

**DEPARTMENT OF HEALTH AND HUMAN SERVICES****Food and Drug Administration****21 CFR Parts 201 and 331**

[Docket No. 95N-0254]

RIN 0910-AA63

**Labeling of Orally Ingested Over-the-Counter Drug Products Containing Calcium, Magnesium, and Potassium**

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

**SUMMARY:** The Food and Drug Administration (FDA) is proposing to amend the general labeling provisions for over-the-counter (OTC) drug products to require that the labeling of all OTC drug products intended for oral ingestion include the calcium content per dosage unit when the product contains 20 milligrams (mg) or more per single dose; a warning statement that persons with kidney stones and persons on a calcium-restricted diet should not take the product unless directed by a doctor when the product contains more than 3.2 grams (g) of calcium in the labeled maximum daily dose; the magnesium content per dosage unit when the product contains 8 mg or more per single dose; a warning statement that persons with kidney disease and persons on a magnesium-restricted diet should not take the product unless directed by a doctor if the product contains more than 600 mg magnesium in the labeled maximum daily dose; the potassium content per dosage unit when the product contains 5 mg or more per single dose; and a warning statement that persons with kidney disease and persons on a potassium-restricted diet should not take the product unless directed by a doctor if the product contains more than 975 mg potassium in the labeled maximum daily dose. The agency is proposing that the calcium, magnesium, and potassium content be labeled in mg per dosage unit, rounded to the nearest whole number. FDA is issuing this notice of proposed rulemaking in order to provide uniform calcium, magnesium, and potassium content and warning labeling for all OTC drug products intended for oral ingestion whether marketed under an OTC drug monograph, an approved application, or no application.

**DATES:** Written comments by July 22, 1996. Written comments on the agency's economic impact determination by July 22, 1996. The agency is proposing that any final rule based on this proposal be

effective 12 months after the date of its publication in the *Federal Register*.

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

**FOR FURTHER INFORMATION CONTACT:** William E. Gilbertson, Center for Drug Evaluation and Research (HFD-105), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2304.

**SUPPLEMENTARY INFORMATION:****I. Background****A. Calcium**

In the advance notice of proposed rulemaking for OTC antacid drug products (38 FR 8714 at 8718, April 5, 1973), the Advisory Review Panel on OTC Antacid Drug Products (Antacid Panel) concluded that calcium carbonate is safe when taken in a dosage of not more than 160 milliequivalents (mEq) of calcium (8 g calcium carbonate) per day. The Antacid Panel stated that hypercalcaemia in response to calcium ingestion is not rare in the population and the danger of renal stone formation has to be considered in determining the intake of calcium-containing antacids.

The maximum daily dose for calcium carbonate or calcium phosphate in § 331.11(d) (21 CFR 331.11(d)) of the antacid monograph is 160 mEq (e.g., 3.2 g calcium). This amount of calcium is contained in 8.0 g calcium carbonate, 18.7 g monobasic calcium phosphate, and 8.3 g tribasic calcium phosphate. The warning in § 331.30(c)(1) (21 CFR 331.30(c)(1)) states: "Do not take more than (maximum recommended daily dosage \* \* \*) in a 24-hour period, or use the maximum dosage of this product for more than 2 weeks, except under the advice and supervision of a physician."

In the advance notice of proposed rulemaking for OTC digestive aid drug products (47 FR 454 at 469, January 5, 1982), the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (Miscellaneous Internal Panel) stated that adverse reactions associated with calcium carbonate, including alkalosis, hypercalcaemia, acid rebound, milk-alkali syndrome, and constipation, usually occur with ingestion of larger than recommended doses and/or with chronic ingestion. The Miscellaneous Internal Panel stated that some antacids decrease the effectiveness of many other drugs. The Miscellaneous Internal Panel recommended the following labeling for drug products containing calcium

carbonate: (1) "If you are taking other drugs, consult your physician as this drug may interfere with their effectiveness," and (2) "Do not take for longer than 2 weeks or in greater than recommended amounts, except on the advice of a physician." However, these warnings were never finalized because no calcium salt attained monograph status as an active ingredient for use as an OTC digestive aid drug product.

**B. Magnesium**

In the advance notice of proposed rulemaking for OTC antacid drug products (38 FR 8714 at 8719), the Antacid Panel stated that in normal renal function it is difficult to reach excessive magnesium blood levels via the oral route, because magnesium enters and leaves the cells rapidly. However, the Antacid Panel stated that hypermagnesaemia toxicity may occur in renal dysfunction and therefore a warning is necessary. The Antacid Panel concluded that for those products in which the maximal daily dose exceeds 50 mEq of magnesium, the labeling should state: "Do not use this product if you have kidney disease except under the advice and supervision of a physician."

In the final monograph for OTC antacid drug products (39 FR 19862 at 19868, June 6, 1974), the agency noted that at some of its early meetings the Antacid Panel initially considered 150 mEq per day of magnesium as the level for requiring a warning, but upon reconsideration reduced the amount to 50 mEq. The Antacid Panel gave several reasons for lowering this level: (1) The normal individual consumes from 20 to 40 mEq of magnesium per day and about one-third of that amount is absorbed into the body; (2) if a person is taking a magnesium-containing antacid, approximately 15 to 30 percent of that magnesium is absorbed, and (3) if a person does not have normal renal function, it is possible to have hypermagnesaemia toxicity, i.e., the level of magnesium in the body may reach a toxic level.

The final monograph for OTC antacid drug products includes a warning in § 331.30(c)(4) for products containing more than 50 mEq of magnesium in the recommended daily dosage, which states: "Do not use this product except under the advice and supervision of a physician if you have kidney disease." Although persons with normal renal function can easily tolerate more than 50 mEq of magnesium a day, the agency included this warning in the monograph because large doses of an antacid could present a serious problem for

individuals with reduced renal function.

In the advance notice of proposed rulemaking for OTC laxative drug products (56 FR 12902 at 12905, March 21, 1995), the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products (Laxative Panel) stated that OTC laxative drug products containing more than 50 mEq (600 mg) magnesium in the maximum recommended daily dose should include a warning which states that people with kidney disease should not use the product except under the advice and supervision of a physician. In the **Federal Register** of January 15, 1985 (50 FR 2124 at 2153), the agency published a tentative final monograph for OTC laxative drug products that included the warning recommended by the Laxative Panel. This rulemaking has not been completed at this time.

In the advance notice of proposed rulemaking for OTC digestive aid drug products (47 FR 454 at 471), the Miscellaneous Internal Panel stated that high serum magnesium levels may result from magnesium ingestion by persons with kidney damage. The Miscellaneous Internal Panel agreed with the Antacid Panel that a warning statement should be present on any magnesium hydroxide preparation (47 FR 470) and on any magnesium trisilicate preparation (47 FR 471) for which the maximal daily dose exceeds 50 mEq (600 mg) of magnesium. The Miscellaneous Internal Panel also stated that magnesium hydroxide has the potential for drug interactions with certain anticoagulants and antibiotics. Similarly, the Miscellaneous Internal Panel noted that magnesium trisilicate absorbs various alkaloids and antibiotics in vitro. However, this warning was never finalized because no magnesium salt attained monograph status as an active ingredient for use as an OTC digestive aid drug product.

#### C. Potassium

In the advance notice of proposed rulemaking for OTC antacid drug products (38 FR 8714 at 8719), the Antacid Panel stated that hyperkalemia is rare for normal persons who can easily tolerate the potassium content of antacid drug products. The Antacid Panel concluded, however, that potassium can accumulate in the body of persons with impaired renal function and exert toxic effects. The Antacid Panel recommended the following warning for products containing more than 25 mEq (975 mg) potassium in the maximum recommended daily dose: "Do not use this product if you have kidney disease except under the advice

and supervision of a physician." This warning appears in § 331.30(c)(6) of the antacid final monograph, slightly rephrased to read: "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

In the advance notice of proposed rulemaking (56 FR 12902 at 12905), the Laxative Panel recommended that if a laxative product contains more than 25 mEq (975 mg) of potassium in the maximum recommended daily dose, the labeling should advise consumers with kidney disease not to use the product except under the advice and supervision of a physician. The agency is aware that some effervescent laxative drug products contain significant amounts of potassium as inactive ingredients. The Laxative Panel recommended that the inactive ingredients be listed (with or without the amounts) for OTC laxative drug products and that the availability of sodium, potassium, and magnesium in the maximum recommended daily dose be stated in the labeling. The Laxative Panel noted that certain inactive ingredients (including calcium hydroxide and potassium carbonate) are added to some laxative preparations to enhance their formulation or to contribute to the effervescent qualities.

In the tentative final monograph for OTC laxative drug products (50 FR 2124 at 2153), the agency agreed with the Laxative Panel's recommendation and proposed the following warning for those products containing more than 975 mg potassium in the maximum recommended daily dose: "Do not use this product if you have kidney disease unless directed by a doctor." This rulemaking has not been completed at this time.

#### D. Rulemaking for Sodium Labeling of OTC Drug Products

The agency has already addressed sodium labeling in a final rule published elsewhere in this issue of the **Federal Register**. That rule amends the general labeling provisions for OTC drug products to include sodium labeling and provides for across-the-board uniform sodium content and warning labeling for all OTC drug products intended for oral ingestion. New § 201.64 requires sodium content labeling of all products containing 5 mg or more sodium per single recommended dose and requires that products containing more than 140 mg sodium per maximum recommended daily dose be labeled with a general warning that states: "Do not use this product if you are on a sodium-restricted diet unless directed by a doctor." Section 201.64 also provides

for the voluntary use of certain descriptive terms ("sodium free," "very low sodium," and "low sodium"). These descriptive terms are the same terms used to describe sodium content in food labeling.

Sodium content is expressed in mg per single dosage unit (e.g., tablet, teaspoonful), rounded-off to the nearest whole number, and includes the total amount of sodium regardless of the source (both active and inactive ingredients). OTC drug products "intended for oral ingestion" also include gum and lozenge dosage forms, but do not include dentifrices, mouthwashes, or mouth rinses. Because some OTC drug products not intended for oral administration can contain very high levels of sodium that may be absorbed from both active and inactive ingredients, the agency has asked for comments from interested individuals on whether the final rule should be amended to include sodium labeling for OTC rectal, vaginal, dentifrice, mouthwash, and mouth rinse drug products. The agency will address this subject in a future issue of the **Federal Register**.

Two comments received to the tentative final monograph for OTC laxative drug products contended that sodium labeling of OTC laxative and other drug products should be consistent with FDA's food labeling terminology. The comments stated that food products already bear FDA terminology and the food terminology will become the dominant system. Thus, other mandatory FDA labeling systems should be made consistent with that system. The agency has used this approach in the final rule for sodium labeling of OTC drug products published elsewhere in this issue of the **Federal Register**.

#### E. Food Labeling Regulations

FDA regulations for food products address calcium and magnesium labeling. Section 101.9 (21 CFR 101.9) requires the labeling of food products to declare the content, as a percent of the Reference Daily Intake (RDI), of calcium, iron, vitamin C, and vitamin E. Other vitamins and minerals for which a RDI has been established, including magnesium, may be listed voluntarily, unless they are added as a nutrient supplement or a claim is made about them, in which case they must be declared.

Section 101.9(c)(5) provides for the voluntary declaration of potassium content in a labeled serving size. However, when a claim is made about potassium, the declaration is mandatory and is placed on the nutrition label

immediately following the sodium content. When the potassium content is less than 5 mg per serving, the content is expressed as zero.

Vitamins and minerals, other than calcium, iron, vitamin C, and vitamin E, present at less than 2 percent of the RDI are not required to be declared in nutrition labeling but may be declared as zero or by use of an asterisk referring to a footnote that states, "Contains less than 2% of the Daily Value of this (these) nutrient (nutrients)" (§ 101.9(c)(8)(iii)). The RDI for calcium is 1,000 mg and for magnesium is 400 mg (§ 101.9(c)(8)(iv)). Thus, for foods containing less than 20 mg of calcium per serving, a declaration of zero is required on the nutrition label. For foods containing less than 8 mg of magnesium per serving, content declaration is not required (unless a claim is made about the nutrient) or may be declared as zero or as less than 2 percent of the Daily Value.

The regulations in § 101.36(b)(3) (21 CFR 101.36(b)(3)) for nutrition labeling of dietary supplements of vitamins and minerals require that potassium be declared except when present in quantitative amounts by weight that allow a declaration of zero.

The regulations for health claims related to calcium and osteoporosis in § 101.72(c)(2)(i)(E) (21 CFR 101.72(c)(2)(i)(E)) require the labeling of food products to state that a total dietary intake greater than 2,000 mg of calcium has no further known benefit to bone health. This requirement applies when the food or supplement contains more than 400 mg of calcium per reference amount. A recently published NIH Consensus Statement on optimal calcium intake states that up to a total intake of 2,000 mg per day appears to be safe in most individuals ("Optimal Calcium Intake," NIH Consensus Statement, 12(4):1-31, June 6-8, 1994).

## II. The Agency's Tentative Conclusions on Labeling of Orally Ingested OTC Drug Products Containing Calcium, Magnesium, and Potassium

### A. Basis for Rulemaking

FDA believes that the public interest in, and the public health consequences of, calcium, magnesium, and potassium intake have produced a need for more informative and consistent labeling information for these ingredients in OTC drug products. The agency believes certain labeling requirements are needed to alert persons with renal failure, kidney stones, or other conditions, and persons taking other medications who wish to monitor their intake of calcium, magnesium, and

potassium. Consumers need to consider their intake from foods, dietary supplements, and drugs. Therefore, the agency is proposing calcium, magnesium, and potassium content and warning labeling for all OTC drug products intended for oral ingestion that contain certain levels of these ingredients (including both active and inactive ingredients).

### B. Criteria for Content and Warning Labeling

In order to establish uniform content declarations and warnings relating to calcium, magnesium, and potassium for orally ingested OTC drug products and to establish content labeling similar to that used in food labeling, the agency is proposing to adopt: (1) 20 mg of calcium, 8 mg of magnesium, and 5 mg of potassium as the amount per single recommended dose in an OTC drug product (which may involve one or more dosage units, e.g., tablets, teaspoonsful, etc.) that requires a content declaration; and (2) 3.2 g calcium, 600 mg magnesium, and 975 mg potassium as the amounts present in the maximum labeled daily dose above which a warning is required. The agency is therefore proposing to amend the general drug labeling provisions in part 201 (21 CFR part 201) to include these labeling requirements for OTC drug products intended for oral ingestion.

The proposed levels for requiring content labeling are similar to those used in food labeling. In contrast, the proposed levels for requiring warnings are based on recommendations of FDA advisory review panels in the early 1970's. The agency acknowledges that there may be more recent scientific information to consider in setting requirements for OTC drug product labeling. The agency specifically encourages comment and data on this aspect of the proposal.

### C. Basis for Amount Requiring Content Labeling

#### 1. Calcium and Magnesium Content

As stated in section I.E. of this document, a serving of food containing 20 mg or more of calcium requires a content declaration, and a serving of food containing 8 mg or more of magnesium (if added as a supplement or if a claim is made) requires a content declaration in the nutrition labeling of foods. Thus, the agency is using 20 mg calcium and 8 mg magnesium per single recommended dose as the amounts at which OTC drug products should include content labeling for these ingredients.

#### 2. Potassium Content

As noted in section I.E. of this document, potassium labeling for foods is optional unless a claim is made about the potassium content; but, if declared, it is expressed in mg per serving for those foods containing 5 mg or more. In § 201.64(a) of the final rule for sodium labeling of OTC drug products, the agency required a declaration of the sodium content for all OTC drugs intended for oral ingestion if the sodium content per single recommended dose is 5 mg or more. The agency believes it is not necessary to declare potassium amounts below 5 mg per dose. However, the agency believes it is appropriate to declare the potassium content if the product contains 5 mg or more per single recommended dose.

### D. Basis for Amount Requiring Warning Statements

The agency believes that for uniformity in labeling, warnings should be required across-the-board for calcium, magnesium, and potassium for those OTC drug products intended for oral ingestion containing a certain concentration of these ingredients.

#### 1. Calcium Warning

Based on the current requirements in the monograph for OTC antacid drug products and the recommendations of the Miscellaneous Internal Panel (see section I.A. of this document), the agency is proposing to require the following warning for all OTC drug products containing more than 3.2 g calcium (equivalent to 8 g calcium carbonate) per labeled maximum daily dose: "Do not use this product if you have kidney stones or if you are on a calcium-restricted diet unless directed by a doctor." The NIH Consensus Statement on optimal calcium intake suggests that a 2,000 mg total daily intake is safe, but it does not give a definitive conclusion as to what level is unsafe. When the 3,200 mg daily dosage level, proposed as the level requiring a warning, is added to the 1,000 mg recommended daily intake that may be included in a person's diet, the resulting 4,200 mg daily intake is considerably higher than the 2,000 mg level found to be safe in the NIH consensus statement. The agency invites comments on whether the proposed 3.2 g level requiring a warning should be lowered.

#### 2. Magnesium Warning

The agency is proposing to require the following warning for all OTC drug products that contain more than 600 mg magnesium per labeled maximum daily dose: "Do not use this product if you have kidney disease or if you are on a

magnesium-restricted diet unless directed by a doctor." This warning is similar to the warning in § 331.30(c)(4) of the final monograph for OTC antacid drug products.

### 3. Potassium Warning

The agency is proposing to require the following warning for all OTC drug products that contain more than 975 mg potassium per maximum recommended dose: "Do not use this product if you have kidney disease or if you are on a potassium-restricted diet unless directed by a doctor." This warning is similar to the warning in § 331.30(c)(6) of the final monograph for OTC antacid drug products.

### E. Units of Measure

The agency believes the units of measure, where possible, should be similar for foods and drugs. The unit of measure in declaring the content of these components in foods is mg or g per serving of food. While a serving of food is not the same as a dosage of a drug, the agency believes it is logical to declare the content in mg per dosage unit of the drug and to require a content declaration if the ingredient per dose (which could be contained in one or more active or inactive ingredients and in one or more dosage units) is equal to the amount in a serving of food that requires a declaration in the nutrition labeling. This is similar to the agency's approach in the final rule for sodium labeling of OTC drug products. Section 201.64(b) states: "The sodium content shall be expressed in milligrams per dosage unit and shall include the total amount of sodium regardless of the source, i.e., from both active and inactive ingredients."

### F. Rounding to Whole Number

While the food labeling regulations allow for the content declaration of certain ingredients (e.g., sodium and potassium) to be labeled as "zero" up to a certain level (5 mg per serving) (§ 101.9(c)(8)(i) and (c)(8)(ii)), the agency believes these ingredients in drugs should not be labeled as zero content except when the content is zero (based on rounding to the nearest whole number, as in the regulation for sodium labeling of OTC drug products). As discussed in the sodium labeling final rule, most OTC drug products are manufactured and the concentration of ingredients can be strictly controlled. Thus, the concentration of specific ingredients is expected to be less variable in OTC drug products than in foods. For consistency in labeling, the agency believes the labeling of these ingredients should be expressed in mg

per dosage unit rounded to the nearest whole number for those products containing less than 1 g. For those products containing 1 g or more per dosage unit, the content labeling may be rounded to the nearest tenth of a g.

### G. Implementation of Labeling Requirements

The agency encourages manufacturers to comply voluntarily with the provisions of this proposed rule despite the fact that revisions in the requirements may occur in the final rule in response to submitted comments. Should any manufacturer choose to adopt the labeling described in this proposed rule, and should any revisions occur in the final rule, the agency will permit the use of existing stocks of labels for those products labeled according to the proposed rule for a period of 1 year following publication of the final rule.

Should this proposed amendment to part 201 relating to calcium, magnesium, and potassium content and warning labeling of all OTC drug products intended for oral ingestion be published as a final rule, then the existing requirements relating to magnesium labeling in § 331.30(c)(4) and potassium labeling in § 331.30(c)(5) of the final monograph for OTC antacid drug products and the proposed labeling requirements for magnesium and potassium being considered in other ongoing OTC drug rulemakings will be deleted. The agency advises that on or after 12 months after publication of a final rule any OTC drug product subject to this rule that does not meet these labeling requirements and that is initially introduced or initially delivered for introduction into interstate commerce will be misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(n) and 352(a) and (f)).

### III. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives, and when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant

regulatory action as defined by the Executive Order and, thus, is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Should this proposed rule become a final rule, one-time label modification costs associated with changing product labels would be incurred by some manufacturers. FDA estimates those costs to total less than \$500,000 for the entire industry. This projected cost is based on estimates of the number of products that will be affected by the proposed rule, the number of distinct label changes that will be required, and the cost of printing new labels.

OTC antacid drug products are the primary products having a significant number of orally administered active ingredients containing calcium, magnesium, and potassium. The monograph for those products has been in effect since 1974 and these products currently bear magnesium and potassium warning labeling. For these products, the labeling change would involve a slight change in wording, resulting only in a minor cost to have a labeling revision printed. For those products containing calcium, a new warning would be required in product labeling. In almost all cases, this revision would be routinely done at the next labeling printing so that minimal costs should be incurred. Manufacturers will have up to 12 months after publication of a final rule in the **Federal Register** to revise their product labeling. It is anticipated that most antacid drug products would undergo a label printing within a 12-month period. Products containing magnesium and potassium would need only minor revisions, and products containing calcium would need to add some new labeling.

Other OTC drug products (i.e., antidiarrheals, laxatives, and internal analgesics) having one or a few calcium, magnesium, and potassium-containing active ingredients that would be affected by mandatory calcium, magnesium, and potassium labeling currently are not required to bear the labeling recommended in this proposed rule. These products would need to have new labels printed to incorporate the labeling requirements of this rulemaking. These products will also need to have new labeling printed in the future when the final monographs for OTC antidiarrheal, laxative, and internal analgesic drug products are published. This again involves one-time label modification costs. For products that will be undergoing such labeling

changes, the incremental costs attributable to this rule for calcium, magnesium, and potassium labeling would be negligible. A limited number of OTC antidiarrheal, laxative, and internal analgesic drug products contain calcium, magnesium, and potassium-containing active ingredients.

Accordingly, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC drug products intended for oral ingestion. Types of impact may include, but are not limited to, costs associated with relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC drug products should be accompanied by appropriate documentation. A period of 90 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. 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.

#### IV. Paperwork Reduction Act of 1995

FDA tentatively concludes that the labeling requirements proposed 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 proposed warning 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)). The calcium, magnesium, and potassium content per dosage unit is product formulation information that manufacturers have on hand as part of their usual and customary business practice.

#### V. Environmental Impact

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.

#### VI. Request for Comments

Interested persons may, on or before July 22, 1996, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Written comments on the agency's economic impact determination may be submitted on or before July 22, 1996. Three copies of all comments are to be submitted, except that individuals 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. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

#### List of Subjects

##### 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

##### 21 CFR Part 331

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act, it is proposed that title 21 of the Code of Federal Regulations be amended in parts 201 and 331 as follows:

#### PART 201—LABELING

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

**Authority:** Secs. 201, 301, 501, 502, 503, 505, 506, 507, 508, 510, 512, 530–542, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 360gg–360ss, 371, 374, 379e); secs. 215, 301, 351, 361 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 264).

2. New § 201.70 is added to subpart C to read as follows:

##### § 201.70 Calcium labeling.

(a) The labeling of over-the-counter (OTC) drug products intended for oral ingestion shall contain the calcium content per dosage unit (e.g., tablet, teaspoonful) if the calcium content of a single recommended dose of the product (which may be one or more dosage units) is 20 milligrams or more. OTC drug products intended for oral ingestion include gum and lozenge dosage forms, but do not include dentifrices, mouthwashes, or mouth rinses.

(b) The calcium content shall be expressed in milligrams or grams per dosage unit and shall include the total amount of calcium regardless of the source, i.e., from both active and inactive ingredients. If less than 1 gram,

milligrams should be used. The calcium content shall be rounded-off to the nearest whole number in milligrams (or tenth of a gram if over 1 gram) and shall be listed on a separate line after the heading "Calcium Content" as the last sentence in the ingredients section.

(c) The labeling of OTC drug products intended for oral ingestion shall contain the following warning under the heading "Warning" (or "Warnings" if it appears with additional warning statements) if the amount of calcium present in the labeled maximum daily dose of the product is more than 3.2 grams: "Do not use this product if you have kidney stones or if you are on a calcium-restricted diet unless directed by a doctor."

(d) Any product subject to this paragraph that is not labeled as required by this paragraph and that is initially introduced or initially delivered for introduction into interstate commerce after (date 1 year after publication of the final rule), is misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

3. New § 201.71 is added to subpart C to read as follows:

##### § 201.71 Magnesium labeling.

(a) The labeling of over-the-counter (OTC) drug products intended for oral ingestion shall contain the magnesium content per dosage unit (e.g., tablet, teaspoonful) if the magnesium content of a single recommended dose of the product (which may be one or more dosage units) is 8 milligrams or more. OTC drug products intended for oral ingestion include gum and lozenge dosage forms, but do not include dentifrices, mouthwashes, or mouth rinses.

(b) The magnesium content shall be expressed in milligrams or grams per dosage unit and shall include the total amount of magnesium regardless of the source, i.e., from both active and inactive ingredients. If less than 1 gram, milligrams should be used. The magnesium content shall be rounded-off to the nearest whole number in milligrams (or tenth of a gram if over 1 gram) and shall be listed on a separate line after the heading "Magnesium Content" as the last sentence in the ingredients section.

(c) The labeling of OTC drug products intended for oral ingestion shall contain the following warning under the heading "Warning" (or "Warnings" if it appears with additional warning statements) if the amount of magnesium present in the labeled maximum daily dose of the product is more than 600 milligrams: "Do not use this product if

you have kidney disease or if you are on a magnesium-restricted diet unless directed by a doctor.”

(d) Any product subject to this paragraph that is not labeled as required by this paragraph and that is initially introduced or initially delivered for introduction into interstate commerce after (date 1 year after publication of the final rule), is misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

4. New § 201.72 is added to subpart C to read as follows:

**§ 201.72 Potassium labeling.**

(a) The labeling of over-the-counter (OTC) drug products intended for oral ingestion shall contain the potassium content per dosage unit (e.g., tablet, teaspoonful) if the potassium content of a single recommended dose of the product (which may be one or more dosage units) is 5 milligrams or more. OTC drug products intended for oral ingestion include gum and lozenge dosage forms, but do not include dentifrices, mouthwashes, or mouth rinses.

(b) The potassium content shall be expressed in milligrams or grams per dosage unit and shall include the total amount of potassium regardless of the source, i.e., from both active and inactive ingredients. If less than 1 gram, milligrams should be used. The potassium content shall be rounded-off to the nearest whole number in milligrams (or tenth of a gram if over 1 gram) and shall be listed on a separate line after the heading “Potassium Content” as the last statement in the ingredients section.

(c) The labeling of OTC drug products intended for oral ingestion shall contain the following warning under the heading “Warning” (or “Warnings” if it appears with additional warning statements) if the amount of potassium present in the labeled maximum daily dose of the product is more than 975 milligrams: “Do not use this product if you have kidney disease or if you are on a potassium-restricted diet unless directed by a doctor.”

(d) Any product subject to this paragraph that is not labeled as required by this paragraph and that is initially introduced or initially delivered for

introduction into interstate commerce after (date 1 year after publication of the final rule), is misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

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

5. 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).

**§ 331.30 [Amended]**

6. Section 331.30 *Labeling of antacid products* is amended by removing paragraphs (c)(4) and (c)(5) and by redesignating paragraph (c)(6) as paragraph (c)(4).

Dated: March 30, 1996.

**William K. Hubbard,**

*Associate Commissioner for Policy Coordination.*

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