DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201 and 331

[Docket No. 1995N–0254]

Display Date 3-23-04
Publication Date 3-24-04
Modifier Sheese

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending 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 ask a doctor before using 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 ask a doctor before using 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 ask a doctor before using if the product contains more than 975 mg potassium in the labeled maximum daily dose.

NFR1

FDA is issuing this final rule 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, the ongoing OTC drug review, a new drug application (NDA) or abbreviated new drug application (ANDA), or no application.

DATES: *Effective Date*: This final rule is effective [*insert date 30 days after date of publication in the* **Federal Register**].

Compliance Dates: The compliance date for any single entity and combination products subject to drug marketing applications approved on or after [*insert date 30 days after date of publication in the* **Federal Register**], is immediately upon approval of the application. The compliance date for all other OTC drug products, whether subject to drug marketing applications approved before [*insert date 30 days after date of publication in the* **Federal Register**], subject to any OTC drug monograph, or not yet the subject of any OTC drug monograph, is [*insert date 18 months after date of publication in the* **Federal Register**].

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 17807), FDA proposed to amend the general labeling provisions for OTC drug products to require that the labeling of all OTC drug products intended for oral ingestion include: (1) Content labeling for the cations calcium, magnesium, and potassium when a dosage unit of the product contains certain levels of the ingredient(s); and (2)

warning statement(s) when the labeled maximum daily dose of the product contains a certain level of the ingredient(s). FDA proposed this labeling because of public interest in, and health consequences related to, calcium, magnesium, and potassium intake. These labeling requirements are needed to alert people with renal failure, kidney stones, or other conditions, and to assist people who wish to monitor their intake of calcium, magnesium, and potassium. Ingestion of large amounts of calcium can result in renal stones, and both potassium and magnesium can cause serious toxicity in people with impaired renal function (see 61 FR 17807 for a more complete discussion). Many consumers need to know their intake of these cations from foods, dietary supplements, and drugs. Therefore, FDA is issuing a final rule for 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). This final rule establishes calcium, magnesium, and potassium content labeling of OTC drug products similar to that used in food labeling.

Interested persons were invited to submit comments by July 22, 1996. In response to two requests for extension of time to file comments to the proposed rule, FDA published a notice in the **Federal Register** of July 22, 1996 (61 FR 38047), extending the comment period until September 20, 1996. Four manufacturers and one trade association submitted comments.

II. FDA's Response to the Comments

A. Effective Date of the Final Rule

(Comment 1) One comment stated that it is currently performing the testing required to implement the sodium labeling final rule (61 FR 17798, April 22, 1996), and that it plans to perform the required calcium, magnesium,

and potassium testing after publication of that final rule. The comment requested that FDA provide 1 year for implementation. Another comment requested at least 18 months for implementation for economic reasons (see also section II.G, comment 8 of this document), and that FDA coordinate the date with any label changes required for products containing sodium.

FDA agrees that the effective date of this final rule and the effective date of the sodium labeling final rule should provide for implementation at the same time. Elsewhere in this issue of the **Federal Register**, FDA has provided the same compliance dates for the sodium labeling requirements. The same dates for both final rules allow a single labeling revision, thereby reducing the economic impact of phasing in labeling changes for two separate but related rulemakings. In addition, FDA is providing 18 months for implementation.

B. Situations Where Rule Should Not Apply

(Comment 2) Two comments disagreed with across-the-board calcium, magnesium, and potassium labeling for all orally ingested OTC drug products. The comments favored a category-by-category approach for cation labeling as was done for OTC antacid and laxative drugs. One comment added that the across-the-board approach ignores the OTC drug review's well-established category-by-category mechanism for considering warnings related to levels of magnesium, potassium, and sodium in OTC antacid and laxative drug products. The comment contended that FDA gave no documented evidence for the need for the proposed warnings, that requiring warnings without adequate support results in the dilution of all warnings, and asked whether FDA conducted any label comprehension studies to support the proposed labeling.

Another comment endorsed the proposed declaration of cation content on OTC drug labels for the benefit of people who monitor intake for medical reasons, but opposed a warning statement. The comment stated that cation content per dose is much more useful than a warning to inform consumers. The comment concluded that a warning statement does not help people on a calcium, magnesium, or potassium-restricted diet make decisions, is unnecessary for the general population, tends to confuse consumers, and is inconsistent with FDA's position that warning statements be clinically significant and important for the safe and effective use of a product by consumers.

Another comment stated that the proposed rule would be helpful to people who have a condition that requires close monitoring of various cation intakes, but for only a small group, mainly end-stage renal failure patients. The comment said cation information might detract from other important labeling information and recommended that cation information be provided directly to individual patients by pharmaceutical companies rather than in product labeling.

FDA disagrees with the comments' arguments that the warning statements are unnecessary, do not need to appear in product labeling, and should not apply to all orally ingested OTC drug products. FDA addressed the issue of across-the-board labeling in comment 4 of the sodium labeling final rule (61 FR 17798 at 17799 to 17800). FDA stated that across-the-board content and warning labeling is important, useful information for OTC drug products intended for oral ingestion containing calcium, magnesium, and potassium, as well as sodium.

In the proposed rule, FDA stated that it 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 (61 FR 17807 at 17809). FDA added that it believes that certain labeling requirements are needed to alert people with renal failure, kidney stones, or other conditions; and to alert people taking medications who wish to monitor their intake of calcium, magnesium, and potassium (61 FR 17807 at 17809). Certain levels of calcium, magnesium, and potassium present a potential safety problem, regardless of the source, and this rule affects thousands of OTC drug products. Implementation of warnings on a category-by-category basis would result in lack of uniformity in OTC drug product labeling until FDA's evaluation of each drug category is completed. Therefore, FDA finds an across-the-board labeling approach more appropriate than the category-by-category approach.

In the March 17, 1999, final rule for labeling requirements for OTC drug products (64 FR 13254 at 13263) (the March 17, 1999, final rule), in discussing present and future requirements for information to be included in the labeling of OTC drug products containing these ingredients, FDA stated: "This information is significant for individuals who monitor their intake of certain nutrients, including persons with hypertension and renal insufficiency, and for persons who want to increase their intake of certain nutrients (e.g., calcium). The agency is requiring this important information to be the first statement under 'Other information' to draw attention to it." FDA considers it misleading for consumers looking for this information not to have it uniformly in place and provided at the same time for all OTC drug products that contain certain levels of these ingredients.

FDA has required a magnesium and potassium warning on OTC antacid drug products for almost 30 years, and there is no evidence that these warnings have confused consumers. FDA has no reports of any consumer label comprehension concerns and does not believe that label comprehension studies are necessary to support this type of labeling change. FDA concludes that the cation warning statements will help consumers who have kidney disease, get kidney stones, or wish to monitor their calcium, magnesium, or potassium intake, make better-informed decisions, resulting in safer use of OTC drug products containing these cations.

In discussing calcium, the Advisory Review Panel on OTC Antacid Drug Products (Antacid Panel) stated that hypercalcuria 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 antacids (see 61 FR 17807). The Advisory Review Panel on OTC Miscellaneous Internal Drug Products stated that adverse reactions associated with calcium carbonate, including hypercalcemia, alkalosis, acid rebound, milk-alkali syndrome, and constipation, usually occur with ingestion of larger than recommended doses and/or with chronic ingestion (see 61 FR 17807). In discussing magnesium, the Antacid Panel stated that hypermagnesemia toxicity may occur in renal dysfunction (see 61 FR 17807). In discussing potassium, the Antacid Panel concluded that potassium can accumulate in the body of people with impaired renal function and exert toxic effects (see 61 FR 17807 at 17808). FDA believes there is a large consumer population who will use this information, and that it is not practical for these individuals to have to obtain it directly from a manufacturer when it can be readily provided in the product's labeling.

(Comment 3) Three comments opposed cation content labeling for OTC drug products that are not intended for oral ingestion. The comments considered the labeling unnecessary, and said consumers may view such labeling as indicating that the product is for oral ingestion. Two comments contended that there is no reason to require cation content declarations on products such as dentifrices, mouthwashes, and mouth rinses, because the amount of cation absorbed or incidentally ingested is negligible. The comments stated that consumers would be confused by cation labeling on OTC vaginal or rectal drug products and could assume such products are meant for ingestion because this information is viewed as nutritional content labeling.

At this time, FDA is not aware of any safety issues related to the calcium, magnesium, or potassium content of OTC dentifrice, mouthwash, mouth rinse, rectal, or vaginal drug products and is not requiring cation labeling for these products.

C. Dose That Triggers Labeling Requirements

(Comment 4) One comment stated that the language regarding the criteria for requiring a cation declaration may cause confusion, and FDA should clearly state in the rule the specific recommended dose that triggers the requirement for a cation content declaration. The comment contended that the word "single" in "single recommended dose" was the problem. The comment argued that for products whose active ingredient has an established dosage range, a "single recommended dose" could be interpreted to be the "minimum recommended dose," which would be given on the product label, whereas FDA more likely intends it to mean the "maximum recommended dose." The comment concluded that if FDA intends the criteria to be the quantity of a

specific cation in the "maximum recommended dose," then the word "maximum" should be used in place of the word "single."

The proposed regulations in §§ 201.70(a), 201.71(a), and 201.72(a) (21 CFR 201.70(a), 201.71(a), and 201.72(a)) state the amount of cation per single recommended dose (calcium 20 mg, magnesium 8 mg, and potassium 5 mg, respectively) that triggers the content labeling requirements. The intent of the proposal was to require content declaration based on the amount of cation present in the maximum number of dosage units recommended for a single dose. Thus, if one tablet of a product contains 15 mg of calcium and the dosage range is "one or two tablets," calcium content labeling (in mg per dosage unit) would be required because two tablets exceed the 20 mg threshold. FDA agrees that the term "single recommended dose" could be confusing because a single recommended dose may consist of more than one dosage unit. However, the term "maximum recommended dose" could be confused to mean "maximum recommended daily dose." Therefore, FDA is revising the language in §§ 201.70(a), 201.71(a), and 201.72(a) to state the amount of cation in a "single maximum recommended dose" that triggers the content labeling requirements.

D. Percentage Criterion for Cation Labeling

(Comment 5) One comment noted that not all OTC drug ingredient specifications contain limits for cation content, and that some ingredients of natural origin are subject to the same variability in cation content as food products. Therefore, the additive effect of these cations as an unassayed component in multiple raw materials could result in a product containing more than the threshold limit of a given cation, resulting in inaccurate labeling of an OTC drug product. Another comment stated that establishing a criteria of ± 10 percent for cation labeling would meet the needs of many products but

might be problematic for some products (e.g., antacids and laxatives). Another comment mentioned that according to the compendial monograph for magnesium stearate, the magnesium content can vary by ± 10 percent. Thus, lot-to-lot variation can occur for products manufactured in accord with compendial materials and good manufacturing practices. The comment recommended that the labeling provide an expected maximum level of the cation(s). The comment also asked whether it is necessary to test or report the amounts for cations not expected to be present in the final product as they are not contained in the product formula. The comment added that routine testing for cations in a product would be costly and recommended periodic testing to confirm the expected amount of cation(s) calculated from the product formula.

FDA recognizes that some ingredients of natural origin have variable cation content and that there is some acceptable variation between different product lots that bear the same labeling. The amount declared in the labeling is a composite value derived from a number of product samples. Some content determinations for some lots may be based, in part, on average values (taken from historical lots) and on known lot-to-lot variation. However, manufacturers should be able to ascertain when it is necessary to do new analyses, e.g., when a raw material is purchased from a new supplier or the raw material contains a cation declaration that differs from previous lots. Manufacturers should also be able to ascertain when it may be necessary to analyze the raw material or the finished product for a cation(s) not expected to be present in the ingredient or product. Many compendial monographs provide that a product contains no less than 90 percent and no more than 110 percent of the labeled amount of an active ingredient. FDA considers this criterion acceptable for cation content

labeling. Manufacturers need to follow good manufacturing practices (21 CFR part 211) and general guidance provided by the United States Pharmacopeia/ National Formulary in determining a product's cation content.

E. Drug Labeling Versus Food Labeling

(Comment 6) Three comments stated that cation content labeling on OTC drug products should be consistent with food labeling regulations. One comment endorsed the proposal to declare cation content on OTC drug labels if consistent with food labeling practices. However, the comments pointed out that the proposed drug regulations were different from the food labeling regulations in several ways. First, the "rounding" rules are different. Two of the comments requested that manufacturers be permitted to round cation content labeling to the nearest 5 mg level, more consistent with food labeling, rather than to the nearest whole number. Second, FDA regulations (§ 101.9 (21 CFR 101.9)) do not require magnesium or potassium content labeling on food products that do not make claims about these cations. Third, FDA regulations (§ 101.9) require that the percent of daily value for calcium be labeled to the nearest 2-percent increment up to and including the 10-percent level, the nearest 5-percent increment above 10 percent and up to and including the 50-percent level, and the nearest 10-percent increment above the 50-percent level. One comment added that using these criteria for drug products would help reduce the cost of label changes for lot-to-lot variations in calcium content.

The comments contended that magnesium and potassium content labeling should be optional unless magnesium or potassium claims are made. One comment added that it seems inconsistent to require magnesium and potassium declarations for OTC drug products when foods can contain as much as 451 mg potassium in a medium banana or 97 mg magnesium in 1

cup of boiled baby lima beans and not list these amounts on their labels. One comment concluded that FDA should not require a cation content declaration on an OTC drug product that would not be required on a food when the same amount of the cation was present in a serving of the food and a dose of the drug product.

FDA is aware that the cation content of foods and OTC drug products is different. Cations present in food are naturally occurring and information about the amount present appears in numerous publications. Most OTC drug products do not make claims about the cation present because the cation is often part of an inactive ingredient, e.g., magnesium hydroxide, potassium bicarbonate. Many consumers who must or wish to monitor specific cation intake would not know that many OTC drug products contain these cations, or the amount present, unless the labeling contains the information. While health professionals may generally advise consumers about the cation content of many foods (e.g., bananas contain large amounts of potassium), these health professionals would not be able to advise consumers of the cation content of OTC drug products unless the product labeling contains this information. Thus, FDA has determined it is important for OTC drug products to declare their calcium, magnesium, and potassium content. As one comment to this rulemaking noted, the proposed rule would affect thousands of OTC drug products. Accordingly, FDA concludes that OTC drug products containing magnesium or potassium must declare their content if it equals or exceeds the amounts listed in §§ 201.71 and 201.72, and that such labeling should not be optional.

Section 101.9(c)(8) provides that the labeling of food products shall contain a statement of the amount per serving of the vitamins and minerals

described in this paragraph as a percent of the reference daily intake (RDI) and expressed as a percent of the daily value. The percent of the daily value is required for calcium in all cases and for magnesium when it is added or when a claim is made about it. Section 101.9(c)(8)(iii) provides for stating the percentages for vitamins and minerals as one comment previously noted, and § 101.9(c)(8)(iv) establishes RDIs for calcium (1,000 mg) and magnesium (400 mg). FDA does not find this labeling scheme practical to use for OTC drug products containing calcium or magnesium because consumers do not routinely relate drug products to RDIs for vitamins and minerals and, in general, the space available on OTC drug labels is more limited than on food labels. Thus, FDA is including the necessary information (in mg units only) on OTC drug labels, using a minimum amount of space.

Section 101.9(c)(5) provides that potassium content shall be expressed as zero when the serving contains less than 5 mg of potassium, to the nearest 5-mg increment when the serving contains less than or equal to 140 mg of potassium, and to the nearest 10-mg increment when the serving contains more than 140 mg. FDA notes that the proposed regulations in §§ 201.70(b), 201.71(b), and 201.72(b) already provide that the amount of calcium, magnesium, and potassium can be rounded-off to the nearest tenth of a g if over 1 g. This flexibility in rounding-off the higher levels of cation content in the labeling of OTC drug products is similar to the broader flexibility provided in § 101.9(c) of the food labeling regulations when products contain larger amounts of these cations.

FDA is willing to allow rounding of the calcium, magnesium, and potassium content declaration to the nearest 5 mg for two reasons. First, the amounts of calcium (3.2 g), magnesium (600 mg), and potassium (975 mg) that

trigger the requirement for a warning are much greater than the amount of sodium (140 mg) that triggers the requirement for a warning in § 201.64(c) (21 CFR 201.64(c)). Second, the calcium, magnesium, and potassium regulations do not contain a provision for descriptive terms, such as "____ free," "very low ____," "low ____," as in the sodium regulation. In comment 3 of the preamble of the sodium labeling final rule (61 FR 17798 at 17799), FDA provided an example of how this rounding rule could work to a manufacturer's disadvantage and, thus, this concern was sufficient reason not to use the 5-mg rounding rule for sodium labeling. Because this concern does not apply to calcium, magnesium, or potassium labeling, FDA sees no reason to not allow the 5-mg rounding rule for the labeling of OTC drug products containing these three cations. FDA concludes that the ability to round the calcium, magnesium, and potassium content declaration to the nearest 5 mg along with a ± 10 percent declaration range should help reduce the burden on industry in establishing the proper content declaration due to the variability of the cation content of some raw ingredients used in manufacturing OTC drug products.

In conclusion, FDA has revised this aspect of the cation labeling requirements for OTC drug products to parallel the food labeling requirements.

F. Placement of the Cation Content Declarations

(Comment 7) Two comments requested clarification on how the cation content declarations should appear in product labeling when the product contains more than one cation. The comments pointed out that each proposed content declaration regulation stated that the (name of cation) content shall be listed on a separate line after the heading "(name of cation) Content" as the last statement in the ingredients section. The comments requested guidance as to the order these declarations should follow when more than one is

required to appear. One comment requested that the information be allowed to be part of a paragraph listing of ingredients that would include other cations and appear as follows: "Each tablet contains: sodium (____ mg), calcium (____ mg), magnesium (____ mg), potassium (____ mg)." The comment contended that flexibility was important for small packages when economy of space is critically important and it would be difficult to place each cation content on a separate line.

As another alternative, the comment also requested that other means, such as color, boldface, underlining, etc., be allowed to give prominence to a new type of information within the listing of ingredients so that the cation content declarations are readily visible within the paragraph listing of inactive ingredients. Another comment requested that this information be allowed to be included in the inactive ingredient list if the labeling contains such information.

Because the calcium, magnesium, and potassium labeling proposed rule was published on April 22, 1996, FDA addressed this issue in the March 17, 1999, final rule. The March 17, 1999, final rule establishes a specific order and format in which information must appear in OTC drug product labeling. New § 201.66(c)(7)(i) states that required information about certain ingredients in OTC drug products (e.g., sodium in § 201.64(b)) shall appear as follows: "each (insert appropriate dosage unit) contains:" [in bold type] (insert name(s) of ingredient(s) and the quantity of each ingredient). This information shall be the first statement under the heading "Other information."

When § 201.66(c)(7)(i) was finalized, calcium, magnesium, and potassium were not referenced because the regulations for these cations were not completed at that time. Now that those regulations are being finalized, FDA

is amending § 201.66(c)(7)(i) to cross-reference these three cations in addition to sodium. FDA has also determined that there is a need for uniformity in when more than one cation content declaration needs to appear in the labeling. Therefore, FDA is further revising § 201.66(c)(7)(i) to state that when more than one cation declaration is required, the declarations shall appear in alphabetical order. Revised § 201.66(c)(7)(i) now reads as follows:

Required information about certain ingredients in OTC drug products (e.g, sodium in § 201.64(b), calcium in § 201.70(b), magnesium in § 201.71(b), and potassium in § 201.72(b)) shall appear as follows: "each (insert appropriate dosage unit) contains:" [in bold type] (insert name(s) of ingredient(s) (in alphabetical order) and the quantity of each ingredient). This information shall be the first statement under this heading.

G. Economic Impact

(Comment 8) One comment stated that the OTC drug industry was not currently able to provide an estimate of the total economic impact of the proposed rule on industry because individual companies do not yet know how to estimate their full costs. The comment added that the industry's expenditure of labor and other resources to comply with the sodium labeling final rule has made it difficult to gather data on the precise contents of other cations in finished drug products. The comment noted that there would be additional relabeling and other technical costs and asked FDA to be open to receiving additional data on the economic impact of the proposed cation labeling requirements when those costs were calculated.

Another comment identified the following several cost factors: (1) The testing of multiple lots of finished products to determine a "mean" for each specific cation was resource intense, (2) a large number of products requiring

analysis would be a sizable resource investment, and (3) the relabeling costs included both the printing of new labels and the loss of some label inventory that would no longer be in compliance. A third comment stated that costs included label obsolescence and analytical, marketing, and regulatory review costs. The comment mentioned that it would incur label conversion costs of $2.7 million due to the far-reaching scope of the proposed rule. The comment concluded that coordinating the calcium, magnesium, and potassium labeling changes with the sodium labeling changes and allowing an 18-month implementation date would permit it to handle the labeling changes at current staff levels, to use preprinted labeling, and to reduce the cost of compliance significantly.

A fourth comment stated that validation of classical cation measurements and methods would be time consuming and expensive for OTC drug products. The comment mentioned that it did not currently test any of its products for these measurements, and testing would involve incremental costs and resources to validate these methods for its products.

To date, the industry has not provided any additional comments on the economic impact of this rule. This final rule provides for coordination of the calcium, magnesium, and potassium, labeling requirements with the sodium labeling requirements and with an 18-month implementation period to reduce the economic impact of this rule. FDA previously encouraged industry to concomitantly plan product analyses for all of the cations at the same time to reduce costs and obtain the needed information at the earliest possible time (Ref. 1).

III. Summary of Significant Changes

1. The calcium, magnesium, and potassium content per dosage unit follows the "Other information" heading and appears in alphabetical order as stated in revised § 201.66(c)(7). (See section II.F, comment 7 of this document.)

2. FDA is allowing the calcium, magnesium, and potassium content declaration to be rounded-off to the nearest 5 mg instead of the nearest whole number in milligrams. (See section II.E, comment 6 of this document.)

3. FDA is revising the language in §§ 201.70(a), 201.71(a), and 201.72(a) to state the amount of cation in a "single maximum recommended dose" that triggers the content labeling requirements. (See section II.C, comment 4 of this document.)

4. FDA is changing the format of the warning statements to follow the new OTC drug labeling requirements in § 201.66(c)(5)(iv). The warning statements appear in the following format in this final rule: "Ask a doctor before use if you have [in bold type] [bullet][1] kidney disease [or stones in one case] [bullet] a (insert name of cation)-restricted diet". If more than one cation is present in the product, the names of the cations can be inserted in the blank space in alphabetical order, e.g., a magnesium or potassium-restricted diet.

IV. FDA's Final Conclusions on Calcium, Magnesium, and Potassium Labeling

A. New Labeling Requirements

FDA concludes that public interest and public health consequences related to calcium, magnesium, and potassium intake have produced a need for more informative and consistent cation content and warning information in the labeling of OTC drug products. This is especially true for individuals with

[1] See § 201.66(b)(4) of this chapter for definition of bullet symbol.

kidney disease or kidney stones, or who need or want to monitor their intake of any or all of these cations.

FDA is implementing the following content and warning requirements for OTC drug products intended for oral ingestion: Content—if the product contains 20 mg calcium, 8 mg magnesium, or 5 mg potassium or more per single maximum recommended dose; warning—if the product contains more than 3.2 g calcium, 600 mg magnesium, or 975 mg potassium in the labeled maximum daily dose. The content labeling may be rounded-off to the nearest 5 mg (if less than 1 g) or nearest tenth of a g (if over 1 g) and shall appear after the heading "Other information." The new calcium, magnesium, and potassium labeling requirements apply to OTC drug products intended for oral ingestion, whether marketed under an OTC drug monograph, the ongoing OTC drug review, an approved application, or no application. The existing requirements relating to magnesium and potassium labeling in § 331.30(c)(4) and (c)(5) (21 CFR 331.30(c)(4) and (c)(5)) of the final monograph for OTC antacid drug products are being deleted because they are superseded by the new requirements of this final rule. Any proposed calcium, magnesium, or potassium labeling requirements in other ongoing OTC drug rulemakings will be deleted when final monographs for those drug classes are issued in a future issue of the **Federal Register**.

B. Statement About Warnings

Mandating warnings in an OTC drug product regulation does not require a finding that any or all of the OTC drug products covered by the regulation actually caused an adverse event, and FDA does not so find. Nor does FDA's requirement of warnings repudiate the prior OTC drug monographs and regulations under which the affected drug products have been lawfully

marketed. Rather, as a consumer protection agency, FDA has determined that warnings are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the Federal Food, Drug, and Cosmetic Act (the act). This judgment balances the benefits of these drug products against their potential risks (see 21 CFR 330.10(a)).

FDA's decision to act in this instance need not meet the standard of proof required to prevail in a private tort action (*Glastetter* v. *Novartis Pharmaceuticals Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)). To mandate warnings, or take similar regulatory action, FDA need not show, nor do we allege, actual causation. For an expanded discussion of case law supporting FDA's authority to require such warnings, see Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use final rule (67 FR 72555, December 6, 2002).

C. Statutory Authority

In this final rule, FDA is addressing legal issues relating to the agency's action to require cation content labeling for OTC drug products. FDA is relying on section 502(e) of the act (21 U.S.C. 352(e)) to require disclosure in the labeling of OTC drug products of: (1) The presence and quantity of cations that are active ingredients and (2) the presence of cations that are inactive ingredients. To require disclosure of the quantity of cations that are inactive ingredients, FDA is relying on sections 502(a) and 201(n) of the act (21 U.S.C. 352(a) and 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, 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) of the act. 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 which 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 § 1.21 (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 IV of this document and in the proposed rule (61 FR 17807), FDA has determined that for OTC drug products containing more than the specified amount of cations, the quantity of these substances as inactive ingredients in OTC drug products is material with respect to consequences that may result from use of such products within the meaning of section 201(n) of the act. Certain levels of calcium, magnesium, and potassium present a potential safety problem. People with renal failure, kidney stones, or other conditions need to monitor their intake of calcium, which can result in kidney stones, and both potassium and magnesium can cause serious toxicity in persons with impaired renal function. Many people are on calcium,

magnesium, or potassium-restricted diets. Other people must monitor their intake of calcium, magnesium, and potassium from foods (including dietary supplements) and OTC drugs for other medical or health reasons. Absent mandatory cation content labeling, these people would not be able to understand the relative contribution that OTC drug products make to their intake of cations, and would not be able to compare the cation contents of various OTC drug products.

D. The First Amendment

This final rule passes muster under the First Amendment. FDA's requirement of cation content labeling for OTC drug products (where cations are inactive ingredients and are 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 consumption of quantities of cations that do not threaten the health of people for whom cation use has material consequences. Some people, newly informed by the required labeling, will properly reduce or discontinue their intake of cation-containing OTC 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 cation consumption. Finally, it is not "unduly burdensome" to require an additional disclosure of this kind.

In any event, this final 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 drug products containing cations in excess of the threshold amount to be non-misleading (Id. at 563–564). As discussed in this document, FDA has determined that the failure to disclose in an OTC drug product's labeling the amount of cations in the product when they are 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 cation content labeling requirement satisfies each of these parts. With respect to the second part, FDA's interest in requiring cation content labeling under this final rule is to ensure that people who must monitor their intake of cations for health reasons have information necessary to understand the relative contribution that OTC drug products make to their intake of cations and to compare the cation contents of OTC drug 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 Hudso*n test, because by requiring labeling disclosure of the presence and quantity of cations in OTC 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 cation content labeling of OTC 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 cation content in the labeling of their products, would ensure that people have the information they need about cation content at the point of sale or ingestion. And establishing limits on cation 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 cation intake from OTC drug products. Further, some consumers may wish to use OTC drug products to enrich the amount of cations in their diets. Finally, for many products, the cation 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 cations above a specified level in OTC drug product labeling.

V. Analysis of Impacts

FDA has examined the impacts of this final 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 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

FDA concludes that this final rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. As discussed in this section of the document, the final rule will not be economically significant as defined by the Executive order. With respect to the Regulatory Flexibility Act, the rule may have a significant economic impact on a substantial number of small entities. 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 final rule, because the final 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 final rule is to add calcium, magnesium, and potassium content and warning information to the labeling of OTC drug products containing these ingredients. This rule is intended to help ensure the safe and effective use of all OTC drug products that contain these ingredients. Potential benefits include reduced toxicity when consumers use such products.

OTC antacid drug products containing the threshold amounts of magnesium and potassium have had a magnesium or potassium warning in their labeling since 1974. The final rule revises the wording of this warning and requires the magnesium and potassium content to be added to product labeling if the amount exceeds the threshold amounts. The final rule also requires calcium, magnesium, and potassium labeling for other OTC drug products for the first time if those products contain above the threshold amounts stated in the final rule.

FDA discussed the impacts of the calcium, magnesium, and potassium labeling requirement in the proposed rule (61 FR 17807 at 17810). Four of the comments submitted in response to the proposal addressed FDA's economic impact determination. (See section II.G, comment 8 of this document.)

One of the comments stated that the rule would affect thousands of OTC drug products. However, the comment provided no additional information. Another comment discussed the large number of formulations requiring analyses, stating that there would be over 50 for its company, and the company would be faced with sizable resource investments. However, the comment did not provide any estimates of the cost of product analyses for calcium, magnesium, or potassium content or the cost of its resource investments.

FDA's Drug Listing System (DLS) and standard texts can identify OTC drug products containing calcium, magnesium, and potassium as active ingredients. However, these sources do not identify those products containing these cations as inactive ingredients or indicate whether the inactive ingredient quantities meet the threshold levels that require content labeling and warnings to appear in product labeling. Therefore, FDA is unable to accurately estimate the number of products that will be affected by this final rule. However, FDA

agrees with one comment that states that thousands of OTC drug products are likely to be affected.

FDA's DLS identifies a large number of products that contain calcium, magnesium, and potassium as active ingredients. For example, the DLS identifies 129 manufacturers, 319 marketers, and 744 products containing a number of calcium salts (acetate, carbonate, citrate, lactate, oxide, phosphate, polycarbophil, and sulfate). The DLS identifies 202 manufacturers, 613 marketers, and 1,553 products containing magnesium (aluminosilicates, carbonate, chloride, citrate, glycinate, hydroxide, magaldrate, oxide, phosphate, phosphate dibasic, salicylate, sulfate, and trisilicate). The DLS identifies 84 manufacturers, 149 marketers, and 445 products containing potassium (bicarbonate, carbonate, phosphate, phosphate dibasic or tribasic, salicylate, and tartrate). There are also a number of other less frequently used calcium, magnesium, and potassium salts included in the DLS. Some of these products contain more than one of these salts. Thus, the number of manufacturers and marketers affected by this final rule is less than the totals (415 manufacturers and 1,081 marketers) of the numbers stated herein. However, the total number of products (2,742) provides an estimate of the number of products that may need analyses. In addition, a number of these products are likely to have more than one stockkeeping unit (SKU) (individual products, packages, and sizes) that requires relabeling. For example, one private label manufacturer informed FDA that it has 91 products that would be affected by this final rule (that would need product analyses done), but these 91 products represent 4,000 SKUs that would require relabeling. (Note—these figures also included products containing sodium.) Another manufacturer informed FDA that it had 42 formulations affected by the

calcium, magnesium, potassium, and sodium labeling requirements, but did not mention the number of SKUs affected. Based on these numbers, FDA estimates that 10,000 SKUs may need labeling revisions.

FDA is aware of varying cost estimates for conducting an individual cation analysis for an individual lot of a specific formulation. These estimates range from $150 for private label products to between $300 and $400 for nationally branded products. If more than one cation is tested at the same time, there would likely be a slight cost savings ($400 for four cations (including sodium if sodium is also done) for one product), but not a significant savings because a separate sample analysis would need to be done for each cation. FDA has also been informed that some manufacturers plan to perform tests on three lots of each specific formulation; thus, the cost per formulation would be $450 to $1,200 per cation, and $1,200 to $3,600 if the analysis had to be done for all three cations (calcium, magnesium, and potassium). For certain cations, the need for analysis would be clear from the batch formulation. However, in some cases, manufacturers might have to test for all three cations to obtain baseline data.

To estimate the cost of product analysis, FDA weighted the cost of product testing to reflect the difference in testing costs reported by private label and branded product manufacturers. FDA estimates that branded products account for about 20 percent of all OTC drug products, and private label products account for the remaining 80 percent. The weighted cost of product testing for one cation, assuming that all product manufacturers will conduct tests on three lots, is $570 (($150 x .8 x 3)+($350 x .2 x 3)). Most manufacturers will know by their product formulations how many cations they will need to test. To estimate testing cost, FDA assumes that 50 percent of the products will

require testing for 2 or 3 cations (midpoint of 2.5 used for estimation purposes). Assuming 3,000 products may need to be tested, the total cost of this requirement is $3.0 million (($570 x 1,500)+($570 x 2.5 x 1,500)).

All products containing over the threshold amounts of the cations will be required to be relabeled. Estimates of relabeling costs for the type of changes required by this rule vary greatly and range from $500 to $15,000 per SKU, depending on whether the products are nationally branded or private label. Because of the large number of products affected by this rule, FDA used the same weighted average cost to relabel (i.e., $3,600 per SKU) that was estimated for the final rule for the standardized format and content labeling requirements of OTC drug products (64 FR 13254 at 13279 to 13281). If 10,000 SKUs need to be relabeled, therefore, the one-time costs will be $36 million. The cost of this rule may be mitigated to the extent that manufacturers can coordinate the testing and relabeling required by this final rule with that of the OTC drug sodium content labeling rule, published elsewhere in this issue of the **Federal Register**, and to the extent that the relabeling can be coordinated with the general OTC drug products labeling rule (64 FR 13254).

In addition to the above costs, some manufacturers may incur one-time and annually recurring costs if they need to increase the label and/or package size of some SKUs because of the additional information required by this final rule. FDA had estimated that about 6,400 of the almost 100,000 marketed OTC drug SKUs may require increased label and/or package sizes to comply with the final labeling rule (64 FR 13254). As about one-half of these 6,400 SKUs were for products subject to this final rule, much of the costs for increasing label and/or package sizes may have already been accounted for in the impact analysis of that broader rule. FDA estimates that the additional few lines of

labeling required by this final rule could compel an additional 3 percent of the approximately 10,000 affected SKUs to increase their label and/or package size. These costs were not accounted for in the prior rule.

Because of the large number of products affected by this final rule, FDA assumes that the average cost per SKU to increase label and/or package size would be essentially the same as FDA previously estimated in its analysis of the standardized format and content labeling requirements for OTC drug products. The model used to estimate the cost to change label/package sizes for the standardized format and content labeling requirements rule was developed by the Eastern Research Group, Inc. (ERG), a private economics consulting firm under contract to FDA (Ref. 2). ERG assigned probabilities to several options for package changes, including adding a carton (if not already present), adding a fifth panel, increasing the size of the packaging, or switching to a nonstandard form of labeling such as peel-back or accordion labels. Where applicable, the costs for changing a container size included container inventory loss, adjustment of the packaging line, and stability testing. Based on this model, FDA had estimated that the cost to increase label/package sizes to comply with the standardized format and content labeling requirements for OTC drug products in § 201.66 was $38.1 million for 6,313 SKUs, with an annual recurring cost of $11.5 million. Consequently, the average per SKU one-time cost was $6,038, and the average per SKU recurring cost was $1,820. Under the same assumptions, this final rule would impose additional one-time costs for increasing label/package sizes of $1.8 million (0.03 x 10,000 x $6,038) with annual recurring costs of $0.5 million (0.03 x 10,000 x $1,820). Thus, FDA estimates the overall costs of this final rule to be $40.8 million in one-

time costs (i.e., $36 million to relabel, $3 million for testing, and $1.8 million to increase label/package sizes) and $0.5 million in annual recurring costs.

This final rule will not require any new reporting and recordkeeping activities. Therefore, no additional professional skills are needed. There are no other Federal rules that conflict with this final rule.

This final rule may have a significant economic impact on some small entities. It will affect the information content of all OTC drug products that contain above the threshold amounts of calcium, magnesium, and potassium. Firms that manufacture or relabel these OTC drug products will need to change the labeling for each affected product. FDA estimates that there are at least 400 firms that manufacture OTC drug products. Based on the Small Business Administration's determination that a small firm in this industry has fewer than 750 employees, roughly 70 percent of the firms are considered small.

The economic impact on any particular small firm is very difficult to measure because it will vary with the number of products affected, the number of SKUs per product, the ability to coordinate these label changes with those required for other purposes, the number of cation tests that must be performed, and the size of the required labeling compared to the space available on existing packaging. For example, assuming average industry costs, a small firm that would need to change labels for 5 products with 3 SKUs each, for a total of 15 SKUs, could experience a one-time cost from $50,000 to $120,000, plus some annually recurring costs. If only one cation test were required for each product and the labeling fit on existing packaging, the one-time cost to comply with the rule would be about $57,000 and there would be no annually recurring costs. However, if the products required tests for all three cations and one SKU from each product required a larger label/package size, the cost

to comply would increase to $92,750 with an annual recurring cost of approximately $9,100. A small private label manufacturer with the same product line and 10 customers for each SKU would face costs of $562,500 and $848,650, with $91,000 in annually recurring costs, respectively. These costs would be largely offset, however, to the extent that OTC drug manufacturers can coordinate these label changes with those already required by the final rule for the labeling requirements of OTC drug products (64 FR 13254), the sodium labeling rule, and any voluntary market-driven label changes that would be completed within the permitted compliance period.

FDA has taken the following steps to minimize the impact on small entities: (1) Providing sufficient time for implementation to enable entities to use up existing labeling stock and (2) coordinating the labeling revisions in this final rule with the revisions required by the final rule for sodium content labeling. FDA believes that these actions provide substantial flexibility and reductions in cost for small entities.

FDA considered but rejected the following several labeling alternatives: (1) A shorter or longer implementation period, and (2) an exemption from coverage for small entities. While FDA believes that consumers would benefit from having this new labeling in place as soon as possible, we also acknowledge that a shorter implementation period could significantly increase the compliance costs and these costs could be passed through to consumers. A longer time period for this rule may cost more if firms would have to undertake two successive labeling revisions. In addition, a longer time period would unnecessarily delay the benefit of the new labeling to consumers who self-medicate with these OTC drug products. FDA rejected an exemption for

small entities because the new labeling information 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 final regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

VI. Paperwork Reduction Act of 1995

FDA concludes that the labeling requirements in this document are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the labeling 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)). The calcium, magnesium, and potassium content per dosage unit for active ingredients is product formulation information that many manufacturers should have on hand as part of their usual and customary business practice. Some manufacturers may need to do content analysis for inactive ingredients.

VII. 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.

VIII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects 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 concludes that the 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. References

The following references are on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Letter from D. Bowen, FDA, to L. Totman, Nonprescription Drug Manufacturers Association, January 14, 1997, coded LET3, Docket No. 95N–0254, Division of Dockets Management.

2. Eastern Research Group, Inc., "Cost Impacts of the Over-the-Counter Pharmaceutical Labeling Rule," in OTC vol. 28 FR, Docket No. 96N–0420, Division of Dockets Management.

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, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 201 and 331 are 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 201.66 is amended by revising paragraph (c)(7)(i) to read as follows:

§ 201.66 Format and content requirements for over-the-counter (OTC) drug product labeling.

* * * * *

(c) * * *

(7) * * *

(i) Required information about certain ingredients in OTC drug products (e.g., sodium in § 201.64(b), calcium in § 201.70(b), magnesium in § 201.71(b), and potassium in § 201.72(b)) shall appear as follows: "each (insert appropriate dosage unit) contains:" [in bold type (insert name(s) of ingredient(s) (in alphabetical order) and the quantity of each ingredient). This information shall be the first statement under this heading.

* * * * *

■ 3. Section 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 maximum 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 the dosage unit contains less than 1 gram of calcium, milligrams should be used. The calcium

content per dosage unit shall be rounded-off to the nearest 5 milligrams (or nearest tenth of a gram if over 1 gram). The calcium content per dosage unit shall follow the heading "Other information" as stated in § 201.66(c)(7).

(c) The labeling of OTC drug products intended for oral ingestion shall contain the following statement 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: "Ask a doctor before use if you have [in bold type] [bullet][1] kidney stones [bullet] a calcium-restricted diet". The warnings in §§ 201.64(c), 201.70(c), 201.71(c), and 201.72(c) may be combined, if applicable, provided the ingredients are listed in alphabetical order, e.g., a calcium or sodium restricted diet.

(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 the following dates is misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

(1) As of the date of approval of the application for any single entity and combination products subject to drug marketing applications approved on or after [*insert date 30 days after date of publication in the* **Federal Register**].

(2) [*Insert date 18 months after date of publication in the* **Federal Register**], for all OTC drug products subject to any OTC drug monograph, not yet the subject of any OTC drug monograph, or subject to drug marketing applications approved before [*insert date 30 days after date of publication in the* **Federal Register**].

■ 4. Section 201.71 is added to subpart C to read as follows:

[1] See § 201.66(b)(4) of this chapter for definition of bullet symbol.

§ 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 maximum 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 the dosage unit contains less than 1 gram of magnesium, milligrams should be used. The magnesium content shall be rounded-off to the nearest 5 milligrams (or nearest tenth of a gram if over 1 gram). The magnesium content per dosage unit shall follow the heading "Other information" as stated in § 201.66(c)(7).

(c) The labeling of OTC drug products intended for oral ingestion shall contain the following statement 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: "Ask a doctor before use if you have [in bold type] [bullet][1] kidney disease [bullet] a magnesium-restricted diet". The warnings in §§ 201.64(c), 201.70(c), 201.71(c), and 201.72(c) may be combined, if applicable, provided the ingredients are listed in alphabetical order, e.g., a magnesium or potassium-restricted diet.

(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

[1] See § 201.66(b)(4) of this chapter for definition of bullet symbol.

introduction into interstate commerce after the following dates is misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

(1) As of the date of approval of the application for any single entity and combination products subject to drug marketing applications approved on or after [*insert date 30 days after date of publication in the* **Federal Register**].

(2) [*Insert date 18 months after date of publication in the* **Federal Register**], for all OTC drug products subject to any OTC drug monograph, not yet the subject of any OTC drug monograph, or subject to drug marketing applications approved before [*insert date 30 days after date of publication in the* **Federal Register**].

■ 5. Section 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 maximum 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 the dosage unit contains less than 1 gram of potassium, milligrams should be used. The potassium content shall be rounded-off to the nearest 5 milligrams (or nearest tenth of a gram if over 1 gram). The potassium content per dosage unit shall follow the heading "Other information" as stated in § 201.66(c)(7).

(c) The labeling of OTC drug products intended for oral ingestion shall contain the following statement 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: "Ask a doctor before use if you have [in bold type] [bullet][1] kidney disease [bullet] a potassium-restricted diet". The warnings in §§ 201.64(c), 201.70(c), 201.71(c), and 201.72(c) may be combined, if applicable, provided the ingredients are listed in alphabetical order, e.g., a magnesium or potassium-restricted diet.

(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 the following dates is misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

(1) As of the date of approval of the application for any single entity and combination products subject to drug marketing applications approved on or after [*insert date 30 days after date of publication in the* **Federal Register**].

(2) [*Insert date 18 months after date of publication in the* **Federal Register**], for all OTC drug products subject to any OTC drug monograph, not yet the subject of any OTC drug monograph, or subject to drug marketing applications approved before [*insert date 30 days after date of publication in the* **Federal Register**].

---

[1] See § 201.66(b)(4) of this chapter for definition of bullet symbol.

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

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

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

§ 331.30 [Amended]

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

Dated: _____
March 15, 2004.

_____
Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. 04–????? Filed ??–??–04; 8:45 am]

BILLING CODE 4160–01–S

CERTIFIED TO BE A TRUE
COPY OF THE ORIGINAL