§ 330.17 Deposit insurance training.

(a) *Purpose.* The purpose of this section is to maintain confidence in Federally insured depository institutions and to protect depositors by requiring insured depository institution employees with authority to open accounts and/or respond to customer inquiries regarding deposit insurance coverage ("employees"), to complete training on basic deposit insurance principles once in any twelve month period. New employees must complete the training within 30 days of commencing employment. Current employees are required to complete the training within 60 days of the effective date of the final rule.

(b) *Applicability.* The requirements in this section shall apply to all insured depository institution employees who have the authority to open accounts and/or respond to customer inquiries regarding deposit insurance coverage.

(c) *Procedure.* (1) *Insured Depository Institution Personnel Education.* (i) *Training.* An insured depository institution must require each employee with the authority to open accounts and/or respond to customer inquiries regarding deposit insurance coverage to complete basic deposit insurance training annually, using an FDIC-provided training module. Each new employee with the authority to open accounts and/or respond to customer inquiries regarding deposit insurance coverage must be required to undergo such training within 30 days of commencing employment.

(ii) *Training Materials.* The FDIC will provide the training module in the form of a self-administered computer-based instructional program.

(2) *Ascertaining Insured Status.* An insured depository institution must implement procedures so that, whenever a customer opens a new deposit account at an insured depository institution, the employee opening the account shall inquire whether the customer has an ownership interest in any other accounts at the IDI and, if so, whether the customer's aggregate ownership interest in deposit accounts, including the new account, exceeds the Standard Maximum Deposit Insurance Amount. If the customer responds affirmatively, then the IDI employee shall provide the customer with the FDIC's *Deposit Insurance Summary* publication. In the case of deposit accounts opened by mail or via the Internet or other technology, these inquiries can be included in the paper or electronic application form, with the link to *the Deposit Insurance Summary* publication provided.

(d) *Definitions.* (1) *Account* shall mean a deposit account at a depository institution that is held by or offered to a customer. It includes time, demand, savings, and negotiable order of withdrawal accounts. The term does not include a fiduciary account as to which the insured depository institution does not, in the normal course of business, keep records of beneficial owners of the deposits in the account.

(2) *New Account* shall mean any deposit account at an insured depository institution to which the insured depository institution assigns a unique identifier that serves to distinguish the account from other, existing accounts at the depository institution.

By order of the Board of Directors.

Dated at Washington, DC, this 7th day of February, 2011.

Federal Deposit Insurance Corporation.

Robert E. Feldman,

Executive Secretary.

[FR Doc. 2011–3085 Filed 2–10–11; 8:45 am]

BILLING CODE 6714–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310 and 334

[Docket No. FDA–1978–N–0021; Formerly Docket No. 78N–036L]

RIN 0910–AF38

Professional Labeling for Laxative Drug Products for Over-the-Counter Human Use; Proposed Amendment to the Tentative Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a proposed rulemaking to amend the tentative final monograph (1985 TFM) for over-the-counter (OTC) laxative drug products (products that relieve occasional constipation). FDA is proposing that sodium phosphate salts (dibasic sodium phosphate, monobasic sodium phosphate, and the combination of dibasic sodium phosphate/monobasic sodium phosphate salts in a solution dosage form) are not generally recognized as safe (GRAS) for bowel cleansing. This document also would withdraw the professional labeling proposed for sodium phosphate salts in the 1985 TFM. Professional labeling is additional information about an OTC drug that is directed to healthcare professionals who prescribe, administer, or dispense medications and is not included in OTC drug product labeling for consumers. FDA is issuing this proposed rule after a careful review of new data and information on the serious side effects that have been associated with the customary dose of OTC sodium phosphates solution (approximately 60 grams (g) of sodium phosphates taken in two 45-milliliter (mL) doses 12 hours apart or approximately 50 g of sodium phosphates taken in a 45-mL dose followed by a 30-mL dose 12 hours later) for bowel cleansing prior to colonoscopy. This proposed rule is part of FDA's ongoing review of OTC drug products.

DATES: Submit electronic or written comments by March 14, 2011. *See* section VI of this document for the effective date of any final rule that may publish based on this proposal.

ADDRESSES: You may submit comments, identified by Docket No. FDA–1978–N–0021 (formerly Docket No. 78–N–036L) and RIN number 0910–AF38, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- *FAX:* 301–827–6870.
- *Mail/Hand delivery/Courier (For paper, disk, or CD–ROM submissions):* Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the agency name, docket number (Docket No. FDA–1978–N–0021) (formerly Docket No. 78N–036L) and Regulatory Information Number (RIN) (RIN 0910–AF38) for this rulemaking. All comments received may be posted without change to *http://www.regulations.gov* including any personal information provided. For additional information on submitting comments, *see* the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket, to read background documents or comments received, go to *http://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts

and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Mary S. Robinson, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, MS5411, Silver Spring, MD 20993–0002, 301–796–2090.

SUPPLEMENTARY INFORMATION:

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I. Glossary

As used in this document:

ACE inhibitor means angiotension-converting enzyme inhibitor; a prescription drug for hypertension.

Acute phosphate nephropathy means a type of nephrocalcinosis attributed to the use of oral sodium phosphate products.

Acute kidney failure means sudden inability of the kidney to remove wastes, concentrate urine, and conserve electrolytes.

ARB is an abbreviation for angiotension receptor blocker, a prescription drug for hypertension.

Biologic plausibility means a causal association (or relationship between two factors) that is consistent with existing medical knowledge.

Bowel cleansing means clearing the lower digestive tract in preparation for a colonoscopy.

Bowel cleansing system means a laxative product containing a combination of several different laxative ingredients for sequential administration at specified intervals for use in cleansing the bowel prior to surgery, colon x-ray, or endoscopic examination.

Electrolyte disturbance means abnormal levels of electrolytes such as sodium, potassium, calcium, or phosphorous found in the blood and other body fluids.

End stage kidney disease means complete or near complete failure of the kidneys to function.

GFR is an abbreviation for glomerular filtration rate; is a measure of kidney function. GFR can be obtained by measuring creatinine clearance or by estimating creatinine clearance. The creatinine clearance is measured by using the values of urine creatinine concentration, urine flow rate, and plasma creatinine concentration, while the estimated creatinine clearance is calculated by using a formula that uses measured serum creatinine. Creatinine clearance is not a precise GFR measurement, but rather an accepted surrogate for GFR.

Nephrocalcinosis means a condition characterized by precipitation of calcium phosphate in the tubules of the kidney resulting in kidney injury.

NSAID is an abbreviation for nonsteroidal anti-inflammatory drug; OTC and prescription drugs that relieve pain and inflammation.

OSP is an abbreviation for oral sodium phosphates, the combination of dibasic sodium phosphate and monobasic sodium phosphate salts in a tablet or solution dosage form.

PEG is an abbreviation for polyethylene glycol, a prescription drug used for bowel cleansing.

II. Background

A. Purpose of the Rule

Oral sodium phosphates (OSP) products are frequently recommended by physicians for bowel cleansing prior to a colonoscopy and other medical procedures. Both prescription tablet dosage forms and OTC OSP solution have been used for this purpose. This document addresses the use of OTC OSP solutions for bowel cleansing. The customary dose of OTC OSP solution used in medical practice for bowel cleansing is approximately 60 g of sodium phosphates (dibasic sodium phosphate and monobasic sodium phosphate salts) solution taken orally as two 45-mL doses 12 hours apart or approximately 50 g of sodium phosphates taken as a 45-mL dose followed by a 30-mL dose 12 hours later. In the tentative final monograph for OTC laxative drug products published January 15, 1985 (50 FR 2124), FDA proposed labeling for healthcare professionals for the use of OTC sodium phosphates solution for bowel cleansing. Subsequently, FDA approved sodium phosphates tablets for prescription use for bowel cleansing through the new drug application (NDA) approval process. However, over the years concerns have been raised about the safety of all OSP, both solutions and tablets, for bowel cleansing.

Most recently, FDA received a petition requesting that FDA either withdraw the marketing authorization of OSP for bowel cleansing or limit the marketing of these products to prescription only and require a "black box" warning (Ref. 1). The petition presented the following arguments to support these requests:

- Trend data on adverse events demonstrate an increase in the number of reports of acute renal failure and nephrocalcinosis associated with the use of OSP for bowel cleansing.
- The available published data suggest that the problem is larger in scope than initially believed.
- The occurrence of nephrocalcinosis in individuals with no identifiable risk factors renders screening insufficient.
- There are equally effective and safer alternative bowel preparation agents that are available.

The petition stated that new safety information warrants reconsideration of the risk/benefit ratio to the public of the continued OTC and prescription use of OSP products for bowel cleansing under their present labeling.

FDA concluded that the currently available information was not sufficient to warrant the withdrawal of OSP products from the market. However, FDA also concluded that the use of OSP for bowel cleansing poses a serious risk of adverse events in some patients and that current measures of mitigating these risks have been unsuccessful. Therefore, on December 11, 2008, FDA granted the petition's request to limit the marketing of OSP products for bowel cleansing to prescription only and to require a boxed warning in product labeling (Ref. 2). We also concluded that additional measures were necessary to manage the potential

risks associated with the use of prescription OSP products for bowel cleansing. Under new authority granted by the Food and Drug Administration Amendments Act of 2007, FDA stated that it had notified the NDA holder of prescription OSP products that it must develop a risk evaluation and mitigation strategy (REMS) that includes the development of a Medication Guide and a communication strategy targeted at healthcare providers who are likely to prescribe or dispense OSP products and/or perform followup assessments of patients following bowel cleansing. We also determined that prospective clinical trials are necessary to assess the risk of acute kidney injury in patients using prescription OSP products for bowel cleansing, and to better define the risk factors that predispose patients to such injury.

Specifically, this document addresses the proposed professional labeling for OTC sodium phosphate salts for bowel cleansing described in § 334.80 of the 1985 TFM. Under the 1985 TFM, this additional labeling would have been provided only to healthcare professionals and not the general public, and the labeling would not have been included as part of the OTC drug product label. Professional labeling may be provided to health professionals in separate labeling distributed by pharmaceutical sales representatives. The proposed labeling would have provided certain information to healthcare professionals about the use of sodium phosphate products for bowel cleansing use. In this document we are proposing that the professional labeling for the use of sodium phosphates salts for bowel cleansing use be removed from the 1985 TFM because of our safety concern with the bowel cleansing use of OSP products. This proposed rule does not address the proposed professional labeling for bowel cleansing for other active ingredients included in § 334.80. FDA intends to address the proposed professional labeling of these active ingredients in a future **Federal Register** publication.

This proposed rule is consistent with the agency's determination that OSP products indicated for bowel cleansing should be limited to prescription only. In this document FDA also proposes to classify, the individual sodium phosphate salts (*i.e.,* dibasic sodium phosphate and monobasic sodium phosphate), as not GRAS (*i.e.,* nonmonograph) for the professional labeling indication proposed in the 1985 TFM, *i.e.,* "For use as part of a bowel cleansing regimen in preparing the patient for surgery or for preparing the colon for x-ray endoscopic examination." Thus, this proposed rule would amend § 310.545 (21 CFR 310.545) to include sodium phosphate salts, singly and in combination for bowel cleansing use as described in § 334.80 of the 1985 TFM.

In addition, the safety issues raised by the prescription and professional use of OSP for bowel cleansing has led FDA to reconsider the appropriateness of bowel cleansing, as described in § 334.66, as an OTC indication. FDA will address the status of bowel cleansing as an OTC indication in a future **Federal Register** publication.

*B. Chronology of the **Federal Register** Publications Addressing Professional Labeling for Sodium Phosphate Salts in the OTC Laxative Drug Products Rulemaking*

The current proposal is part of FDA's ongoing review of OTC drug products. There are earlier **Federal Register** publications relevant to the use of OTC sodium phosphate salts for bowel cleansing. A summary of relevant **Federal Register** publications is provided in table 1 of this document as follows:

TABLE 1—OTC LAXATIVE DRUG PRODUCTS RULEMAKING FOR MONOBASIC SODIUM PHOSPHATE AND DIBASIC SODIUM PHOSPHATE [1]

Federal Register publication	Information in document
March 21, 1975 (40 FR 12902), advance notice of proposed rulemaking (ANPR) for OTC laxative drug products.	Recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products (Panel) Panel recommends: • General recognition of the safety and effectiveness of sodium phosphate salts and the combination of sodium phosphate salts for laxative use. • A professional labeling warning (for healthcare professionals) "Do not use in patients with megacolon, as hypernatremic dehydration may occur. Use with caution in patients with impaired renal functions as hyperphosphatemia and hypocalcaemia may occur." The Panel did not recommend that the sodium phosphates salts bear an indication for preparation of the colon for x-ray and endoscopic examination. (50 FR 12902 at 12940 and 12942)
January 15, 1985 (50 FR 2124), tentative final monograph (TFM) for OTC laxative drug products.	FDA adds a provision for OTC bowel cleansing systems in § 334.32. FDA also adds the following professional labeling indication for sodium phosphates oral and rectal solutions, USP: [2] "For use as part of a bowel cleansing regimen in preparing the patient for surgery or for preparing the colon for x-ray endoscopic examination." The proposed professional labeling did not contain directions for the proposed bowel cleansing indication. (50 FR 2124 at 2157)
March 31, 1994 (59 FR 15139) Amendment to TFM for OTC laxative drug products.	Based on a number of deaths related to the OTC availability of a 240-milliliter (mL) container size for sodium phosphates oral solution, FDA proposes an amendment to the 1985 TFM to limit the container size for these products to not greater than 90 mL (3 ounces (oz)) and to add a new overdose warning alerting consumers that exceeding the recommended dose can be harmful as follows: "Do not exceed the recommended dose unless directed by a doctor. Serious side effects may occur from excess dosage."

TABLE 1—OTC LAXATIVE DRUG PRODUCTS RULEMAKING FOR MONOBASIC SODIUM PHOSPHATE AND DIBASIC SODIUM PHOSPHATE [1]—Continued

Federal Register publication	Information in document
May 21, 1998 (63 FR 27836), final rule, package size limitation and warning and directions statements for sodium phosphates oral solutions.	FDA determines that the continued OTC availability of a 240-mL container size of sodium phosphates oral poses a serious safety concern and that it cannot wait for a laxative final rule to address this concern. FDA publishes a final rule that limits the container sizes to not greater than 90 mL and adds warnings and direction statements for sodium phosphates oral and rectal solutions marketed for laxative and bowel cleansing use that includes the following: • "Do not (take or use) more unless directed by a doctor." • "Adults and children 12 years of age and over; Oral dosage is dibasic sodium phosphate 3.42 to 7.56 grams and monobasic sodium phosphate 9.1 to 20.2 grams (20 to 45 mL dibasic. sodium phosphate/monobasic sodium phosphate oral solution) "Do not take more than 45 mL (9 teaspoons or 3 tablespoons in a 24-hour period." FDA also indicates its intention to incorporate the information in 21 CFR 201.307 into the final monograph for OTC laxative drug products at a later date. *See* 21 CFR 201.307. Effective date of the package size limitation portion of the final rule was June 22, 1998, and effective date of the relabeling portion was September 18, 1998.
May 21, 1998 (63 FR 27886), amendment to TFM for OTC laxative drug products.	In an amendment to the 1985 TFM, FDA proposes extensive additional labeling for the professional use of oral and rectal sodium phosphate drug products that: • Warns healthcare professionals about the use of sodium phosphates products in the elderly, in patients taking drugs that may affect electrolyte levels, or in patients with: ○ congestive heart failure ○ impaired renal function ○ heart disease ○ acute myocardial infarction ○ unstable angina ○ preexisting electrolyte disturbances (such as dehydration, or those secondary to the use of diuretics) • Advises monitoring electrolytes and giving sufficient fluid replacement to prevent dehydration. • Describes the adverse effects on electrolyte balance that can occur when one or more doses of sodium phosphates is given in a 24-hour period. • Provides recommendations for the treatment of electrolyte imbalance. FDA also proposes additional warnings about the use of rectal dosage forms of sodium phosphate drug products that: • Warns about the use of rectal dosage forms of sodium phosphate products in children under 2 or in patients with ○ megacolon ○ imperforate colon ○ colostomy ○ rectal abnormalities ○ and about forcing the enema tip into the rectum FDA also states that it will not include a dosage greater than 7.56 gm of dibasic sodium phosphate and 20.2 g monobasic sodium phosphate in a 24-hour period in the OTC or professional labeling in the final monograph for OTC laxative drug products.
December 7, 1998 (63 FR 67399)	Final rule; stay of compliance with the relabeling requirements for rectal sodium phosphates in 21 CFR 201.307 until September 8, 1998, to allow manufacturer's additional time to relabel their products.
December 9, 1998 (63 FR 67817), notice of withdrawal of TFM amendment of May 21, 1998 (63 FR 27886).	FDA withdraws its proposed amendment of § 334.80(b)(2) of the 1985 TFM to add expanded professional labeling for oral and rectal sodium phosphates drug products and states the intent to further expand the professional labeling in a future proposed rule.
November 29, 2004 (69 FR 69278)	Final rule to extend the sodium content labeling requirement to sodium phosphates rectal products.

[1] In the 1985 TFM (50 FR 2124), FDA referred to dibasic sodium phosphate as "sodium phosphate," and monobasic sodium phosphate as "sodium biphosphate." This document uses "dibasic sodium phosphate" and "monobasic sodium phosphate," the official names listed in the USP Dictionary of USAN and International Drug Names, 2008. The document uses the term "sodium phosphate salts" to refer to dibasic sodium phosphate" and "monobasic sodium phosphate" separately or in combination.

[2] Sodium phosphates oral solution is the official name for a solution of dibasic sodium phosphate and monobasic sodium phosphate in the U.S. Pharmacopeia 31/National Formulary 26, 2008. Sodium phosphates rectal solution is the official name for a solution of dibasic sodium phosphate and monobasic sodium phosphate in the U.S. Pharmacopeia 31/National Formulary 26, 2008.

C. Other Regulatory History Relevant to This Rulemaking

1. Citizen Petition To Include Bowel Cleansing Systems Containing Sodium Phosphates Oral Solution

In the 1985 TFM, FDA proposed that certain combination bowel cleansing systems could be considered generally recognized as safe and effective (GRASE) for OTC use as bowel cleansers (50 FR 2124 at 2153). The proposed combinations did not include sodium phosphate ingredients. In a petition dated November 12, 1987, and a subsequent supplemental submission to the petition, a manufacturer requested that FDA amend the 1985 TFM to include six bowel cleansing systems (Refs. 3 and 4). In a letter dated October 26, 1989, FDA responded to the petition and found that two of the six requested kits could be GRASE for OTC use for bowel cleansing (Ref. 5). Both kits include sodium phosphates oral solution as a component. One kit contains three laxatives for sequential

administration as follows: sodium phosphates oral solution (7.56 g sodium phosphate and 20.2 g sodium biphosphate as a 45-mL solution), followed by bisacodyl (20 mg) in an oral dosage form taken at least 3 hours after the sodium phosphates oral solution, followed by a bisacodyl suppository (10 mg) taken at least 9 hours after the oral bisacodyl and at least 1 hour before the scheduled procedure. The other kit substitutes a bisacodyl enema (10 g) for the bisacodyl suppository. In its response, FDA indicated that the Agency intended that both kits would be added as GRASE OTC bowel cleansing systems in § 334.32 of the final monograph. In a letter dated December 27, 2010, FDA subsequently informed the manufacturer of its intention to withdraw its proposal to include § 344.66 Bowel Cleansing Systems in the OTC laxative final monograph based on concerns about the safety of bowel cleansing in the OTC setting (Ref. 6).

2. Citizen Petition To Include in Professional Labeling a Sodium Phosphates Oral Solution Two 45-mL Dose Regimen

In response to the 1985 TFM, one manufacturer filed a petition dated March 23, 1993, and supplements to the petition, requesting that the professional labeling (§ 334.80) be amended to include a bowel cleansing regimen consisting of two 45-mL doses of sodium phosphates oral solution, administered sequentially 10 to 12 hours apart (Refs. 7 through 12). A comment on the petition dated September 23, 1993, expressed concern about the March 23, 1993, petition request, stating that there is a potential for sodium phosphates to induce electrolyte and hemodynamic changes when ingested in two sequential doses within 24 hours (Ref. 13).

On March 1, 1996, FDA responded to the citizens petition mentioned previously, stating that the available data supported the effectiveness of the proposed bowel cleansing regimen of two 45-mL doses 10 to 12 hours apart (Ref. 14). However, FDA emphasized it was concerned about the safety of this dosage regimen because of the electrolyte and vascular volume changes that could occur. FDA explained that, should adequate safety data to support the proposed regimen become available, it might be possible for the Agency to consider this dosage regimen of two 45-mL doses, administered 10 to 12 hours apart, for inclusion in the monograph by professional labeling only. FDA ultimately denied this petition (Ref. 7) in a letter dated August 22, 1997, because we remained concerned about the safety of that dosing regimen (Ref. 15).

3. Citizen Petition To Limit Sodium Phosphates for Bowel Cleansing to Prescription Marketing

Subsequently, FDA received another citizen petition dated August 23, 2000, requesting that FDA limit the marketing of sodium phosphates oral solution for bowel cleansers to prescription status and to require a boxed warning (Ref. 16). On July 19, 2001, FDA denied the petition, stating that based on the available data and information; there was insufficient evidence at that time to support the petition's request (Ref. 17). However, FDA stated that it intended to propose in a future issue of the **Federal Register** to limit the package size of sodium phosphates oral solution to 45 mL and to require revised labeling to include more information on the safe use of these products by consumers and health professionals.

4. Citizen Petition to Include Professional Labeling for Two 30-mL Doses to Two 45-mL Doses

FDA received another citizen petition dated June 25, 2003, requesting that the Agency amend the 1985 TFM to include professional labeling for two 30-mL to two 45-mL doses of sodium phosphates oral solution given sequentially at a 10- to 12-hour dosing interval for bowel cleansing prior to diagnostic procedures (Refs. 18 and 19). The petition also included recommendations for amending the proposed professional labeling (§ 334.80).

FDA also received a number of comments objecting to the petition's requested dosing regimen (Refs. 21, 22, and 23). One comment stated that the regimen of two doses in 24 hours is not safe, primarily because it can cause dangerous electrolyte shifts. The comment asserted that the problem is exacerbated because a patient's susceptibility to electrolyte changes is not adequately evaluated prior to administration for bowel cleansing use, in spite of labeling (Ref. 21). Another comment stated that sodium phosphates oral solution should be subject to prescription control when used for bowel cleansing (Ref. 22). As an alternative to prescription status for sodium phosphates oral solution, the comment recommended that FDA limit the bowel cleansing indication to situations where sodium phosphates oral solution is included in a bowel cleansing system to be administered at a total dose of not more than 7.56 g sodium phosphate and 20.2 g sodium monobasic sodium phosphate (45 mL). The third comment stated that the sodium phosphate bowel cleansing labeling is inadequate to address the continuing problems resulting from the electrolyte derangements and volume depletion caused by these products (Ref. 23).

On December 11, 2008, FDA denied this petition (Ref. 20). Based on a review of the available data and the lack of data establishing a safe dose of OSP for bowel cleansing in the OTC setting, FDA concluded that the use of sodium phosphates oral solution for bowel cleansing in the OTC setting according to professional labeling in an OTC monograph poses an unacceptable risk of serious adverse events. FDA also concluded that the use of sodium phosphate oral solution products for bowel cleansing meets the statutory standard for prescription products set forth in the Federal Food, Drug, and Cosmetic Act (FD&C Act).

5. FDA's Educational Efforts

FDA has made a number of attempts outside the rulemaking process to educate healthcare professionals and consumers about the potential risks associated with the use of sodium phosphates oral solution for bowel cleansing. In September 17, 2001, a Science Background Paper was issued on the "Safety of Sodium Phosphates Oral Solution" (Ref. 24), in which FDA stated that physicians need to be aware that people at increased risk for electrolyte disturbances (*e.g.,* those with congestive heart failure, ascites, renal insufficiency, and dehydration) may experience serious adverse events if they use a sodium phosphates oral solution for bowel cleansing (*see* section III of this document).

In 2006, FDA issued a health alert and a second Science Background Paper stating that a rare but serious form of kidney failure has been associated with the use of OSP products for bowel cleansing (Refs. 25 and 26). In 2008, FDA issued another health alert and provided healthcare professionals with updated information on the risks associated with the use of OSP for bowel cleansing (Refs. 27 and 28). The alert stated that as a result of new safety information, FDA would require a Boxed Warning on prescription OSP products as well as the development of a REMS for these products (Ref. 27). FDA also stated its intention to publish a proposed rule to remove professional labeling for OTC OSP for bowel cleansing from the 1985 TFM (50 FR 2124 at 2157). FDA posted this information on its Web site at *http://www.fda.gov/cder/drug/infopage/osp_solution/default.htm.*

III. Safety Concerns About the Use of Oral Sodium Phosphate Products for Bowel Cleansing

A. Summary of FDA's Adverse Event Reporting System Data

As described previously, FDA has previously made a number of attempts to educate healthcare professionals and consumers about the risk of adverse effects on the kidneys that have been associated with the use of OSP products for bowel cleansing. In addition to measures taken by FDA, in 2005 a major manufacturer of OTC sodium phosphates oral solution products distributed updated professional labeling containing detailed safety information and dosing instructions (60 g of sodium phosphates (dibasic sodium phosphate and monobasic sodium phosphate salts) solution taken orally as two 45-mL doses 12 hours apart or approximately 50 g of sodium phosphates taken as a 45-mL dose followed by a 30-mL dose 12 hours later) (Ref. 29). Despite these measures and the development of products with a reduced sodium phosphate dose, FDA's Adverse Event Reporting System (AERS) continues to receive reports of acute kidney injury that have been associated with the customary dose of these products for bowel cleansing.

To date, AERS has received over 100 serious adverse event reports associated with the use of prescription and nonprescription OSP products for bowel cleansing at the customary dose. Acute renal injury associated with this use of OSP for bowel cleansing has led to kidney transplant, dialysis, long term renal failure and, in rare instances, death. The majority of these cases occurred in patients with additional risk factors for kidney injury as identified in the May 2006 Health Alert (*see* section II.C.5 of this document). There were cases, however, that occurred in patients without additional risk factors.

From 1969 to 2005, FDA received 33 reports of acute kidney injury reported to be associated with the use of OTC sodium phosphates oral solution for bowel cleansing. Among the 33 reports, 4 cases developed end-stage kidney disease with one case requiring a kidney transplant. At least 22 of the 33 cases developed chronic kidney failure, with at least 9 cases requiring hospitalization and 7 requiring dialysis. Only 5 of the 33 cases of acute kidney injury involved a dose of sodium phosphate in excess of 59.4 g.[1] In addition to the cases of acute kidney injury, there were reports of 11 fatalities, 2 cases of seizure, and 12 serious cardiac events. Most of the cases with cardiac events had electrolyte abnormalities. However, the dose of sodium phosphates involved in most of these cases was well in excess of 59.4 g.

Since 2005, there have been an additional 46 reports of acute kidney failure that have been associated with the use of OTC sodium phosphates oral solution for bowel cleansing. Twelve of these cases were reported in a published abstract (Ref. 30) with only limited information. The remaining 34 cases were reported in the AERS data base. Of the AERS cases, one required a kidney transplant, one was placed on a kidney transplant list, six required dialysis, and four cases had long term decreased kidney function. More recently (January 2008), FDA received two reports of acute kidney injury associated with a lower dose sodium phosphate oral solution regimen, *i.e.,* a 45-mL dose followed by 30-mL dose administered 10 to 12 hours apart. Both of these cases resulted in hospitalization.

An OSP in a tablet dosage form has been approved for prescription use as a bowel cleanser since 2000. The sodium phosphate dose of this product is 60 g. In 2006, FDA approved a sodium phosphate tablet with a lower sodium phosphate dose (48 g) for the same indication. There have also been a number of reports of acute kidney injury associated with the use of both of these products.

Since 2001, FDA has received 16 cases of acute kidney injury that were likely associated with the use of the 60-g prescription product. Ten of these cases required hospitalization, and at least two required dialysis. Direct evidence of calcium phosphate precipitation in kidney tubules was obtained by biopsy in one case. There were also 10 cases of seizure. In at least nine of these cases there was no previous history of seizure, and seizures began between 2 to 16 hours after use of OSP. In all 10 seizure cases, the patient had low blood sodium levels, and required hospitalization. Five of the cases of renal failure and two of the cases of seizure did not follow labeled directions for use, which may have contributed to the adverse event.

Since approval of the 48-mg dosage form of sodium phosphate tablets in 2006, 20 unique cases of kidney injury associated with the use of this lower dose 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 the product. 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 in 11 cases, diuretic use in 6 cases, NSAID use in 4 cases; and 1 patient received a contrast dye. 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 kidney impairment that continued for at least 2 to 4 weeks. The status of renal impairment is unknown for seven patients.[2]

B. Summary of the Available Published Data

In addition to the FDA AERS cases described previously, there are also reports of acute kidney injury associated with the use of sodium phosphate products for bowel cleansing in the published literature. It is not clear from the reports whether these adverse events were associated with the use of an OTC or prescription product.

The 21 cases of acute phosphate nephropathy cited in the May 2006 Health Alert were identified by Markowitz *et al.* (Ref. 31) from kidney biopsy archives at the Columbia University Renal Pathology Laboratory. From 2000 to 2004, the laboratory processed a total of 7,349 native renal biopsies (transplanted kidneys were excluded), from which 31 cases were retrieved with findings of kidney tubule injury and abundant calcium deposits. Of these 31 cases, 21 had normal calcium levels and met the criteria for acute phosphate nephropathy and had a recent colonoscopy preceded by OSP use. The incidence of acute phosphate nephropathy reported in this study was 0.29 percent (21 of 7,349).

Clinical followups were available for all 21 cases (mean 16.7 months). All 21 cases had increased serum creatinine, an indication of decreased kidney function, (mean 3.9 mg/deciliter (mg/dL)) at a median of 1 month after colonoscopy. Four cases (19 percent) progressed to end stage kidney failure 9 to 18 months (mean 13.8 months) after colonoscopy and required dialysis. These four patients required kidney replacement therapy, and one of the four underwent successful kidney transplant. Although 16 of the remaining 17 cases (94 percent) had a subsequent improvement in kidney function, none returned to baseline creatinine levels and were left with some degree of renal impairment.

The demographic and clinical findings for these 21 cases suggest that age and the co-administration of agents

[1] Outcomes are not mutually exclusive.

[2] Outcomes are not mutually exclusive.

that may reduce kidney circulation are risk factors for the condition. Eighteen of the 21 cases were 51 years or older, and 3 were older than 62. Sixteen of 21 cases (76.2 percent) had a history of hypertension, and 14 of the 16 patients with hypertension (87.5 percent) were being treated with either an ACE inhibitor or ARB for their hypertension. Four cases were taking diuretics and three were on non-steroidal anti-inflammatory drugs (NSAIDs). Five cases were taking more than one of these agents simultaneously. One patient who was 39 years old did not have any of the risk factors noted in the series. Also noteworthy, but of unclear significance, was that 17 (81 percent) of the 21 cases were women.

Subsequent to the report by Markowitz and the 2006 FDA Health Alert, there continued to be reports (Refs. 32 and 33) of acute kidney injury associated with the use of OSP. Ma *et al.* reported cases of acute kidney injury in two patients (75-year old male and an 80-year old female) who had a history of diabetes mellitus (Ref. 32). Baseline serum creatinine was within normal limits, but one patient had microalbuminuria (small amounts of protein in the urine), an early marker of diabetic kidney disease. Acute kidney injury developed within days of receiving OSP bowel prep for colonoscopy. Biopsies were not conducted, but the kidney injury was attributed to OSP because of the temporal relationship to OSP exposure. The male patient required 5 days of dialysis for the acute injury. Both cases resolved, but serum creatinine remained elevated above their baseline values. The authors noted that patients with diabetes often have decreased renal perfusion despite normal serum creatinine and may be at risk for kidney injury with OSP.

Gonlusen *et al.* reported the case of a 56-year-old woman with Crohn's Disease who presented with acute kidney injury approximately 2 weeks after a colonoscopy (Ref. 33). She received two doses of sodium phosphates oral solution (45 ml each dose) prior to the colonoscopy. Her baseline creatinine was 0.8 mg/dL. Serum creatinine was 3.5 mg/dL at the time of presentation. Kidney biopsy showed calcium phosphate deposition in the kidney tubules, that was likely related to the use of sodium phosphates oral solution. The acute kidney injury resolved, but her serum creatinine remained elevated at 1.6 mg/dL 10 months later.

The author reviewed the literature and speculated that there are two types of acute kidney injury associated with OSP. One type is related to the precipitation of calcium phosphate in the kidney tubules, such as the case described in this report. The other type occurs within several days and is associated with severe electrolyte abnormalities and symptoms related to these abnormalities. In the literature reviewed by Gonlusen *et al.,* none of the cases had kidney biopsies. Some patients had residual elevation of creatinine at followup while others had normal creatinine. In some of the reviewed cases, abnormalities of blood urea nitrogen or creatinine may have reflected severe dehydration.

Recently published observational, retrospective studies have attempted to assess the incidence of subclinical (without symptoms) kidney injury after OSP use for bowel preparation (Refs. 34 through 39). It is not entirely clear how the observations in these studies relate to cases of acute phosphate nephropathy that became evident because of the development of clinical symptoms that 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 receiving OSP. Nevertheless, it is useful to review the data in light of our concerns about OSP products for bowel cleansing.

Hurst *et al.* found an increased risk of acute kidney injury that was associated with OSP use in an observational, retrospective, cohort study (Ref. 34). The study included 9,799 subjects over the age of 50 who had a colonoscopy using either OSP or PEG products and had serum creatinine values available within 365 days before and after their procedure. Acute kidney injury was defined as greater than or equal to a 50-percent increase in serum creatinine over the 12 months following colonoscopy.

A total of 114 patients out of 9,799 developed acute kidney injury. Of these, 83 (1.29 percent, 83/6,432) were in the OSP group and 31 (0.92 percent, 31/3,367) were in the PEG group. On univariate analysis, the risk for the developing acute kidney injury was not significantly different between the two groups (odds ratio = 1.41; 95 percent confidence interval 0.93 to 2.13, $p = 0.113$). The PEG group, however, included high-risk subjects who were significantly older and had a higher incidence of diabetes, hypertension, cardiovascular disease, chronic kidney disease, and were more likely to be using a diuretic, ACE inhibitor, or ARB (all $p < 0.05$).

After adjustment for significant covariates and risk factors such as age, diabetes, hypertension, acute cardiovascular disease, ACE inhibitor or ARB use, and other factors suspected to be associated with acute kidney injury, OSP use was found to be associated with an increased risk of acute kidney injury (odds ratio = 2.35, 95 percent confidence interval 1.51 to 3.66, $p < 0.001$). Using a more stringent definition of acute kidney injury (doubling of serum creatinine), an even stronger association between OSP use and acute kidney injury emerged (odds ratios = 3.52, 95 percent confidence interval 1.13 to 10.93, $p = 0.03$). Followup creatinine values in patients with acute kidney injury remained significantly higher, with only 16 percent of cases returning to their previous creatinine levels. The changes in creatinine levels seen in this study were less severe than those seen in the case series compiled by Markowitz *et al.* (Ref. 31). Hurst *et al.* noted, however, that even small increases in creatinine levels have been shown to be associated with increased mortality (Ref. 34).

Brunelli *et al.* evaluated 2,237 subjects who underwent colonoscopy with a baseline serum creatinine of less than 1.5 mg/dL and compared cases that developed acute kidney injury to those who did not in a case-controlled study (Ref. 35). Acute kidney injury was defined as either a 25-percent or a 0.5-mg/dL increase in serum creatinine from baseline (measured within 6 months before the colonoscopy) to 6 months after colonoscopy. There were 116 cases of acute kidney injury with exposure data that were compared with 349 controls. These authors found no association between acute kidney injury and the use of OSP. However, a significant interaction ($p = 0.03$) was found indicating an increased risk for kidney injury from OSP products in patients who were simultaneously receiving ACE inhibitors or ARBs.

Abaskharoun *et al.* (Ref. 36) conducted a retrospective analysis of a database of patients who underwent a colonoscopy at their institution between 2004 and 2005 in order to detect the occurrence of kidney injury in patients who received either OSP or PEG. The study was supported by a manufacturer of OSP. The study included only patients who had undergone two colonoscopy procedures and had serum creatinine measured prior to each procedure. A total of 767 patients were included in the study. OSP was used by 618 patients and PEG was used by 149 patients. The timeframe between the two colonoscopies for the patients ranged from 3 months to 9 years.

Serum creatinine and estimated creatinine clearance, calculated by the Cockroft-Gault equation, were compared between patients receiving OSP and PEG. Chronic renal failure was defined as an abnormal creatinine or creatinine clearance on the repeat measurement. The change in serum creatinine was significantly different (p = 0.005) between OSP (−2.0 micromole/liter (μmol/L)) and PEG (0.9 μmol/L), suggesting that OSP had less of an effect than PEG, but this difference was not felt to be clinically significant by the authors, and there was no significant difference in the number of patients with abnormal second creatinine values between the two groups. In addition, the results were difficult to interpret because:

1. There is a possibility that selection bias eliminated people who developed renal injury from the prep from their first colonoscopy. The study only enrolled patients who used the same bowel prep prior to each colonoscopy. If a patient received OSP or PEG before their first colonoscopy and developed kidney damage as a result, they may not receive the same prep again prior to the second colonoscopy. They would be excluded from this study because they would have had to receive the same prep prior to each procedure. Also, other patients who had only one colonoscopy were not included.

2. There was a wide range of time between measurements of serum creatinine. No analysis was provided that looked at potential differences related to the time between measurements.

3. A greater percent of the PEG patients were receiving antihypertensive therapy, nonsteroidal anti-inflammatory drugs or had a diagnosis of diabetes mellitus, coronary artery disease and hypertension. The patients in the PEG group were older than the OSP patients. Many of these factors have been reported to be risk factors for the development of kidney injury from OSP. Age and use of antihypertensives were found in this study to be predictors of renal failure.

4. Chronic renal failure is not adequately defined and may include many people who did not have significant kidney injury.

5. The study is too small to make conclusions about renal function decline related to OSP.

Khurana *et al.* reported a retrospective study of 286 patients (out of more than 3,000 patients) who had undergone colonoscopy or flexible sigmoidoscopy between January 1998 and February 2005 and used OSP as the bowel prep (Ref. 37). The patients had serum creatinine measured at 6 months and 12 months after the procedure. Baseline serum creatinine had to be less than 1.5 mg/dL and obtained within 6 months prior to colonoscopy. Glomerular filtration rate (GFR), a measure of kidney function, was calculated using a formula from the Modification in Diet in Renal Disease study group (Ref. 38). The formula uses age and serum creatinine in the calculation.

A control group of 125 patients was derived from their database of patients who did not have colonoscopy at any time or who had undergone colonoscopy prior to 1996 and had post-colonoscopy serum creatinine unchanged from prior to colonoscopy. There were no significant differences between the two groups regarding demographic and base line characteristics as well as the use of concomitant medications. The patients were predominately white and female and the mean age was about 68 years. In the study group, 95 percent had hypertension, 45 percent had diabetes, 61 percent were taking an ACE inhibitor and/or ARB and 47 percent were taking diuretics, which were not significantly different as compared to the control group.

Serum creatinine increased by 0.09 mg/dL in the OSP group and 0.02 mg/dL in the control group at 6 months ($p < .001$; 2 sample t test). At 1 year, the change from baseline was 0.12 mg/dL for OSP and 0.04 mg/dL for the controls ($p < .001$; 2 sample t-test). Because calculated GFR used serum creatinine, similar trends were seen when GFR values were compared between groups. The authors concluded that OSP is associated with a decline in GFR in elderly patients with normal creatinine.

It is difficult to make definitive conclusions from this study for the following reasons:

1. Less than one-tenth of the patients who had a colonoscopy were included in the study. The study size is small and sampling may not be random.

2. The control group included patients who had the same creatinine after a previous colonoscopy. This could introduce a selection bias because it picked people with stable renal function. The number of these patients in the control group, which included patients without colonoscopy, is not provided.

3. The majority of subjects had conditions that may predispose them to kidney injury (*e.g.* hypertension) or were receiving drugs that may make them susceptible to toxicity with OSP. It is also unclear how these findings can be extrapolated to people without risk factors for kidney injury.

4. Serum creatinine and calculated GFR are not adequate surrogates to detect small changes in glomerular filtration rate as a function of time.

5. It would have been helpful to describe the number of patients who exceeded some percent increase in creatinine or some absolute value. The upper range of creatinine is greater than 3.0 mg/dL at 1 year in both groups.

This study, however, raises important issues that need to be addressed. Patients will undergo multiple colonoscopies over the years, and it is important to understand whether exposure to OSP can lead to small amounts of kidney damage that may be cumulative after repeated exposure.

A retrospective study by Russman *et al.* compared the risk of kidney impairment in patients who used OSP or PEG prior to colonoscopy based on clinical and electronic records from the Henry Ford Health System (HFHS) in Detroit, MI (Ref. 39). The base study population (7,897 patients) consisted of patients who had a colonoscopy at the HFHS Detroit Center gastroenterology clinic between November 1999 and October 2005. Patients were included if they had a creatinine determination 12 months prior to and 6 months after colonoscopy and a GFR greater than or equal to 60 (milliliter per minute (mL/min). Patients with preexisting kidney disease within 12 months of colonoscopy were excluded from further evaluation based on prespecified criteria (*e.g.,* undergoing dialysis, history of kidney transplant, acute as well as chronic renal failure, or GFR < 60 mL/min). Impaired renal function after colonoscopy was defined as a GFR of less than 60 mL/min and a decrease of at least 10 mL/min from the last value before colonoscopy, and/or at least a two-fold increase in creatinine from baseline within 6 months after colonoscopy. Patients with an identifiable, likely cause of renal impairment that was not clearly related to OSP or PEG use were excluded.

Of a total of 2,352 eligible patients, 269 used PEG and 2,083 used OSP. Compared to the patients receiving OSP, those receiving PEG were on average older (≥ 65 years of age), had a higher prevalence of heart failure, were using diuretics or an ARB, were more likely to have an inpatient colonoscopy procedure, and, in general, were more likely to be hospitalized during 12 months prior to the colonoscopy. The proportion of patients with mild renal impairment (GFR between 60 and 90 mL/min) at baseline was similar between the OSP and PEG groups (49 and 45 percent, respectively).

A total of 88 patients were identified as having renal impairment after colonoscopy. The proportion of patients with renal impairment after colonoscopy was similar between OSP users (79/2083 (3.8 percent)) and PEG users (9/269 (3.3 percent)). Of these 88 cases, 50 patients had a GFR decrease of 20 mL/min, and 13 had at least a twofold increase in creatinine after colonoscopy. In 21 out of those 88 cases, GFR remained < 60 mL/min 6 months after colonoscopy, and out of these 17 had used OSP and 4 had used PEG. The relative risk (RR) estimate for renal impairment comparing OSP and PEG was 1.13 (95 percent confidence interval 0.58–2.23) without adjustment, and the Odds Ratio after multivariate adjustment was 1.14 (0.55–2.39). Significant risk factors were those identified by earlier studies and include age greater than or equal to 65, African American race, low baseline GFR, hypertension and use of ACE inhibitors, ARBs, or thiazide diuretics. The authors of the study concluded that in patients without preexisting kidney disease, the risk of kidney impairment after colonoscopy appears to be similar between OSP and PEG users.

It is difficult to make definitive conclusions from this study for the following reasons:

1. A significantly greater proportion of OSP users who underwent colonoscopy were excluded from the study, which may introduce a potential selection bias.

2. There is a wide range of time between measurements of serum creatinine. Although the authors claimed that adjustment for differences in the latency time from colonoscopy to creatinine determination did not alter the risk estimates, analysis of such data was not provided.

3. PEG users tended to have a higher prevalence of co-morbid conditions (*e.g.,* congestive heart failure, liver cirrhosis) or used agents that potentially impair kidney perfusion.

4. Two different criteria were used for identification of patients with renal impairment post colonoscopy.

There are limitations in the design of all of the five studies discussed previously, 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 from these studies, and additional studies are needed to further assess subclinical changes in kidney function.

C. Consensus Statement on Bowel Preparation Before Colonoscopy

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 (Ref. 40). The task force performed a critical scientific review of the available data, which included 21 randomized, controlled trials in the published literature. The scope of the task group consensus statement included not only the customary dose of OSP but also other treatment modalities for bowel preparation, including PEG. Both oral solutions and the tablet formulations of OSP were assessed.

In their consensus statement the Task Force acknowledges the risks associated with the customary dose of OSP for bowel cleansing. The Task Force drew the following conclusions based on its evaluation of the data:

1. The use of OSP for bowel preparation prior to a colonoscopy is associated with abnormalities in serum electrolytes and altered extracellular fluid volume, which can cause significant losses of both fluid and electrolytes in the stool, resulting in volume contraction and dehydration.

2. Rarely adverse events such as nephrocalcinosis with acute kidney failure have occurred after use of OSP.

3. OSP use has been shown to cause elevated blood urea nitrogen levels, decreased exercise capacity, increased plasma osmolality, hypocalcemia, and significant hyponatremia and seizures.

4. Although usually asymptomatic, hyperphosphatemia is seen in as many as 40 percent of healthy patients completing OSP preparations, and hypokalemia developed in as many as 20 percent of patients using OSP preparations.

The Task Force advised physicians to select a preparation for each patient based on the safety profile of the agent and the overall health of the patient, their comorbid conditions and currently prescribed medications. They further advised that in certain circumstances such as bowel preparation in children, the elderly, patients with renal insufficiency, and those with hypertension taking an ACE inhibitor or an ARB, it may be advisable to adhere to PEG-based solutions because of the risk of occult physiologic disturbances that may contraindicate the use of sodium phosphates regimens.

D. FDA's Tentative Conclusions on the Safety of Nonprescription Sodium Phosphate Oral Solutions for Bowel Cleansing

FDA has tentatively concluded that the customary dose of OTC sodium phosphate salts for bowel cleansing (*i.e.,* two 45-mL doses taken 12 hours apart or a 45-mL dose followed by a 30-mL dose of sodium phosphates oral solution 10 to 12 hours later) in an OTC setting based on professional labeling in an OTC monograph poses an unacceptable risk of serious adverse events. Some patients have experienced sudden and severe acute kidney failure which may require kidney dialysis, while others have had a less serious course that resolves with minimal intervention. The outcome has varied from complete recovery to, in rare instances, death. Some patients may have residual kidney damage and may never return to the kidney function present prior to OSP use.

Some of the retrospective studies that have reviewed the serum creatinine of large numbers of patients who underwent bowel preparation for colonoscopy at the customary OSP doses suggest that the percent of cases leading to serious injury with symptoms is relatively rare. However, there is no accurate estimate of the incidence of acute kidney injury in patients receiving these doses of OSP for bowel cleansing. Some studies have identified populations who appear to be at risk, but data from prospective studies are needed to better define the risk of acute kidney injury in patients using OSP at the current doses as preparation for colonoscopy and to determine the risk factors that may predispose patients to such injury.

The study by Hurst also raises questions about the possible effects of small changes in serum creatinine that may occur after OSP use at the customary doses for bowel cleansing (Ref. 34). This is an important question that needs to be addressed. There are about 14 million screening colonoscopies per year in the United States., for which an estimated 50 percent will use OSP for bowel cleansing (Ref. 31). Given the magnitude of the exposure, the possibility of low grade declines in GFR after exposure to OSP is troubling when one considers that many patients undergo colonoscopies more than once in their lifetime and the damage that occurs with every exposure could be cumulative for some individuals. Other studies have not supported the findings of Hurst. Thus, it is important that this issue be addressed with clinical trials

using more exact measurements of glomerular filtration rate. For these reasons, FDA has required the NDA holder of prescription OSP products to conduct prospective, randomized, active-controlled clinical trials to determine the absolute and relative risk of kidney injury (including acute phosphate nephropathy) following the use of these products.

Further, because of continuing reports of acute kidney injury associated with the prescription and customary dose of OTC OSP products for bowel cleansing, despite repeated educational efforts by FDA and the detailed professional labeling provided by a drug manufacturer for these products, we have tentatively concluded that OSP for bowel cleansing at the currently used doses poses a serious risk of adverse events in some patients. Therefore, additional measures are needed to manage the risk posed by this use of OSP products for bowel cleansing to assure that the benefits outweigh the potential risks. The need for these additional measures precludes the continued use of the current regimen of sodium phosphates oral solution for bowel cleansing under the professional labeling of an OTC monograph.

Under the current professional labeling provisions of the 1985 TFM 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 not been sufficient to manage the risk that has been associated with the customary dose of OTC sodium phosphates oral solution for bowel cleansing. 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 affect patients' decisions to use these products, and thus help prevent serious adverse effects. 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 consumer labeling for these products. Manufacturers marketing OTC products under the 1985 TFM cannot provide consumers with labeling information on the OTC package related to those indications or uses that are not part of the drug facts labeling allowed under the 1985 TFM. For all of these reasons, we are proposing in this document that the professional labeling for bowel cleansing use be removed from the tentative final monograph because of our safety concern with the bowel cleansing use of sodium phosphate products.

We also believe that the safe use of OSP as presently used for bowel cleansing requires the continuing involvement of a doctor to monitor its effects on kidney function. Section 503(b)(1) of the FD&C Act establishes the standards under which the marketing of a drug must be limited to prescription. Among these is the need for collateral measures for the safe use of the product and the need for the involvement of a licensed practitioner to ensure the safe use of the product. For the reasons already given, the customary dose of OSP solution for bowel cleansing meets the statutory definition of a prescription product. Thus, in this document FDA proposes to classify OTC sodium phosphate salts, singly or in combination with each other, as not GRAS (*i.e.,* nonmonograph) for the professional labeling indication proposed in the 1985 TFM, *i.e.,* "For use as part of a bowel cleansing regimen in preparing the patient for surgery or for preparing the colon for x-ray endoscopic examination." This proposed rule would amend § 310.545 to include sodium phosphate salts for bowel cleansing use, as described in § 334.80 of the 1985 TFM, as nonmonograph.

Screening colonoscopy can lead to the early detection of colon cancer and polyps, which, if not removed, can progress to cancer. Early detection of colon cancer can result in more effective treatment and a survival advantage. Inadequate preparation for colonoscopy can lead to missed lesions. OSP products have been shown to be effective in cleansing the colon, thereby allowing better visualization of cancers and polyps. FDA believes it is important to have multiple options available for bowel cleansing because no single product is tolerated by all individuals. It is important, however, to make sure that the risk for serious injury is very low and the appropriate populations are identified who can use these products safely.

IV. FDA's Tentative Conclusions on the Safety and Effectiveness of Other Doses of Sodium Phosphates Oral Solution for Bowel Cleansing

FDA has previously acknowledged the effectiveness of the bowel cleansing regimen that is currently the standard of practice for OTC sodium phosphates oral solution, *i.e.,* 60-g sodium phosphate administered in two 45-mL doses of sodium phosphates oral solution taken 10 to 12 hours apart (Ref. 14). However, the available data raise serious concerns about the safety of this regimen.

There are some data that suggest a lower sodium phosphate dose may be similar in effectiveness to the regimen currently in use. An unpublished study comparing the effectiveness of sodium phosphates oral solution at two dose levels, the standard 2 x 45-mL dose (60 g sodium phosphate) and a reduced 2 x 30-mL dose (37 g sodium phosphate), with PEG solution was included in a citizen petition from a manufacturer of sodium phosphate laxative products (Ref. 18). The study, PS–9902, was a randomized, single-blind, parallel group design. The two regimens were administered as divided doses 10 to 12 hours apart. A total of 238 subjects were randomized to one of the three treatments. Seventy-four subjects took the 2 x 45-mL dose, and 75 subjects took the 2 x 30 mL dose. There were 73 subjects who took PEG. The study excluded all patients with current labeling contraindications to OSP use and all patients for whom use is allowed with caution.

The manufacturer's evaluation of physicians' assessments of bowel preparation indicated no statistically significant differences between the 2 x 30-mL sodium phosphates oral solution group and the PEG group for any of the effectiveness endpoints: Residual stool, stool consistency, and bowel wall visualization parameters. Bowel cleansing with the two 45-mL doses was found to be superior to the lower dose OSP regimen and PEG. The observed electrolyte changes and side effects were milder with the two 30-mL doses of OSP compared to the two 45-mL dose. Elevation in serum sodium was the only significant electrolyte change between the OSP groups. Four patients on the two 45-mL dose regimen had post-prep sodium levels that exceeded the upper limit of normal but remained below 150 millimole/Liter.

While the results of this study are worth noting, they are not sufficient to demonstrate the safety and effectiveness of the reduced phosphate regimen. It is noteworthy that 32 percent (23/73) of the PEG subjects 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, the study results can not be considered a conclusive demonstration of the effectiveness of these products. In addition, while the electrolyte changes and side effects were milder with the two 30-mL doses of sodium phosphates oral solution, the number of subjects exposed to the proposed lower dose regimen (79 subjects) is too small to allow any conclusions about the safety of the lower dose regimen.

V. Summary of Significant Changes From the 1985 Proposed Rule for OTC Laxative Drug Products

1. FDA is classifying sodium phosphate salts described in § 334.16(d), (e) and (f), as nonmonograph and removing them as acceptable active ingredients for the use as a bowel cleansing agent described in § 334.80(a)(2).

2. FDA is removing the warning in § 334.80(b)(2) for sodium phosphate salts. The warning will be revised and included in a proposed rule to be published at a future date.

VI. Proposed Effective Date

The existing evidence is inadequate to establish the safety of OTC sodium phosphate salts (dibasic sodium phosphate, monobasic phosphate and dibasic sodium phosphate/monobasic sodium phosphate (sodium phosphates) solution) for professional use as a bowel cleansing preparation prior to surgery or endoscopic examination. Accordingly, sodium phosphate salts cannot be considered GRAS for OTC use for bowel cleansing.

If this proposal becomes a final rule, the conditions under which drug products subject to this rule are not GRASE and are misbranded will be effective 30 days after the date of the final rule's publication in the **Federal Register**. On or after that date, any OTC laxative products containing dibasic sodium phosphate or monobasic phosphate and dibasic sodium phosphate/monobasic sodium phosphate (sodium phosphates) marketed for bowel cleansing will be misbranded and will require an approved NDA for bowel cleansing use and marketing. Any OTC drug product subject to the final rule that is repackaged or relabeled after the effective date of the final rule must be in compliance with the final rule, regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce.

VII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is not a significant regulatory action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this proposed rule only affects labeling provided to healthcare professionals for the indication of bowel cleansing and does not affect the marketing of sodium phosphates oral solution for consumer use as a laxative for the relief of occasional constipation, the agency proposes to certify that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and Tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $135 million, using the most current (2009) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

The purpose of this proposed rule is to remove the professional labeling relating to the use of sodium phosphates oral solution laxatives for bowel cleansing in the 1985 TFM (50 FR 2124 at 2157). Professional labeling is information directed to health professionals who prescribe, administer, or dispense medications, and may not be included in labeling directed to the consumer. This proposed rule amends § 334.80 to remove the bowel cleansing indication for sodium phosphates oral solution laxatives based on concerns about serious adverse reactions associated with the use of these OTC drug products in preparation for colonoscopy and x-ray before surgery.

A. Background

FDA has taken a number of measures to mitigate the risk of serious adverse events associated with the use of OSP products in preparation for colonoscopy and x-ray endoscopic examination. As discussed in the preamble, FDA has limited the acceptable container sizes that can be marketed and added warnings and direction statements to OTC sodium phosphates solutions marketed for laxative and to healthcare professionals for bowel cleansing use. Separate from this proposed rule, the agency has also made several attempts to educate and alert both healthcare professionals and consumers about potential risks associated with customary dose of OSP products for bowel cleansing. Despite these measures, FDA's AERS has continued to receive reports of acute kidney injury that have been associated with the customary dose of OSP products for bowel cleansing.

For this reason, on December 12, 2008, FDA took steps to limit the marketing of OSP products for bowel cleansing to prescription only and to increase the prominence of risk information by requiring a boxed warning on prescription OSP products (Ref. 1). In addition, the continued marketing of prescription OSP products will require the development of a risk evaluation and mitigation strategy that includes the development of a Medication Guide and a communication strategy targeted at healthcare providers who are likely to prescribe OSP products. FDA has also instructed the holders of NDAs for OSP products to conduct prospective clinical trials to assess the risk of acute kidney injury in patients using sodium phosphate products for bowel cleansing and to better define the risk factors that predispose patients to such injury. FDA has taken these steps in an attempt to increase the level of risk communication for these products and thereby reduce the incidence of adverse events that has been associated with these products.

B. Need for the Proposed Rule

This proposed rule is consistent with the Agency's determination that the customary dose of OSP products for bowel cleansing (*i.e.,* approximately 60 g of sodium phosphates taken as two 45-mL doses 12 hours apart or approximately 50 g of sodium phosphates taken as a 45-mL dose followed by a 30-mL dose 12 hours later) poses a serious risk to some individuals and that the marketing of

these products for bowel cleansing should be limited to prescription only. In this document FDA proposes to classify OTC sodium phosphate salts, singly or in combination with each other, as not GRAS (*i.e.,* nonmonograph) for bowel cleansing. Furthermore, FDA is proposing to remove professional labeling for bowel cleansing use from the monograph. Manufacturers of OTC OSP laxative products would no longer be able to promote the use of these products to healthcare professionals for bowel cleansing use. Consequently, the marketing of sodium phosphates oral solution marketed under an OTC drug monograph would be limited to laxative use at a lower sodium phosphates dose to relieve occasional constipation.

C. Impact of the Proposed Rule

Executive Order 12866 and OMB Circular A–4 direct agencies to consider and provide a description of any important distributional effects that might be attributed to a regulation, where applicable. To the extent that OTC OSP products for bowel preparation remain on the market, this rule would shift those sales to prescription products only. Any such shift in sales represents a transfer payment between manufacturers within the industry and is not a social cost of this rule. The agency believes that most of this transfer has already occurred through voluntary withdrawal of OTC products by their manufacturers.

An informal in-store review of several national drug and mass merchandise stores found that there were no OTC liquid OSP products on those store shelves. Pharmacists indicated that OSP liquid products were removed from the shelves in response to information from FDA. Therefore, the agency believes that any shift in sales from OTC to prescription products for bowel cleansing that would have been attributed to this rule most likely has already occurred.

According to proprietary data from A.C. Nielsen, annual retail sales for OSP products totaled about $30 million in 2006. The vast majority of these sales are attributed to one manufacturer. That manufacturer has already voluntarily removed its OSP laxative products from the shelves. We believe that other suppliers have similarly removed their products. The agency requests specific comments on this assumption.

To the extent that any OSP products for laxative use might remain on the market, there would be no relabeling or reformulation costs attributed to this rule. If, however, manufacturers have chosen to improperly label their OSP products with a bowel cleansing indication, these manufacturers will incur the cost of relabeling to remove the bowel cleansing use from their labels. These costs would be incurred without this rule, because professional uses of OTC drugs are not properly included in labeling directed to consumers.

We analyzed proprietary data from SDI Health on the total number of retail prescriptions dispensed for bowel preparation products from March 2004 through February 2009. We included PEG products and OSP products that are considered alternatives to the OTC OSP products for bowel cleansing. The number of prescriptions for PEG products has grown significantly over this time period, whereas the number of OSP products remained relatively constant over most of this period and began to decline in late 2008. The average annual growth rate for all prescription bowel preparation products was 17 percent from 2006 to 2008. From 2006 through the third quarter of 2008, the monthly share of sodium phosphate prescriptions dispensed for bowel preparation was about 13 to 15 percent of total prescriptions, but declined to a monthly low of 7 percent by February 2009. This apparent decline in dispensed prescription sodium phosphate products may be a market response to recent agency actions, including the boxed warning requirement, that are separate from this rule. However, it is too soon to determine market changes. Nonetheless, the data on the number of prescriptions dispensed suggest that prior agency actions may have had a dampening market effect on the use of OSP products for bowel preparation.

D. Benefits of the Proposed Rule

Section III.A of this document presents data on the reports of serious adverse events associated with prescription and OTC products containing sodium phosphates for bowel cleansing. More than 100 adverse events have been reported that are associated with the customary dose of OSP products as presented in section III. A of this document. Although these serious events are rare, the public health consequences can be substantial. Acute phosphate nephropathy that has been associated with the customary dose of OSP for bowel cleansing can result in permanent impairment of kidney function that ultimately may require chronic dialysis or kidney transplant, and may result in long term renal failure and, in rare instances, death.

The economic consequences of this severity of renal impairment are significant. The cost of hospitalization resulting from acute renal failure without dialysis has been estimated at $22,251 (51 FR 77314 at 77344, December 26, 2006). Recent analyses have reported Medicare payments for a year's treatment of a dialysis patient of about $67,000. Employer group health insurance costs are much higher at $180,000 per year (Ref. 41).

Estimates of the cost of kidney transplants also vary. Associated medical costs for transplants average about $102,000 in the year of the transplant (Ref. 42). The mean cost of hospitalization for a kidney transplant procedure was $128,000 in 2006 (Ref. 43). In addition, patients with kidney transplants require immunosuppressive drugs for years after their transplant.

We believe, based on the available data, that sodium phosphates solution marketed under an OTC drug monograph for bowel cleansing may be a significant cause of severe adverse events. However, we note that there is uncertainty about the baseline risk of serious adverse events associated with customary dose of OSP products (for both OTC and prescription uses). It is not possible to predict a specific level of reduction in the incidence of these serious adverse events that might be attributable to limiting OSP products for bowel cleansing use to prescription drug use. Moreover, to the extent that OSP products have been voluntarily withdrawn from the market, this rule would not have an impact on the incidence of these serious adverse events.

E. Alternatives

The agency considered but rejected several alternatives: (1) Requiring additional (OTC or professional) labeling that describes potential adverse effects, the subpopulations at greatest risk, and detailed directions about hydration, (2) a longer implementation period for this rule if finalized, and (3) product withdrawal, including prescription use. We do not believe that the first two alternatives to the proposed regulation would be adequate to provide for the safe use of OTC sodium phosphates oral solution for bowel cleansing (*e.g.,* preparation for colonoscopy). Various attempts at conveying the risk associated with OTC sodium phosphates oral solution products, including detailed professional labeling describing potential adverse events and at risk populations (Ref. 29) by a manufacturer of an OTC sodium phosphates oral solution product have not been successful in reducing the number of serious adverse events attributed to these products. The agency also

considered but rejected a longer implementation period for this proposed rule if finalized, because of the overriding safety considerations. We rejected the third alternative, to withdraw the product, because OSP has been demonstrated to be effective for bowel cleansing, and we believe that it is important to continue to have multiple options available for bowel cleansing because no single product is tolerated by all individuals.

F. Impact on Small Businesses

The Small Business Administration (SBA) defines an entity as small in the pharmaceutical manufacturing industry if the business has fewer than 750 employees. Over 90 percent of manufacturers in the OTC pharmaceutical industry are classified as small. To the extent that there continue to be manufacturers of OSP products for bowel preparation that remain on the market, those sales would be shifted to prescription products. This is a transfer payment and not a social cost of this rule. The agency believes that most of this impact has already occurred with manufacturers voluntarily withdrawing products from the market prior to this rule.

We estimate that there are about 10 manufacturers that could be affected by this proposed rule and that all of them are small businesses. The economic impact on any remaining individual firms will vary based on the amount of lost production and lost sales revenue that is derived from sales of the OSP products for bowel cleansing. Without knowing the volume of OTC OSP sales that can be attributed to this use, it is difficult to estimate the impact of this proposed rule on small business entities. As noted above, a major manufacturer of OTC OSP labeled for professional use for bowel cleansing has already voluntarily withdrawn its bowel cleansing products from the market. The remaining suppliers may have done the same.

Given the small number of manufacturers of these products, we believe that it is unlikely that this proposed rule will have a significant economic impact on a substantial number of small entities. Nonetheless, the agency requests detailed comments on small businesses impacts. The proposed rule will not require any new recordkeeping and no additional professional skills are needed.

This analysis shows that this proposed rule is not economically significant under Executive Order 12866. Thus, this economic analysis, together with other relevant sections of this document, serves as the agency's initial regulatory flexibility analysis as required under the Regulatory Flexibility Act. Finally, this analysis shows that the Unfunded Mandates Reform Act does not apply to this proposed rule because it would not result in an expenditure in any 1 year by State, local, and Tribal governments in the aggregate, or by the private sector of $135 million.

FDA invites public comment regarding any significant economic impact that this proposal would have on affected manufacturers of sodium phosphates oral solutions. Comments regarding the impact of this proposal should be accompanied by appropriate documentation. FDA will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to any final rule.

VIII. Paperwork Reduction Act of 1995

This proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

IX. Environmental Impact

FDA has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires agencies to "construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute." The sole statutory provision giving preemptive effect to the proposed rule is section 751 of the FD&C Act (21 U.S.C. 379r).

We believe that the preemptive effect of this proposed rule, if finalized, would be consistent with Executive Order 13132. Through the publication of this proposed rule, we are providing notice and an opportunity for State and local officials to comment on this rulemaking.

XI. References

The following references are on display in the Division of Dockets Management (HFA–305), 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, under Docket No. FDA–1978–N–0021 (formerly Docket No. 78N–036L) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Document Id. FDA–2007–P–0345–0003, Federal Dockets Management System.

2. Document Id. FDA–2007–P–0345–0005, Federal Dockets Management System.

3. Comment No. CP8, Docket 1978N–036L, Division of Dockets Management.

4. Comment No. SUP5, Docket No. 1978N–036L, Division of Dockets Management.

5. Comment No. LET41, Docket No. 1978N–036L, Division of Dockets Management.

6. Document Id. FDA–1978–N–0021–0032–0036, Federal Dockets Management System.

7. Comment No. CP14, Docket No. 1978N–036L, Division of Dockets Management.

8. Comment No. SUP8, Docket No. 1978N–036L, Division of Dockets Management.

9. Comment No. AMD10, Docket No. 1978N–036L, Division of Dockets Management.

10. Comment No. LET71, Docket No. 1978N–036L, Division of Dockets Management.

11. Comment No. SUP11, Docket No. 1978N–036L, Division of Dockets Management.

12. Comment No. SUP10, Docket No. 1978N–036L, Division of Dockets Management.

13. Comment No. C146, Docket No. 1978N–036L, Division of Dockets Management.

14. Comment No. LET109, Docket No. 1978N–036L, Division of Dockets Management.

15. Comment No. PDN4, Docket No. 1978N–036L, Division of Dockets Management.

16. Comment No. CP1, Docket No. 00P–1472, Division of Dockets Management.

17. Comment No. PDN1, Docket No. 00P–1472, Division of Dockets Management.

18. Comment No. CP28, Docket No. 1978N–036L, Division of Dockets Management.

19. Comment No. LET204, Docket No. 1978N–036L, Division of Dockets Management.

20. Document Id. FDA–1978N–0021–0031, Federal Dockets Management System.

21. Comment No. C207, Docket No. 1978N–036L, Division of Dockets Management.

22. Comment No. C208, Docket No. 1978N–036L, Division of Dockets Management.

23. Comment No. SUP18, Docket No. 1978N–036L, Division of Dockets Management.

24. FDA Science Background Paper: "Safety of Sodium Phosphates Oral Solution" September 17, 2001 in OTC Volume 09OSPPR.

25. FDA Science Background Paper: "Acute Phosphate Nephropathy and Renal Failure Associated with the Use of Oral Sodium Phosphate Bowel Cleansing Products," May 2006 in OTC Volume 09OSPPR.

26. FDA Information for Healthcare Providers: Oral Sodium Phosphate Products for Bowel Cleansing, May 2006 in OTC volume 09OSPPR.

27. FDA Alert: Oral Sodium Phosphate (OSP) Products for Bowel Cleansing (marketed as Visicol and OsmoPrep, and oral sodium phosphate products available without a prescription), December 11, 2008 in OTC volume 09OSPPR.

28. FDA Information for Healthcare Professionals: Oral Sodium Phosphate (OSP) Products for Bowel Cleansing (marketed as Visicol and OsmoPrep, and oral sodium phosphate products available without a prescription), December 11, 2008, in OTC volume 09OSPPR.

29. Professional Labeling for Fleets Phosphasoda in OTC volume 09OSPPR.

30. Khurana, A. *et al.,* "Acute Phosphate Nephropathy," *Journal of the American Society of Nephrology,* 17: 163A, 2006.

31. Markowitz, G. S. *et al.,* "Acute Phosphate Nephropathy Following Oral Sodium Phosphate Bowel Purgative: An Unrecognized Cause of Chronic Renal Failure," *Journal of the American Society of Nephrology,* 16:3389–3396, 2005.

32. Ma, R. C. *et al.,* "Acute Renal Failure Following Oral Sodium Phosphate Bowel Preparation in Diabetes," *Diabetes Care,* January: 30(1):182–3. 2007.

33. 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,* January: 130(1):101–6, 2006.

34. Hurst, F. P. *et al.,* "Association of Oral Sodium Phosphate Purgative Use with Acute Kidney Injury," *Journal of the American Society of Nephrology,* 18:1–6, 2007.

35. Brunelli, S. M. *et al.,* "Risk of Kidney Injury Following Oral Phoshphasoda Bowel Preparations," *Journal of the American Society of Nephrology,* 18: 199–3205, 2007.

36. Abaskharoun, R., W. Depew, and S. Vanner, "Changes in Renal Function Following Administration of Oral Sodium Phosphate or Polyethylene Glycol for Colon Cleansing Before Colonoscopy," *Canadian Journal of Gastroenterology,* April: 21(4):227–31, 2007.

37. Khurana A., L. McLean, S. Atkinson, and C. J. Foulks, "The Effect of Oral Sodium Phosphate Drug Products on Renal Function in Adults Undergoing Bowel Endoscopy," *Archives of Internal Medicine,* March 24:168(6):593–7, 2008.

38. Levey, A. S., T. Greene, J. Kusek, and G. Beck, "A Simplified Equation to Predict Glomerular Filtration Rate from Serum Creatinine (abstract), *Journal of the American Society of Nephrology,* 11: p.155A, 2000.

39. Russman, S. *et al.,* "Risk of Impaired Renal Function After Colonoscopy: A Cohort Study in Patients Receiving Either Oral Sodium Phosphate or Polyethylene Glycol," *American Journal of Gastroenterology,* 102:2655–2663, 2007.

40. Wexner, S.D. *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), *Gastrointestinal Endoscopy;* 63:894–909, 2006.

41. Just, P. M. *et al.,* "Reimbursement and Economic Factors Influencing Dialysis Modality Choice around the World," *Nephrology Dialysis Transplantation,* 23(7):2365–2373, 2008.

42. St. Peter, W., "Introduction: Chronic Kidney Disease: A Burgeoning Health Epidemic," *Journal of Managed Care Pharmacy,* 13(9):S2–S5, 2007.

43. Agency for Healthcare Research and Quality, HCUPnet National and regional estimates on hospital use for all patients from the HCUP Nationwide Inpatient Sample (NIS) (2006), data accessed March 11, 2009.

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 334

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 310 and 334 (as proposed in the **Federal Register** of January 15, 1985 (50 FR 2124)), October 1, 1986 (51 FR 35136), September 2, 1993 (58 FR 46589), March 31, 1994 (59 FR 15139), September 2, 1997 (62 FR 46223), May 21, 1998 (63 FR 27886), June 19, 1998 (63 FR 33592), March 24, 2004 (69 FR 13765), November 29, 2004 (69 FR 69278), be amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

2. Section 310.545 is amended by redesignating paragraph (a)(12)(ii) as paragraph (a)(12)(ii)(A), by adding paragraph (a)(12)(ii)(B), by revising paragraph (d) introductory text and paragraph (d)(1), and by adding paragraph (d)(53) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(12) * * *

(ii) * * *

(B) Saline laxatives—Approved as of [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION OF THE FINAL RULE IN THE **FEDERAL REGISTER**].

Dibasic sodium phosphate, monobasic sodium phosphate, and sodium phosphates (dibasic sodium phosphate monobasic sodium phosphates in a solution dosage form administered as 59.4 grams (g) of sodium phosphates taken in two 45-milliter (mL) doses 12 hours apart or 49.5 g of sodium phosphates taken as a 45-mL dose followed by a 30-mL dose 12 hours later) for use as part of a bowel cleansing regimen in preparing the patient for surgery or for preparing the colon for x-ray endoscopic examination.

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(53) of this section.

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(2)(i), (a)(3)(i), (a)(4)(i), (a)(6)(i)(A), (a)(6)(ii)(A), (a)(7) (except as covered by paragraph (d)(3) of this section), (a)(8)(i), (a)(10)(i) through (a)(10)(iii), (a)(12)(i)(A), (a)(12)(ii)(A), (a)(12)(iii), (a)(12)(iv)(A), (a)(14) through (a)(15)(i),

(a)(16) through (a)(18)(i)(A), (a)(18)(ii) (except as covered by paragraph (d)(22) of this section), (a)(18)(iii), (a)(18)(iv), (a)(18)(v)(A), and (a)(18)(vi)(A) of this section.

* * * * *

(53) [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION OF THE FINAL RULE IN THE **FEDERAL REGISTER**], for products subject to paragraph (a)(12)(ii)(B) of this section.

PART 334—LAXATIVE DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

3. The authority citation for 21 CFR part 334 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

§ 334.80 [Amended]

4. Section 334.80 as proposed on January 15, 1985 (50 FR 2124), is amended by removing "sodium phosphate/sodium biphosphate identified in § 334.16(d)" from paragraph (a)(2), and by removing paragraph (b)(2) and redesignating paragraph (b)(3) as paragraph (b)(2).

Dated: February 3, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2011–3091 Filed 2–10–11; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Parts 1 and 31

[REG–146097–09]

RIN 1545–BJ01

Guidance on Reporting Interest Paid to Nonresident Aliens; Correction

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Correction to notice of proposed rulemaking; notice of a public hearing; and withdrawal of previously proposed rulemaking.

SUMMARY: This document contains corrections to notice of proposed rulemaking; notice of a public hearing; and withdrawal of previously proposed rulemaking (REG–146097–09) that was published in the **Federal Register** on Friday, January 7, 2011 (76 FR 1105). The proposed regulations provide guidance on the reporting requirements for interest on deposits maintained at U.S. offices of certain financial institutions and paid to nonresident alien individuals.

FOR FURTHER INFORMATION CONTACT: Kathryn Holman at (202) 622–3840 (not a toll-free number).

SUPPLEMENTARY INFORMATION:

Background

The notice of proposed rulemaking; notice of a public hearing; and withdrawal of previously proposed rulemaking that is the subject of this document is under section 6049 of the Internal Revenue Code.

Need for Correction

As published, the notice of proposed rulemaking; notice of a public hearing; and withdrawal of previously proposed rulemaking (REG–146097–09) contains errors that are misleading and are in need of clarification.

Correction to Publication

Accordingly, the notice of proposed rulemaking; notice of a public hearing; and withdrawal of previously proposed rulemaking which is the subject of FR Doc. 2011–82 is corrected as follows:

On page 1105, in the preamble, column 3, under the caption **DATES**, line 4, the language "public hearing scheduled for April 28," is corrected to read "public hearing scheduled for April 27,".

On page 1107, in the preamble, column 2, under the paragraph heading "Comments and Public Hearing", line 14, the language "for April 28, 2011, beginning at 10 a.m." is corrected to read "for April 27, 2011, beginning at 10 a.m."

LaNita VanDyke,

Branch Chief, Publications and Regulations Branch, Legal Processing Division, Associate Chief Counsel, (Procedure and Administration).

[FR Doc. 2011–2922 Filed 2–10–11; 8:45 am]

BILLING CODE 4830–01–P

DEPARTMENT OF HOMELAND SECURITY

Coast Guard

33 CFR Part 181

[Docket No. USCG–2007–29236]

Hull Identification Numbers for Recreational Vessels

AGENCY: Coast Guard, DHS.

ACTION: Follow-up to request for comments.

SUMMARY: The Coast Guard announces its decision to not initiate a rulemaking addressing an expanded hull identification number (HIN). The Coast Guard's decision-making process included consideration of comments submitted in response to its request for comments on the costs and benefits of expanding the existing 12-character HIN in order to provide additional information identifying vessels.

ADDRESSES: The docket for this action is available for inspection or copying at the Docket Management Facility (M–30), U.S. Department of Transportation, West Building Ground Floor, Room W12–140, 1200 New Jersey Avenue, SE., Washington, DC 20590, between 9 a.m. and 5 p.m., Monday through Friday, except Federal holidays. You may also find this docket on the Internet by going to *http://www.regulations.gov,* inserting "USCG–2007–29236" in the "Keyword" box, and then clicking "Search."

FOR FURTHER INFORMATION CONTACT: If you have questions about this notice, call or e-mail Mr. Jeffrey Ludwig, Coast Guard; telephone 202–372–1061, e-mail *Jeffrey.A.Ludwig@uscg.mil.* If you have questions on viewing material in the docket, call Ms. Renee V. Wright, Program Manager, Docket Operations, telephone 202–366–9826.

SUPPLEMENTARY INFORMATION: On March 17, 2008, we published a request for public comments on the costs and benefits of expanding the existing 12-character HIN in order to provide additional information identifying vessels (73 FR 14193). The notice specifically requested comments on: (1) The expected benefits and costs of an expanded HIN; (2) the manner in which the Coast Guard should exempt small entities and builders of high-volume, low-cost vessels; (3) the estimated collection of information burdens to vessel manufacturers if the current 12-character HIN regulations were revised to require additional characters; and (4) possible alternatives to an expanded HIN. The Coast Guard also sought specific data to support its decision-making process about whether to initiate a rulemaking addressing an expanded HIN.

In response to the request for comments, we received 29 comments. The Coast Guard has decided not to initiate a rulemaking addressing an expanded HIN based on consideration of the comments received as well as the challenges from data uncertainty in describing, estimating, and quantifying potential costs and benefits of such a rulemaking.

Background

The Coast Guard has been looking into the possibility of an expanded HIN for several years. In 1994, the Coast Guard initiated a rulemaking to create