

concludes that the proposed use of the additive is safe, that the additive will achieve its intended technical effect, and therefore, that the regulations in § 178.2010 should be amended as set forth below.

In accordance with § 171.1(h) (21 CFR 171.1(h)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition are available for inspection at the Center for Food Safety and Applied Nutrition by appointment with the information contact person listed above. As provided in § 171.1(h), the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch

(address above) between 9 a.m. and 4 p.m., Monday through Friday.

Any person who will be adversely affected by this regulation may at any time on or before June 22, 1998, file with the Dockets Management Branch (address above) written objections thereto. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this

document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 178

Food additives, Food packaging. Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to the Director, Center for Food Safety and Applied Nutrition, 21 CFR part 178 is amended as follows:

PART 178—INDIRECT FOOD ADDITIVES: ADJUVANTS, PRODUCTION AIDS, AND SANITIZERS

1. The authority citation for 21 CFR part 178 continues to read as follows:

Authority: 21 U.S.C. 321, 342, 348, 379e.

2. Section 178.2010 is amended in the table in paragraph (b) by alphabetically adding a new entry under the headings "Substances" and "Limitations" to read as follows:

§ 178.2010 Antioxidants and/or stabilizers for polymers.

* * * * *
(b) * * *

| Substances | Limitations |
|---|--|
| 1, 11-(3, 6, 9-Trioxaundecyl) bis-3-(dodecylthio) propionate (CAS Reg. No. 64253-30-1). | For use only as provided in § 175.300(b)(3)(xxxi) of this chapter at 4.0 parts per 100 parts rubber. |

Dated: May 11, 1998.

L. Robert Lake,

Director, Office of Policy, Planning and Strategic Initiatives, Center for Food Safety and Applied Nutrition.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 78N-036L]

RIN 0910-AA01

Package Size Limitation for Sodium Phosphates Oral Solution and Warning and Direction Statements for Oral and Rectal Sodium Phosphates for Over-the-Counter Laxative Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule to limit the container size for sodium phosphates oral solution

(dibasic sodium phosphate/monobasic sodium phosphate oral solution) to not greater than 90 milliliters (mL) (3 ounces (oz)) when used as an over-the-counter (OTC) laxative drug product. FDA is limiting the container size because of reports of deaths associated with an overdosage of sodium phosphates oral solution when the product was packaged in a larger-size container and a larger than intended dose was ingested inadvertently. The agency is also requiring warning and direction statements to inform consumers that exceeding the recommended dose of oral and rectal sodium phosphates products in a 24-hour period can be harmful. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

DATES: The regulation is effective June 22, 1998, however compliance with

201.307(b)(2) and (b)(3) is not mandatory until September 18, 1998.
FOR FURTHER INFORMATION CONTACT:
 Cheryl A. Turner, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2222.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of March 21, 1975 (40 FR 12902), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC laxative, antidiarrheal, emetic, and antiemetic drug products, together with the recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products (the Panel), which was the Advisory Review Panel responsible for evaluating data on the active ingredients in these classes. The Panel recommended monograph status for phosphate salts, such as sodium phosphate oral solution (40 FR 12902 at 12940), but did not recommend any container size limitations.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC laxative drug products was published in the Federal Register of January 15, 1985 (50 FR 2124). The agency also proposed monograph status for sodium phosphates oral solution (50 FR 2124 at 2152 and 2155), but did not recommend any container size limitations. The agency proposed the following dosage for sodium phosphates oral solution for adults and children 12 years of age and over: 3.42 to 7.56 grams (g) of dibasic sodium phosphate and 9.1 to 20.2 g of monobasic sodium phosphate¹ in a single daily dose. (See proposed § 334.58(d)(5)(i) (21 CFR 334.58(d)(5)(i)), 50 FR 2124 at 2155.) In addition to its use as an OTC laxative for the relief of occasional constipation, sodium phosphates oral solution² is used as part of a bowel cleansing

¹ In the tentative final monograph for OTC laxative drug products, published in the Federal Register of January 15, 1985 (50 FR 2124), and in the proposed rule for package size limitation for OTC laxative drug products published in the Federal Register of March 31, 1994 (59 FR 15139), the agency referred to dibasic sodium phosphate as "sodium phosphate," and monobasic sodium phosphate as "sodium biphosphate." The current nomenclature in the *USP Dictionary of USAN and International Drug Names, 1997* is "dibasic sodium phosphate" and "monobasic sodium phosphate," respectively. This final rule uses the current nomenclature.

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 23/National Formulary 18, 1995*.

regimen in preparing a patient for surgery or for preparing the colon for x-ray or endoscopic examination. (See proposed § 334.80(a)(2), 50 FR 2124 at 2157.) Sodium phosphates oral solution and sodium phosphates enema³, respectively, are the current United States Pharmacopeia (USP) names for the oral and rectal dosage forms of the combination of sodium phosphates ingredients.

In the Federal Register of March 31, 1994 (59 FR 15139), the agency proposed to amend the tentative final monograph for OTC laxative drug products to limit the OTC container size for sodium phosphates oral solution to not greater than 90 mL. The agency also proposed a warning for all oral and rectal dosage forms of sodium phosphates products to inform consumers not to exceed the recommended dosage unless directed by a doctor. Interested persons were invited to submit written comments on the proposed regulation and on the agency's economic impact determination by May 31, 1994.

In response to the proposal, two manufacturers of laxative drug products submitted comments. Neither comment addressed the agency's economic impact determination. Copies of these comments are on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. Additional information that has come to the agency's attention since publication of the proposal is also on public display in the Dockets Management Branch.

In the proposal, the agency discussed its reasons for limiting the package size for sodium phosphates oral solution (59 FR 15139). The agency noted that the major trade product containing sodium phosphates oral solution was marketed in 45-mL, 90-mL, and 240-mL bottles. The purgative dose or dose used for colonoscopy is 45 mL. Because the product was available in three sizes, the manufacturer's labeling advised physicians to prescribe by volumes and not to prescribe by the bottle and not to exceed the recommended dosage, as serious side effects may occur. Despite this labeling, the multiple container sizes available in the marketplace have caused consumer confusion and appear to have been involved in several consumer deaths.

The agency determined that the OTC availability of the 240-mL container of

³ Sodium phosphates enema is the official name for a solution of dibasic sodium phosphate and monobasic sodium phosphate in the *U.S. Pharmacopeia 23/National Formulary 18, 1995*.

sodium phosphates oral solution creates a potential safety risk, particularly for elderly persons who are likely to use the product for bowel cleansing prior to surgery or a diagnostic procedure involving the colon. Because of the reported cases of accidental overdosing and the confusion that has occurred between 240-mL and 90-mL container sizes, the agency proposed that the 240-mL size container of sodium phosphates oral solution should no longer remain in the OTC marketplace. In the interest of safety, the agency proposed to limit the maximum OTC container size for this product to 90 mL.

The agency proposed to include the package size limitation and warning in the monograph for OTC laxative drug products. However, that monograph has not been finalized to date. Because of the potential safety risk involved, the agency has decided to finalize both the package size limitation and several new warning and direction statements prior to completion of the final monograph for OTC laxative drug products. The agency has decided to include this information in part 201 (21 CFR part 201) at this time and to incorporate it into the final monograph for OTC laxative drug products at a later date.

In the Federal Register of February 27, 1997 (62 FR 9024), FDA proposed to establish a standardized format for the labeling of OTC drug products. Until the proposal is finalized, manufacturers, distributors, and packagers must comply with the final rule published herein and all other currently applicable labeling regulations. The agency will eventually use the final labeling rule to incorporate the information included herein in part 201 into the final monograph for OTC laxative drug products.

II. The Agency's Conclusions on the Comments

1. One comment stated that, according to the USP 22 (Ref. 1), the current terminology for sodium phosphate is monobasic sodium phosphate and for sodium biphosphate it is dibasic sodium phosphate. The comment stated that the tentative final monograph should be amended accordingly.

Under agency regulations in 21 CFR 299.4(e), the established name of a drug is the current compendial name or the USAN (U.S. Adopted Names Council) adopted name listed in the USP Dictionary of USAN and International Drug Names. Both the U.S. Pharmacopeia 23/National Formulary 18 (Ref. 2) and the USP Dictionary of USAN and International Drug Names, 1997 (Ref. 3) list the current name for sodium phosphate as "dibasic sodium phosphate," and for sodium

biphosphate as "monobasic sodium phosphate." (See footnote 1, supra.) It appears that the comment inadvertently reversed the names of the ingredients.

2. One comment stated that the agency's proposal that the final rule be effective 30 days after its publication in the Federal Register is insufficient time. The comment argued that 30 days would not be enough time for relabeling of its sodium phosphates products and requested that the final rule be effective 120 days after its publication in the Federal Register.

The agency is instituting a split effective date for this final rule. Because of the potential serious safety risk involved, the agency has determined that initial introduction or initial delivery for introduction into interstate commerce of any container size of sodium phosphates oral solution greater than 90 mL should cease as soon as possible (within 30 days of this final rule). However, the agency concurs with the comment that manufacturers need more than 30 days to relabel these drug products and is granting the 120 days requested by the comment. Because of the potential serious safety risks, the agency has determined that manufacturers need to work promptly to relabel their products. The agency is providing manufacturers the option to use supplementary labeling (e.g., stick-on labeling) to add the new warning and direction information to currently manufactured products not yet introduced into interstate commerce or on package labeling that has not yet been incorporated into the manufacturing process. If manufacturers choose not to use stick-on labeling, they are encouraged to have new labeling containing the new warning and direction information printed as expeditiously as possible in the interest of safe use of these products.

3. One comment stated that sodium phosphates oral solution should not be marketed in packages containing more than 45 mL. The comment argued that 45 mL of this product equals the "single daily dose" of solution generally recognized as safe and effective for use as a laxative and bowel cleansing agent in the tentative final monograph. The comment provided data to show that taking more than this amount has been shown to cause significant changes in blood levels of sodium, potassium, phosphate, chloride, and calcium, thereby imposing a risk of serious injury (Refs. 4, 5, and 6).

The agency does not agree with the comment that packages containing more than 45 mL of sodium phosphates oral solution should not be marketed. Problems that previously occurred

involved confusion resulting from the availability of a 240-mL container size (59 FR 15139). (In 1993, the manufacturer of the major trade product containing this solution ceased manufacture and initiated a market withdrawal of the 240-mL container size.) The oral solution is currently marketed in 45-mL and 90-mL containers. The agency has not received any reports that a one-time 90 mL dose has resulted in a death or a serious adverse reaction requiring medical treatment.

The agency has reviewed the submitted data (Refs. 4, 5, and 6) and agrees that taking more than 45 mL of sodium phosphates solution over a 10- to 12-hour period can result in significant changes in electrolytes and may impose a risk of serious injury. (See comment 4 in section II of this document.) Therefore, the agency is requiring specific warning and direction statements to ensure that the correct dose is used and that consumers do not use more than the recommended dose in a 24-hour period. The agency proposed to amend the tentative final monograph for OTC laxative drug products to include in § 334.58(c)(2)(iv) the following warning for oral and rectal dosage forms of sodium phosphates products: "Do not exceed recommended dose unless directed by a doctor. Serious side effects may occur from excess dosage" (59 FR 15139).

In this final rule, the agency is revising the proposed warning by adding 24-hour dosing information and by simplifying the language. The agency is also requiring separate warnings for oral and rectal enema drug products. For oral sodium phosphates drug products, the new warning states: "Taking more than the recommended dose in 24 hours can be harmful." For rectal sodium phosphates drug products, the new warning states: "Using more than one enema in 24 hours can be harmful." Both warnings must be in boldface type and appear as the first statement under the heading "Warnings." (See comment 5 in section II of this document.)

The agency is also adding new directions in boldface type immediately preceding the dosage information, which state: "Do not" ("take" or "use") "more unless directed by a doctor. See Warnings." (See comment 4 in section II of this document.) The new directions appear in § 201.307(b)(3)(i).

The agency notes that sodium phosphates oral solution is available for general laxative use for relief of occasional constipation at a single daily dose of 20 mL to 45 mL for adults and children 12 years of age and over. Thus,

a larger size container (90 mL) may be more convenient for consumers to purchase and have available for future use. The agency is also aware that the 45-mL and 90-mL container sizes are often recommended and prescribed by physicians for bowel cleansing prior to surgery and diagnostic procedures of the colon. Accordingly, the agency is allowing the 90-mL container of sodium phosphates oral solution to remain on the OTC market. However, in an effort to prevent consumers from taking an entire 90-mL container in 1 day (24 hours), the agency is adding additional statements in the directions in § 201.307(b)(3)(ii) to inform consumers how much of the oral solution may be taken as a single daily dose and not to take more than the recommended daily dose in a 24-hour period. The agency has also revised the format for stating children's ages from that proposed in § 334.58(d)(5)(i) of the tentative final monograph (50 FR 2124 at 2155). The directions now state:

Adults and children 12 years of age and over: Oral dosage is dibasic sodium phosphate 3.42 to 7.56 grams (g) and monobasic sodium phosphate 9.1 to 20.2 g (20 to 45 mL dibasic sodium phosphate/monobasic sodium phosphate oral solution) as a single daily dose. "Do not take more than 45 mL (9 teaspoonfuls or 3 tablespoonfuls) in a 24-hour period."

Children 10 and 11 years of age: Oral dosage is dibasic sodium phosphate 1.71 to 3.78 g and monobasic sodium phosphate 4.5 to 10.1 g (10 to 20 mL dibasic sodium phosphate/monobasic sodium phosphate oral solution) as a single daily dose. "Do not take more than 20 mL (4 teaspoonfuls) in a 24-hour period."

Children 5 to 9 years of age: Oral dosage is dibasic sodium phosphate 0.86 to 1.89 g and monobasic sodium phosphate 2.2 to 5.05 g (5 to 10 mL dibasic sodium phosphate/monobasic sodium phosphate oral solution) as a single daily dose. "Do not take more than 10 mL (2 teaspoonfuls) in a 24-hour period." Children under 5 years of age: ask a doctor.

The agency notes that the directions for sodium phosphates oral solution contain separate dosages for children 10 and 11 years of age and for children 5 to 9 years of age. These age ranges are not consistent with age ranges used for the majority of OTC laxative drug products, which recommend dosages for children 6 to 11 years of age. Therefore, elsewhere, in this issue of the Federal Register, the agency is proposing to revise the directions for sodium phosphates oral solution to limit the OTC use of these products to children 6 years of age and above.

The proposed directions state:
* * * Children 6 to 9 years of age: Oral dosage is dibasic sodium phosphate 0.86 to 1.89 g and monobasic sodium phosphate 2.2 to 5.05 g (5 to 10 mL dibasic sodium phosphate/monobasic sodium phosphate oral

solution) as a single daily dose. 'Do not take more than 10 mL (2 teaspoonfuls) in a 24-hour period.' Children under 6 years of age: ask a doctor.

4. One comment requested that sodium phosphates oral solution products bear a warning against consuming more than 45 mL in a 24-hour period unless directed by a physician. The comment contended that there are potentially serious health problems associated with high doses of this product. The comment submitted data to show that consuming more than 45 mL of sodium phosphates oral solution in 24 hours has resulted in significant changes in blood levels of sodium, potassium, phosphate, chloride, and calcium, thereby imposing a risk of serious injury (Refs. 4, 5, and 6).

The agency has reviewed the submitted data and agrees that ingesting more than 45 mL of sodium phosphates oral solution in a 24-hour period may be harmful. Clarkston et al. (Ref. 4) compared a polyethylene glycol (PEG) based gastrointestinal lavage to a sodium phosphates oral regimen. In this randomized trial, 26 subjects took 4 liters (L) of the PEG solution and 25 subjects took two 45-mL doses of sodium phosphates oral solution 11 hours apart. The subjects had a chemistry panel and ionized calcium done prior to taking the drug and on the morning of the colonoscopy. The results indicated that the sodium phosphates solution caused a decrease in ionized serum calcium and serum potassium, with concomitant increases in phosphate. The investigators stated that the sodium phosphates oral regimen resulted in statistically significant changes in serum sodium, potassium, phosphorus, and calcium ($p < 0.01$). The investigators concluded that the risk of symptoms of hypocalcemia must be considered due to the abnormal low levels of ionized calcium that frequently occur with this regimen.

Vanner et al. (Ref. 5) compared a standard PEG based gastrointestinal solution to a sodium phosphates oral solution prior to colonoscopy. In this parallel, single-blinded, randomized study, 54 subjects received two 45-mL doses of the sodium phosphates oral solution 11 hours apart, and 48 subjects received 4 L of the PEG solution. The subjects had blood tests on admission and the morning of the procedure. The authors concluded that the sodium phosphates oral solution was safe and effective because serial measurements of blood tests, postural pulse, and blood pressure changes did not reveal any clinically significant changes in intravascular volume. One "syncopal

episode" occurred in the sodium phosphates group. The authors mentioned that the subject's vital signs did not appear to indicate that hypovolemia (abnormally decreased volume of circulating plasma) was the cause. The authors reported that hyperphosphatemia occurred with sodium phosphates, but serum phosphate values returned to normal within 24 hours, and no concomitant decrease in calcium was seen. They added that histological assessment for possible preparation-induced changes revealed no difference between the two drugs.

The agency notes that numerous induced electrolyte abnormalities occurred in this study. The data showed statistically significant decreases in potassium and increases in hematocrit, sodium, chloride, osmolality, and phosphate. Extreme serum phosphate levels reached 11.6 milligrams/deciliter (mg/dL) in the sodium phosphates group and 4.7 mg/dL in the PEG group; normal values are 2.5 to 4.1 mg/dL. In hyperphosphatemia, excessive complexing of calcium with phosphate may contribute to a decrease in plasma ionized calcium, which results in hypocalcemia. Calcium levels were not reported for the entire sodium phosphates group nor was the risk of hypokalemia mentioned. The agency notes that the postural changes in pulse, systolic blood pressure, and the one "syncopal episode" were most likely due to decreased intravascular volume in subjects in the sodium phosphates group.

Because elevated phosphate levels are known to occur with sodium phosphates use, 15 subjects were randomly selected to have serum phosphate and calcium levels measured at 4 p.m. on the day of colonoscopy and at 8 a.m. the following day. Seven of the fifteen subjects received the sodium phosphates regimen. Vanner et al. reported that 2 hours after the second dose, the mean serum phosphorus was 7.2 mg/dL (nearly twice the pre-study value of 3.7 mg/dL), while the total calcium values continued to decline for at least 24 hours after the dose was taken.

The agency believes that the Vanner et al. study showed that postural increases in pulse, decreases in systolic blood pressure, and serum electrolyte and plasma volume shifts were greater in the sodium phosphates group than in the PEG group. The incidence of postural elevation in heart rate, indicating significant reduction in intravascular volume, was also three times higher in the sodium phosphates group than in the PEG group. Because

of the small sample size, the fact that none of the study subjects died or had serious side effects that required hospitalization cannot be interpreted to mean that two 45-mL doses of sodium phosphates oral solution are safe to ingest without a physician's supervision.

Warner and DiPalma (Ref. 6) stated that sodium phosphates oral solution is extremely popular for use as a bowel cleansing agent because it is effective, easy to administer, and well tolerated. However, they contended that little data are available concerning its safety. They mentioned that the majority of trials evaluating the product for use as a bowel cleanser have not systematically monitored electrolytes. They asserted that the solubility product of calcium and phosphate, when exceeded, leads to soft tissue calcification in areas where an alkaline internal environment enhances calcium phosphate salt deposit, primarily in the kidneys, heart, blood vessel, cornea, lungs, and gastric mucosa. They stated that the normal calcium-phosphate product is 40 mg/dL, which is tightly regulated through absorption, excretion, and intracellular/extracellular ion shifts; and that the in vitro solubility product of calcium is 58 mg/dL, well above the normal value (Ref. 6). Warner and DiPalma mentioned that Vanner et al. (Ref. 5) and Kolts (Ref. 7) have presented limited data to show phosphate levels rising to as high as 7 mg/dL with relatively unchanged serum calcium values. According to Warner and DiPalma, the increase in phosphate levels appeared quite transient, but because sampling was so infrequent, it is impossible to ascertain whether even these high values represent the peak phosphate concentrations after administration of sodium phosphates oral solution.

Kolts (Ref. 8) responded to Warner and DiPalma, and argued that sodium phosphates oral solution should be the preparation of choice for most endoscopy outpatients due to its low cost, comfort for the patient, and low incidence of adverse side events. Kolts stated that the sodium phosphates oral solution used in his study (Ref. 7) had been sold OTC for more than 100 years and the manufacturer had not reported any serious side effects, except when the solution was taken in massive overdoses or if used when contraindicated. Kolts added that there were no reports of adverse events such as ectopic calcification in the literature from 1966 to 1993 from the use of phosphate catharsis in people with normal renal function. Kolts concluded that his (Ref. 7) and Vanner's (Ref. 5) studies documented the minor changes

in clinically relevant electrolytes as well as the lack of adverse symptoms from sodium phosphates oral solution.

The agency finds that the data show that sodium phosphates oral solution can cause alterations in serum levels of sodium, potassium, phosphate, chloride, and calcium. In some people, such changes can be life-threatening. The agency has particular concerns about hypocalcemia occurring due to its reported frequency when two 45-mL doses of sodium phosphates oral solution are given over a 24-hour period. The reduction of calcium levels reflects changes in ionized calcium (Ref. 9). Hypocalcemia with subsequent low levels of ionized calcium may result in neuromuscular irritability, heart block, and cardiovascular failure (Ref. 9).

In the tentative final monograph for OTC laxative drug products (50 FR 2124 at 2155), the agency proposed a maximum single daily oral dose of 7.56 g of dibasic sodium phosphate and 20.2 g of monobasic sodium phosphate. The major manufacturer of sodium phosphates products recommends (as part of a bowel cleansing regimen in preparation for surgery or preparation of the colon for x-ray or endoscopic examination) (Ref. 10) that 45 mL be given at 7 p.m. and again at 6 a.m. the following morning. The agency notes that 0.9 g/5 mL of dibasic sodium phosphate is equivalent to 17.1 to 18.9 g/100 mL of sodium phosphates oral solution, and that 2.4 g/5 mL of monobasic sodium phosphate is equivalent to 45.6 to 50.4 g/100 mL of sodium phosphates oral solution according to the USP 23 (Ref. 2). Therefore, over an 11-hour period, 90 mL of solution (approximately 16.2 g of dibasic sodium phosphate and 43.2 g of monobasic sodium phosphate) containing 9.9 g of sodium could be consumed. The manufacturer of this product has not submitted sufficient data to demonstrate the safety of more than 45 mL of this solution in a 24-hour period (Ref. 11). Thus, the agency concludes that the safe oral use of more than 7.56 g of dibasic sodium phosphate and 20.2 g of monobasic sodium phosphate in a 24-hour period has not been demonstrated at this time. Therefore, the agency will not include a greater dosage in a 24-hour period in the OTC or professional labeling in the final monograph for OTC laxative drug products, which will be published in a future issue of the Federal Register.

The agency agrees with the comment that the labeling for sodium phosphates oral solution should include a warning not to ingest more than the recommended dose in a 24-hour period. Accordingly, the agency is including the

following warning in § 201.307(b)(2)(i) for oral products that contain sodium phosphates: "Taking more than the recommended dose in 24 hours can be harmful." The sentence is required to appear in boldface type as the first statement under the heading "Warnings." The agency is also requiring in § 201.307(b)(3)(i) that the directions for oral and rectal sodium phosphates products contain the following statements in boldface type immediately preceding the dosage information: "Do not" ("take" or "use") "more unless directed by a doctor. See Warnings." (See comment 5 in section II of this document.) These additional statements are intended to refer consumers to the warnings when they read the directions for the product.

5. One comment disagreed with the proposed warning in § 334.58(c)(2)(iv) for rectal enema sodium phosphates drug products, which states: "Do not exceed recommended dose unless directed by a doctor. Serious side effects may occur from excess dosage." The comment argued that the agency provided no concrete or specific evidence to support this warning. The comment stated that its sodium phosphates enema contains 19 g/118 mL (equivalent to 16 g/100 mL) of monobasic sodium phosphate and 7 g/118 mL (equivalent to 7 g/100 mL) of dibasic sodium phosphate. In contrast, the oral product contains 2.4 g/5 mL (equivalent to 48 g/100 mL) of monobasic sodium phosphate and 0.9 g/5 mL (equivalent to 18 g/100 mL) of dibasic sodium phosphate. The comment stated that because the phosphate concentration of the enema is only one-third that of the oral product, use of the enema is not likely to result in overdosage. The comment added that an overdosage is unlikely to occur due to the way enemas are used and the results they produce. The comment mentioned that the enema product is clearly labeled "Not intended for oral consumption," and that the current labeling clearly states the appropriate dosage. Thus, the comment concluded that the warning should not be required for sodium phosphates enema products. Another comment stated that the dosage and administration section of products containing sodium phosphates should be allowed to contain statements similar to the following proposed warning: "Do not exceed recommended dose unless directed by a doctor. Serious side effects may occur from excess dosage." The comment indicated that such statements should be allowed, but do not need to be included in the final rule.

The agency notes that the first comment made an error in its statement

of the amount of dibasic sodium phosphate per 100 mL. It should have been approximately 6 g/mL, which is consistent with USP 23 (Ref. 2), which states that each 100 mL of sodium phosphates enema solution contains not less than 5.7 g and not more than 6.3 g of dibasic sodium phosphate.

The agency is aware of numerous reports of misuse of sodium phosphates enemas that resulted in adverse effects (Refs. 12 through 23). Wason et al. (Ref. 12) reported the case of a normal 5-month-old child who was given an entire adult sodium phosphates enema by her mother. Within 30 minutes, the child became extremely ill; consciousness decreased; and shock, hyperphosphatemia, hypocalcemia, and acidosis developed. The child was hospitalized and responded to intravenous (IV) fluid replacement and aluminum hydroxide gel. Oxnard, O'Bell, and Grube (Ref. 13) reported that a 4-year-old child with chronic renal failure became profoundly hyperphosphatemic and hypocalcemic after receiving an entire adult sodium phosphates enema. The child developed muscle twitching, acidosis, severe diarrhea, and tachycardia, and was hospitalized, subsequently responding to IV calcium gluconate, calcium chloride, and sodium bicarbonate.

Other authors have reported that children (4 months to 2 1/2 years old) with gastrointestinal anomalies, such as Hirschsprung's disease (congenital megacolon), and chronic renal failure were at high risk for complications after the use of sodium phosphates enemas (Refs. 13 through 20). These children received varying amounts of adult or pediatric sodium phosphates enemas for constipation and bowel cleansing prior to surgery. Three of the children had cardiac arrest after the use of hypertonic sodium phosphates enemas (Refs. 17, 19, and 20). Martin et al. (Ref. 19) reported that an 11-month-old child died after receiving four adult sodium phosphates enemas. Loughnan and Mullins (Ref. 17) reported that a 9-month-old child suffered severe and permanent brain damage after receiving a pediatric sodium phosphates enema. Reedy and Zwiren (Ref. 20) reported that a 17-month-old child received two pediatric sodium phosphates enemas as a "bowel prep" on the day of surgery and was successfully resuscitated after experiencing cardiac arrest during induction of anesthesia. The authors noted that the child had received sodium phosphates enemas chronically but that a possible electrolyte imbalance was not suspected, and the child was not screened for any possible electrolyte problems prior to surgery.

Other authors (Refs. 21, 22, and 23) have reported acidosis, hypocalcemia, and hyperphosphatemia that occurred in adults and children after the use of sodium phosphates enema products. Davis et al. (Ref. 21) state that these products can cause electrolyte imbalances, which can cause severe reactions and could result in death, when administered in the recommended doses to individuals with normal renal function.

The agency is also aware of serious electrolyte imbalances occurring in individuals who used more than one sodium phosphates enema in a 24-hour period (Refs. 15, 16, 24, 25, and 26). Thus, an electrolyte imbalance can result from an excess dose of either the oral solution or the enema dosage form. Because of the serious side effects that can occur from overdosage, the agency considers it important to include information against exceeding the recommended dose of sodium phosphates drug products in both the warnings and directions sections of product labeling. The agency concludes that this information needs to be required, not just voluntarily included at a manufacturer's discretion.

III. References

The following references are on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. The United States Pharmacopeia 22/ The National Formulary 17, The United States Pharmacopoeial Convention Inc., Rockville, MD, pp. 1265-1267, 1989.
2. The United States Pharmacopeia 23/ The National Formulary 18, The United States Pharmacopoeial Convention Inc., Rockville, MD, pp. 1428-1430, 1994.
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IV. Summary of Significant Changes From the Proposed Rule

The agency is making the following changes based on comments submitted in response to the proposal (59 FR 15139) and other relevant information that has come to the agency's attention. The agency had proposed to include the package size limitation and the labeling in the final monograph for OTC laxative drug products (proposed 21 CFR part 334). However, that final monograph has not been completed to date. Therefore, at this time the agency is including this information in part 201 subpart G, Specific Labeling Requirements for Specific Drug Products. New § 201.307 will be titled *Sodium phosphates; package size limitation, warnings, and directions for over-the-counter sale*. When the laxative final monograph is complete, it will incorporate the requirements in § 201.307. A summary of the changes made by the agency follows:

1. The package size limitation of 90 mL (3 oz) for sodium phosphates oral solution proposed in § 334.25 appears in § 201.307(b)(1) and is effective 30 days after date of publication of this final rule in the Federal Register. The relabeling requirements in § 201.307 are effective 120 days after date of publication of this final rule in the Federal Register. (See comment 2 in section II of this document.)
2. The agency has revised the warning for oral and rectal dosage forms of sodium phosphates proposed in § 334.58(c)(2)(iv). The agency is adding a new warning for oral sodium phosphates products, which appears in § 201.307(b)(2)(i) and states: "Taking more than the recommended dose in 24 hours can be harmful." (See comment 5 in section II of this document.) The agency is adding a new warning for rectal sodium phosphates products, which appears in § 201.307(b)(2)(ii) and states: "Using more than one enema in 24 hours can be harmful." These warnings must appear in boldface type and must be the first statement in product labeling under the heading "Warnings."

3. The agency is adding new directions in § 201.307(b)(3)(i) for oral and rectal sodium phosphates that state: "Do not" ("take" or "use") "more unless directed by a doctor. See Warnings." (See comment 4 in section II of this document.) These directions must be in boldface type and immediately precede the dosage information.

4. The agency is including specific directions in § 201.307(b)(3)(ii) that inform consumers not to take more than the recommended daily dose in a 24-hour period. (See comment 3 in section II of this document.)

V. The Agency's Final Conclusions on OTC Laxative Drug Products Containing Sodium Phosphates

The agency has determined that there is sufficient evidence to show that an overdose of sodium phosphates products can cause an electrolyte imbalance. This imbalance can occur if an excess dose of either the sodium phosphates oral solution or the sodium phosphates enema were used. This electrolyte imbalance can cause severe reactions and result in death. Accordingly, this final rule establishes a container size limit for oral sodium phosphates products and new warning and direction statements for OTC laxative drug product containing sodium phosphates. To better protect consumers who use products containing these ingredients, the agency concludes that the container size must be limited to 90 mL (3 oz). In addition, labeling needs to alert consumers not to exceed the recommended dose of an oral or rectal sodium phosphates product in a 24-hour period. Therefore, the agency is requiring the following warning for oral dosage forms of sodium phosphates in § 201.307(b)(2)(i): "Taking more than the recommended dose in 24 hours can be harmful." The agency is also requiring a similar warning for rectal dosage forms of sodium phosphates in § 201.307(b)(2)(ii): "Using more than one enema in 24 hours can be harmful." Furthermore, the agency is requiring that the directions for oral and rectal sodium phosphates products in § 201.307(b)(3)(i) state: "Do not" ("take" or "use") "more unless directed by a doctor. See Warnings." These additional statements are intended to refer consumers to the warnings when they read the directions for the product. Because of the dire consequences that can occur from an overdose of sodium phosphates, the warnings are required to appear in boldface type as the first sentence under the heading "Warnings." The direction statements are required to appear in boldface type immediately preceding the dosage

information. In addition, the agency is including specific directions that inform consumers not to take more than the recommended daily dose in a 24-hour period in § 201.307(b)(3)(ii). (See comment 3 in section II of this document.)

VI. Analysis of Impacts

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (59 FR 15139 at 15141). FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601-612). 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). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that minimize any significant impact of the rule on small entities.

Title II of the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*) requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation). The proposed rule that has led to the development of this final rule was published on March 31, 1994, before the Unfunded Mandates Reform Act was enacted. The agency explains in this final rule that the final rule will not result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million.

The agency believes that this final rule is consistent with the principles set out in the Executive Order and in these two statutes. The purpose of this final rule is to limit the OTC container size of one laxative drug product (sodium phosphates oral solution) to not more than 90 mL and to add warning and direction statements to the labeling of oral and rectal OTC sodium phosphates drug products. This container size limitation and the warning and direction statements concern product toxicity and are intended to help ensure the safe and effective use of all OTC sodium phosphates drug products. Potential benefits include reduced

toxicity when consumers use these products.

The manufacturer of the only major trade product containing sodium phosphates oral solution marketed in a container size larger than 90 mL has already withdrawn that size product from the market. The agency is not able to identify any other sodium phosphate oral solution marketed by another manufacturer in a container exceeding 90 mL.

Regarding relabeling, the agency has been informed that relabeling costs of the type required by this final rule generally average about \$2,000 to \$3,000 per stock keeping unit (SKU) (individual products, packages, and sizes). The agency is aware of 3 manufacturers that together produce 4 SKUs of oral sodium phosphates drug products and approximately 125 SKUs of rectal sodium phosphates drug products. There may be a few additional small manufacturers or a few additional products in the marketplace that are not identified in the sources FDA reviewed. Assuming that there are about 130 affected OTC SKUs in the marketplace, total one-time costs of relabeling would be \$260,000 to \$390,000. The agency believes that actual cost could be lower for several reasons. First, most of the label changes will be made by private label manufacturers that tend to use simpler and less expensive labeling. Second, the agency is allowing supplementary labeling (e.g., stick-on labeling) to be used for those products not undergoing a new labeling printing within 120 days.

The final rule would not require any new reporting and recordkeeping activities. Therefore, no additional professional skills are needed. There are no other Federal rules that duplicate, overlap, or conflict with the final rule.

The agency considered but rejected several container size and labeling alternatives: (1) A container size limit of 45, 60, or 120 mL; (2) voluntary relabeling; (3) publication of the labeling information in the FDA Drug Bulletin or professional journals; and (4) an exemption from coverage for small entities. The alternate container sizes were not selected because 90 mL represents the upper limit of the two doses per container and physicians often prescribe this amount for bowel cleansing prior to surgery and diagnostic procedures of the colon. The agency does not consider voluntary relabeling or an exemption from coverage acceptable because they do not assure that consumers or health professionals will have the most recent needed information for safe and effective use of these sodium

phosphates drug products. The agency considers the third alternative useful and may proceed with such publications. However, such publications do not provide a permanent labeling requirement, which the agency considers necessary for these products.

This final rule may have a significant economic impact on the manufacturers of this product, all of which are considered small entities, using the U.S. Small Business Administration designations for this industry (750 employees). The agency believes that any other unidentified manufacturer of these products may also be a small entity. These manufacturers will need to change the information panel of each affected sodium phosphates SKU. Among the steps the agency is taking to minimize the impact on these small entities are: (1) To provide 120 days for implementation, as one comment requested, to enable entities to use up some existing labeling stock, and (2) to provide for the use of supplementary labeling (e.g., stick-on labeling) if necessary. The agency believes that these actions should help reduce the relabeling cost for small entities.

The agency considered a longer implementation period. The agency proposed a 30-day effective date, considered extending this to 60 days, and in response to public comment has extended the effective date to 120 days to reduce the economic burden on small entities. The agency considered but rejected a longer effective date because it would not assure that consumers have the most recent needed information for safe and effective use of OTC sodium phosphates drug products at the earliest possible time. The agency concludes that the overriding safety considerations warrant a 120-day implementation period.

The analysis shows that this final rule is not economically significant under Executive Order 12866 and that the agency has undertaken important steps to reduce the burden to small entities. Nevertheless, some entities, especially those private label manufacturers that provide labeling for a number of the affected products, may incur significant impacts. Thus, this economic analysis, together with other relevant sections of this document, serves as the agency's final regulatory flexibility analysis, as required under the Regulatory Flexibility Act. Finally, this analysis shows that the Unfunded Mandates Act does not apply to the final rule because it would not result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million.

VII. Paperwork Reduction Act of 1995

FDA concludes that the labeling requirements in this document are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the labeling statements are a "public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

VIII. Environmental Impact

The agency has determined under 21 CFR 25.31(c) 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.

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements. Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 201 is amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

2. Section 201.307 is added to subpart G to read as follows:

§ 201.307 Sodium phosphates; package size limitation, warnings, and directions for over-the-counter sale.

(a) Reports in the medical literature and data accumulated by the Food and Drug Administration indicate that multiple container sizes of sodium phosphates oral solution available in the marketplace have caused consumer confusion and appear to have been involved in several consumer deaths. Sodium phosphates oral solution has been marketed in 45-milliliter (mL), 90-mL, and 240-mL container sizes. The 45-mL and 90-mL container sizes of sodium phosphates oral solution are often recommended and prescribed by physicians for bowel cleansing prior to surgery and diagnostic procedures of the colon. Sodium phosphates oral solution (adult dose 20 mL to 45 mL) is also used as an over-the-counter (OTC) laxative for the relief of occasional constipation. Accidental overdosing and deaths have

occurred because the 240-mL container was mistakenly used instead of the 45-mL or 90-mL container. The Food and Drug Administration is limiting the amount of sodium phosphates oral solution to not more than 90 mL (3 ounces (oz)) per OTC container because of the serious health risks associated with the ingestion of larger than intended doses of this product. Further, because an overdose of either oral or rectal enema sodium phosphates can cause an electrolyte imbalance, additional warning and direction statements are required for the safe use of any OTC laxative drug product containing sodium phosphates.

(b) Any OTC drug product for laxative or bowel cleansing use containing sodium phosphates as an active ingredient when marketed as described in paragraph (a) of this section is misbranded within the meaning of section 502 of the Federal Food, Drug, and Cosmetic Act unless packaged and labeled as follows:

(1) Package size limitation for sodium phosphates oral solution: Container shall not contain more than 90 mL (3 oz).

(2) Warnings. The following sentences shall appear in boldface type as the first statement under the heading "Warnings."

(i) Oral dosage forms. "Taking more than the recommended dose in 24 hours can be harmful."

(ii) Rectal enema dosage forms. "Using more than one enema in 24 hours can be harmful."

(3) Directions—(i) The labeling of all orally or rectally administered OTC drug products containing sodium phosphates shall contain the following directions in boldface type immediately preceding the dosage information: "Do not" ("take" or "use") "more unless directed by a doctor. See Warnings."

(ii) For products containing dibasic sodium phosphate/monobasic sodium phosphate identified in § 334.16(d) marketed as a solution. Adults and children 12 years of age and over: Oral dosage is dibasic sodium phosphate 3.42 to 7.56 grams (g) and monobasic sodium phosphate 9.1 to 20.2 g (20 to 45 mL dibasic sodium phosphate/monobasic sodium phosphate oral solution) as a single daily dose. "Do not take more than 45 mL (9 teaspoonfuls or 3 tablespoonfuls) in a 24-hour period." Children 10 and 11 years of age: Oral dosage is dibasic sodium phosphate 1.71 to 3.78 g and monobasic sodium phosphate 4.5 to 10.1 g (10 to 20 mL dibasic sodium phosphate/monobasic sodium phosphate oral solution) as a single daily dose. "Do not take more than 20 mL (4 teaspoonfuls) in a 24-