

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 1990N-0309]

DDM

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Drug Labeling; Sodium Labeling for Over-the-Counter Drugs

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a proposed rule that would amend the regulations for sodium labeling for over-the-counter (OTC) drug products by extending the sodium content labeling requirement to rectal drug products containing sodium phosphate/sodium biphosphate (sodium phosphates). FDA is taking this action because people with certain medical conditions are at risk for an electrolyte imbalance to occur when using rectal sodium phosphates products. Serious adverse events and deaths have occurred because of the high level of sodium present in these products. This proposal is part of FDA's ongoing review of OTC drug products.

DATES: Submit written or electronic comments by [*insert date 90 days after date of publication in the **Federal Register***]. Submit written or electronic comments on FDA's economic impact determination by [*insert date 90 days after date of publication in the **Federal Register***]. See section IX of this document for the effective date of any final rule that may publish based on this proposal.

ADDRESSES: Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061,

Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Robert L. Sherman, 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 April 22, 1996 (61 FR 17798), FDA issued a final rule on sodium labeling for OTC drug products that included sodium content labeling for products intended for oral ingestion. FDA provided an opportunity for comment on whether the final rule should be amended to include sodium content labeling for OTC rectal laxative, vaginal, dentifrice, mouthwash, and mouth rinse drug products. FDA noted that sodium labeling is important because a substantial portion of daily sodium intake can come from OTC drugs, especially those used frequently, such as laxatives. Interested persons were given until July 22, 1996, to submit comments on labeling for those products. In the **Federal Register** of July 22, 1996 (61 FR 38046), FDA published a notice extending the comment period until September 20, 1996.

Elsewhere in this issue of the **Federal Register**, FDA responds to the comments submitted in response to the final rule. At this time, FDA is not requiring sodium labeling for OTC vaginal, dentifrice, mouthwash, or mouth rinse drug products. Because of reports of problems associated with rectal enemas containing sodium phosphates and because the sodium is absorbed in the body when the product has not produced a bowel movement and has been retained in the body, FDA is proposing sodium content labeling for these products. These products contain a high sodium content (9.5 grams (g)

monobasic sodium phosphate and 3.5 g dibasic sodium phosphate per 59 milliliters) and the sodium content per delivered dose is 4.4 g for the adult product and 2.2 g for the children's product (Ref. 1). This amount of sodium may represent problems to people who need to limit sodium intake.

In the **Federal Register** of May 21, 1998 (63 FR 27886), FDA published a proposal to amend the tentative final monograph for OTC laxative drug products to include additional general and professional labeling for oral and rectal sodium phosphates drug products. That proposal includes a discussion of a number of situations where people with different medical conditions are at risk for an electrolyte imbalance to occur with use of oral and rectal sodium phosphates products. Because of this risk for an electrolyte imbalance to occur, FDA proposed new warnings and directions for these sodium phosphates products. However, that proposal did not contain any requirement for the sodium phosphates enemas to bear sodium content labeling. FDA considers it important for both consumers and health care professionals to have such information. The current proposal is intended to require sodium content labeling for these rectal products.

II. FDA's Proposal

FDA considers it important that consumers be aware of the sodium content of OTC sodium phosphates rectal drug products and that this information appear in product labeling so that it will be readily available to physicians. Section 201.64 (21 CFR 201.64) requires orally ingested sodium phosphates products to bear this information. Some OTC laxative drug products intended for rectal administration can contain very high levels of sodium from both active and inactive ingredients. Significant amounts of some of these products may be absorbed causing an electrolyte imbalance (61 FR 17798 at 17800).

Therefore, FDA is proposing to add paragraph (k) to § 201.64 to require sodium content information to appear in the labeling of rectal drug products containing dibasic sodium phosphate and/or monobasic sodium phosphate.

III. FDA's Tentative Conclusions on Sodium Labeling for Rectal Drug Products

A. Proposed New Labeling Requirements

FDA concludes that public interest and public health consequences related to sodium intake have produced a need for more informative and consistent sodium content and warning information in the labeling of OTC drug products. This is especially true for individuals with hypertension, heart failure, or other conditions, who must monitor their sodium intake.

FDA is proposing to require sodium content information to appear in the labeling of OTC rectal drug products containing dibasic sodium phosphate and/or monobasic sodium phosphate. Warnings for these products will be addressed in the final monograph for OTC laxative drug products.

B. Statutory Authority

In this proposed rule, FDA is addressing legal issues relating to the agency's action to require sodium content labeling for OTC rectal drug products. FDA is relying on section 502(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(e)) to require disclosure in the labeling of OTC rectal drug products of the following: (1) The presence and quantity of sodium that is an active ingredient and (2) the presence of sodium that is an inactive ingredient. To require disclosure of the quantity of sodium that is an inactive ingredient, FDA is relying on sections 502(a) and 201(n) of the act (21 U.S.C. 321(n)).

Section 502(e) of the act deems a drug to be misbranded unless its label bears the established name and quantity of each active ingredient or, if

determined to be appropriate by the Secretary of Health and Human Services (the Secretary), the proportion of each active ingredient (21 U.S.C. 352(e)(1)(A)(ii)). That provision also deems a drug to be misbranded unless its label bears the established name of each inactive ingredient on the outside container, and if determined appropriate by the Secretary, on the immediate container (21 U.S.C. 352(e)(1)(A)(iii)). Under section 502(a) of the act, a drug is deemed to be misbranded if its labeling is “false or misleading in any particular.” Section 201(n) of the act amplifies what is meant by “misleading” in section 502(a). Section 201(n) of the act states that, in determining whether labeling is misleading, FDA shall take into account not only representations made about the product, but also the extent to which the labeling fails to reveal facts material in the light of such representations or material with respect to consequences that may result from the use of the article to which the labeling relates under the conditions of use prescribed in the labeling, or under such conditions of use as are customary or usual (see 21 CFR 1.21). Finally, FDA has authority under section 701(a) of the act (21 U.S.C. 371(a)) to issue regulations for the efficient enforcement of the act.

As discussed in sections I, II, and III of this document, FDA has tentatively determined that for OTC rectal drug products containing more than the specified amount of sodium, the quantity of this substance as an active or inactive ingredient in these drug products is material with respect to consequences that may result from their use. Certain levels of sodium present a potential safety problem. People with hypertension, heart failure, or other conditions need to monitor their intake of sodium, which can cause serious toxicity in persons with these conditions. Many people are on sodium-restricted diets. Other people must monitor their intake of sodium from foods

(including dietary supplements) and OTC drugs for other medical or health reasons. Without mandatory sodium content labeling, these people would not be able to understand the relative contribution that OTC rectal drug products containing sodium make to their intake of sodium, and would not be able to compare the sodium content of various OTC rectal drug products.

C. The First Amendment

This proposed rule passes muster under the first amendment. FDA's proposed requirement of sodium content labeling for OTC rectal drug products (where sodium is an active or inactive ingredient and is present beyond the specified threshold level) is constitutionally permissible because it is reasonably related to the Government's interest in preventing deception of consumers and because it is not an "unjustified or unduly burdensome" disclosure requirement that offends the First Amendment. (See *Zauderer v. Office of Disciplinary Counsel*, 471 U.S. 626, 651 (1985); see also *Ibanez v. Florida Dep't of Bus. and Prof'l Regulation*, 512 U.S. 136, 146 (1994)). Such a reasonable relationship is plain here. The prescribed labeling disclosure would contribute directly to the use of products containing quantities of sodium that do not threaten the health of people for whom sodium use has material consequences. Some people, newly informed by the required labeling, will properly reduce or discontinue using sodium-containing OTC rectal drug products and thereby protect and promote their own health. By encouraging such changes in behavior, the labeling requirement is rationally related to the Government's goal of ensuring appropriate use of rectal drug products containing sodium. Finally, it is not "unduly burdensome" to require an additional disclosure of this kind.

In any event, this proposed rule passes muster when analyzed under the four-part test in *Central Hudson Gas & Electric Corporation v. Public Service Commission*, 447 U.S. 557 (1980), because it is necessary for the labeling of OTC rectal drug products containing sodium in excess of the threshold amount to be nonmisleading (*Id.* at 563–564). As discussed in this document, FDA has determined that the failure to disclose in an OTC rectal drug product’s labeling the amount of sodium in the product when it is present in amounts exceeding a certain threshold misbrands the product because the failure causes the labeling to be false or misleading under sections 502(a) and 201(n) of the act.

Although this determination obviates the need for FDA to address the other three parts of the *Central Hudson* test, we believe that the sodium content labeling requirement satisfies each of these parts. With respect to the second part, FDA’s interest in requiring sodium content labeling under this proposed rule is to ensure that people who must monitor their sodium intake for health reasons have information necessary to understand the relative contribution that OTC rectal drug products make to their sodium intake and to compare the sodium content of such products. FDA’s interest in protecting the public health has been previously upheld as a substantial government interest under *Central Hudson*. (See *Pearson v. Shalala*, 164 F.3d 650, 656 (D.C. Cir. 1999) (citing *Rubin v. Coors Brewing Co.*, 514 U.S. 476, 484–485 (1995))). The labeling requirement directly advances this interest, thereby satisfying the third part of the *Central Hudson* test, because by requiring labeling disclosure of the presence and quantity of sodium in OTC rectal drug products, the rule gives people the precise information they need to determine whether a particular product is consistent with their health requirements.

Finally, under the fourth part of the *Central Hudson* test, there are not numerous and obvious (*Cincinnati v. Discovery Network*, 507 U.S. 410, 418 n. 13 (1993)) alternatives to mandatory sodium content labeling of OTC rectal drug products that directly advance the Government's interest but are less burdensome to speech. Consumers are accustomed to using the label as their primary source of information about a product's contents. Neither a public education campaign, nor encouraging OTC drug product marketers to provide information on sodium content in the labeling of their products, would ensure that people have the information they need about sodium content at the point of sale or use. And establishing limits on sodium content would be more harmful to the public health. It is unnecessary for consumers who are not at risk to reduce or closely monitor their added daily sodium intake from OTC rectal drug products. For these rectal products, sodium content is linked to product design and determined by pharmaceutical necessity. Requiring disclosure here meets the fourth part of the test.

In conclusion, FDA believes it has complied with its burdens under the First Amendment to support mandatory disclosure of the amount of sodium above a specified level in OTC rectal drug product labeling.

IV. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). 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 would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits 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).

FDA believes that this proposed rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. As discussed in this section, the proposed rule will not be economically significant as defined by the Executive order. With respect to the Regulatory Flexibility Act, FDA does not believe the rule would have a significant economic impact on a substantial number of small entities, but FDA cannot be certain. Thus, this preamble contains FDA's regulatory flexibility analysis. The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of costs and benefits for the proposed rule, because the proposed rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation. The current inflation adjusted statutory threshold is about \$110 million.

The purpose of this proposed rule is to extend the requirement for sodium content labeling to OTC rectal drug products that contain sodium phosphates so that the information is available to individuals who need to limit their sodium intake. The proposed rule would require minor relabeling of sodium phosphates rectal products. There are fewer than five manufacturers of these products in the OTC drug marketplace. One company manufactures a

nationally branded product with the others producing private label products. One large manufacturer produces about one-half to two-thirds of the products covered by this proposed rule. Three small manufacturers account for the remainder of the market. There may be other manufacturers/marketers not identified in sources FDA reviewed, but FDA believes there are a limited number and they would be small manufacturers. FDA does not believe that this proposed rule would have a significant economic impact on small entities, using the U.S. Small Business Administration designations for this industry (750 employees). Together, the manufacturers will have to relabel fewer than 300 stockkeeping units (SKUs). The manufacturer of the nationally branded product and some private label manufacturers of these products already include sodium content information in the labeling of their products. This relabeling (addition of sodium content labeling) will impose direct one-time costs on some manufacturers. FDA has been informed that the cost to relabel these products ranges from \$500 to \$3,500. Using the conservative estimate of \$3,500 per SKU, and assuming all SKUs would need to be relabeled, the total one-time cost to relabel these products would be \$1,050,000. Actual costs will be lower because of current voluntary compliance.

Manufacturers that have not voluntarily included sodium content information may also incur one-time costs to test their products. The cost to test for one cation is about \$150 for private label manufacturers. Assuming they repeat the testing, the total one-time costs for an estimated 10 products would be \$3,000.

FDA considered but rejected several labeling alternatives: (1) A longer implementation period and (2) an exemption from coverage for small entities. A longer time period would unnecessarily delay the benefit of the new labeling

to consumers who self-medicate with these products. FDA rejected an exemption for small entities because the labeling is also needed by consumers who purchase products marketed by those entities.

This analysis shows that FDA has considered the burden to small entities. Thus, this economic analysis, together with other relevant sections of this document, serves as FDA's initial regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

FDA invites public comment regarding any substantial or significant economic impact that this proposed rule would have on manufacturers or marketers of OTC rectal drug products containing sodium phosphates. Comments regarding the impact of this proposed rule on OTC rectal drug products containing sodium phosphates should be accompanied by appropriate documentation. FDA is providing a period of 90 days from the date of publication of this proposed rule in the **Federal Register** for development and submission of comments on this subject. FDA will evaluate any comments and supporting data that are received and will reassess the economic impact of this proposed rule in the preamble to the final rule.

V. Paperwork Reduction Act of 1995

FDA tentatively concludes that the labeling requirement proposed in this document is not subject to review by the Office of Management and Budget because it does not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the proposed labeling statement is 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)).

VI. 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.

VII. Request for Comments

FDA is providing interested persons 90 days after the date of publication of this proposed rule in the **Federal Register** to submit written or electronic comments on the proposed rule and FDA's economic impact determination to the Division of Dockets Management (see **ADDRESSES**). Three copies of all written comments are to be submitted. Individuals submitting written comments or anyone submitting electronic comments may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. FDA is requesting that comments be submitted within 90 days because it wants to finalize this proposal as quickly as possible to coordinate this proposed labeling addendum with other labeling changes that are occurring for these products. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

VIII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effect on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, FDA tentatively concludes that the proposed rule

does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

IX. Proposed Effective Date

FDA proposes that any final rule based on this proposal become effective 12 months after its date of publication in the **Federal Register**.

X. Reference

The following reference is on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Enema label, OTC Vol. 090TFM3, Docket No. 78N-036L.

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, it is proposed that 21 CFR part 201 be 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, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

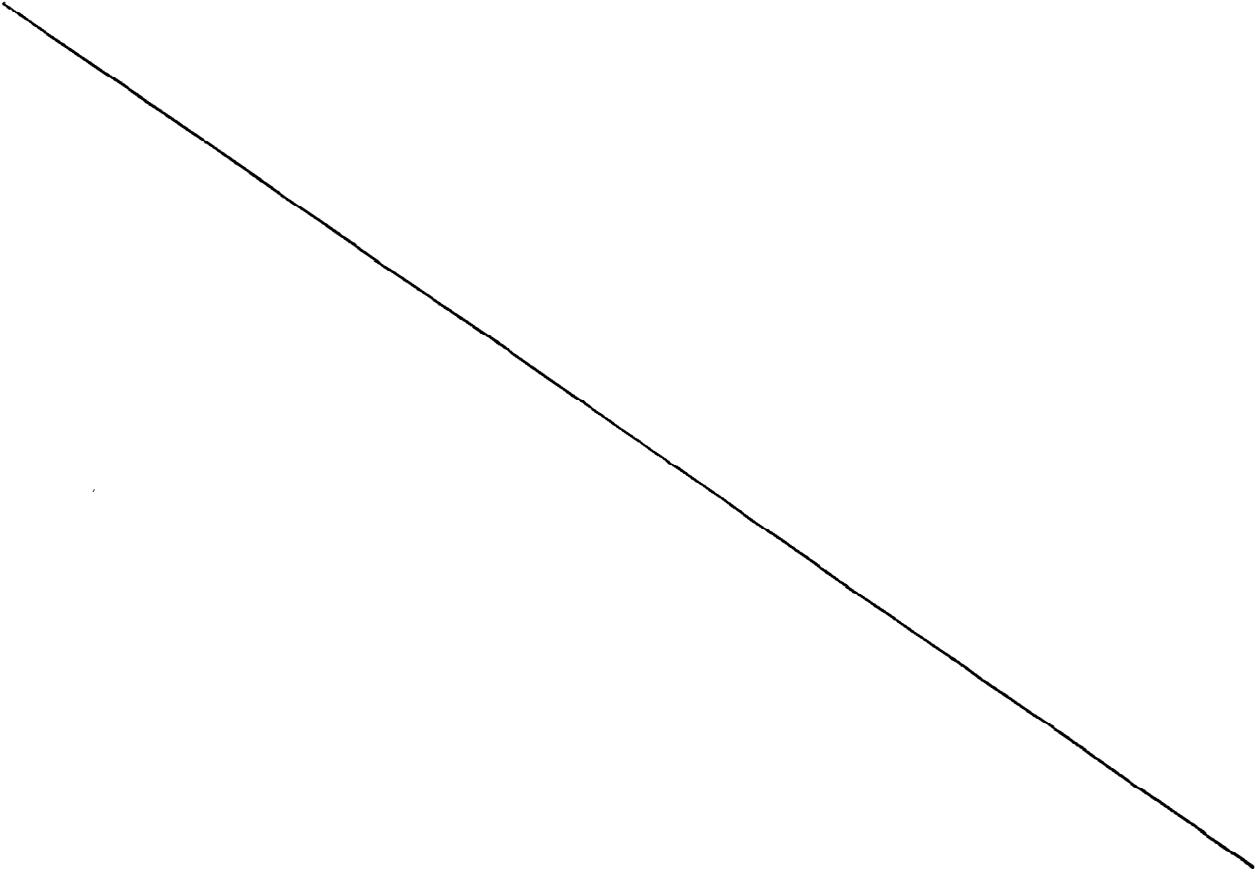
■ 2. Section 201.64 is amended by adding paragraph (k) to read as follows:

§ 201.64 Sodium labeling.

* * * * *

(k) The labeling of OTC drug products intended for rectal administration containing dibasic sodium phosphate and/or monobasic sodium phosphate

shall contain the sodium content per delivered dose if the sodium content is 5 milligrams or more. The sodium content shall be expressed in milligrams or grams. If less than 1 gram, milligrams should be used. The sodium content shall be rounded-off to the nearest whole number if expressed in milligrams (or nearest tenth of a gram if expressed in grams). The sodium content per delivered dose shall follow the heading "Other information" as stated in § 201.66(c)(7). Any product subject to this paragraph that contains dibasic sodium phosphate and/or monobasic sodium phosphate as an active ingredient intended for rectal administration and that is not labeled as required by this paragraph and that is initially introduced or initially delivered for introduction into interstate commerce after [date 12 months after date of publication in the **Federal Register**], is misbranded under sections 201(n) and 502(a) and (f) of the act.



Dated: 3/15/04
March 15, 2004.



Jeffrey Shuren,
Assistant Commissioner for Policy.

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