLytely) in the Preparation of Patients for Colonoscopy, " The American Journal of Gastroenterology, 85:422-427, 1990; Haroon, N., et al., "A Randomized Clinical Trial Comparing Oral Sodium Phosphate with Standard Polyethylene Preparation of Patients for Colonoscopy (Abstract), "American Gastroenterological Association, A-529:2112, 1992; Golub, R. W., et al., "Colonoscopic Bowel Preparations--Which One? A Blinded, Prospective, Randomized Trial, " Diseases of the Colon and Rectum, Vol. 38, No. 6, June 1995, 594-599; Bawani, M., et al., "A Single Blinded, Prospectively Randomized Comparison of Oral Phospho-Soda with Polyethylene Glycol Based Solution as a Colonic Lavage for Colonoscopy (Abstract)," The American Journal of Gastroenterology, 86:9, 1991; Del Piano, M. et al., "Comparison Between Three Methods

In May of 1993, at the Agency's request, Fleet withdrew the larger (8 fluid ounce/240 mL) packages of Fleet® Phospho-soda® from the market. The Agency's request arose out of a death that resulted after a nurse administered an entire 240 mL bottle to a patient in lieu of a single 45 mL dose that had been ordered by the physician.

On September 23, 1993, Braintree Laboratories, Inc., manufacturer of PEG lavage products, filed comments opposing Fleet's March 1993 Citizen Petition, asserting that there were safety issues relating to what it termed "electrolyte and hemodynamic effects" associated with the two-dose regimen, and suggesting it should be regulated as a "new drug" requiring approval of a new drug application ("NDA") and also that it should be regulated as a prescription drug. Fleet responded on December 22, 1993, by supplying additional information, and by pointing out that the single patient death emphasized by Braintree and reported in a 1971 *JAMA* article involved a 48-year-old female with chronic constipation who ingested a sodium phosphates-like compound daily in massive overdosages.

Several months later, on March 31, 1994, FDA published a proposed rule to amend the TFM by limiting the container size for oral sodium phosphate laxatives to 90 mL, noting that

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*footnote continued from previous page*

in Preparation for Colonoscopy (unpublished report)," The Greater Charity Hospital, Novara, Italy; Rosetti, C. et al. "Comparison of Two Methods of Preoperative Colonic Cleansing. Results of a Randomized Clinical Trial (Abstract)," presented at the Second World Week of Professional Updating in Surgery and in Surgical and Oncological Disciplines of the University of Milan, July 15-21, 1990; Corman, M.L., Colon and Rectal Surgery, 3rd ed., J.B. Lippincott Co., Phil., PA, pp. 32-35, 1993; Raymond, P.L., et al., "Colonoscopy Preparation, Tolerance, and Efficacy: Polyethylene Glycol Lavage Versus Phospho-Soda Laxative or Avatar 2100 PIEE (Abstract)," American Gastroenterological Association, 87:1273, 1992.

Fleet had already voluntarily withdrawn the 240 mL (8 fl. oz.) package, and also proposing warnings for oral and rectal sodium phosphate products not to exceed the recommended dose. ("Do not exceed recommended dose unless directed by a doctor. Serious side effects may occur from excess dosage.") In the preamble, the Agency stated that:

> Sodium phosphate/sodium biphosphate oral solution is considered safe when taken in the recommended dosage. The 45 mL and 90 mL container sizes are often recommended and prescribed by physicians for bowel cleansing prior to surgery and diagnostic procedures of the colon. However, consumer and health professional confusion with resulting deaths have occurred as a result of the availability of a 240 mL container size . . . In the interest of safety, the agency is proposing to limit the maximum OTC container size of this product to 90 mL . . . This container size will provide enough laxative to use for bowel cleansing. . . .

59 Fed. Reg. 15139, 15140-41. On May 18, 1994, Fleet submitted its comments on the proposed rule, in which it concurred with the package size limitation for oral (but not rectal) sodium phosphates products and noted that it had already, voluntarily, withdrawn the larger packages from the market. Emphasizing that many of the problems relating to the larger package were caused by physician error or patient dosing error, Fleet also requested that the Agency require professional warnings on the product label. It had included such professional warnings on its label for Fleet® Phospho-soda® since the mid-1980's. Braintree followed shortly thereafter with its comments; it again suggested that the two-dose regimen causes dangerous electrolyte changes and that the product therefore should require an NDA to be marketed and should be regulated as a prescription drug. It also requested that the Agency eliminate any packages greater than 45 mL, and it requested a warning against use of more than 45 mL of Sodium Phosphates Oral Solution in a 24-hour period.

Shortly after that, Fleet submitted a new study in support of the then pending Citizen Petition, the Cohen study[2] (Exhibit C), which added further support to its contention that the 2 x 45 mL bowel preparation regimen, administered 10-12 hours apart, had been found safe and effective, and pointed out that Braintree's comments were based on selective use of data. Fleet also submitted the then newly published Huynh[3] study as further evidence of the bowel preparation regimen's safety. In that study, two 45 mL doses administered 5 hours apart -- a worst case scenario, using a dosing regime not advocated by Fleet -- caused a slight increase in serum phosphate levels, which returned to normal within 24 hours, and a slight drop in serum calcium levels, without any evidence of adverse effects.

On March 1, 1996, the Agency issued a letter (Exhibit D) responding to Fleet's March 1993 Citizen Petition. The Agency concluded that the data supported the effectiveness of the two-dose regimen, but the Agency indicated it had concerns about the OTC use of the 2 x 45 mL regimen, 10-12 hours apart, because of electrolyte and vascular volume changes that may occur with its use.[4] It did not raise any issue about the safety of a daily dose of 45 mL of the product. The Agency indicated in that letter that it would not include the two-dose regimen in the Final

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[2] Cohen, S.M., et al., "Prospective, Randomized, Endoscopic-Blinded Trial Comparing Precolonosopy Bowel Cleansing Methods," Diseases of the Colon and Rectum, Vol. 37, No. 7, July, 1994.

[3] Huynh, et al, "Safety Profile of 5-Hour Oral Sodium Phosphate Regimen for Colonoscopy Cleansing: Lack of Clinically Significant Hypocalcemia or Hypovolemia," The American Journal of Gastroenterology, 90:104-107, 1995.

[4] Letter from Debra Bowen, M.D., Director, Division of OTC Drug Evaluation, Office of Drug Evaluation V, Center for Drug Evaluation and Research, to Peter S. Reichertz, counsel for C. B. Fleet Co., Inc. (Exhibit D).

Monograph on Laxative Drug Products for OTC Human Use ("Final Monograph") when published.

However, the Agency also indicated that it was willing to consider the dosage regimen for professional use labeling in the Final Monograph if adequate supporting safety data (as to electrolyte and vascular volume changes) were submitted. As a result of that letter, since that time, Fleet has undertaken a number of studies to address the safety concerns noted above. (These are discussed herein on pages 15 to 19.)

On March 14, 1996, Fleet responded to FDA's March 1, 1996, letter with a submission summarizing the five most recent published studies on the use of Sodium Phosphates Oral Solution regimen for bowel cleansing. Two were previously submitted as abstracts; three were newly submitted with that letter. In that submission, Fleet noted that three of these studies (Golub,[5] Thomson[6] and Clarkston[7]) fell within the dosing scheduling requested in the March 1993 Citizen Petition, a 10-12 hour separation between the two (2) 45 mL doses. The other two

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[5] Golub, R. W., et al., supra. at fn. 1.

[6] Thomson, A. et al., "Bowel Preparation for Colonoscopy: A Randomized Prospective Trial Comparing Sodium Phosphate and Polyethylene Glycol in a Predominantly Elderly Population," Journal of Gastroenterology and Hepatology, 11, 1996, 103-107.

[7] Clarkston, et al., "Oral Sodium Phosphate versus Sulfate-Free Polyethelene Glycol Electrolyte Lavage Solution in Outpatient Preparation for Colonoscopy: A Prospective Comparison," Gastrointestinal Endoscopy, Vol. 43, No. 1, 1996, 42-48.

studies, Afridi[8] and Henderson,[9] which utilized a shorter three (3) to four (4) hour interval, provided even more stringent evidence of the safety of the two-dose, 10-12 hours apart, regimen. The fifth study discussed in that submission, Clarkston, was sponsored by Braintree, and reported that the Fleet® Phospho-soda® two-dose bowel preparation regimen caused statistically significant changes in some serum electrolytes, but it drew no conclusion as to the safety of the regimen.

Also in its March 14, 1996 submission, Fleet pointed out the long history of use of both the one-dose and two-dose Fleet® Phospho-soda® bowel cleansing preparation regimens. Fleet acknowledged that both it and FDA had long recognized that a Sodium Phosphates Oral Solution can have an effect on serum electrolyte levels and had accepted the usefulness of appropriate professional labeling and warnings for patients in whom its use was contraindicated. Importantly, Fleet also noted that, based on FDA's spontaneous reporting system, there was a history of significantly fewer adverse events occurring for the almost 10-year period of 1985 through June 1995, with Fleet® Phospho-soda® (14 reports, 5 hospitalizations, and 4 deaths) than with the PEG lavage (211 reports, 77 hospitalizations, and 11 deaths), and, significantly, that a vast majority of the Fleet® Phospho-soda® adverse event reports that could be identified

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[8] Afridi, Shariq A., et al., "Prospective, Randomized Trial Comparing a New Solution Phosphate-Bisacodyl Regimen with Conventional PEG-ES Lavage for Outpatient Colonoscopy Preparation," Gastrointestinal Endoscopy, Vol. 41, No.5, 1995, 485-489.

[9] Henderson, Joseph M., et al., "Single-Day, Divided Dose Oral Sodium Phosphate Laxative versus Intestinal Lavage as Preparation for Colonoscopy: Efficacy and Patient Tolerance," Gastrointestinal Endoscopy, Vol. 42, No. 3, 1995, 238-243.

and reviewed related to massive overdosing or use in contraindicated conditions or patients. (Fleet acknowledges that reporting adverse events is voluntary for its OTC product, Fleet® Phospho-soda®, while it is mandatory for prescription PEG lavage products.) Finally, Fleet reiterated its position that providing a specific, approved dosing interval would further improve safety of the two-dose regimen, administered 10-12 hours apart.

About 18 months later, on October 8, 1997, undersigned counsel for Fleet notified the Agency of changes that Fleet was making to the professional labeling for Fleet® Phospho-soda® published in the *Physicians' Desk Reference*®. The letter noted that the TFM also proposed, in addition to use as an OTC laxative product, Sodium Phosphates Oral Solution can be used as a purgative for the bowel in preparation for diagnostic procedures or surgery, as reflected by proposals 21 C.F.R. §334.80 (a)(2) and (b)(2), citing 50 Fed. Reg. 2157-8.

About six months after that, on May 21, 1998, the Agency published a final and a proposed rule regarding Sodium Phosphates Oral Solution. First, the Agency published a final rule limiting container sizes for the product to 90 mL and changing the labeling for warnings and dosages for all OTC sodium phosphates preparations, rectal and oral. The rule was codified at 21 C.F.R. §201.307 (Exhibit E) with the stated intention of later moving it to the Final Monograph when published. It also contained language in the preamble indicating that at that time the Agency did not believe that sufficient data to demonstrate the safety of more than 45 mL of Sodium Phosphates Oral Solution within a 24 hour period had been submitted to it (63 Fed. Reg. 27837, 27840). In response to that rule, Fleet relabeled its Fleet® Phospho-soda® product to comply with the new labeling rule. Fleet had at that time already complied with the rule limiting

the size of containers to 90 mL. The Agency also indicated that it would not include professional labeling for the sodium phosphates products in the Final Monograph when published.

The Agency also published that same day a proposed rule that amended the TFM to propose several changes to both the OTC and the professional labeling for both the oral and enema forms of sodium phosphates. (63 Fed. Reg. 27886, May 21, 1998.) As proposed, professional labeling contained a "do not use" warning for patients with congestive heart failure, and a "use with caution" warning for certain patients, including those with impaired renal function, heart disease, preexisting electrolyte disturbances, and the elderly. The proposed professional labeling also recommended monitoring of electrolytes and taking sufficient fluids. Finally, the proposed professional labeling indicated that the reason for these cautions was the risk of hypocalcemia, hyperphosphatemia, hypernatremia, hypokalemia, and acidosis, and that "these conditions are more likely to occur when more than one dose of sodium phosphates is given in a 24 hour period." (63 Fed. Reg. 27888.) Clearly this did not evince the Agency's intention to prohibit the appropriate professional use of the two-dose bowel preparation regimen or evidence any concern about its effectiveness or safety when used properly, but was done just to ensure its safety.

Subsequently, on December 9, 1998, at 63 Fed. Reg. 67817, the Agency published a notice in which it partially withdrew the May 21, 1998 Notice of Proposed Rulemaking (the notice that proposed to amend the TFM). The Agency withdrew those portions of the notice that pertained to the proposed professional labeling. FDA indicated in the December 9, 1998 *Federal Register* notice that it intended to further expand the professional labeling for these products, and

that it would re-propose the professional labeling in the future. To date, the Agency has yet to do so.

On August 23, 2000, Braintree filed yet another Citizen Petition requesting again that oral drug products containing sodium phosphates and labeled for use as bowel cleansing preparations be subject to prescription limitations under Section 503 of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), be regulated as "new drugs" under the FFDCA, and, for the first time, requesting that they bear a boxed warning. Fleet responded to Braintree's Citizen Petition on April 6, 2001, arguing that the requested relief was inappropriate in light of the long history of safe use of the products and the then draft report, now submitted in final as Exhibit A, demonstrating the safety of 2 x 45 mL dosing of the product administered 10-12 hours apart. By letter dated July 19, 2001 (Exhibit F), FDA denied Braintree's Citizen Petition in large part, specifically denying the requests that the product be regulated as a prescription drug and as a "new drug." The Agency also stated "the data do not support the use of a boxed warning." The Agency did state it would propose to eliminate the 90 mL container size of Sodium Phosphates Oral Solution and limit the container size to 45 mL, and that it intended to revise labeling "to inform health professionals and consumers of contraindications and potential adverse effects" associated with use of the products. To date, FDA has yet to issue a rule on limiting the container size to 45 mL or professional labeling. The Agency did, however, post on its web site in October, 2001, a document dated September 17, 2001, entitled "Food and Drug Administration: Science Background Safety of Sodium Phosphates Oral Solution" (Exhibit G), providing such information in the form of a notice to health professionals.

On June 19, 2002, Fleet met with officials of FDA's Division of Gastrointestinal and Coagulation Drug Products, Office of New Drug Evaluation III, and FDA's Office of OTC Drug Evaluation to discuss proposed professional labeling for Fleet® Phospho-soda®, submitted to the Agency for review, along with the studies FDA had requested in its March 1, 1996 letter (Exhibit D). The Agency indicated that it was not at that time prepared to rule on whether the proposed professional labeling submitted by Fleet was appropriate. The Agency stated its concerns about professional labeling for Fleet® Phospho-soda®, and requested certain additional information relating to the studies and use of the product be submitted for review. The Agency indicated that Fleet should file a Citizen Petition seeking approval of its proposed professional labeling as a modification to the TFM after it had developed the requested additional information. The Agency indicated, however, that Fleet need not conduct any further safety studies of the product, and that filing of a Citizen Petition is all that would be required.

**B. THE EVIDENCE SUBMITTED DEMONSTRATES THAT 2 x 30 mL to 2 x 45 mL DOSING 10-12 HOURS APART OF FLEET® PHOSPHO-SODA® (SODIUM PHOSPHATES ORAL SOLUTION) IS SAFE AND EFFECTIVE**

Fleet has now completed two studies that demonstrate, as requested by the Agency, the safety of Fleet® Phospho-soda®, specifically with regard to changes in electrolyte levels and vascular volume - the items raised in the March 1996 letter from the Agency. They are submitted herewith as Exhibits A and B. Combined with other data, submitted previously, and herewith, they demonstrate Sodium Phosphates Oral Solution is safe for use as a bowel purgative given in two doses of 30 mL to 45 mL administered 10-12 hours apart.

**1. Based on clinical studies, Fleet® Phospho-soda® has been shown to be a very safe bowel cleanser when used as directed in a dosing regimen of 2 x 45 mL administered 10-12 hours apart.**

As indicated, Fleet conducted several studies to examine the safety (and effectiveness) of Fleet® Phospho-soda® when used in the 2 x 45 mL dosing regimen administered 10-12 hours apart. Those studies, submitted herewith, support the safety of the product when used as directed. Fleet has submitted herewith two unpublished studies – Exhibit A, PS9902 "A Multi-Center Randomized, Single-Blind, Parallel Group Evaluation of the Effectiveness, Tolerance and Effect on Serum Electrolytes of Two Treatment Regimens of Oral Phospho-soda Solution, USP and GoLYTELY for Bowel Preparation for Colonoscopy" and Exhibit B – "The Time Course and Effect on Serum Electrolytes Following Administration of Phospho-soda® Oral Solution in Healthy Male and Female Volunteers." The results of these studies are summarized in Exhibit H, pages 5-11, and 11-20, and in the following brief discussion.

**a. Unpublished Studies – PS9902 and F00.020**

Fleet is submitting a final report of a clinical trial (PS9902) that demonstrates the excellent safety profile of its Fleet® Phospho-soda® bowel preparation regimen using 2 x 45 mL doses administered 10-12 hours apart. It also demonstrates the safety and efficacy (at lower level of effectiveness) of a 2 x 30 mL dosing of the product also administered 10-12 hours apart. Attached hereto as Exhibit A is the study report for Fleet PS-9902, a clinical trial comparing the effects of two different Fleet® Phospho-soda® bowel preparation regimens and a PEG lavage bowel preparation system (GoLYTELY®).

This clinical study had three parallel treatment arms which compared 2 x 45 mL doses of Fleet® Phospho-soda®, 2 x 30 mL doses of Fleet® Phospho-soda®, and the labeled PEG lavage

bowel preparation regimen, in 222 patients undergoing an elective colonoscopy performed on an outpatient basis. The Fleet® Phospho-soda® doses were administered 10-12 hours apart. GoLYTELY® was administered per its approved labeling. Patients with history of congestive heart failure, recent heart attacks, renal insufficiency, or uncontrolled high blood pressure were excluded. Serum electrolytes were measured during screening, on the morning of the colonoscopy, and at a follow-up visit 24 hours following the colonoscopy. The blinded colonoscopist provided an overall assessment of the bowel preparation and assessments of the amount and consistency of residual stool.

The results of this study demonstrate that the Fleet® Phospho-soda® 2 x 45 mL regimen (10-12 hours apart) was significantly better than the lower-dose (2 x 30 mL) Fleet® Phospho-soda® regimen (also administered 10-12 hours apart) and the PEG lavage regimen in terms of the quality of the bowel preparation as assessed by the colonoscopist, based on the primary as well as the secondary assessment variables. The study also demonstrates that, as to patient tolerability, the subjects generally preferred either Fleet® Phospho-soda® regimen over the PEG lavage regimen (based on expression of outright preference or by the expressed willingness to repeat the regimen for their next colonoscopy).

Most important, however, are the safety data from this study. The incidence of adverse events in the body as a whole was approximately equal across all three treatment groups, and there were no unexpected adverse events, serious or otherwise. As to changes in electrolyte levels, serum phosphorus levels initially increased by an average of 3.2 and 2.4 mg/dL in patients receiving the 2 x 30 mL to 2 x 45 mL Fleet® Phospho-soda® preparations, respectively, but these increases were transient. Small but statistically significant increases in serum sodium, and

decreases in serum potassium, calcium, and magnesium were observed in patients treated with Fleet® Phospho-soda®. There were no changes in vital signs indicating any greater risk of orthostatic hypotension with either Fleet® Phospho-soda® regimen compared to the PEG regimen. **None of the electrolyte changes were associated with any adverse experiences or clinical sequelae. There were no patient deaths, serious adverse experiences, or patients who discontinued the study because of an adverse experience**.

Also enclosed, as Exhibit B, is the final report of a study entitled "The Time Course and Effect on Serum Electrolytes Following Administration of Phospho-soda® Oral Solution in Healthy Male and Female Volunteers." (F00.020). This was a study in 24 healthy adult male and female subjects, balanced for age and gender, reflecting the electrolyte levels at 0, 1, 2, 3, 4, 6, 12, 13, 14, 15, 16, 18, 24, 36, 60 and 84 hours, and vascular volume at 0, 1, 2, 4, 13, 14, 16, 24, 36, 60 and 84 hours after administration of 45 mL of Fleet ® Phospho-soda® at 0 and 12 hours.

The results of the study showed the following:

- Net fluid loss was relatively small.
- Mean serum sodium fluctuated within the normal range, and serum phosphorus concentrations exceeded the upper limits of normal, rising to a peak of 6.86 mg/dL following the second dose. Mean serum sodium and phosphorus concentrations returned to within the range of baseline values by 24 hours after administration of the second dose. The changes in mean serum sodium and phosphorus were associated with decreases in mean serum potassium and calcium (both of which fluctuated within the normal range).

- Mean serum potassium and calcium concentrations returned to within the range of baseline values by 12 hours after administration of the second dose. No individual subjects had clinically significant hypocalcemia or hypokalemia.
- None of the observed ECG changes were considered clinically significant by the investigator.
- The serum electrolyte changes associated with the preparation were not clinically significant, and they resolved within 12 to 24 hours after taking the bowel preparation regimen.

As would be expected from the historical data summarized and analyzed in Exhibit H, the results of this study also demonstrate that the Fleet® Phospho-soda® bowel cleansing regimen of 2 x 45 mL doses administered 10-12 hours apart is both safe and effective when administered to an appropriate patient population. The most significant findings were that there were minor:

- changes in electrolyte levels; and,
- observations consistent with vascular volume changes.

The studies conducted by Fleet thus confirm the safety of the dosing regimen of 2 x 45 mL doses administered 10-12 hours apart, and demonstrate there are no clinically significant changes in electrolytes and/or vascular volume. For ease of reference, attached as Exhibit H which contains a summary of those findings at pages 5-19.

## C. ISSUES RAISED BY FDA RELATING TO THE SAFETY STUDIES.

FDA raised seven issues during the June 19, 2002, meeting with Fleet it said should be addressed in the Citizen Petition it recommended Fleet file to propose to amend the TFM to include the 2 x 30 mL to 2 x 45 mL dosing regimen administered 10-12 hours apart. Those issues were:

1. **Whether clinically significant electrolyte shifts and changes in blood pressure (orthostasis) occur in the healthy elderly population and at what doses (i.e., 2 x 45 mL, 2 x 30 mL).**

2. **Whether 40 ounces of oral fluid intake is the optimum volume to recommend as part of the bowel preparation.**

3. **Whether titrating the dose of the product according to the body mass would preserve efficacy and diminish the incidence of adverse events (i.e. to adequately prepare the colon, does a small, elderly woman need to take the same dose as a large middle-aged man?).**

4. **Whether we need to be concerned about this potential interaction with antiresorptive agents considering the number of women who take them for osteoporosis. (We have one case report about severe hypocalcemia occurring with oral sodium phosphate laxatives in a woman on alendronate.)**

5. **How safe is it to use the product "with caution" in the people with conditions listed in this category in your proposed label? Should those patients receive the preparation in a monitored, hospitalized setting? What information should be provided to the physician?**

6. **We realize that serious adverse events are not common, but we do not know how rare they are. This is an OTC product and the incidence of serious events as a consequence of its use should be as low as possible.**

7. **With regard to efficacy, in study PS9902 the 2 x 30 mL dose is not statistically different from the GoLYTELY (an approved Rx product), but may be associated with fewer adverse events than the 2 x 45 mL dose. It may be that after the data are analyzed, it will be appropriate to recommend the lower instead of the higher oral sodium phosphates dose.**

Fleet has re-evaluated the studies submitted and the available scientific and medical information, and provides the following response to each specific question raised by the Agency as follows:

1. **Whether clinically significant electrolyte shifts and changes in blood pressure (orthostasis) occur in the healthy elderly population and at what doses (i.e., 2 x 45 mL, 2 x 30 mL).**

**Orthostasis**. In Study PS9902 (Exhibit A), orthostasis was defined as a 20mm Hg or greater drop in systolic blood pressure or a 10mm Hg or greater drop in diastolic blood pressure upon moving from a supine to an erect position. The results showed that there were no clinically or statistically significant differences between the three treatment groups (2 x 45 mL; 2 x 30 mL; GoLYTELY) for orthostatically induced differences. This held true whether measuring systolic or diastolic blood pressure at baseline, after bowel preparation or at follow-up (see Table 16, Exhibit A). Orthostatically-induced changes in systolic blood pressure were noted following preparation in one subject (1.4%) in the 2 x 45 mL group and one subject (1.3%) in the 2 x 30 mL group: both of these patients were males, ages 76 and 72, respectively. The second patient also demonstrated an orthostatically induced drop of 10-mm Hg in diastolic pressure. Again after preparation, two subjects (2.9%) in the 2 x 45 mL group showed orthostatically-derived changes in diastolic blood pressure: both of these patients were males, ages 60 and 78. Other than the case described above, there were no additional incidents in the 2 x 30 mL group.

In their review article, Hookey *et al,* (2002; Exhibit I) report that in five studies where 405 patients received a 2 x 45 mL dose of Sodium Phosphates Oral Solution, orthostatic changes occurred in 16% to 28% of patients. However, in studies where sodium phosphate and PEG solutions were compared, there were either no significant differences between the two treatments

or there was a greater percentage of change with PEG. The authors concluded that, while it is difficult to determine the clinical relevance of these changes, they appear to be minor.

**Electrolyte Shifts.** Electrolyte shifts occur in the healthy elderly population. They are not associated with the occurrence of serious adverse experiences or clinical sequelae. Fleet has electrolyte data on an individual subject basis from two studies. In the first study (Cohen *et al.*, 1994, Exhibit C) serum electrolytes were determined during the screening visit and after bowel preparation in subjects who used either GoLYTELY (138 patients), NuLYTELY (141) or the 2 x 45 mL regimen of Fleet® Phospho-soda® (143). About half of the subjects were 70 years of age or older. In the second study, PS9902 unpublished (Exhibit A), serum electrolytes were determined at screening, after bowel preparation and one day after the colonoscopy procedure in subjects who used GoLYTELY (73), a conventional 2 x 45 mL dose of Fleet® Phospho-soda® (74) or a low dose 2 x 30 mL regimen of Fleet® Phospho-soda® (75). Individual patient data from both of these studies were reanalyzed to determine the electrolyte shifts and their effect in the elderly population. The analysis is attached as Exhibit J; a summary of the findings for the most clinically significant electrolytes is presented below.

Combined data from both studies show that, as expected, the serum phosphate increased for both Fleet® Phospho-soda® doses following bowel preparation. This increase was age related, with elderly subjects showing a greater increase. Elderly females showed greater increases than did elderly males. Using data from the Cohen study (Exhibit C), and calculating values adjusted for a set weight of 160 pounds, the increase in elderly (over age 70) females was 3.8 mg/dL while the increase in non-elderly females was 2.8 mg/dL. Similarly, for elderly versus

non-elderly males, the changes were 3.3 mg/dL and 2.5 mg/dL, respectively. These differences for gender and age were statistically significant ($p<.001$).

Overall, some subjects in both studies developed a slight hypernatremia following administration of Fleet® Phospho-soda®. In the Cohen study, 22 of 143 patients (15%) had sodium values between 146 and 148 mEq/L (normal range: 135-145 mEq/L; NCI Grade I hypernatremia: >145 but <150 mEq/L). The change in serum sodium was more variable in females than in males, and was related to age and weight. Since older females tended to have lower weights, it is unclear as to the degree to which each of these factors contributed to the increase. From the clinical perspective, the degree of hypernatremia was minor. The results for change in serum sodium levels in the PS9902 study were similar, with four subjects, age range 57-67, developing Grade I hypernatremia following the 2 x 45 mL dose of Fleet® Phospho-soda®. In three of these subjects, the sodium level had returned to the normal range 24 hours after colonoscopy (the last subject, a 62-year-old male, remained mildly hypernatremic, 148 mEq/L). In this study, none of the 75 subjects who used the 2 x 30 mL regimen developed hypernatremia.

The data from the PS9902 study also showed that mean serum calcium decreased slightly for both Fleet® Phospho-soda® doses following bowel preparation: 0.3 mg/dL and 0.4 mg/dL for the 2x 45mL and 2 x 30 mL dosages, respectively. In contrast to the results observed for serum phosphate, the changes in serum calcium were not age, sex or dose related. The mean decrease in calcium in the Cohen study was 0.28 mEq/L, which mirrors the decrease observed in the PS9902 study. The lowest post-administration values observed in any subject were 8.1

mg/dL in the Cohen study and 7.8 mg/dL in PS9902. These levels are well above the critical value of 6.0 mg/dL.

Finally, in both studies, the average potassium decreased following Fleet® Phospho-soda® administration. Gender, dose and age were not significant predictors of the change in serum potassium, although females exhibited a significantly larger variation in change than did males. No subject in either of the two studies reached the critical value of 2.5 mEq/L. A relatively large increase in serum phosphorus was observed in the limited sample of females over age 70 who were given the standard dosage regimen (2 x 45 mL). This was associated with a relatively large decrease in potassium.

Even though there were no serious adverse experiences associated with the use of Fleet® Phospho-soda® in either of the two studies described above, in order to further enhance its safety Fleet recommends Professional Labeling for Fleet® Phospho-soda® to include elderly patients in the "Use with Caution" section, and also a recommendation that the physician consider using the lower end of the dosage range (2x30 mL) in these patients.

**2. Whether 40 ounces of oral fluid intake is the optimum volume to recommend as part of the bowel preparation.**

The TFM, proposed 21 C.F.R. § 334.66, Labeling of Bowel Cleansing Systems, states that: "The manufacturer should include a detailed set of instructions for intake of at least 40 ounces of clear fluids...during the course of the bowel cleansing regimen." 50 Fed. Reg. 2157, January 15, 1985. The origin of the 40 fluid ounces specified in the TFM is not clear from the TFM comments. It is, however, a well-accepted medical premise that adequate hydration during a bowel-cleansing regimen helps to prevent dehydration and improve cleansing efficacy.

Fleet is not aware of any published clinical study on the relationship of different levels of hydration to the success or safety of the bowel prepping process with two-dose Sodium Phosphates Oral Solution. The scientific literature does, however, reveal a diversity of hydration practices in the published clinical studies involving bowel preparations. Table I lists the published clinical studies clearly utilizing two 45 mL doses of Sodium Phosphate Oral Solution in a pm/am regimen separated by at least 10 hours, along with the amount of hydration specified in each publication. Five of the nine studies specified less than 40 ounces of fluids. There is no correlation between the amount of liquid specified and the cleansing efficacy reported in these studies. The range of fluids in these studies, 22 fluid ounces to 61 fluid ounces, could represent a broad range of hydration practices, or it may only represent an inadequate reporting of the fluid intake during some of the studies.

One unpublished two-site colonoscopy bowel preparation clinical study conducted by Fleet, with a total of 77 patients using 2x45 mL doses of Fleet® Phospho-soda® taken 11 hours apart, did capture on a patient questionnaire the number of glasses of liquids consumed. Table II provides a tabulation of the glasses of water consumed and the corresponding gastroenterologist-rated overall bowel cleansing efficacy. Seventy-one percent of the patients consumed 48 ounces (6 glasses) of fluids, 12% less than 48 ounces and 17% more than 48 ounces. The table shows no clear evidence of a relationship between efficacy of the bowel preparation and the number of glasses that were reported to have been consumed during the administration of Fleet® Phospho-soda®. In fact, in this relatively small study, 92% of the patients who reported taking 48 ounces (6 glasses) of fluids or less had excellent or good overall cleansing, while only 84% of the subjects reporting more than 48 ounces had excellent or good cleansing ratings. Omitted from

this data, however, is the amount of total fluid intake during the time prior to preparation when subjects were encouraged to drink additional clear liquids. No significant adverse events were reported during this study.

Another source of information on hydration practices during bowel preparation is the patient instructions of commercially available bowel cleansing systems (available as kits or through professionally prescribed patient instructions). The patient instructions in saline-laxative-based systems were examined for specified hydration quantities and are tabulated in Table III. These commercially available OTC bowel-cleansing systems specify 48 to 80 ounces of liquid for hydration. Each system also encourages additional hydration through clear liquid meals and statements such as "You must drink all the glasses of the clear liquids listed in the instructions. You may drink more but not less."

In summary, no published scientific study of the ideal hydration during a bowel preparation using saline laxatives (such as Sodium Phosphates Oral Solution or tablets, or magnesium citrate oral solution) has been identified. The TFM recommendation of "at least 40 ounces of clear fluids" is being followed in commercially available kits and professional patient instructions for bowel preparation. The 40 fluid ounce minimum specified quantity of clear liquids is apparently not necessarily followed in all independent clinical practices not using drug manufacturer's patient instructions. The average consumption during a recent two-dose Fleet® Phospho-soda® clinical study was 48 ounces of liquid and no correlation between efficacy and clear liquid consumed was found.

In the proposed professional labeling requested in this Citizen Petition Fleet recommends that the Agency increase the minimal specified intake of clear fluids in both the two-dose

Sodium Phosphates Oral Solution professional labeling and in the other bowel cleansing systems from 40 ounces to 48 ounces. Fleet believes that this would increase the safety margin for hydration during bowel prepping and that this would reflect the most common practice.

**Table I. Published Clinical Studies using Fleet® Phospho-soda® 2 x 45 mL pm/am by Liquids Consumed**

**Liquid Lunch and Dinner**

| Study | Dose | Times | Specified Total Fluids | "Liquid Only" Meals | Clinical Outcome #pts | Clinical Outcome % Excellent/Good | Comments |
|---|---|---|---|---|---|---|---|
| Young (2000) | 2 x 45 mL | 7pm, 6am | ≥61 oz. | Lunch & Dinner | 169 | 85% | |
| Berkelhammer (2002) | 2 x 45 mL | 7pm, 6am | 50.8 oz. | Lunch & Dinner | 297 | 84% in right colon<br>87% in left colon | Dilution Solution (each 45 mL dosage divided into three portions) |
| Kolts (1993) | 2 x 45 mL | 6pm, 6am | 39 oz. | Lunch & Dinner | 34 | 79% (38% = excellent) | |
| Ünal (1998) | 2 x 45 mL | 7pm, 6am | 27 oz. | Lunch & Dinner | 18 | 83% (39% = excellent) | |

**Liquid Dinner, and possibly Lunch**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cohen (1994) | 2 x 45 mL | 4pm, 6am | ≥40 oz. | Lunch (see comment) Dinner | 143 | 90% (65% = excellent) | Patients had 'light lunch' (soup) |
| Clarkston (1996) | 2 x 45 mL | 7pm, 6am | 40 oz. | Dinner | 49 | 82% (45% = excellent) | "Clear liquids after noon" |

**Table I. Published Clinical Studies using Fleet® Phospho-soda® 2 x 45 mL pm/am by Liquids Consumed (continued)**

**Liquid Dinner only**

| Study | Dose | Times | Specified Total Fluids | "Liquid Only" Meals | Clinical Outcome #pts | % Excellent/Good | Comments |
|---|---|---|---|---|---|---|---|
| Chia (1995) | 2 x 45 mL | 6pm, 6am | 22.2 oz. | Dinner | 39 | 85% (unknown in 5% of pts)<br><br>ascending = 0.94<br>transverse = 0.58<br>descending = 0.53<br>rectum = 0.30 | "Regular lunch day before"<br>Segmental grading based: 0= none, 4=solid |
| Marshall (1993) | 2 x 45 mL | 6pm, 6am | 32 oz. | Dinner | 70 | 69% (39% = excellent) | "Usual diet through lunch" |
| Vanner (1990) | 2 x 45 mL | 7pm, 6am | ≥3 oz. | Dinner | 54 | >80% | "Patients received fluids for evening meal" |

1 Berkelhammer C, Ekambaram A, Slva RG. Low-volume oral colonoscopy bowel preparation sodium phosphate and magnesium citrate. *Gastrointest Endosc* 2002 Jul;56(1).89-94
2 Chia YW, Cheng LC, Goh PM, *et al.* Role of oral sodium phosphate and its effectiveness in large bowel preparation for out-patient colonoscopy *J R Coll Surg Edinb* 1995;40(6).374-6
3 Clarkston WK, Tsen TN, Dies DF, *et al* Oral sodium phosphate versus sulfate-free polyethylene glycol electrolyte lavage solution in outpatient preparation for colonoscopy a prospective comparison. *Gastrointest Endosc* 1996,43(1).42-8
4 Cohen SM, Wexner SD, Binderow SR, *et al* Prospective, randomized endoscopic-blinded trial comparing pre-colonoscopy bowel cleansing methods *Dis Colon Rectum* 1994,37(7)·689-96
5 Kolts BE, Lyles WE, Achem SR, *et al.* A comparison of the effectiveness and patient tolerance of oral sodium phosphate, castor oil and standard electrolyte lavage for colonoscopy or sigmoidoscopy preparation *Am J Gastroenterology* 1993,88(8)·1218-23
6 Marshall JB, Pineda JJ, Barthel JS, *et al.* Prospective, randomized trial comparing sodium phosphate solution with polyethylene glycol-electrolyte lavage for colonoscopy preparation *Gastrointest Endosc* 1993;39(5) 631-4
7 Ünal S, Doğan ÜB, Öztürk Z, *et al* A randomized prospective trial comparing 45 and 90 mL oral sodium phosphate with X-prep in the preparation of patients for colonoscopy *Acta Gastroenterol Belg* 1998;61(3).281-284
8 Vanner SJ, MacDonald PH, Paterson WG, *et al* A randomized prospective trial comparing oral phosphate with standard polyethylene glycol-based lavage solution (Golytely) in the preparation of patients for colonoscopy. *Am J Gastroenterol* 1990,85(4) 422-7
9 Young CJ, Simpson RR, King DW, *et al* Oral sodium phosphate solution is a superior colonoscopy preparation to polyethylene glycol with bisacodyl *Dis ColonRectum* 2000·43(11) 1568-71

**Table II. Number of Subjects by Total Water Consumed during Administration of Fleet® Phospho-soda® and Physician Overall Efficacy**

The following table gives a tabulation of the number of subjects by the total number of glasses reported during both administrations of Fleet® Phospho-soda® by the overall physician rating of the efficacy of the preparation of the bowel. Data given in the table is from the Fleet® Phospho-soda® arm of two studies comparing the product to Visicol® sodium phosphate tablets, one conducted in Norfolk, Virginia, and the other conducted in Charlottesville, Virginia.

| Total water (8 oz. glasses) | Clinical Efficacy | | | | Total |
|---|---|---|---|---|---|
| | Poor | Fair | Good | Excellent | |
| 2 | 0 | 0 | 1 | 1 | 2 |
| 3.5 | 0 | 0 | 1 | 0 | 1 |
| 4 | 0 | 0 | 1 | 1 | 2 |
| 5 | 0 | 0 | 1 | 2 | 3 |
| 5.5 | 0 | 0 | 0 | 1 | 1 |
| 6 | 1 | 4 | 9 | 41 | 55 |
| 6.5 | 0 | 1 | 0 | 0 | 1 |
| 7 | 0 | 0 | 0 | 4 | 4 |
| 8 | 0 | 1 | 1 | 4 | 6 |
| 10 | 0 | 0 | 1 | 0 | 1 |
| 19 | 0 | 0 | 1 | 0 | 1 |
| Total | **1** | **6** | **16** | **54** | **77*** |

*A total of 78 patients received Fleet® Phospho-soda®, 1 patient did not respond to the question regarding the number of glasses of water consumed.

**Table III. Commercially Available Saline Bowel Cleansing Systems**

| Product/ Ingredients | Specified Liquid with Administration (instructions) | Total Liquid Specified | Additional Liquid Meals | "Other" Hydration Remarks |
|---|---|---|---|---|
| **Fleet Prep Kits:**<br><br>**#1** NaP, bisacodyl tablets, bisacodyl suppository<br><br>**#2** NaP, bisacodyl tablets, bagenema<br><br>**#3** NaP, bisacodyl tablets, bisacodyl enema | *18 Hour Prep:*<br><br>"Pour into one-half glass of cold clear liquid and drink" "Follow immediately with at least 8 oz. clear liquids"<br><br>"Swallow tablets whole with a full glass of water" | 8 oz. Clear liquid every hour from 1 p.m. until 9 p.m. (8 glasses), plus 4 oz. With NaP, and additional 1 glass with bisacodyl tablets<br><br>9 glasses at 8 oz.<br>4 oz. With NaP<br>**76 oz. Total** | *Lunch*: light meal from listed options<br><br>*Dinner:* clear liquid meal | "You must drink all of the glasses of the clear liquids listed in the instructions. You may drink more but not less" |
| | *24 Hour Prep:*<br>(same as above) | 8 glasses throughout day (including lunch), plus 4 oz. With NaP, and additional 1 glass with bisacodyl tablets<br><br>9 glasses at 8 oz.<br>4 oz. With NaP<br>**76 oz.Total** | *Lunch*: clear liquid meal (at least 8 oz.)<br><br>*Dinner*: clear liquid meal | (same as above) |

**Table III. Commercially Available Saline Bowel Cleansing Systems (continued)**

| Product/ Ingredients | Specified Liquid with Administration (instructions) | Total Liquid Specified | Additional Liquid Meals | "Other" Hydration Remarks |
|---|---|---|---|---|
| **Fleet Prep Kit LS**<br><br>magnesium citrate, bisacodyl tablets, bisacodyl enema | *18 Hour Prep:*<br>"Fill a large glass with 8 oz. of cold water. Add powder…drink the entire glassful and follow with 8 oz. of clear liquids"<br><br>Swallow tablets whole with a full glass of water" | 7 glasses of clear liquids throughout day, plus 1 glass with LS, and 1 glass with tablets.<br><br>9 glasses at 8 oz.<br>**72 oz. Total** | *Dinner:* clear liquid meal | "you must drink at least the number of glasses in the time period recommended" |
| | *24 Hour Prep:*<br>(same as above) | 7 glasses of clear liquids throughout the day, 1 glass with prep, additional 1 glass with tablets.<br><br>9 glasses at 8oz.<br>**72 oz. Total** | *Lunch*: clear liquid meal<br><br>*Dinner:* clear liquid meal | (same as above) |

**Table III. Commercially Available Saline Bowel Cleansing Systems (continued)**

| Product/ Ingredients | Specified Liquid with Administration (instructions) | Total Liquid Specified | Additional Liquid Meals | "Other" Hydration Remarks |
|---|---|---|---|---|
| **Fleet Accu-Prep™**<br><br>sodium phosphate | *For Each of Two Doses:*<br><br>*Step 1*: twist top off pre-measured vial<br><br>*Step 2*: pour all contents into 8 fluid ounces of clear liquid<br><br>*Step 3*: Stir and drink the entire contents<br><br>Repeat steps 1-3 in ten minutes, and again in another ten minutes. | *First dose*: 3 glasses with NaP, then additional 3 glasses of clear liquid<br><br>*Second dose*: 3 glasses with NaP<br><br>first dose: 6 glasses at 8 oz (48 oz.)<br>second dose: 3 glasses at 8 oz. (24 oz.)<br>**72 oz. Total** | *Lunch*: clear liquid meal<br><br>*Dinner:* clear liquid meal | "For each dose you will need 24 fluid ounces of a clear liquid…"<br><br>"Drink at least 3 more glasses (8 oz. each) of Clear Liquids (You may then drink all the Clear Liquids you desire)" |
| **Fleet Phospho-soda®**<br><br>sodium phosphate<br><br>*Patient Bowel Preparation Dosing Instructions* | *For Each of Two Doses:*<br><br>Mix 1.5 oz. with at least 4 oz. cold Clear Liquid and drink. Follow with 8 oz. of Clear Liquid | *Throughout Evening*: Drink at least 3 more glasses (8 oz. each) of clear liquids<br><br>PM: 4oz. + 8 oz.<br>Evening: 24 oz.<br>AM: 4 oz. + 8 oz.<br>**48 oz. Total** | *Lunch*: clear liquid meal<br><br>*Dinner:* clear liquid meal | "You may then drink all the Clear Liquids you desire" |

**Table III. Commercially Available Saline Bowel Cleansing Systems (continued)**

| Product/ Ingredients | Specified Liquid with Administration (instructions) | Total Liquid Specified | Additional Liquid Meals | "Other" Hydration Remarks |
|---|---|---|---|---|
| **Visicol®Tablets**<br><br>sodium phosphate tablets | *PM & AM:*<br>"4 Visicol Tablets should be taken with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets" | 5 glasses for each administration<br><br>5 glasses at 8 oz. (40 oz.) each dose<br>**80 oz. Total** | "patients should be advised to take only clear liquids by mouth for at least 12 hours prior to starting the purgative regimen" | (nothing stated) |
| **E-Z-EM®**<br><br>magnesium citrate, bisacodyl tablets, bisacodyl suppository | Slowly combine with 8 oz. water and drink entire contents<br><br>Take all four tablets with one full 8 fl oz glass of water. | 8 glasses of clear liquid throughout the day, 1 glass with the magnesium citrate, and 1 glass with the tablets<br><br>10 glasses at 8 oz.<br>**80 oz. Total** | *Breakfast*: clear liquid meal<br><br>*Lunch*: clear liquid meal | "A high fluid intake is required for this preparation. Drink at least one (1) full 8 fl oz glass of water at each of the times specified." |

**3. Whether titrating the dose of the product according to the body mass would preserve efficacy and diminish the incidence of adverse events (i.e. to adequately prepare the colon, does a small, elderly woman need to take the same dose as a large middle-aged man?)**

Study PS9902 (Exhibit A) provides a limited amount of data regarding age, dose response, body mass and efficacy. "Elderly" was defined as age 65 and older in order to obtain sufficient numbers for analysis. Using this definition, there were 35 patients in the elderly group and 114 in the non-elderly group. When combining the preparation outcomes of "excellent" and "good" together, the percentages of effective preparations for the elderly were 78% in the low

dose (2 x 30 mL) group, and 95% in the conventional dose (2 x 45 mL) group. For the non-elderly, the corresponding values were 77% and 94%, respectively. Thus age was not a factor in the efficacy of the preparation. The overall ratings were then converted to numerical scores (0=poor, 1=fair, 2=good and 3= excellent) and analyzed by ANOVA using age, gender and dose as the variables. In this analysis, and as was documented in the original report, dose was only a significant factor on the effectiveness of the preparation with a mean score of 2.73 in the conventional group and 2.24 in the low dose group.

The Cohen study (Cohen *et al*, 1994, Exhibit C) only tested the conventional 2 x 45 mL treatment regimen; therefore no high vs. low dose response analysis is possible. However, this study did have a large number of elderly subjects (72 over age 70) where weights and preparation effectiveness were determined. Overall, there was no statistically significant association between age or weight in the effectiveness of the preparation. While elderly patients did have a greater proportion of diminished responses ("poor" plus "fair" as rated by the colonoscopist) than did non-elderly patients (12.5% vs. 6.3%, respectively), this difference was not statistically significant (Fisher's Exact Test, p=0.25). Overall, at the 2 x 45 mL dosage used in this study, 123 of 136 ratings (90%) were graded as good or excellent by the examining colonoscopists. The relationship between age and preparation efficacy is presented in Table IV on the following page.

**Table IV. Number of Subjects by Age Group and Overall Efficacy**

| Efficacy Rating | Age Group ≤ 60 | 60 to < 70 | ≥ 70 | Total |
|---|---|---|---|---|
| Excellent | 20 | 23 | 47 | 90 |
| Good | 11 | 6 | 16 | 33 |
| Fair | 0 | 2 | 7 | 9 |
| Poor | 1 | 1 | 2 | 4 |
| Total | 32 | 32 | 72 | 136 |

Of the nine elderly subjects with poor or fair preparations, six were in males and three were in females. The four preparations judged as poor or fair in the younger age groups were evenly divided by gender. When this data is analyzed by weight the 13 poor and fair ratings were distributed as follows:

**Table V. Distribution by Weight of Subjects with Fair or Poor Bowel Preps**

| | |
|---|---|
| >180 pounds | 5 (38%) |
| 150 – 180 pounds | 1 (8%) |
| 130 – 150 pounds | 4 (31%) |
| <130 pounds | 3 (23%) |

Overall, 90% of the clinical evaluations for Fleet® Phospho-soda® were judged as either good or excellent, and these efficacy ratings were not associated with age, weight or gender.

In conclusion, the 2 x 45 mL bowel cleansing regimen is statistically significantly more effective than the 2 x 30 mL regimen and this difference is not influenced by age or body mass. Nevertheless, the lower dose regimen does produce a clinically acceptable, although not a superior, level of bowel cleansing. In view of the electrolyte changes observed in elderly individuals, particularly older females, the physician should consider using the lower dose in

these cases; the proposed professional labeling requested in this Citizen Petition reflects this finding in both the "Warnings" and "Directions" sections.

**4. Whether we need to be concerned about this potential interaction with antiresorptive agents considering the number of women who take them for osteoporosis. (We have one case report about severe hypocalcemia occurring with oral sodium phosphate laxatives in a woman on alendronate.)**

Of the 10,551 adverse events reported to FDA's spontaneous adverse event reporting system between November 2, 1997, and January 31, 2003, involving one or more of the six marketed antiresorptive agents for osteoporosis (bisphosphonates), Actonel®, Didronel®, Zometa®, Skelid®, Aredia® or Fosamax®, only one literature case involved oral sodium phosphates solution. (Exhibit K.) That article reported on a single patient who had many confounding factors that could have contributed to the tetany observed, including ileum resection and glucocorticoid effects. Therefore, separating all of the factors is impossible. In addition, an incorrect dose of Fleet® Phospho-soda® was used. Further, the total dose of Fosamax® received by the patient would have been only about 11 grams for three years of daily dosing of 10 mg/day. It seems unlikely that the expected small surface occupancy of bone by bisphosphonates would significantly alter the normal response to hyperphosphatemia. There were no other reports in the published literature. Other than that one report, which had confounding factors, there is no evidence to support a conclusion that there is such an interaction. In conclusion, patients on bisphosphonates in whom the use of Fleet® Phospho-soda® is otherwise not contraindicated should not be at increased risk for hypocalcemic-induced tetany when Fleet® Phospho-soda® is administered properly.

**5. How safe is it to use the product "with caution" in the people with conditions listed in this category in your proposed label? Should those patients receive the preparation in a monitored, hospitalized setting? What information should be provided to the physician?**

The **"Use with Caution"** statement proposed in this Citizen Petition is as follows: "**Use with Caution** in patients with impaired renal function, heart disease, acute myocardial infarction, unstable angina, pre-existing electrolyte disturbances or increased risk for electrolyte disturbances (e.g. dehydration, gastric retention, bowel perforation, colitis, ileus, inability to take adequate oral fluid, concomitant use of diuretics or other medications that affect electrolytes), with debilitated or elderly patients or with patients who are taking medications known to prolong the QT interval."

The proposed professional labeling requested in this Petition described above was derived from a number of sources.

1) In the Federal Register of May 21, 1998, (63 Fed. Reg. 27886), FDA published proposed professional labeling for oral monobasic sodium phosphate/dibasic sodium phosphate drug products. In proposed 21 C.F.R. § 334.80 Professional labeling (b) (2) (B), FDA proposed the following: "**Use with Caution** in patients with impaired renal function, heart disease, acute myocardial infarction, unstable angina, pre-existing electrolyte disturbances (such as dehydration or secondary to the use of diuretics), the elderly, or people taking drugs that may affect electrolyte levels." While this proposed rule was subsequently withdrawn with intent to repropose (63 Fed. Reg. 67817, December 21, 1998), it does illustrate Agency thinking on this caution.

2) The approved labeling for Visicol® (sodium phosphate monobasic monohydrate, USP, and sodium phosphate dibasic anhydrous, USP tablets) (NDA 21-097, 9/21/00) states the

following in the "Use with Caution" section. "Use with caution in patients with impaired renal function, pre-existing electrolyte disturbances (such as dehydration or those secondary to the use of diuretics), or people taking drugs that may affect electrolyte levels. People with electrolyte abnormalities such as hypernatremia, hyperphosphatemia, hypokalemia, or hypocalcemia should have them corrected before treatment with Visicol® tablets." (Exhibit L).

3) In the Precautions section of the approved labeling for Visicol® tablets, the following caution is made: "Visicol® Tablets should be used with caution in patients who are taking medications known to prolong the QT interval, since serious complications may occur."

The "**Use with Caution**" section proposed in the professional labeling requested in this Citizen Petition includes the statements previously approved in an NDA by FDA made in Nos. 1-3 above, and further elaborates upon the list of conditions that can lead to electrolyte disturbances. The proposed labeling also includes the following recommendation to the physician:

> "**In at-risk patients, including elderly patients, consider obtaining baseline and post-treatment sodium, potassium, calcium, chloride, bicarbonate, phosphate, blood urea nitrogen and creatinine values and consider using the lower end of the dosage range.** There is a risk of elevated serum levels of sodium and phosphate and decreased levels of calcium and potassium; consequently hypocalcemia, hypokalemia, hyperphosphatemia, hypernatremia, and acidosis may occur."

Fleet believes that all of this information should be provided to the physician as part of professional labeling, in all communications to the health professional including medical journal advertising and in publications such as the *Physicians' Desk Reference®*. The informed judgment of the physician on a case-by-case basis is essential in determining whether or not Fleet® Phospho-soda® can or should be used in any particular case. Likewise, Fleet believes it is

up to the physician to determine on a case-by-case basis the setting in which bowel cleansing will be conducted.

6. **We realize that serious adverse events are not common, but we do not know how rare they are. This is an OTC product and the incidence of serious events as a consequence of its use should be as low as possible.**

From 1991 through the end of 2002, the incidence of Serious Adverse Events (SAEs) associated with the use of Fleet® Phospho-soda® in the United States was 1.46 SAEs per million bowel prep doses sold (see Table VI on the following page). A more extensive analysis of SAE's on a worldwide basis is provided in a Benefit-Risk Analysis (Exhibit M) which was submitted to Health Canada in March 2003. The Council for International Organizations of Medical Sciences (CIOMS) classifies SAEs occurring at a rate of <1 per 10,000 exposures as "very rare" (Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals; Report of CIOMS Working Group IV; Geneva 1998, page 47) (Exhibit N). The SAE rate associated with bowel cleansing doses of Fleet® Phospho-soda® is slightly more than one order of magnitude below that which is classified as "very rare".

The majority of SAE's associated with the use of Fleet® Phospho-soda® are due to inappropriate dosing or use in patients with known contraindications. Fleet believes that providing information to physicians as to the appropriate dose and the appropriate patient population in whom the drug should be used and not be used will enhance the safety of an already safe drug.

**Table VI. Fleet® Phospho-soda® Serious Adverse Experience Rate**

**(USA only)**

| YEAR | Total Bowel Prep Dosage Sales* | Serious Adverse Experiences** | SAE/Million Bowel Prep Doses Sold |
|---|---|---|---|
| 1991 | 988,920 | 3 | 3.03 |
| 1992 | 1,220,172 | 1 | 0.82 |
| 1993 | 1,176,326 | 6 | 5.10 |
| 1994 | 1,409,172 | 2 | 1.42 |
| 1995 | 1,687,752 | 2 | 1.19 |
| 1996 | 2,097,792 | 8 | 3.81 |
| 1997 | 2,425,464 | 3 | 1.24 |
| 1998 | 3,036,996 | 3 | 0.99 |
| 1999 | 3,902,820 | 4 | 1.02 |
| 2000 | 4,489,848 | 7 | 1.56 |
| 2001 | 5,382,168 | 1 | 0.19 |
| 2002 | 5,674,956 | 9 | 1.59 |
| **Total** | **33,492,386** | **49** | Average = 1.46 |

* Dosage is expressed in terms of the number of 3 fluid ounce (90 mL) equivalents sold; this is the usual bowel cleansing dose (2 x 45 mL). This does not include the individual 1.5 fluid ounce units which are sold as part of Fleet Prep Kits. Inclusion of these would artificially lower the SAE rate.

** Serious Adverse Experiences were obtained from the literature, from reports made directly to C. B. Fleet Co, Inc. and from FDA's spontaneous reporting system database. The 2002 data does not include any possible SAE's from FDA as of this date (3/21/03); update is in-process.

7. **With regard to efficacy, in study PS9902 the 2 x 30 mL dose is not statistically different from the GoLYTELY (an approved Rx product), but may be associated with fewer adverse events than the 2 x 45 mL dose. It may be that after the data are analyzed, it will be appropriate to recommend the lower instead of the higher oral sodium phosphates dose.**

The results of Study PS9902 (Exhibit A) demonstrate that on a 0-to-3 scale, where 0 is poor cleansing and 3 is excellent cleansing as rated by experienced colonoscopists, cleansing scores with the 2 x 45 mL dose of Fleet® Phospho-soda® (score of 2.7) were superior to that of the 2 x 30 mL dose of Fleet® Phospho-soda® (2.2) and that of a PEG lavage product,

GoLYTELY® (2.0). These results were highly significant (p =0.0001), while the slight difference between cleansing scores with the 2 x 30 mL dose of Fleet® Phospho-soda® and GoLYTELY® was not. While clinical relevance of these differences is debatable, superior colon cleansing minimizes patient risks of missed lesions, eliminates the need to repeat the procedure if cleansing is not adequate, decreases the likelihood of a more technically difficult procedure because of poor visualization of the lumen and limits delays in diagnosis if procedures need to be canceled because of inadequate cleansing (Exhibit I, Hookey).

The results of Study PS9902 do show that the 2 x 30 mL dose of Fleet® Phospho-soda® is associated with fewer adverse events than is the 2 x 45 mL dose. However, in terms of the potentially most significant adverse events, hypokalemia and hypocalcemia, there were no significant differences between the doses. As would be expected, the higher dose was associated with a greater incidence of hyperphosphatemia (15% vs 8%, respectively), but this transient mild hyperphosphatemia did not translate into an increased incidence of hypocalcemia. The higher dose also caused an increased incidence of nausea (46% vs 27%) and vomiting (7% vs 0%), although this difference was not reflected in the patients' assessment of their colonoscopy preparation regimens. In each group, 95% or more of patients reported that they had completed the entire prep regimen and, when asked if they would use the same prep for their next colonoscopy, they responded affirmatively.

There is a tradeoff between a superior degree of cleansing that is associated with a higher incidence of nausea and vomiting, and a lesser degree of cleansing associated with a decreased incidence of these events. Fleet believes that these facts can be provided to physicians through professional publication of these results in the *Physicians' Desk Reference®*, journal articles and

advertising. Having been provided with these data, physicians will then be in the best position to make informed bowel cleansing recommendations based on their evaluation of their patients and their patient's individual needs. As noted in response to other questions in this Citizen Petition, the use of 2 x 30 mL dosing may be indicated with certain groups of patients, particularly the elderly, although it is at the cost of reduced bowel cleansing efficacy. For most patients, the more effective 2 x 45 mL dosing will and should remain the standard.

### D. OTHER PUBLISHED STUDIES

An additional 24 reports have been published of clinical trials of Fleet® Phospho-soda® using the product in 2 x 45 mL dosing administered less than 24 hours apart. See Exhibit H, pages 20-30. These studies included 2,213 patients treated with Fleet® Phospho-soda®, and include data on electrolyte levels in 623 patients. None of the patients in any of the studies had significant complications resulting from the observed changes in serum electrolytes. See Exhibit H, pages 24-27. See pages 30-34 for a discussion of other studies, not randomized or controlled, reporting electrolyte changes with use of the product.

The other published literature supports the fact that the electrolyte and vascular volume changes resulting from use of this dosing of the product are clinically insignificant, and serious adverse events do not occur when the product is used as directed.

#### 1. Other Data on Serious Adverse Events Experience Demonstrate the Safety of the 2 x 45 mL Dosing Regimen

While reports of SAEs are not as inherently reliable as those from published clinical studies, the results of actual marketing – as reflected in spontaneous reporting to FDA and other

authorities, and reports in the published literature – confirm that Fleet® Phospho-soda® dosed 10-12 hours apart is safe, when used as directed.

The results of reporting of serious adverse events to Fleet and FDA, and in the published literature, in the U.S., were analyzed for the period January, 1991, to February, 2003, for Fleet® Phospho-soda®. During that time, only 49 events occurred that were fatal, life-threatening or required hospitalization out of almost 33,492,386 90 mL equivalents (2 x 45 mL) sold. See Table VI. Similarly, reports from July, 1995, to January, 2002, had similar results. See Table 12, p. 35, Exhibit H. Many of these reactions involved misuse of the product, by either overdosages or use of the product in patients in whom its use is clearly contraindicated.

Results in other countries are similar. While there have been five deaths in Australia, two involved use of Fleet ® Phospho-Soda® **and** PEG, two involved elderly (80 and 90 years) men with congestive heart failure (contraindicated in the labeling for the product) and one involved changes in electrolyte levels in a 77-year-old woman whose findings are not consistent with hypovolemia from sodium phosphates.

Published case reports of adverse events contain similar findings. See Exhibit H, pages 37 to 41. There have been 27 published reports of SAEs to Sodium Phosphates Oral Solution between 1968 and 2002. While there were five deaths reported, the other patients recovered. All of the deaths were associated with overdoses, as were many of the other SAEs.

The reports of published and spontaneous adverse events demonstrate that the vast majority involve overdoses or use in patients in whom the product is contraindicated. Marketing experience confirms a known, predictable physiological response. Fleet® Phospho-soda® has been labeled to take into account the known physiologic response, and to prevent use of the

product when its use would be contraindicated. There is nothing unknown or unexpected about these findings; they merely confirm that, while adverse events can and do occur rarely, the product is safe as labeled when used properly. The proposed professional labeling required in this Citizen Petition would help assure its safe use for these products.

**E. IT IS APPROPRIATE TO REGULATE THE PURGATIVE USE OF 2 x 30 mL to 2 x 45 mL DOSING (10-12 HOURS APART) OF SODIUM PHOSPHATES ORAL SOLUTION FOR BOWEL CLEANSING BY PROFESSIONAL LABELING UNDER THE LAXATIVE MONOGRAPH**

As indicated above, as recently as July 19, 2001 (Exhibit F), the Agency has concluded that the use of Sodium Phosphates Oral Solution as a bowel cleansing preparation does not require an NDA or the use of the prescription legend and that it is effective for that use. The Agency has, however, questioned the use of a 90 mL bottle and the adequacy of warnings/ contraindication language. Thus, while the Agency has questioned the labeling of this dosing regimen, it has accepted that it is appropriate to continue to regulate it as professional labeling under the Final Monograph on Laxative Drug Products OTC for Human Use when published. Fleet believes the information submitted herewith reconfirms that conclusion. To address the Agency's concerns, Fleet has undertaken on its own initiative a number of actions to increase the safety of the use of Fleet® Phospho-soda® as a bowel purgative.

To this end, Fleet has, first of all, committed to cease all distribution of a 90 mL bottle when required by the Agency. Furthermore, it has revised its professional labeling, taking into account the findings of its studies and the issues raised by FDA in the Science Background document posted on the Agency web site on September 17, 2001. This labeling is attached as Exhibit O. In this labeling, as proposed above, Fleet includes a recommendation, to address the

concerns raised by the Agency, to consider use of the 2 x 30 mL dosing in at risk patients, such as the elderly.

These steps reflect Fleet's ongoing program of routinely providing important prescribing information to the physician as to the warnings and contraindications for use of Fleet® Phospho-soda® and to amend the labeling for the product as needed to address safety concerns. See, for example, the web site for the product, www.phospho-soda.com, which provides information on the professional-use warnings for the product and which contains full prescribing information for the product. In addition, for almost 15 years, Fleet included "Professional Use Warnings" on the package of the product. It discontinued this practice only because the Agency had declared it inappropriate (see 63 Fed. Reg. 27888, May 21, 1998) and in order for Fleet to comply with the OTC DRUG FACTS format.

**F. THE PROPOSED PROFESSIONAL LABELING ADDRESSES ALL SAFETY ISSUES AND REFLECTS THE FINDINGS OF THE STUDIES SUBMITTED HEREWITH**

Fleet has prepared the proposed professional labeling described above, taking into account the Agency's prior proposals; the information contained in the September 17, 2001, FDA web site posting; the labeling for the NDA approved VISICOL® tablets, and the results of the clinical studies submitted herewith, as well as all of the other published literature and results of prior marketing experience. It believes the proposed labeling proposed herein fully addresses all safety issues which result from the findings of the studies submitted herewith, and the Agency's concerns raised in the June 19, 2002, meeting.

## III. ENVIRONMENTAL IMPACT

The undersigned claims categorical exclusion from the requirement for an environmental assessment, pursuant to 21 C.F.R. § 25.24.

## IV. CERTIFICATION

The undersigned certify that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and that it includes representative data and information known to the petitioner that are unfavorable to this Petition as of this date, unless otherwise indicated.

Respectfully submitted,

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