DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 331

[Docket No. 93N-0164]

RIN 0905-AA06

Antacid Drug Products for Over-the-Counter Human Use; Proposed Amendment of Antacid Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the final monograph for over-the-counter (OTC) antacid drug products to require specific indication, warning, and direction statements in the labeling of products containing sodium bicarbonate as an active ingredient. The new labeling would be required only for oral dosage forms intended to be dissolved in liquid prior to administration, such as powders and effervescent granules or tablets. As proposed, no such oral dosage forms containing sodium bicarbonate as an active ingredient would be allowed to make a claim for "relief of overindulgence in food and drink." The proposed warnings would alert consumers to avoid antacid drug products containing sodium bicarbonate when the stomach is overly full from eating or drinking. The proposed directions would inform consumers that sodium bicarbonate should be completely dissolved before drinking and that the recommended dose should not be exceeded. FDA is issuing this notice of proposed rulemaking after receiving reports of gastric (stomach) rupture following ingestion of sodium bicarbonate to relieve gastrointestinal distress. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by April 4, 1994; written comments on the agency's economic impact determination by April 4, 1994. The agency is proposing that any final rule that may issue based on this proposal become effective 6 months after the date of publication in the **Federal Register.**

ADDRESSES: Written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5000.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of June 4, 1974 (39 FR 19862), FDA issued a final monograph for OTC antacid drug products that established conditions in part 331 (21 CFR part 331) under which these drug products are generally recognized as safe and effective and not misbranded. Sodium bicarbonate is listed as a permitted active ingredient in § 331.11. Permitted indications for products containing sodium bicarbonate are in § 331.30 and include relief of the symptoms of "heartburn," "sour stomach," and/or "acid indigestion." In the **Federal Register** of August 31, 1982 (47 FR 38481), permitted indications for OTC antacid drug products were changed to the following: "For the relief of" (optional, any or all of the following:) "heartburn," "sour stomach," and/or "acid indigestion" (which may be followed by the optional statement:) "and upset stomach associated with" (optional, as appropriate) "this symptom" or "these symptoms." The agency recognized that "upset stomach" is a general term used by consumers to describe symptoms associated with gastric hyperacidity such as acid indigestion, heartburn, or sour stomach (47 FR 38481 at 38482).

In the **Federal Register** of November 16, 1988 (53 FR 46204), the agency published the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products (internal analgesic tentative final monograph). This proposal permitted combinations of acetaminophen and any monograph antacid ingredient and combinations of aspirin and any monograph antacid ingredient (see proposed § 343.20(b)(1) and (b)(3) (53 FR 46204 at 46255)). As proposed in § 343.60(b)(2) and (b)(4), indications for these combination products included concurrent antacid and internal analgesic symptoms (53 FR 46204 at 46258). In the same issue of the **Federal Register** (53 FR 46190), the agency proposed amendments to the final monograph for OTC antacid drug products so that the antacid and internal analgesic final monographs would be consistent. The agency proposed to revise § 331.15(b) to include antacid/acetaminophen and antacid/aspirin combinations as generally recognized as safe and effective. The agency also proposed to add a new § 331.60 (entitled "*Labeling of permitted combinations of active ingredients*") to reflect that the new combinations included in § 331.15(b) should use the indications that were proposed in § 343.60(b)(2) and (b)(4) of the internal analgesic tentative final monograph.

In the **Federal Register** of October 1, 1982 (47 FR 43540), FDA published an advance notice of proposed rulemaking for OTC orally administered drug products for relief of symptoms associated with overindulgence in alcohol and food. The notice included a report prepared by the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (the Panel). The Panel had reviewed data on drug products containing antacid, analgesic, and stimulant ingredients in various combinations and recommended conditions for their safe and effective use. The Panel concluded that the following combinations of Category I ingredients were safe and effective for use in relief of the symptoms of hangover: (1) Antacids and analgesics, (2) antacids and stimulants, (3) analgesics and stimulants, and (4) antacids, analgesics, and stimulants. The Panel also classified two ingredients, bismuth subsalicylate and sodium citrate in solution, in Category I (generally recognized as safe and effective) for relief of symptoms of upset stomach due to overindulgence in food and drink.

In the tentative final monograph for OTC orally administered drug products for relief of symptoms associated with overindulgence in food and drink, published in the **Federal Register** of December 24, 1991 (56 FR 66742), the agency recognized that the overindulgence rulemaking significantly overlaps other OTC drug monographs, including antacid (21 CFR part 331), stimulant (21 CFR part 340), and internal analgesic (proposed 21 CFR part 343). To avoid unnecessary monograph duplication, the agency proposed to amend the final monographs for OTC antacid and stimulant drug products and to amend the tentative final monograph for OTC internal analgesic drug products to include conditions for relief of hangover symptoms. Similarly, the agency found that the Panel's recommended claim for relief of symptoms of upset stomach due to overindulgence in food and drink overlaps claims in the antacid monograph. Therefore, the agency proposed to amend the final monograph for OTC antacid drug products to include appropriate conditions for relief of the symptoms of upset stomach due to overindulgence in food and drink. In a proposed amendment of § 331.30 of the antacid final monograph (56 FR

66754 at 66756, December 24, 1991), the agency proposed to add a claim for the relief of upset stomach due to overindulgence in food and drink for all antacid ingredients, including sodium bicarbonate.

Likewise, in a proposed amendment to the internal analgesic tentative final monograph (56 FR 66762 at 66764, December 24, 1991), the agency proposed to include a claim for relief of symptoms of hangover and a claim for relief of symptoms of overindulgence in food and drink for internal analgesic/antacid combinations proposed in § 343.60(b)(2) and (b)(4). At that time, the agency was not aware of the number of reports of adverse effects associated with the ingestion of sodium bicarbonate for the relief of gastrointestinal distress. These adverse effects include the possibility of stomach rupture and, in rare cases, death. (See discussion in section II of this document.) Based on a review of these reports of adverse effects, the agency is proposing labeling changes for OTC antacid drug products containing sodium bicarbonate as an active ingredient in dosage forms that are intended to be dissolved in liquid before administration. The agency considers these labeling changes necessary for the safe use of these products.

Elsewhere in this issue of the Federal Register, the agency is also proposing to amend § 343.60(b)(2) and (b)(4) of the internal analgesic tentative final monograph to include labeling indications, warnings, and directions specifically for internal analgesic/antacid combination products containing sodium bicarbonate as an active ingredient in a dosage form intended to be dissolved in liquid before administration.

II. Stomach Rupture Associated With Sodium Bicarbonate

After reviewing the literature and the case reports, the agency concludes that the ingestion of sodium bicarbonate may, under certain circumstances, induce acute gastric dilatation (stretching of the stomach beyond normal dimensions) and rupture.Sodium bicarbonate reacts with gastric acid to form sodium chloride, water, and carbon dioxide. A rapid accumulation of carbon dioxide in the stomach may occur if sodium bicarbonate is ingested before it is fully dissolved (i.e., before all the gas has evolved) (Refs. 1 through 4). In this case, an individual may not have ingested a solution of sodium bicarbonate, but rather a suspension of sodium bicarbonate, that is, partially dissolved material with the complete dissolution likely to occur inside the stomach. As long as the effervescent reaction of sodium bicarbonate continues in the stomach, carbon dioxide is produced. The increased amount of carbon dioxide may induce gastric dilatation. If the stomach is overly full, such as after ingestion of a large meal, especially with large amounts of liquids, there is limited space for expansion and a rupture can occur (Refs. 1 through 4).

A. Summary of Literature Case Reports

In 1986, Lazebnik, Iellin, and Michowitz (Ref. 5) reviewed eight cases of rupture of the normal stomach following ingestion of sodium bicarbonate. The cases had been reported from 1926 to 1986. Seven of these cases had previously been reported individually in the literature (Refs. 6 through 12). Six cases involved overindulgence in food and/or alcoholic beverages, while in two cases, no meal was ingested. However, in one case where no meal was ingested, the subject drank an entire bottle of citrate of magnesia prior to ingestion of sodium bicarbonate. Although in most cases the person took higher than recommended doses of the antacid, in some cases the person took smaller amounts. In some cases, it is not clear whether the sodium bicarbonate was taken directly without mixing with liquid or was taken as a solution or suspension. All of the people who experienced gastric rupture in 1963 or earlier died. In the more recent cases, the people underwent repair of the ruptured stomach. Although serious complications, such as formation of abscesses, atelectasis, and gastric fistula occurred, in all of the cases occurring after 1963, the people survived.

Brismar, Strandberg, and Wiklund (Ref. 13) reported a case of spontaneous stomach rupture after ingestion of sodium bicarbonate that took place in Sweden in 1986. A 43-year-old male consumed a large meal consisting of new potatoes, herring pickled in vinegar, and aerated water. At the end of this meal, the man ingested approximately 30 grams (g) of sodium bicarbonate. (The report does not describe the method of administration.) Immediately afterwards he experienced a rapidly increasing sensation of filling, with abdominal distention, very severe abdominal pain, and a sensation that something had "burst" in his abdomen. He was transported to the hospital and was found to have a 5-centimeter (cm)-long rupture on the posterior aspect of his stomach close to the lesser curvature. The authors state that at the recommended dose of sodium bicarbonate, corresponding to approximately 1.8 g, only 20 milliliters (mL) of gas is released within 3 minutes. However, if 8.4 g of sodium bicarbonate is added to the same volume of gastric juice (1,000 mL with a concentration of 100 milliequivalents (meq) per liter (L)), 470 mL of gas will be produced. The ingestion of 30 g of sodium bicarbonate resulted in enormous gas development with resultant stomach rupture.

In 1989, Downs and Stonebridge (Ref. 14) reported a case of stomach rupture in Scotland in which a 70-year-old man took 2 teaspoons (12 g) of sodium bicarbonate in water following a large meal. His abdomen rapidly distended, becoming tense and uncomfortable. He experienced increasing difficulty in breathing and could neither vomit nor belch. This was followed by a severe, sudden epigastric pain, as though "something had burst." A 6-cm tear on the anterior surface of the lesser curvature of the stomach had occurred. The authors estimated that the approximate volume of gas produced from the chemical reaction of 12 g of sodium bicarbonate is 3.4 L, approaching the 4 L estimate necessary to cause stomach rupture.

B. Summary of Case Reports

The agency has identified a total of 29 cases of adverse effects associated with the ingestion of sodium bicarbonate for the relief of gastrointestinal distress. These cases were obtained from a search of the FDA Spontaneous Reporting System (SRS), a literature review, and voluntary submissions from a manufacturer covering the period from 1926 to May 1993. Included in this total are 21 cases of stomach rupture. Death occurred in five of these cases. All of these case reports are on file in the Dockets Management Branch (Refs. 15 and 16). The agency's summary of these case reports follows.

In August 1979 a 52-year-old male ate a large meal and consumed several alcoholic beverages. Shortly after going to bed, he awakened with indigestion. He then mixed a teaspoon of baking soda with a small amount of water, drank the mixture, and less than a minute later collapsed in agony because of sudden onset of severe abdominal pain. An exploratory laparotomy revealed a 6-cm tear in the stomach extending from the gastroesophageal junction down the lesser curvature of the stomach.

In the second case report (June 1981), a 31-year-old male ingested a large Mexican meal, felt uncomfortable, put one dosage (amount unknown) of baking soda in a glass with water, and quickly drank the mixture. He immediately experienced severe, intense abdominal

pain, could neither vomit nor belch, and his abdomen became markedly distended. Exploratory surgery revealed a 5-cm linear tear along the lesser curvature of the stomach.

The third case report (April 1982) involved a 56-year-old female who had been on a liquid protein diet for 1 month prior to her hospitalization. She ate a large dinner accompanied by champagne and bicarbonate of soda. No information was provided on the amount of the dose or how it was taken. She was admitted to the hospital with acute abdominal pain, and exploratory laparotomy revealed a 12-cm tear extending from the distal esophagus onto the posterior aspect of the lesser curvature of the stomach. The size of the gastric tear was so big that it allowed the extrusion of gastric contents into the peritoneal cavity. It is conceivable that in this case the patient's stomach had been modified and even became atrophic because of the liquid diet and, thereby, sustained more damage as a consequence of the sodium bicarbonate-induced distention.

The fourth case report (December 1983) involved a 37-year-old male who developed progressive abdominal pain after dinner. He drank soda with some sodium bicarbonate and then experienced severe chest and back pain, and shock. At laparotomy, a tear of the stomach just below the gastroesophageal juncture was found. In this case, the ingestion of soda and sodium bicarbonate may have aggravated the situation because soda is very acidic and produces carbon dioxide in addition to that produced by the sodium bicarbonate.

The fifth case report (October 1984) involved a 42-year-old male with a history of slight burning epigastric pain an hour following heavy meals and exacerbated by strong foods such as onions, cabbages, and spicy foods. On the night of his admission to the hospital, he had eaten a large meal of hot, spiced chili and then promptly ingested two beers. He then ingested bicarbonate of soda and experienced a spontaneous onset of abdominal pain. An exploratory laparotomy revealed a perforation along the lesser curvature of the stomach. Initially, this case appeared to be one of a perforated gastric or duodenal ulcer, but during the ensuing operation and under subsequent microscopic examination, no ulcer was found.

The sixth case report (December 1988) describes a 23-year-old male who had increasingly severe abdominal pain with subsequent vomiting after eating a spaghetti dinner. At some time the subject took sodium bicarbonate, but there was no information on how much was ingested, whether it was completely dissolved, how much water was taken with it, or exactly when it was taken. However, on exploratory laparotomy, a 6- to 7-cm linear tear in the lesser curvature of the stomach was found.

The seventh report (June 1989) involved a 37-year-old male who experienced heartburn, for which he took a bismuth subsalicylate-containing product. He then developed severe diffuse abdominal pain. On the trip to the emergency room, he stated that he had eaten a lot of food and had taken some baking soda when the pain became very severe. However, that statement is the only indication in the medical records that the subject ingested sodium bicarbonate prior to his injury. Thus, there is some question whether sodium bicarbonate ingestion actually occurred in this case.

The eighth case report (July 1991) involved a 39-year-old male with no previous history of gastrointestinal disease. He had a large Mexican meal and developed epigastric distress for which he took some sodium bicarbonate. When his sleep was interrupted by continuing epigastric distress, he arose and took at least 2 tablespoons of sodium bicarbonate. (This amount is higher than the recommended dose.) Within 2 minutes, he experienced an acute onset of severe epigastric pain. An exploratory laparotomy revealed a 4-cm perforation on the lesser curvature of the stomach. Neither the surgeon nor the pathologist could definitely document the presence of an ulcer. However, the patient did have a moderate narrowing of the pylorus due to mucosal scarring. Because this condition interfered with gastric emptying, it may have contributed to the reported problem.

C. Additional Data

In December 1990, a probability sample survey was conducted to determine the number of doses of sodium bicarbonate taken by American adults annually to settle an upset stomach (Ref. 17). In this survey, 20 percent of the U.S. adult population 18 years of age and older answered affirmatively when asked if they ever use baking soda or bicarbonate of soda to help settle an upset stomach. Based on an estimated adult population of 186.4 million, the survey indicated that 37.3 ± 6.5 million adults used sodium bicarbonate for an upset stomach. The average (mean) frequency with which these people use bicarbonate is 19.7 times during a 1-year period, which indicates that 734.8 million doses of sodium bicarbonate are taken by American adults annually (S.D. 235.8 million). Further statistical analysis revealed that the median dose frequency was five times per year per user.

An independent estimate of doses of sodium bicarbonate ingested per year calculated from the weight of consumer baking soda sold each year and the amount used by consumers for indigestion, as gauged by consumer surveys, was also provided to the agency (Ref. 18). Although not identical, the number of doses estimated, based on this information, is within the range of the survey discussed above. Regardless of the method of calculation used, the agency concludes that the number of doses-per-year of sodium bicarbonate is very large.

The agency also considers the 21 identified cases of gastric rupture that have occurred in association with sodium bicarbonate to be a very serious but uncommon event. The agency is proposing changes in the labeling of OTC drug products containing sodium bicarbonate so that such products can be used safely and the incidence of untoward effects reduced to the lowest possible levels.

III. Additional Agency Concerns

In addition to the serious adverse reactions described above, the agency has identified several other problems that could occur when sodium bicarbonate is used as an OTC antacid. These include systemic metabolic alkalosis, occurrence of milk-alkali syndrome, increased sodium load for certain susceptible individuals, and the overall risk-to-benefit ratio of sodium bicarbonate as an OTC antacid drug product.

Sodium bicarbonate is readily absorbed and may produce systemic metabolic alkalosis and/or sodium overload, particularly if taken in large doses or for a prolonged period of time. Rapid alkalization may precipitate tetany in people having hypocalcemia and cause cardiotoxicity and paralysis in people having hypokalemia (Refs. 1, 2, 3, and 19 through 24). These occurrences can be life-threatening medical emergencies. The agency is aware of one death attributed to complications resulting from severe metabolic alkalosis caused by ingestion of sodium bicarbonate (Ref. 19). In this case, a 45-year-old man was admitted to an emergency room in alert and stable condition but complaining of burning pain in his arms and legs. He admitted taking baking soda for epigastric pain over the past several days. Although the total amount consumed was not ascertained, the man had a half empty 8-ounce box of baking soda in his

pocket. Shortly after admission, the man had a sudden, unexpected cardiopulmonary arrest. During this period, no medications were given (including sodium bicarbonate). A diagnosis of severe metabolic alkalosis was made after laboratory results revealed a primary elevation in serum bicarbonate concentration. The man remained comatose and died (due to infectious complications) 14 days after admission.

Large doses or chronic administration of sodium bicarbonate with milk or calcium may lead to an increase in calcium absorption and may precipitate the milk-alkali syndrome. This syndrome is characterized by hypercalcemia, reduced secretion of parathyroid hormone, retention of phosphate, precipitation of calcium salts in the kidney, alkalosis, and renal insufficiency or failure. Symptoms include nausea, vomiting, headache, mental confusion, and anorexia. This may be particularly important in pregnancy where milk or calcium intake is emphasized (Refs. 1, 2, 3, and 25).

Each g of sodium bicarbonate contains 12 meq of sodium. This large quantity may cause problems for people who are pregnant, on low-salt diets, receiving diuretics, or have a tendency toward fluid overload (Ref. 2). Even moderate amounts of sodium bicarbonate may expand plasma volume, increase blood pressure, and lead to edema (Ref. 1). The final monograph for OTC antacid drug products limits the daily dosage for sodium to 200 meq for persons up to 60 years old and to 100 meq for persons 60 years or older. Limitations for bicarbonate ion are also 200 meq for persons up to 60 years old and 100 meq for persons 60 years or older. (See § 331.11(b) and (k)(1).)

Because of the potential severity of the adverse effects of sodium bicarbonate, the agency is concerned that the risk to consumers from ingestion of sodium bicarbonate in antacid doses may outweigh the benefit. There are many other OTC antacid ingredients currently available that do not pose the possibility of such serious side effects. Based on the concerns discussed above, the agency is considering the need for additional changes and/or additions to the indications and/or warnings provided for sodium bicarbonate in the antacid monograph (21 CFR part 331).

For example, the agency has concerns how the presently allowed portion of the indications in § 331.30(b) that mentions "upset stomach" may be confusing to consumers in light of the new warning being proposed in this document. The agency questions whether consumers will be able to recognize that sodium bicarbonate should not be used to relieve an "upset stomach" caused by excessive eating or drinking. The agency invites specific comment on how the indications for sodium bicarbonate antacid products might be changed and on any of the other issues discussed above or any additional issues that relate to the safe and effective use of sodium bicarbonate as an OTC antacid drug product. For example, the agency notes that a major manufacturer of baking soda currently voluntarily labels its product with warnings similar to those proposed in this document (Ref. 26).

References

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(14) Downs, N. M., and P. A. Stonebridge,"Gastric Rupture Due to Excessive SodiumBicarbonate Ingestion," *Scottish Medical Journal*, 34:534–535, 1989.

(15) Medical records submitted by Church & Dwight Co., Inc., included in OTC Vol. 01AM2, Docket No. 93N–0164, Dockets Management Branch.

(16) Memorandum from M. Chen, FDA, to W. Gilbertson, FDA, dated December 1, 1991, in OTC Vol. 01AM2, Docket No. 93N–0164 Dockets Management Branch.

(17) Survey Center, Inc., "Use of Soda Bicarbonate to Settle an Upset Stomach," draft of unpublished consumer survey in OTC Vol. 01AM2, Docket No. 93N–0164, Dockets Management Branch.

(18) Letter from W. Sorenson, Church & Dwight Co., Inc., to H. Gallo-Torres, FDA, dated April 23, 1992, copy included in OTC Vol. 01AM2, Docket No. 93N–0164, Dockets Management Branch.

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(24) "Drug Evaluations," 6th ed., American Medical Association, Chicago, p. 833, 1986.

(25) "Drug Evaluations Subscription,"Vol. 2, American Medical Association, Chicago, p.1–18, Spring 1990.

(26) Copy of labeling for Arm & Hammer Baking Soda in OTC Vol. 01AM2, Docket No. 93N–0164, Dockets Management Branch.

IV. The Agency's Proposal for Revised Labeling for Sodium Bicarbonate in OTC Antacid Drug Products

The case reports have shown that the ingestion of sodium bicarbonate may cause gastric dilatation and rupture of the stomach, particularly if the stomach is overly full from food or drink. The reports indicate that this problem occurs with dosage forms intended to be dissolved in liquid before administration, e.g., powders or effervescent granules or tablets. In some cases, the person drank a solution or suspension of sodium bicarbonate, while in other cases the person ingested the sodium bicarbonate in a dry form. The agency is aware of OTC antacid drug products in chewable tablet dosage form, in which sodium bicarbonate is an inactive ingredient. However, the agency is not aware of any reports of gastric dilatation and stomach rupture resulting from ingestion of these

products. Accordingly, the agency is proposing to amend § 331.30 to include specific indication, warning, and direction statements for all OTC antacid drug products containing sodium bicarbonate as an active ingredient in dosage forms intended to be dissolved in liquid before administration. Separate indications are proposed in § 331.30(b) for products that either do or do not contain sodium bicarbonate as an active ingredient intended to be dissolved in liquid before administration. Antacid products containing sodium bicarbonate as an active ingredient will not be allowed to include a claim for relief of overindulgence in food and drink. In addition, the agency is proposing that these sodium bicarbonate products bear new warnings and directions.

Because of the potential serious health risk involved, the agency is proposing that the new warnings appear after the header "STOMACH WARNING." Portions of the new warnings must appear in bold print and in capital letters. The proposed warnings read as follows:

"To avoid serious injury, do not take until" (insert product dosage form, e.g., "tablet," "powder") "is completely dissolved. It is very important not to take this product when overly full from food or drink. [first two sentences in boldface type and all capital letters] Consult a doctor if severe stomach pain occurs after taking this product."

Additional directions, proposed to appear after the header "DIRECTIONS," read as follows:

"Dissolve completely in water" [*For effervescent dosage forms add*: "and be sure all bubbling has stopped"] "before drinking. Do not exceed recommended dose. [second sentence in boldface type and all capital letters] See Warnings."

The agency has examined the economic consequences of this proposed rulemaking and has determined that it does not require either a regulatory impact analysis, as specified in Executive Order 12866, or a regulatory flexibility analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96-354). This rulemaking for OTC antacid drug products containing sodium bicarbonate as an active ingredient is not expected to have an impact on small businesses. The final rule will impose direct one-time costs associated with changing product labels, but that cost is estimated to be less than $1 million. Also, there appears to be a limited number of products involved. Further, a major manufacturer of baking soda currently voluntarily labels its product with statements similar to those proposed in this amendment. Manufacturers will have 6 months after the date of publication of the final rule in which to implement this relabeling. However, manufacturers of OTC antacid drug products are encouraged to voluntarily implement this labeling as of the date of publication of this proposal, subject to the possibility that FDA may change the wording as a result of comments filed in response to this proposal. Because FDA is encouraging the proposed labeling changes to be used on a voluntary basis at this time, the agency advises that manufacturers will be given ample time after publication of a final rule to use up any labeling implemented in conformance with this proposal. The impact of the proposed rule, if implemented, appears to be minimal. Therefore, the agency concludes that the proposed rule is not a major rule as defined in Executive Order 12866. Further, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC antacid drug products. Types of impact may include, but are not limited to, costs associated with relabeling or repackaging.

Comments regarding the impact of this rulemaking on OTC antacid drug products should be accompanied by appropriate documentation. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined under 21 CFR 25.24(c)(6) 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.

Interested persons may, on or before April 4, 1994, submit written comments on the proposed regulation and the agency's economic impact determination to the Dockets Management Branch (address above). Three copies of all comments are to be submitted, except that individuals may submit one copy. Comments should 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. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 331

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 part 331 be amended as follows:

PART 331—ANTACID PRODUCTS FOR OVER-THE-COUNTER (OTC) HUMAN USE

1. The authority citation for 21 CFR part 331 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

2. Section 331.30 is amended by revising paragraph (b), and by adding new paragraphs (c)(8), (e)(1), and (e)(2) to read as follows:

§ 331.30 Labeling of antacid products.

* * * * *

(b) *Indications.* The labeling of the product states under the heading "Indications," any of the phrases listed in this paragraph, as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For products containing active ingredients identified in § 331.11(a) through (j), (k)(2), (l), and (m).* "For the relief of" (select any or all of the following: "heartburn," "sour stomach," and/or "acid indigestion") which may be followed by the statement: "and upset stomach associated with" (select one or more of the following, as appropriate: "this symptom," "these symptoms," or "overindulgence in food and drink.")]

(2) *For products containing sodium bicarbonate as an active ingredient in a dosage form intended to be dissolved in liquid before administration identified in § 331.11(k)(1).* "For the relief of" (select any or all of the following: "heartburn," "sour stomach," and/or "acid indigestion") (which may be followed by the statement: "and upset stomach associated with" (select one of the following, as appropriate: "this symptom" or "these symptoms".)) These products may not bear any claims that relate to use for "overindulgence in food and drink."

(c) * * *

(8) For products containing sodium bicarbonate as an active ingredient in a dosage form intended to be dissolved in liquid before administration identified in § 331.11(k)(1), portions of the warning statements must appear in bold print and in capital letters as follows: "STOMACH WARNING: To avoid serious injury, do not take until" (insert product dosage form, e.g., "tablet," "powder") "is completely dissolved. It is very important not to take this product when overly full from food or drink. [first two sentences in bold print and all capital letters] Consult a doctor if severe stomach pain occurs after taking this product."

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(e) * * *

(1) The labeling for products containing sodium bicarbonate as an active ingredient in a dosage form intended to be dissolved in liquid before administration identified in § 331.11(k)(1) contains the following additional directions: "Dissolve completely in water" [*For effervescent dosage forms add*: "and be sure bubbling has stopped"] "before drinking. Do not exceed recommended dose. [second sentence in bold print and all capital letters] See Warnings."(2) [Reserved]

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Dated: November 3, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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