December 11, 2008

Peter S. Reichertz, Esq.
Christopher A. Brown, Esq.
Sheppard Mullin Richter & Hampton LLP
1300 I Street, Suite 11E
Washington, D.C. 20005

Re: Docket No. FDA-1978-N-0021
(fomerly 78N-036L)
Comment Nos. CP28 and SUP 12

Dear Mr. Reichertz and Mr. Brown:

This letter responds to your citizen petition dated June 25, 2003, filed on behalf of C.B. Fleet, Incorporated of Lynchburg, Virginia. The petition requests that FDA modify the Tentative Final Monograph (TFM) for OTC Laxative Drug Products (50 FR 2124, January 15, 1985) to include professional labeling for two 30-milliliter (mL) to two 45-mL doses of sodium phosphates oral solution for sequential administration 10 to 12 hours apart for bowel cleansing. The petition also proposes detailed professional labeling that you believe will allow physicians to instruct patients to safely and effectively use your proposed dosing regimen of sodium phosphates for bowel cleansing in preparation for diagnostic procedures such as colonoscopy or x-ray prior to surgery.

This letter also responds to your submission of March 14, 1996 (SUP12 in Docket FDA-1978-N-0021) that included the results of five published studies to support the safety of the two 45-mL dose regimen. Your March 14, 1996 submission was in response to FDA's March 1, 1996, denial of your petition (CP 14 dated March 23, 1993, in Docket No. FDA-1978-N-002l) requesting that the proposed professional labeling in the 1985 TFM be modified to include two 45-mL doses of sodium phosphates oral solution for sequential administration 10 to 12 hours apart for bowel cleansing.

We have carefully reviewed your petition and the data in your March 14, 1996, submission. For the reasons described in detail in this response, we deny your request that FDA modify the proposed professional labeling for OTC laxative products proposed in the Federal Register of January 15, 1985, to include the use of your proposed dosing regimens of sodium phosphates oral solution for bowel cleansing. The bases for your requests and our responses to each request are discussed in the sections below.

1. Determination on Including Your Proposed Sodium Phosphates Oral Solution Dosing Regimens in the Proposed Professional Labeling of the TFM

Your request that two 30-mL to 45-mL doses of sodium phosphates oral solution be included in the proposed professional labeling for bowel cleansing is based on the following:

- Results from an unpublished study comparing the safety and effectiveness of sodium phosphates oral solution at two dose levels, the most commonly recommended 2 x 45 mL dose (~60 gm sodium phosphate) and a lower 2 x 30 mL dose (~40 gm sodium phosphate), with polyethylene glycol solution (PEG) (PS9902, Exhibit A)
- Results from an unpublished time course study of the effects of two 45-mL doses of Fleet Phospho-soda® on serum electrolytes (study F00.20, petition Exhibit B)
- A summary of the safety and effectiveness data for Fleet Phospha-soda® results of previous human experience (Exhibit H)
- A review article by Hookey et al.[1] evaluating the available safety data from studies of oral sodium phosphate for colon cleansing (petition attachment I)
- An analysis of the effects of Fleet Phospho-soda® on serum electrolytes in the elderly based on data from a study by Cohen et al.[2] and study F9902 (Exhibit J)
- A benefit risk assessment of Fleet Phospho-soda® conducted by Meditrials, Inc. (Exhibit M)
- Proposed professional labeling (Exhibit O)

You believe that the above information provides adequate support for including your requested sodium phosphates oral solution dosing regimens in the proposed professional labeling of the TFM for bowel cleansing when used as directed in patients without additional risk factors.

We have reviewed the information provided in the petition and conducted our own review of the published literature and FDA's Adverse Event Reporting System (AERS). We have concluded that the data are insufficient to support the proposed use of OTC sodium phosphates oral solution for bowel cleansing in the proposed professional labeling based on concerns regarding both safety of the use of sodium phosphates for bowel cleansing in the OTC setting and the effectiveness of the two 30-mL dose regimen.

2. Discussion

2.1 Safety of Oral Sodium Phosphates for Bowel Cleansing

Randomized, controlled clinical trials evaluating the use of sodium phosphates oral solution for bowel cleansing in study populations without significant risk factors for the use of these products have demonstrated statistically significant electrolyte changes

[1] Hookey, L. C., W. T. Depew, and S. Vanner. "The Safety Profile of Oral Sodium Phosphate for Colonic Cleansing Prior to Colonoscopy," Gastrointestinal Endoscopy, 56(6):895-902, 2002.
[2] Cohen, S. M. et al. "Prospective, Randomized, Endoscopic-Blinded Trial Comparing Precolonoscopy Bowel Cleansing Methods. Dis Colon Rectum, 37(7):689-96. 1994

that have not resulted in serious adverse events.[2,3,4,5] These changes occurred after the use of two 45-mL doses of sodium phosphates oral solution administered 10 to 12 hours apart.

However, since 1969, FDA's AERS has received over 100 cases of acute kidney failure associated with prescription and OTC oral sodium phosphates used for bowel cleansing. Seventy-nine of these cases have been associated with the use of an OTC sodium phosphates oral solution, and the majority of these reports (46/79 or 58 percent) have been received since 2005. In addition, there are also reports of acute kidney injury associated with the use of sodium phosphate products for bowel cleansing in the published literature.[6]

An article by Markowitz et al. in 2005 reported cases of acute phosphate nephropathy associated with the use of oral sodium phosphate products. In this study, 21 cases were reported where patients were diagnosed with acute phosphate nephropathy following the use of OSP for bowel preparation for colonoscopy.[7] These cases were identified retrospectively from the kidney biopsy archives of the Columbia University Renal Pathology Laboratory between 2000 and 2004. During the period of study, a number of biopsies were reviewed, from which 31 cases of acute kidney failure were retrieved with histologic findings of acute and/or chronic tubular injury and abundant calcium phosphate deposits. Of these cases, a total of 21 patients met the criteria for the

---

[3] PS9902, Exhibit A

[4] 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," American Journal of Gastroenterology, 85:422-427, 1990.

[5] Lieberman, D. A., J. Ghormley, and K. Flora, "Effect of oral Sodium Phosphate Colon Preparation on Serum Electrolytes in Patients with Normal Serum Creatinine," Gastrointestinal Endoscopy, 43:467-469, 1996.

[6] Other information the agency considered about oral sodium phosphates comes from a 2006, a Joint Task Force from the American Society of Colon and Rectal Surgeons (ASCRS), the American Society for Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). They issued a consensus statement on bowel preparation before colonoscopy. (See Wexner SD, Beck DE, Baron TH et al. A consensus document on bowel preparation before colonoscopy: prepared by a task force from the American Society of Colon and Rectal Surgeons (ASCRS), the American Society for Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). Gastrointest Endosc 2006; 63:894-909.) The task force reported that the use of OSP for bowel preparation prior to a colonoscopy is associated with abnormalities in serum electrolyte and altered extracellular fluid volume, which can cause significant losses of both fluid and electrolytes in the stool, resulting in volume contraction and dehydration. Although usually asymptomatic, hyperphosphatemia is seen in as many as 40 percent of healthy patients completing OSP preparations, and may be significant in patients with renal failure. Also, hypokalemia developed in as many as 20 percent of patients using OSP preparations. In addition, OSP has been shown to cause elevated blood urea nitrogen levels, decreased exercise capacity, increased plasma osmolality, hypocalcemia, and significant hyponatremia and seizures due to electrolyte shifts.

[7] Markowitz GS, et al. "Acute Phosphate Nephropathy Following Oral Sodium Phosphate Bowel Purgative: an Under-Recognized Cause of Chronic Renal Failure," Journal American Society of Nephrology, 16:3389-3396, 2005.

diagnosis of "acute phosphate nephropathy following oral sodium phosphate bowel purgative." These patients were observed for approximately 16 months after the colonoscopy and by then, 4 patients had gone on to require permanent hemodialysis. All of the remaining 17 patients developed chronic renal insufficiency.

The authors state that potential etiologic factors include inadequate hydration, increased patient age, history of hypertension and concurrent use of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). They concluded that, "in the absence of the discovery of acute renal failure immediately after the colonoscopy and in the setting of significant hyperphosphatemia, the causative role of oral sodium phosphate products in the development of acute phosphate nephropathy is likely to be overlooked." Since the publication by Markowitz, there have been several other individual case reports of renal failure from acute phosphate nephropathy associated with the use of oral sodium phosphate products.[8,9,10]

Recently published observational, retrospective studies have attempted to assess the incidence of subclinical (without symptoms) kidney injury after oral sodium phosphate use for bowel preparation. It is not entirely clear how the observations in these studies relate to cases of acute phosphate nephropathy that become evident because of the development of clinical symptoms which lead physicians to conduct testing. These studies only assess changes in serum creatinine function in a cohort of people who received oral sodium phosphates for bowel cleansing in an attempt to determine whether lesser degrees of kidney injury occur in a population of patients receiving oral sodium phosphates. Nevertheless, it is useful to review the data in light of our concerns about OSP products for bowel cleansing.

Brunelli et al. conducted a retrospective, case-control study of outpatient colonoscopy procedures, comparing those who subsequently developed kidney injury, defined as a 25 percent or $\geq$ 0.5 mg/deciliter increase in serum creatinine, to those who did not.[11] The Brunelli study found no statistically significant association between acute kidney injury and exposure to oral sodium phosphates, but found a significant interaction indicating increased risk for kidney injury from oral sodium phosphates in patients who were simultaneously receiving ARBs or ACE inhibitors. The Brunelli study also found that risk factors for the development of acute kidney injury included female gender, heart failure, and diuretic use. Another observational retrospective cohort study by Hurst et al. revealed an increased risk of acute kidney injury, defined as $\geq$ 50% increase in baseline serum creatinine, in patients undergoing bowel cleansing using oral sodium phosphate

---

[8] Gonlusen G. et al. "Renal Failure and Nephrocalcinosis Associated with Oral Sodium Phosphate Bowel Cleansing: Clinical Patterns and Renal Biopsy Findings," Archives of Pathology and Laboratory Medicine, Jan: 130(1):101-6, 2006. .

[9] Ma R. C. et al. "Acute Renal Failure Following Oral Sodium Phosphate Bowel Preparation in Diabetes," Diabetes Care, Jan: 30(1):182-3, 2007.

[10] Aasebo, W et al., "Kidney Biopsies Taken Before And After Oral Sodium Phosphate Bowel Cleansing," Nephrology Dialysis Transplant. 22:920 – 922. 2007.

[11] Brunelli SM, et al., "Risk of Kidney Injury Following Oral Phosphosoda Bowel Preparations," Journal American Society of Nephrology 18: 3 199-3205, 2007.

products compared to polyethylene glycol (PEG) preparations.[12] However, a recent study by Russmann et al. evaluated the risk of impaired kidney function after colonoscopy and revealed that in patients without preexisting kidney disease, the risk of renal impairment, defined as calculated glomerular filtration rate less than 60 mL/minute, after colonoscopy appears to be similar for sodium phosphate and PEG users.[13]

There are limitations in the design of these recently published observational retrospective studies, such as the lack of a consistent definition of acute kidney injury and the exclusion of patients with baseline serum creatinine values above a threshold value. As a consequence, no definitive conclusions can be drawn and prospective studies are needed to further assess subclinical changes in kidney function.

Furthermore, the available data also do not establish that a lower dose regimen, such as the one you proposed, poses less of a safety concern. Data to support the safety of the two 30-mL dose regimen comes from a single study (PS9902, Exhibit A) comparing the effectiveness of sodium phosphates oral solution at two dose levels, the customarily recommended 2 x 45 mL dose and a reduced 2 x 30 mL dose, with PEG in subjects without significant risk factors for the use of sodium phosphates oral solution. In general, the observed electrolyte changes and side effects were milder with the two 30-mL doses of sodium phosphates oral solution and there were no changes in creatinine in any of the groups. However, the number of subjects exposed to the lower dose regimen is too small (79 subjects) to draw any conclusions about renal function decline related to the use of the lower dose regimen.

Based on our review of the available data and the lack of data establishing a safe dose of oral sodium phosphates for bowel cleansing, we have concluded that the use of sodium phosphates oral solution for bowel cleansing poses a serious risk of adverse events in some patients. Educational efforts by FDA have not been successful in mitigating this risk.[14,15,16] Under the current proposed professional labeling provisions of the TFM for OTC Laxative Drug Products published on January 15, 1985, (50 FR 2124), consumers rely on their healthcare provider to provide information on the safe use of the sodium phosphates oral solution for bowel cleansing. This approach has also not been sufficient to manage the risk that has been associated with the use of sodium phosphates oral solution for bowel cleansing in the OTC setting.

---

[12] Hurst FP, Bohen EM, Osgard EM, Oliver DK., Das NP, Gao SW, Abbott KC. Association of oral sodium phosphate purgative use with acute kidney injury. J Am Soc Nephrol 18:31 92-31 98, 2007.
[13] Russmann S, Lamerato L, Marfatia A, Motsko SP, Pezzullo J, Olds G, Jones JK. 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.
[14] FDA Science Background Paper: "Safety of Sodium Phosphates Oral Solution" September 17, 2001
[15] FDA Science Background Paper: "Acute Phosphate Nephropathy and Renal Failure Associated with the Use of Oral Sodium Phosphate Bowel Cleansing Products," May 2006
[16] FDA Information for Healthcare Providers: Oral Sodium Phosphate Products for Bowel Cleansing, May 2006

We believe that consumers need to have detailed information in the form of patient labeling, and information from a physician, regarding the safe use of the product. Risk information in patient labeling could help prevent serious adverse effects and this information could affect patients' decisions to use these products. This kind of patient labeling (see 21 CFR 201.57 and 21 CFR Part 208) cannot be accomplished with professional labeling found in an OTC monograph. Professional labeling is labeling provided only to healthcare professionals who direct patients to use OTC products in ways that differ from the labeling on the marketed product. Manufacturers marketing OTC products under the TFM cannot provide consumers with labeling information on the OTC package, related to indications or uses that are not part of the drug facts labeling allowed under the TFM.

Section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) sets forth the standard under which drug products can only be dispensed with a prescription. If a drug because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug, then the product shall only be dispensed with a prescription. We conclude that the use of oral sodium phosphates oral solution for bowel cleansing meets this statutory standard that defines a prescription product.

In addition, the Food and Drugs Amendments Act of 2007 (FDAAA), Title IX, subtitle A, created a new section (505-l) of the Act that grants FDA new authorities to require risk evaluation and mitigation strategies (REMS) for prescription drugs when FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug. Pursuant to 505-l, FDA has determined that, based on the new safety information described above, a REMS is necessary to ensure that the benefits of the drug outweigh the risks. FDA plans to require the manufacturers of prescription oral sodium phosphate products for bowel cleansing to submit a proposed REMS that includes the development of a Medication Guide and a communication strategy targeted at gastroenterologists, surgeons, primary care physicians, and other healthcare providers who are likely to prescribe oral sodium phosphate products for bowel cleansing. FDA also plans to require the manufacturers of prescription oral sodium phosphate products for bowel cleansing to include in their labeling a boxed warning to alert prescribing physicians of the risks of acute kidney injury (see 505(o)(4)), and to conduct a clinical trial to assess the known risk of acute kidney injury in patients using sodium phosphate products for bowel cleansing and to better define what risk factors may predispose patients to such injury (see 505(o)(3)).

2.2 Effectiveness of the Proposed Two 30-mL Dose Regimen

FDA has previously acknowledged the effectiveness of the proposed two 45-mL dose regimen.[17] However, the data are not sufficient to establish the effectiveness of the petition's proposed lower dose regimen (two 30-mL doses taken 10 to 12 hours apart). Data to support this proposed regimen comes from one randomized single-blind, parallel group design study comparing the effectiveness of sodium phosphates oral solution at two dose levels, the standard 2 x 45 mL dose and a reduced 2 x 30 mL dose, with PEG. While the study reports that the lower dose regimen is slightly less effective than the 45-mL dose regimen and as effective as treatment with PEG, this study cannot be considered a conclusive demonstration of the effectiveness of the reduced phosphate regimen.

It is noteworthy that 32 percent (23/73) of the PEG subjects in this study reported that they did not complete the treatment regimen. This finding may have reduced the efficacy found in the PEG group, thereby minimizing treatment effect differences between PEG and the low dose phosphate regimen. There were also irregularities in randomization. Ten patients were excluded following randomization because they were randomized before all inclusion criteria were verified. In addition, at one study site, six patients were randomized out of order and did not receive the treatments assigned by the randomization protocol. Thus, this study is not sufficient to demonstrate the effectiveness of this regimen. Please be advised that data from two adequate and well-controlled studies are typically needed to support the effectiveness of the two 30-mL sodium phosphates oral solution regimen.

3. FDA's Conclusions

Based on our evaluation of the available data, we have decided not to include your proposed dosing regimens for oral sodium phosphate products for bowel cleansing in the proposed professional labeling of the TFM. FDA has also concluded that the use of sodium phosphates oral solution for bowel cleansing in the OTC setting pursuant to professional labeling in the OTC monograph poses an unacceptable risk of serious adverse events. Please be advised that FDA plans to amend the TFM to remove the proposed professional labeling for oral sodium phosphate products for bowel cleansing. The use of these sodium phosphate oral solution products for bowel cleansing meets the statutory standard for prescription products set forth in the Act. Further, the new safety information about the risks associated with these products requires the use of a REMS to ensure that the benefits of the drug outweigh the risks of the product. Moreover, additional data are needed to assess the known risk of acute kidney injury in patients using sodium phosphate products for bowel cleansing and to better define what risk factors may predispose patients to such injury . Accordingly, we are denying your petition to amend the 1985 TFM for OTC Laxative Drug Products to include professional labeling for your proposed dosing regimens for sodium phosphates oral solution for bowel cleansing.

[17] Comment No. LET109, Docket No. 1978N-036L, Division of Dockets Management.

Any comments you wish to make on the above information should be identified with the appropriate docket number (1978N-036L) and submitted in three copies to the Division of Docket Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.

Sincerely yours,

David J. Horowitz, Esq.
Assistant Commissioner for Policy
U.S. Food and Drug Administration