December 11, 2008

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Washington, D.C. 20001

Re: Docket No. FDA-2007-P-0345

Dear Ms. Leskovsek:

This letter responds to your petition (Petition) dated September 20, 2007.[1] In your petition, you request that the Food and Drug Administration (FDA or the Agency):

- withdraw the commercial marketing authorization for oral sodium phosphate (OSP) products for bowel cleansing, or

- add a black box warning to OSP products regarding the potential risks of renal failure caused by nephrocalcinosis and reclassify all OSP products for bowel cleansing as prescription only medicines.

We have carefully reviewed the petition and comment(s) filed in the docket. For the reasons stated in this response, the petition is granted in part and denied in part.

I. BACKGROUND

A. Oral Sodium Phosphate Products, Acute Phosphate Nephropathy and Nephrocalcinosis

1. Oral Sodium Phosphate Products

a. Over The Counter (OTC) products

OSP products for use as laxatives are being evaluated as part of the OTC drug review. Several OSP products are available OTC in solution dosage form (e.g., Fleet Phospho-soda). The tentative final monograph (TFM) for laxative use (50 FR 2124, January 15, 1985) proposes the

[1] This citizen petition was originally assigned docket number 2007P-0352/CP1. The number was changed to FDA-2007-P-0345 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

following professional labeling for a bowel cleansing indication: "For use as part of a bowel cleansing regimen in preparing patients for surgery or for preparing the colon for x-ray or endoscopic examination" (proposed § 334.80 of FDA regulations (21 CFR 334.80)).

OSP solution available in the OTC setting is frequently recommended by physicians for use in bowel cleansing before colonoscopy. Although no dosing information is included in the TFM, the customary dose used in medical practice is 90 milliliters (mL) administered in two divided doses (two 45-mL doses ingested 12 hours apart, the night before and the morning of the colonoscopy (total sodium phosphate dose 60 grams (g))).

b. Prescription products

In addition to the OSP products available in the OTC setting, two tablet forms of sodium phosphate are approved for cleansing of the colon as a preparation for colonoscopy in adults 18 years of age or older and are available by prescription only. The products are (1) Visicol (sodium phosphate monobasic monohydrate, USP, and sodium phosphate dibasic anhydrous, USP) Tablets, approved September 21, 2000 (new drug application (NDA) 21-097), for which the dosage is 40 tablets or 60 g of sodium phosphate; and (2) OsmoPrep (sodium phosphate monobasic monohydrate, USP, and sodium phosphate dibasic anhydrous, USP) Tablets, approved March 16, 2006 (NDA 21-892), for which the dosage is 32 tablets or 48 g of sodium phosphate. Salix Pharmaceuticals, Inc. is the holder of the approved applications for Visicol Tablets and OsmoPrep Tablets.

2. Acute Phosphate Nephropathy and Nephrocalcinosis

Acute phosphate nephropathy refers to kidney injury caused by diffuse tubular damage as a result of deposition of calcium phosphate in the distal tubules and collecting ducts. Tubular atrophy and interstitial fibrosis, indicators of irreversible tubular injury, may result. Unlike nephrocalcinosis, in which hypercalcemia promotes an insidious loss of kidney function through chronic tubulointerstitial injury secondary to calcification in the renal parenchyma, this new clinico-pathologic entity is typically acute in onset and occurs in the absence of hypercalcemia.

OSP products promote colonic evacuation by drawing large volumes of water into the colon. They induce transient hyperphosphatemia which is most profound in the elderly. Recognizing the pathogenetic role for exogenous oral phosphate ingestion, Markowitz et al. suggested the term *acute phosphate nephropathy* to describe acute renal failure following exposure to OSP products instead of the term *nephrocalcinosis*.[2] Although the true incidence of acute phosphate nephropathy is unknown, it may occur in up to 1 in 1000 patients who receive OSP products and

[2] Markowitz GS, Stokes MB, Radhakrishnan J, D'Agati YD. Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an under-recognized cause of chronic renal failure. J Am Soc Nephrol 16:3389-3396, 2005.

is probably under-recognized.[3]

Factors that promote hyperphosphatemia will predispose OSP users to acute phosphate nephropathy. Such factors include inappropriate dosing of OSP products, increased bowel transit time (e.g., with bowel obstruction), active colitis, and reduced ability to excrete a phosphate load (e.g., in patients with renal impairment).[4]

Factors that promote tubular precipitation of calcium phosphate also predispose OSP users to acute phosphate nephropathy. Such factors include inadequate hydration during phosphate administration, hypertension with arteriosclerosis, and exposure to drugs such as rennin-angiotensin inhibitors, diuretics, and non-steroidal anti-inflammatory drugs (NSAIDs).

Acute phosphate nephropathy may lead to permanent renal impairment or need for dialysis. The clinical manifestations may be difficult to recognize, as many patients may be asymptomatic. Laboratory tests reveal minimal proteinuria, elevated serum creatinine[5] level, and bland urine sediment. Hyperphosphatemia is transient. Acute phosphate nephropathy can be confirmed by taking a kidney biopsy.

Although your petition expresses concerns about the association of OSP products and the potential risk of kidney failure caused by nephrocalcinosis, upon consideration of the published literature, FDA believes the term *acute phosphate nephropathy* is a better descriptor of the renal effects of OSP products. FDA's assessment of OSP-related renal effects and its communications about them will therefore use this term.

B. Previous FDA Statements Regarding OSP Products

1. FDA's Response to August 2000 Citizen Petition

In August 2000, Braintree Laboratories, Inc., submitted a citizen petition (Braintree Petition) requesting, among other things, that FDA reclassify OTC OSP preparations as prescription only

[3] Markowitz GS, Radhakrishnan J, D'Agati YD. Towards the incidence of acute phosphate nephropathy. J Am Soc Nephrol 18:3020-3033, 2007.

[4] Markowitz GS, Stokes MB, Radhakrishnan J, D'Agati YD. Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an under-recognized cause of chronic renal failure. J Am Soc Nephrol 16:3389-3396, 2005; Connor A, Sykes L, Roberts ISD, Weston CE. Acute phosphate nephropathy after sodium phosphate preparations. BMJ 337:a182, 2008; 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 18:3192-3198, 2007.

[5] Creatinine is a compound formed by the metabolism of creatine, found in muscle tissue and blood and normally excreted in the urine as a metabolic waste. Measurement of creatinine levels in the blood is used to evaluate kidney function.

products and require a boxed warning in the labeling to call attention to serious safety concerns associated with the use of OSP products.[6] In July 2001, the Agency issued a response to the Braintree Petition.

In the response to the Braintree Petition, FDA noted that it reviewed the data and information submitted in the petition and determined there was not sufficient evidence to support the request to remove OSP products from the OTC setting, or to add a boxed warning in the labeling. In reviewing the data and information submitted with the Braintree Petition, the Agency concluded that the primary reason for the adverse events appeared to be that physicians were not adequately informed as to how to properly use the product and were prescribing more than the recommended 45-mL dose. Although the Agency denied the petition, the Agency recommended that the container size for OSP products in the OTC setting be limited to no greater than 45 mL and that warning statements be broadened to inform physicians and consumers of potential adverse effects and contraindications for use. The Agency also stated that it planned to propose regulations to limit the package size of OSP to no greater than 45 mL and to require revised labeling to include more information to improve safe use of the products by consumers and health professionals.

2. Labeling Changes, FDA Alert, and Science Background Paper

In March 2006, information regarding the risk of acute phosphate nephropathy associated with the use of OSP products for bowel cleansing was added to the WARNINGS section of the existing labeling for Visicol, as well as incorporated into the labeling for OsmoPrep. In May 2006, the Agency issued an FDA Alert on OSP products for bowel cleansing (2006 FDA Alert),[7] which included information for healthcare professionals and patients, and a science background paper.[8] The 2006 FDA Alert detailed cases of acute phosphate nephropathy associated with the use of OSP for bowel cleansing. At that time, the cases included 21 patients who used OSP solution available in the OTC setting and 1 patient who used Visicol Tablets. Certain individuals (e.g., those of advanced age, those with kidney disease or decreased intravascular volume, and those using medicines that affect renal perfusion or function) were believed to be at an increased risk of acute phosphate nephropathy, and these risk factors were discussed in the 2006 FDA Alert and in the background paper.

[6] See FDA Docket No. 2000P-1472/CP1.

[7] See FDA Alert on "Oral Sodium Phosphate (OSP) Products for Bowel Cleansing," available on the Internet at http://www.fda.gov/cder/drug/infopage/OSP_solution/default.htm.

[8] See FDA "Science Background Paper: Acute Phosphate Nephropathy and Renal Failure Associated With the Use of Oral Sodium Phosphate Bowel Cleansing Products," available at http://www.fda.gov/cder/drug/infopage/OSP_solution/backgrounder.htm.

II. DISCUSSION

As stated previously in this response, you request that FDA (1) withdraw the commercial marketing authorization for OSP products for bowel cleansing, or (2) add a black box warning to OSP products regarding the potential risks of kidney failure caused by nephrocalcinosis and reclassify all OSP products for bowel cleansing as prescription only medicines. In this section of the response, we describe our review of the safety information relating to OSP products, address the specific requests in your petition, and describe related actions that FDA is taking with respect to OSP products.

A. FDA Review of Safety Information

FDA has reviewed recent medical literature and the updated Adverse Event Reporting System (AERS) data on adverse events associated with the use of OSP products. The results of our reviews are discussed in the following subsections.

1. Literature

In 2005, an article by Markowitz et al. reported cases of acute phosphate nephropathy associated with the use of OSP. 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.[9] 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 criteria for the 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. The remaining 17 patients all 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 OSPs 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 OSP.[10]

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[9] Markowitz GS, Stokes MB, Radhakrishnan J, D'Agati YD. Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an under-recognized cause of chronic renal failure. J Am Soc Nephrol 16:3389-3396, 2005.

[10] Gonlusen G et al. Renal failure and nephrocalcinosis associated with oral sodium phosphate bowel cleansing:

In 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) issued a consensus statement on bowel preparation before colonoscopy.[11] This task force performed a critical scientific review of available data, which included 21 randomized, controlled trials in the published literature. The consensus statement was published by the three gastrointestinal (GI) surgery societies after the issuance of the 2006 FDA Alert to healthcare professionals. The scope of the task force consensus statement included not only the use of OSP but also other treatment modalities for bowel preparation, such as polyethylene glycol (PEG). Dosing instructions for OSP were included in the recommendations.[12] The task force assessed both the OTC oral solutions and the prescription-only tablet formulations. The report also identified subgroups in the populations who should not be given OSP.[13]

The task force reported that the use of OSP for bowel preparation before 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

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clinical patterns and renal biopsy findings. Arch of Pathol Lab Med 130(1):101-106, 2006; Ma R C et al. Acute renal failure following oral sodium phosphate bowel preparation in diabetes. Diabetes Care 30(1):182-183, 2007; Aasebo, W et al. Kidney biopsies taken before and after oral sodium phosphate bowel cleansing. Nephrol Dial Transplant 22:920-922, 2007.

[11] Wexner SD, Beck DE, Baron TH et al. A consensus document on bowel preparation before colonoscopy: prepared by a task force from ASCRS, ASGE, and SAGES. Gastrointest Endosc 63:894-909, 2006.

[12] The Wexner et al. task force dosing recommendations regarding the use of OSP for bowel preparation before colonoscopy are as follows:

> Aqueous NaP colonic preparation is an equal alternative to PEG solutions except for pediatric and elderly patients, patients with bowel obstruction, and other structural intestinal disorders, gut dysmotility, renal failure, congestive heart failure, or liver failure (Grade IA). Dosing of aqueous NaP should be 45 mL in divided doses, 10 to 12 hours apart with one of the doses taken on the morning of the procedure (Grade IIB). Apart from anecdotal reports, the addition of adjuncts to the standard NaP regimen has not demonstrated any dramatic effect on colonic cleansing preparation. Carbohydrate-electrolyte solutions such as E-Lyte may improve safety and tolerability. [Note: The term *NaP* is used for OSP in the consensus statement.]

[13] Physicians are advised to select a preparation for each patient based on the safety profile of the agent, sodium phosphate or PEG, in light of the overall health of the patient, their comorbid condition, and currently prescribed medications. In certain circumstances, such as bowel preparation in children, elderly patients, patients with renal insufficiency, and those with hypertension who are receiving ACE inhibitors or ARBs, it may be advisable to adhere to PEG-based solutions because of the risks of occult physiologic disturbances that may potentially contraindicate the use of sodium phosphate-based regimens.

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.[14]

Recently published observational, retrospective studies attempt to assess the incidence of subclinical (without symptoms) kidney injury after OSP 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 OSP for bowel cleansing in an attempt to determine whether lesser degrees of kidney injury occur in a population of patients receiving OSP. 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 patients, comparing those who subsequently developed kidney injury, defined as a 25 percent or $\geq$ 0.5 milligrams/deciliter increase in serum creatinine, to those who did not.[15] The Brunelli study found no statistically significant association between acute kidney injury and exposure to OSP, but found a significant interaction indicating increased risk for kidney injury from OSP 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. In addition, another observational retrospective cohort study by Hurst et al. revealed an increased risk of acute kidney injury, defined as $\geq$ 50 percent increase in baseline serum creatinine, in patients undergoing bowel cleansing using OSP products compared to PEG preparations.[16] 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 that 60 mL/minute, after colonoscopy appears to be similar for sodium phosphate and PEG users.[17]

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

[14] Wexner et al. 2006.

[15] Brunelli SM, Lewis JD, Gupta M, Latif SM, Weiner MG, Feldman HIL. Risk of kidney injury following oral phosphosoda bowel preparations. J Am Soc Nephrol 18:3199-3205, 2007.

[16] 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 18:3192-3198, 2007.

[17] 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.

definitive conclusions can be drawn and prospective studies are needed to further assess subclinical changes in kidney function.

2. Adverse Event Reporting System (AERS) Reports

In the petition, you state that from April 2005 through March 2007, AERS data identified 80 patients with a diagnosis of acute renal failure associated with the use of OSP. You also state that in 50 of these cases, there was no identifiable risk factor for renal impairment reported (Petition at 4). In addition, you state that in the majority of cases there was no histological diagnosis recorded, and in 31 cases there was a diagnosis of nephrocalcinosis or acute phosphate nephropathy associated with renal failure (Petition at 4).

As previously mentioned, we issued an FDA Alert in May 2006 for healthcare professionals and patients detailing cases of acute phosphate nephropathy associated with the use of OSP for bowel cleansing. At that time, the cases included 21 patients who used OSP solution available in the OTC setting and 1 patient who used Visicol Tablets.

Since May 2006, FDA has conducted routine reviews of adverse event reports submitted to AERS and has identified additional cases of acute phosphate nephropathy and renal impairment. This review involved both the prescription products and products available in the OTC setting.

Of the prescription products, we reviewed adverse event reports associated with the use of OsmoPrep, because the number of prescriptions for Visicol appears to have decreased significantly since the introduction of OsmoPrep. OsmoPrep Tablets, which were approved in March 2006, are a reformulation of Visicol Tablets. Patients ingest 48 g (32 tablets) of OsmoPrep rather than 60 g (40 tablets) of Visicol, representing a lower sodium phosphate dose. At the time of the issuance of the 2006 FDA Alert, no cases of acute phosphate nephropathy or acute kidney injury associated with OsmoPrep had been received in AERS.

Since OsmoPrep's approval on March 16, 2006, 20 unique cases of kidney injury associated with the use of the product have been reported to AERS, through September 12, 2008. The onset of the kidney injury occurred from several hours to 21 days after taking OsmoPrep. Three of these patients had a kidney biopsy, the results of which revealed acute phosphate nephropathy. The concomitant use of an ACE inhibitor or ARB was noted for 11 cases, diuretic use in 6 cases, NSAID use in 4 cases, and 1 patient received a contrast dye.[18] Five cases were reported to be life-threatening and 10 resulted in hospitalization. Of these 20 cases, 4 patients required dialysis for an unspecified period of time and 1 patient died from complications of pneumonia. Nine patients were reported to have renal impairment that continued for at least 2 to 4 weeks. The status of renal impairment is unknown for seven patients.

[18] Some patients may fit within more than one category.

In addition, since the issuance of the 2006 FDA Alert, reports of over 50 cases of acute renal failure have been received for OTC OSP solution used for bowel cleansing before colonoscopy.

The data you provided in the petition overlap with the time frame of our review and analysis of the most recent safety information. However, because the time periods are not identical, we cannot compare the specific numbers you provide to our results. As explained more fully in sections II.C, D, and E, we agree that reports of kidney injury, particularly acute phosphate nephropathy, are important information when evaluating the need for additional actions by FDA to address the safety concerns associated with OSP products.

B. Petitioner's Request for Withdrawal of FDA Approval of OSP Products for Bowel Cleansing

In the petition, you request that FDA withdraw the commercial marketing authorization for OSP products for bowel cleansing (Petition at 1). You maintain that because OSP products are used for colonoscopy screening in otherwise healthy populations and because equally effective and safer alternatives for bowel preparations exist, the withdrawal of commercial authorization for OSP products is warranted (Petition at 1). For the reasons stated in the following subsections, FDA denies your request.

1. Standards for Withdrawal of Approval

Section 505(e) of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 355(e)) provides the standards for withdrawal of approval of an NDA. Section 505(e) authorizes FDA to withdraw approval of an application if FDA finds, among other things:

- that clinical or other experience, tests, or other scientific data show that the subject drug product is unsafe for use under the conditions of use upon the basis of which the application was approved;

- that new evidence of clinical experience, not contained in such application or not available to FDA until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to FDA when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or

- on the basis of new information with respect to such drug, evaluated together with the evidence available when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the drug product's labeling.

Section 505(e) further provides that if the Secretary of Health and Human Services finds that

there is an imminent hazard to the public health, FDA may suspend the approval of such application immediately, give the applicant prompt notice of his action, and afford the applicant the opportunity for an expedited hearing under section 505(e). FDA regulations also provide standards for withdrawal of approval of an NDA or abbreviated new drug application (ANDA) under section 505(e) of the FDCA.[19]

2. Risk/Benefit Profile

You state that trend data regarding adverse events demonstrate that reports of acute renal failure and nephrocalcinosis associated with OSP products have grown alarmingly in recent months (Petition at 3). You further state that the published data suggest that the problem is larger in scope than initially believed and warrants reconsideration of the risk/benefit to public health of leaving OSP products on the market under present conditions of access and labeling (Petition at 3).

Although you claim that the incidence of OSP-associated nephrocalcinosis appears higher than previously believed, the increase since 2006 could be associated with increased reporting because there is increased awareness among healthcare professionals and consumers. FDA has previously stated in the 2006 FDA Alert that acute phosphate nephropathy is a rare, but serious adverse event associated with OSP bowel cleansing. Published data, before and after the 2006 FDA Alert, suggest that acute phosphate nephropathy associated with OSP use for bowel preparation may result in progression to chronic renal failure, dialysis, transplant surgery, permanent disability, and/or death. Potential contributing factors include inadequate hydration; increased patient age; history of hypertension and arteriosclerosis; and concurrent use of ACE inhibitors, ARBs, diuretics, or NSAIDs.

[19] Section 314.150(a) (21 CFR 314.150(a)) of the regulations provides that FDA will notify the manufacturer or distributor of the drug product regarding a proposal to withdraw approval if FDA, among other things, finds:

> (i) That clinical or other experience, tests, or other scientific data show that the drug is unsafe for use under the conditions of use upon the basis of which the application or abbreviated application was approved; or
>
> (ii) That new evidence of clinical experience, not contained in the application or not available to FDA until after the application or abbreviated application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when the application or abbreviated application was approved, evaluated together with the evidence available when the application or abbreviated application was approved, reveal that the drug is not shown to be safe for use under the conditions of use upon the basis of which the application or abbreviated application was approved; or
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> (iii) Upon the basis of new information before FDA with respect to the drug, evaluated together with the evidence available when the application or abbreviated application was approved, that there is a lack of substantial evidence from adequate and well-controlled investigations as defined in § 314.126, that the drug will have the effect it is purported or represented to have under the conditions of use prescribed, recommended, or suggested in its labeling.

Although OSP solution and tablets are now marketed with the phosphate content reduced, cases of acute phosphate nephropathy associated with OSP use continue to be reported. However, given the seriousness of colon cancer, screening is a critical part of the process of detecting cancer in people who have no symptoms of the disease. OSP products, when used as a bowel cleanser, play an integral role in the screening process. Thus, although there are risks associated with the use of OSP products for bowel cleansing, there are also important benefits of their use.

3. Risk Factor Screening Not Sufficient

You state that although the selective use of risk factor identification may mitigate the risk of nephrocalcinosis with OSP use, the approach has significant drawbacks. You conclude that the occurrence of nephrocalcinosis in individuals with no identifiable risk factor renders the screening insufficient. You also state that risk factor screening is inadequate in view of the predominant use of OSP in an identified at-risk population (Petition at 4-5).

Current risk factor screening may not be capable of completely eliminating the occurrence of OSP-associated acute phosphate nephropathy. The prior FDA Information for Healthcare Professionals Sheet entitled "Oral Sodium Phosphate Products for Bowel Cleansing,"[20] issued in May 2006, contains several considerations for healthcare professionals when selecting a bowel cleanser for patients. The listed risk factors for OSP-associated acute phosphate nephropathy were inferred from characteristics of the Markowitz et al. study and FDA's AERS reports. However, it is not possible to determine whether the considerations outlined in the 2006 FDA Alert are being followed by doctors.

FDA plans to issue an Information for Healthcare Professionals Sheet that identifies another group who may be at increased risk (persons who are hypovolemic) and specifies an age for increased risk of acute phosphate nephropathy (persons over age 55). Nevertheless, even if the recommendations are being followed universally, FDA does not believe the occurrence of OSP-associated acute phosphate nephropathy would be completely eliminated. Some cases have occurred in patients with no identifiable risk factors. We cannot rule out, however, that some of these patients were dehydrated before taking OSP or they did not drink sufficient fluids after ingesting OSP. Randomized prospective trials may help to clarify which risk factor would be associated with the occurrence of acute phosphate nephropathy and acute kidney injury associated with OSP use.

4. Withdrawal Not Warranted

The standards for withdrawal of an NDA are set forth in section 505(e) of the FDCA and

[20] Available on the Internet at http://www.fda.gov/cder/drug/InfoSheets/HCP/OSP_solutionHCP.htm.

§ 314.150 of the regulations. The risk/benefit profile of OSP does not warrant the withdrawal of OSP products from the market at this time. Based on the evidence provided in the petition and information available to the Agency, we conclude that the standards have not been met and withdrawal is not warranted.

Colorectal cancer is a disease that can be fatal if undetected and left untreated. Colonoscopy is a commonly performed procedure that can provide early detection of colorectal cancer. Before a colonoscopy, it is important to properly prepare the bowel for the procedure. Given that those individuals undergoing a colonoscopy are taking the OSP product to facilitate a screening test rather than for direct therapeutic benefit, it is reasonable to conclude that the benefits of such a therapy should be high and that any risks should be minimal. Although OSP is an effective bowel purgative for use before colonoscopy, acute phosphate nephropathy is a rare complication.[21]

You do not provide evidence to support the claim that other preparation agents provide better safety data compared to OSP. FDA has reviewed the most recent published literature and does not agree with your claim that there are equally effective and safer alternative bowel preparation agents available compared to OSP.[22] Many people cannot tolerate PEG solutions in the quantities used for bowel preparation. Moreover, FDA plans to require the NDA holder of the approved prescription products to conduct a clinical trial comparing safety profiles of OSP and PEG products.

FDA has concluded that prescription OSP products for bowel cleansing should remain available as an option for physicians and patients to determine whether it is appropriate based on an individual analysis of risks and benefits (e.g., patients who cannot take PEG products). OSP solutions available in the OTC setting that are indicated for the relief of constipation can continue to be marketed under the TFM. As explained in section II.C, we believe that based on our current knowledge, the risk of OSP-associated acute phosphate nephropathy can be reduced if the labeling for the prescription OSP products is changed and healthcare providers follow the new warnings that will be in the labeling. Therefore, your request that FDA withdraw the commercial marketing authorization for OSP products is denied.

C. Petitioner's Request to Require a Boxed Warning for All OSP Products Marketed for Bowel Cleansing

In your petition, you request that if OSP products remain on the market for bowel cleansing, then these products should carry a black box warning (Petition at 1, 5). You request that the black box warning include information regarding the potential risks of renal failure, sometimes fatal, caused by nephrocalcinosis (Petition at 1). To support your request, you state that 47 AERS

[21] See Markowitz et al. 2005.

[22] See Hurst et al. 2007; Russmann et al. 2007.

cases of OSP-induced renal damage reported between April 2005 and March 2007, where the mean dosage of OSP solution was 80.3 mL and mean dosage of tablet formulation was 32.9 tablets, indicate that over-dosage no longer was a major reason for observed adverse effects (Petition at 5).

FDA labeling regulations in 21 CFR part 201 state that the WARNINGS AND PRECAUTIONS section of drug product labeling (including the product's package insert) must describe clinically significant adverse reactions,[23] other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur (§ 201.57(c)(6)(i)). Labeling must be revised to include a warning as soon as there is reasonable evidence of a causal association of a clinically significant hazard with a drug. A summary of the most clinically significant warnings and precautions information must be included in the Highlights of Prescribing Information (Highlights) section of labeling for the drug product (§ 201.57(a)(10)).

Under § 201.57(c)(1), a boxed warning (referred to as a "black box warning" by the petitioner) may be required for certain contraindications or serious warnings, particularly those that may lead to death or serious injury. A boxed warning must contain, in uppercase letters, a heading that includes the word "WARNING" and conveys the general focus of information in the box. A boxed warning briefly explains the risk and refers to more detailed information in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section (§ 201.57(c)(1)). A summary of a boxed warning (with the heading WARNING and other words identifying the subject of the warning) must be included in the Highlights in a box and in bold type (§§ 201.56(d)(1) and 201.57(a)(4)).

We have concluded that a boxed warning is appropriate because acute phosphate nephropathy is an adverse reaction so serious in proportion to the potential benefit of using OSP as a bowel cleanser that it is essential that the risk be assessed by a healthcare professional before prescribing the use of the product. In addition, a boxed warning could alert the prescribing physician that acute phosphate nephropathy could be prevented or the risk could be reduced if certain risk factor screening is completed, including taking into consideration whether the person is 55 years of age or older; has kidney problems or heart failure; or is taking medicines to control blood pressure, taking water pills (diuretic), or taking NSAID medicines for arthritis.

In 2008, we conducted a review and new analysis of the AERS reports involving OSP-associated acute phosphate nephropathy, as well as reviewed the recent medical literature on this matter. This review demonstrated that acute phosphate nephropathy may lead to serious injury to the kidney, which may require dialysis or a kidney transplant, and in rare instances, death. However, awareness by healthcare providers to the known risk factors may reduce the frequency of this potentially preventable adverse event. Based on this evidence, we have now concluded that the current labeling of OSP products does not adequately warn healthcare providers and

[23] Section 201.57(c)(7) defines *adverse reaction* as an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

patients about this serious event. In particular, we have determined that taking steps to ensure that healthcare providers and their patients are better informed about the risk of OSP-associated acute phosphate nephropathy might help to decrease the number of these adverse events. Based on this analysis, we have determined that the significance of this risk of OSP-associated acute phosphate nephropathy and the benefits of increased awareness by healthcare professionals of the risk justify the need for a boxed warning under § 201.57(c)(1).

Our updated review and analysis of the AERS reports and literature on OSP-associated acute phosphate nephropathy meets the definition of *new safety information* [24] in Title IX, Subtitle A, section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (see section 505(o)(4) of the FDCA (21 U.S.C. 355(o)(4))). This new safety information provided the basis for our conclusion that a boxed warning regarding OSP-associated acute phosphate nephropathy must be included as part of the safety labeling changes for OSP products (described in more detail in section II.E). In accordance with section 505(o)(4) of the FDCA, we have notified the holder of NDAs for prescription OSP products of the need to revise the product labeling.

Therefore, we grant your request to add a boxed warning to prescription OSP products.

D. Petitioner's Request That All OSP Products for Bowel Cleansing Be Available as Prescription Only Medicines

You state that OSP products remain available in the OTC setting and consumers may not be able to adequately assess the risks of these products without physician guidance, nor adhere to the dosing regimen and recommended levels of fluid intake (Petition at 5). You request that if OSP products remain on the market for bowel cleansing, then these products should be available by prescription only (Petition at 5). To support your request, you observe that simple dose restriction has proven inadequate to prevent the occurrence of renal failure (Petition at 5).

Based on our review of the available data and the lack of data establishing a safe dose of OSP for bowel cleansing, we have concluded that the use of sodium phosphate oral solution for bowel cleansing poses a serious risk of adverse events in some patients. Educational efforts by FDA, such as the 2006 FDA Alert, have not been successful in mitigating this risk. Under the current proposed professional labeling provisions of the TFM for OTC laxative drug products, consumers rely on their healthcare provider to provide information on the safe use of sodium phosphate oral solution for bowel cleansing. This approach has also not been sufficient to

[24] As defined in section 505-1(b)(3) of the FDCA (21 U.S.C. 355-1(b)(3)), *new safety information* is information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3) of the FDCA), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) of the FDCA (21 U.S.C. 355(k)); or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the drug that the Agency has become aware of (that may be based on a new analysis of existing information) since the drug was approved.

manage the risk that has been associated with this use of OSP for bowel cleansing in the OTC setting. 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 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 FDCA (21 U.S.C. 353(b)(1)) sets forth the standard under which drug products can be dispensed only with a prescription. If a drug intended for use, and 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 be dispensed only with a prescription. We conclude that the use of OSP oral solution for bowel cleansing meets this statutory standard that defines a prescription product. Based on the conclusions described above, FDA plans to amend the TFM to remove the proposed professional labeling for OSP products.[25] Therefore, this request in your petition is granted.

E. Additional Safety-Related Actions

In addition to the actions requested in your petition, pursuant to our authority under FDAAA, we have notified the NDA holder of prescription OSP products that they must do the following:

- develop a risk evaluation and mitigation strategy (REMS) that includes the development of and distribution of a Medication Guide and a Communication Plan, and

- conduct a postmarketing clinical trial.

1. Risk Evaluation and Mitigation Strategy (REMS)

In addition to the required safety labeling changes described in section II.C, we also notified the NDA holder that a REMS is necessary for the prescription OSP products. This notification was made under our new authorities under FDAAA (section 505-1(a)(2) of the FDCA (21 U.S.C. 355-1(a)(2)), which authorizes FDA to require the submission of a REMS for an approved drug product if FDA becomes aware of new safety information and makes a determination that such a

[25] FDA is also responding to a citizen petition, submitted on behalf of C.B. Fleet Company, Inc. (Fleet Petition) in June 2003 (Docket No. FDA-1978-N-0021), that requested FDA amend its regulation regarding the use of OSP products in the OTC setting for bowel cleansing. FDA denied the Fleet Petition.

strategy is necessary to ensure that the benefits of the drug outweigh its risks. As previously mentioned, the new safety information is data about acute phosphate nephropathy (discussed in section II.A), an adverse event that can result in permanent impairment of renal function.

a. Medication Guide

We also notified the holder of the NDAs for prescription OSP products that the company is required to develop a Medication Guide as part of the safety labeling changes and their REMS to better educate patients on the risks of acute phosphate nephropathy when using OSP prescription products. A medication guide is FDA-approved patient labeling that conforms to the specifications in 21 CFR part 208 and other applicable regulations. Under section 505-1(e)(2) of the FDCA and part 208, FDA has determined that OSP prescription products pose a serious and significant public health concern requiring distribution of a Medication Guide and that the Medication Guide is necessary for patients' safe and effective use of OSP products. Furthermore, FDA has determined that prescription OSP products have serious risks (relative to its benefits), of which patients should be made aware, because information concerning risks could affect patients' decisions to use or continue to use these products. FDA has also determined that prescription OSP products are products for which patient labeling can help prevent serious adverse events.

b. Communication Plan

In addition, FDA notified the NDA holder of the need to develop a communication plan as part of its REMS that will be targeted at gastroenterologists, surgeons, primary care physicians, and other healthcare providers who are likely to prescribe or dispense OSP products and/or perform follow-up assessments of patients following bowel cleansing. The communication plan will be designed to support implementation of the elements of the REMS.

2. Postmarket Clinical Trial

Section 901 of FDAAA added authority for FDA to require, under certain circumstances, postmarket studies and clinical trials. FDA may require a postapproval study or postapproval clinical trial of a drug product in an approved NDA if FDA becomes aware of new safety information. Under section 505(o)(3)(A) through (B) of the FDCA, the requirement must be based on scientific data and for one or more of the following purposes:

- To assess a known serious risk related to the use of the drug involved.
- To assess signals of serious risk related to the use of the drug.
- To identify an unexpected serious risk when available data indicates the potential for a

serious risk.[26]

In this case, FDA has determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess the known serious risk of acute kidney injury, including acute phosphate nephropathy following OSP use. In addition, the new pharmacoviligance system that FDA is required to establish under section 505(k)(3) of the FDCA has not been established and thus is not sufficient to assess this known serious risk. Finally, FDA determined that only a clinical trial (rather than a nonclinical or observational study) would be sufficient to assess this known serious risk in patients who are taking OSP products for bowel cleansing and to better define what risk factors may predispose patients to such injury. Therefore, we have notified the NDA holder of the requirement to conduct a prospective randomized, active-controlled clinical trial on the risk of developing acute kidney injury, comparing patients undergoing bowel cleansing using prescription OSP products to patients undergoing bowel cleansing using PEG-containing products.

3. Other Action

In addition to providing a response to your petition, we are taking further action with respect to OSP products. We believe that public education is important, and we are working to convey important information to healthcare professionals. In doing so, we have developed an Information for Healthcare Professionals Sheet. In addition, we are issuing a press release and a Frequently Asked Questions (FAQs) document and are arranging telephone calls with the media and stakeholders to discuss these issues. As explained in section II.D of this response, FDA also plans to amend the TFM to remove the proposed professional labeling for OSP products.

III. CONCLUSION

After a thorough review of the information submitted and currently available relevant scientific literature, we conclude that there is new safety information regarding acute phosphate nephropathy that supports granting some of your requests. Accordingly, we have notified the NDA holder for prescription OSP products of the requirement to add a boxed warning to the labeling of these products. We also plan to amend the TFM to remove the proposed professional labeling for OSP products. Therefore, OSP products indicated for bowel cleansing will be available only by prescription. However, your request to withdraw the marketing authorization of prescription OSP products for bowel cleansing is not supported by sufficient evidence. Therefore, your petition is granted in part and denied in part.

[26] Furthermore, before requiring a postapproval study, FDA must make a determination that adverse event reporting under section 505(k)(1) of the FDCA and the active postmarket risk identification and analysis system under section 505(k)(3) of the FDCA are not sufficient to meet the purposes outlined above (section 505(o)(3)(D)(i)). Before requiring a firm to conduct a postapproval clinical trial, FDA must make a determination that a postapproval study will not be sufficient to meet the purposes outlined above (section 505(o)(3)(D)(ii)).

Sincerely,

/s/

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research