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Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

CITIZEN PETITION

The undersigned submits this petition under 21 C.F.R. § 10.30 to request that the Food and Drug Administration (FDA) (i) withdraw the commercial marketing authorization for oral sodium phosphate (OSP) products for bowel cleansing, *or alternatively*, (ii) add a black box warning to their labeling regarding the potential risks of renal failure, sometimes fatal, caused by nephrocalcinosis and reclassify all OSP products for bowel cleansing as prescription only medicines.

ACTION REQUESTED

Petitioner requests that FDA withdraw the commercial marketing authorization for oral sodium phosphate (OSP) products for bowel cleansing *or* immediately add a black box warning to their labeling regarding the potential risks of renal failure, sometimes fatal, caused by nephrocalcinosis and reclassify all OSP products for bowel cleansing as prescription only medicines.

STATEMENT OF GROUNDS

Oral sodium phosphate (OSP) products have historically been regarded as a safe and effective bowel preparation for many patients. It has become increasingly clear, however, that their use presents an avoidable and potentially catastrophic risk of renal failure to some patients and that screening for known risk factors cannot identify all potentially affected patients. Since OSP products are used in a colonoscopy screening context in otherwise healthy populations, and because equally effective and safer alternatives for bowel preparation exist, the withdrawal of commercial authorization for OSP products is warranted.

OSP-Induced Nephrocalcinosis is a Serious Public Health Issue

In 2006, FDA issued an alert to healthcare professionals regarding the risk of acute phosphate nephropathy with use of OSPs for bowel cleansing, summarizing the

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literature reports published as of that time and disclosing some twenty FDA Adverse Event Reporting System (AERS) reports of renal failure following OSP use.¹

Physiologically, the use of OSP as a purgative agent is associated with a transient rise in serum phosphate level and consequent reduction in serum calcium. In some patients active renal tubular excretion mechanisms may be unable to deal with the excess phosphate load.² The consequences of this effect are particularly pronounced in patients with impaired glomerular filtration or in those patients who are taking drugs that impact on tubular mechanisms, such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics or non-steroidal anti-inflammatory drugs (NSAIDs).

FDA's 2006 alert concerned a second aspect of the renal complications of OSP treatment, nephrocalcinosis. Nephrocalcinosis, also known as acute phosphate nephropathy, is characterized by impaired renal function that is first identified weeks or even months after exposure to OSP. For nephrocalcinosis, renal biopsy reveals calcium deposition and extensive tubular injury with atrophy and interstitial fibrosis. Among the 26 cases of OSP-induced nephrocalcinosis reported in the literature thus far,³ all patients suffered some degree of residual renal impairment and four progressed to end stage renal failure. While rare, the severity of this adverse effect is not tolerable in light of the population in which OSPs are prescribed and used and the availability of equally effective alternative bowel preparation agents.

¹ www.fda.gov/cder/drug/InfoSheets/HCP/OSP_solutionHCP.htm

² Ainley EJ, Winwood PJ, Begley JP. Measurement of serum electrolytes and phosphate after sodium phosphate colonoscopy bowel preparation: an evaluation. *Dig Dis Sci* 2005; 50:1319-1323.

³ Aasebo W, Scott H, Ganss R. Kidney biopsies taken before and after oral sodium phosphate bowel cleansing. *Nephrol Dial Transplant* 2007; 22:920-922.

Desmeules S, Bergeron MJ, Isenring P. Acute phosphate nephropathy and renal failure. *N Engl J Med* 2003; 349:1006-1007

Gonlusen G, Akgun H, Ertan A, Olivero J, Truong LD. Renal failure and nephrocalcinosis associated with oral sodium phosphate bowel cleansing: clinical patterns and renal biopsy findings. *Arch Pathol Lab Med* 2006; 130:101-106.

Ma RC, Chow CC, Yeung VT et al. Acute renal failure following oral sodium phosphate bowel preparation in diabetes. *Diabetes Care* 2007; 30:182-183.

Markowitz GS, Nasr SH, Klein P et al. Renal failure due to acute nephrocalcinosis following oral sodium phosphate bowel cleansing. *Hum Pathol* 2004; 35:675-684.

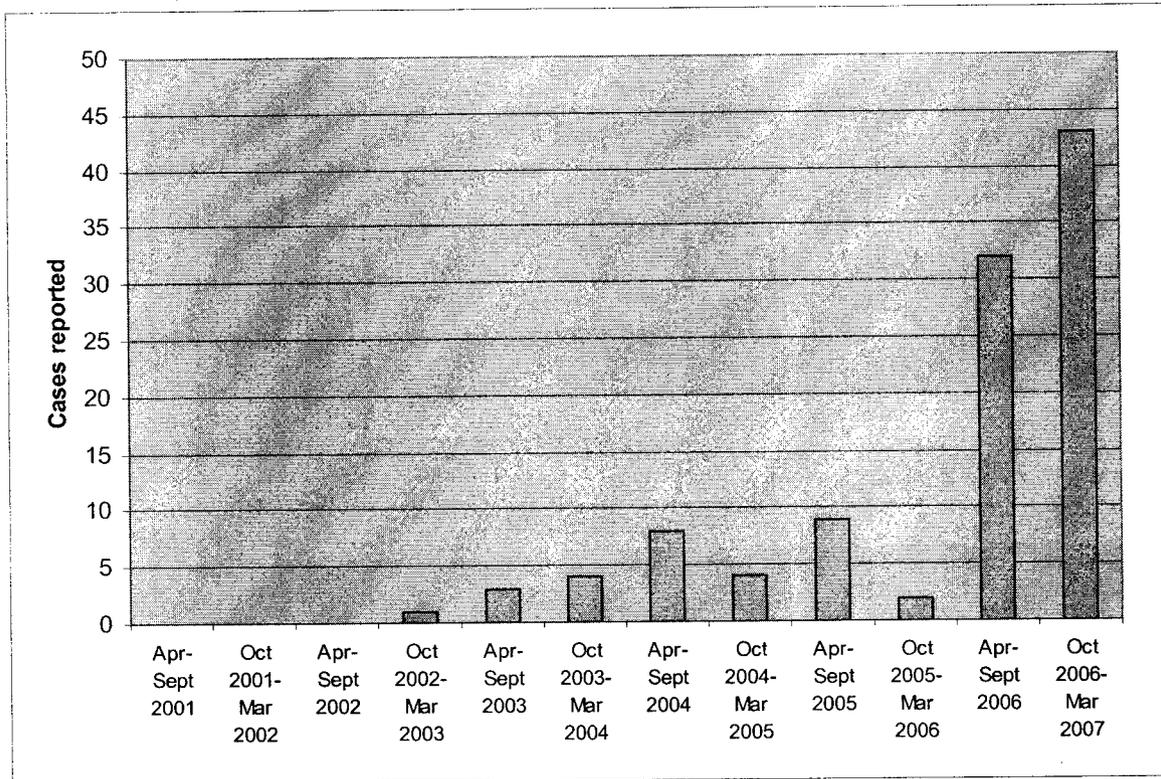
Markowitz GS, Whelan J, D'Agati VD. Renal failure following bowel cleansing with a sodium phosphate purgative. *Nephrol Dial Transplant* 2005; 20:850-851.

Markowitz GS, Stokes MB, Radhakrishnan J, D'Agati VD. Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an underrecognized cause of chronic renal failure. *J Am Soc Nephrol* 2005; 16:3389-3396.

The True Incidence of OSP-Induced Nephrocalcinosis Appears to Be Higher Than Previously Believed

AERS trend data demonstrate that reports of acute renal failure and nephrocalcinosis associated with OSPs have grown alarmingly in recent months (see Figure 1).

Figure 1 – Cases of renal failure and/or nephrocalcinosis reported to FDA April 2001-March 2007 (semiannual rates)⁴



While increased reporting may simply reflect better reporting rather than increased baseline incidence, these data suggest that the problem is larger in scope than initially believed and warrant reconsideration of the risk/benefit to public health of leaving these products on the market under present conditions of access and labeling.

AERS data from April 2005 – March 2007 identified 80 patients with a diagnosis of acute renal failure associated with use of OSP. In an additional 9 cases, there were diagnoses of nephrocalcinosis, nephropathy or renal injury that was not associated with renal failure. Of the 80 patients with renal failure, 7 were identifiable as being aged over 75 (overall mean age was 66), 6 received OSP doses in excess of the recommended amount and 30 were receiving treatment with drugs acting on the renal tubule (7 had

⁴ Center for Drug Evaluation and Research Adverse Event Reporting System; <http://www.fda.gov/cder/aers/extract.htm>.

more than one risk factor). In 50 cases, however, there was no identifiable risk factor for renal impairment reported. In the majority of cases there was no histological diagnosis recorded; in 31 cases there was a diagnosis of nephrocalcinosis or nephropathy associated with the renal failure. These 31 cases post-date publication of the 26 cases previously referred to in the literature.

One single-center study also provides perspective on the potential impact of OSP-induced nephrocalcinosis.⁵ Over a five year period, the Columbia University Medical Center carried out 7,349 renal biopsies on non-grafted kidneys. A retrospective review found that 31 of these had histological findings of nephrocalcinosis. Twenty-seven (27) of those with nephrocalcinosis had undergone recent colonoscopy, of whom 21 had clear evidence indicating OSP as the causal agent in their nephropathy. Of the other six, four had co-existing renal disease preventing establishment of a causal link and the other two cases had no record of the bowel preparation used. Therefore, approximately 0.29% of renal biopsies were attributable to OSP-induced nephropathy. Many of these patients presented with relatively low-grade symptoms that generally improved slowly over a period of months, although none returned to baseline functioning. It is likely that many patients presenting with similar symptoms would simply be diagnosed with non-specific renal impairment owing to the lag time between OSP use and presentation, precluding a link being made.

Finally, in a retrospective long term review of 618 patients who had received oral OSP on two occasions over a 10 year period, 6.8% developed renal insufficiency, although this was not significantly different from the rate of renal impairment developing in a similar smaller group of patients who had received alternative bowel preparations.⁶

Risk Factor Screening Cannot Successfully Eliminate The Occurrence of OSP-Induced Nephrocalcinosis

As stated by the Agency in its 2006 alert to healthcare providers, OSPs are to be used with caution in patients of advanced age, those with kidney disease or decreased intravascular volume, and those using medicines that affect renal perfusion or function (diuretics, ACE inhibitors, ARBs, and possibly NSAIDs). Although the selective use of such risk factor identification may mitigate the risk of nephrocalcinosis with OSP use, this approach has significant drawbacks. Additionally, the occurrence of nephrocalcinosis in individuals with no identifiable risk factor renders this screening mechanism insufficient.

Screening is also inadequate in view of the predominant use of OSP in an identified at-risk population. While no published US data is available for the mean age of patients undergoing colonoscopy, its use as a screening tool is primarily in individuals

⁵ Markowitz GS, Whelan J, D'Agati VD. Renal failure following bowel cleansing with a sodium phosphate purgative. *Nephrol Dial Transplant* 2005; 20:850-851.

⁶ Abaskharoun R, Depew W, Vanner S. Changes in renal function following administration of oral sodium phosphate or polyethylene glycol for colon cleansing before colonoscopy. *Can J Gastroenterol* 2007; 21:227-231.

aged 50 and older.⁷ Data from NHANES III⁸ show that some degree of renal impairment (serum creatinine >1.2 mg/dl) is found in around 15-20% of the population over 50, a level which has been shown to result in significant metabolic disruption following normal doses of OSP.⁹ Finally, and most importantly, further data from NHANES III show that the prevalence of hypertension in older Americans rises from 45% and 54% in men and women aged 55-64 to a peak of 68% and 83% in those over 75.¹⁰ Given that the standard recommended first line treatment is a thiazide diuretic, with ACE inhibitors and ARBs representing popular second line choices, it is clear that a large number, if not a majority of patients presenting for colonoscopy will have at least one risk factor for developing electrolyte imbalance, with the potential for more serious renal damage.

If OSP Products Remain on the Market for Bowel Cleansing, They Should Carry a Black Box Warning and be Available by Prescription Only

In August 2000, a previous Citizen Petition¹¹ requested that OSP bowel preparations be subject to prescription limitations. This petition was denied on the grounds that then-proposed limitations on container size were sufficient, as the majority of renal problems reported in the literature reflected clinicians' failure to observe dosage guidelines.

Current prescribing guidance for bowel preparation recommends that total sodium phosphate dosage should not exceed 60g (90ml phosphosoda solution, 48 tablets) and that this amount should be split into two equal doses, taken 10-12 hours apart.¹² However, among the 47 AERS cases of OSP-induced renal damage reported between April 2005 and March 2007 that also reported the dose administered, mean dosage of OSP solution was 80.3 ml (range 45-240 ml), while mean dosage of the tablet formulation was 32.9 tablets (range 20-48 tabs), indicating that overdosage is no longer a major reason for observed adverse effects. Simple dose restriction has thus proven inadequate to prevent the occurrence of renal failure. Fleet® Phospho-Soda® remains available over-the-counter (OTC), and consumers may not be able to adequately assess the risks of this product's use without physician guidance, nor adhere to the dosing regimen and recommended levels of fluid intake.

⁷ United States Preventive Services Task Force: Screening for Colorectal Cancer (July 2002).

⁸ National Center for Health Statistics. National Health and Nutrition Examination Survey 2003-4. Biochemistry profile. http://www.cdc.gov/nchs/about/major/nhanes/nhanes2003-2004/140_c.xpt

⁹ Ainley EJ. Hyperphosphataemia after bowel preparation with oral sodium phosphate. *Endoscopy* 1006;38:759

¹⁰ National Center for Health Statistics. National Health and Nutrition Examination Survey. Hypertension among persons 20 years of age and over, according to sex, age, race and Hispanic origin: United States, 1988-94 and 1999-2002. <http://www.cdc.gov/nchs/data/hus/04trend.pdf#067>

¹¹ FDA Docket No OOP-1472, CP1.

¹² 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.

In light of the above findings, the Agency should reconsider the request to reclassify OSP products as prescription only and require a black box warning on their labeling.

ENVIRONMENTAL IMPACT

Categorical exclusion is claimed pursuant to 21 C.F.R. § 25.31.

CERTIFICATION

The undersigned certifies 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 which are unfavorable to the petition.

Respectfully Submitted,



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