DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201 and 331

[Docket No. 90N–0309]

RIN 0910–AA63

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule with opportunity for comments.

SUMMARY: The Food and Drug Administration (FDA) is amending the general labeling provisions for over-the-counter (OTC) drug products to require that the sodium content of all OTC drug products intended for oral ingestion be included in labeling when the product contains 5 milligrams (mg) or more sodium per a single dose; require that all OTC drug products intended for oral ingestion containing more than 140 mg sodium in the labeled maximum daily dose bear a general warning that persons who are on a sodium-restricted diet should not take the product unless directed by a doctor; and provide for the voluntary use of certain terms ("sodium free," "very low sodium," and "low sodium") relating to an OTC drug product's sodium content per labeled maximum daily dose. FDA is issuing this final rule in order to provide uniform sodium content labeling for all OTC drug products intended for oral ingestion (whether marketed under an OTC drug monograph, an approved application, or no application), and to provide for the voluntary use in OTC drug labeling of the same terms used to describe sodium content in food labeling.

DATES: This final rule is effective April 22, 1997; written comments by July 22, 1996.

ADDRESSES: 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

In the **Federal Register** of April 25, 1991 (56 FR 19222), FDA proposed to amend the general labeling provisions for OTC drug products to: (1) Require that the sodium content of all orally administered OTC drug products be included in labeling when the product contains 5 mg or more sodium per a single recommended dose; (2) require that orally administered OTC drug products containing more than 140 mg sodium in the maximum recommended daily dose be labeled with a general warning that persons who are on a sodium-restricted diet should not take the product unless directed by a doctor; and (3) provide for the voluntary use of certain descriptive terms relating to the OTC drug product's sodium content. FDA issued the notice of proposed rulemaking in order to provide uniform sodium content labeling for all orally administered OTC drug products, and to provide for the voluntary use in OTC drug labeling of the same descriptive terms as those used to describe sodium content in food labeling. To promote uniformity, the agency also proposed to delete the existing sodium labeling requirements in the final monograph for OTC antacid drug products (21 CFR part 331).

Interested persons were invited to file written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs (the Commissioner) and to file comments on the agency's economic impact determination by June 24, 1991. In the **Federal Register** of June 12, 1991 (56 FR 26946), FDA published a notice extending the comment period until July 24, 1991.

In response to the proposed rule, comments were received from five state governments, five manufacturers, two trade associations, one health professional association, one consumer organization, and FDA employees. No comments were received on the agency's economic impact determination.

Based on comments received, the agency is seeking comments from interested individuals on whether this final rule should be amended to include sodium content labeling for OTC rectal laxative, vaginal, dentifrice, mouthwash, and mouth rinse drug products. (See section I.B., comment 6 of this document.) Comments should be sent to the Dockets Management Branch (address above) by July 22, 1996.

II. The Agency's Conclusions on the Comments

A. General Comments

1. Most comments generally supported the proposal to include sodium content in OTC drug product labeling. A number of the comments stated that this labeling would be especially helpful to those individuals who must restrict their sodium intake, specifically the elderly. Several comments were opposed to the warning statement (see section II.D., comment 12 of this document).

2. Several comments supported uniform sodium labeling for foods and OTC drug products. One comment favored use of the descriptive terms "sodium free," "very low sodium," and "low sodium" for OTC drug products because food labeling has made these terms familiar to consumers on a low-sodium diet. However, the comment strongly opposed sodium warning labeling for OTC drug products, which it considered unnecessary and counterproductive (see also section II.D., comment 12 of this document). Another comment noted that the proposed sodium warning requirement for those OTC drugs containing over 140 mg sodium per maximum recommended daily dose is consistent with the labeling of foods. The comment noted that consumers are familiar with food labeling where a serving containing 140 mg or less sodium is considered "low sodium."

Another comment acknowledged the value of the proposed terms, provided they are consistent with those used in food labeling. However, the comment contended that basing drug labeling on "per maximum daily dosage" is inconsistent with food labeling which is based on "per serving." The comment indicated that "per dose" labeling for drugs would be more consistent with the food labeling. The comment also noted that sodium labeling for foods has no warning threshold, while the proposed sodium labeling for OTC drug products does have a warning threshold. Another comment stated that drugs are not produced, consumed, or regulated like foods and thus should not be treated like foods for warning purposes.

FDA does not consider sodium labeling for OTC drug products to be either unnecessary or counterproductive. The agency has determined that such labeling is important and, wherever possible, should be comparable to that used for foods because consumers are already familiar with that labeling. While consumption patterns for drugs are not the same as those for foods, a substantial portion of daily sodium intake can come from OTC drugs, especially those used frequently, such as antacids, internal analgesics, and laxatives. Thus, the agency concludes that consumers

should be informed about the sodium content of drugs as well as foods.

The agency believes that "maximum daily dose" is the most appropriate basis for sodium descriptor labeling of OTC drug products, even though this basis differs from that for food labeling. Consumers may use multiple doses per day of many OTC drug products, and OTC drug product labeling informs consumers how much of a drug can be safely consumed daily. On the other hand, in many cases only a single serving of many different foods containing sodium is likely to be consumed in 1 day, although there is no upper limit on the number of servings that could be consumed. Thus, the consumption patterns vary for foods and for drugs. Because of food consumption patterns, nutritional labeling, including the descriptive terms used, is based on "per serving," and the consumer must determine the total daily intake of each food. By contrast, OTC drugs have a safe consumption limit, and sodium labeling is more appropriately based on the labeled maximum daily dosage. The agency is using the term "labeled maximum daily dosage" in place of "maximum recommended daily dosage" to indicate that this dosage appears in the product's labeling.

Although the use of descriptive terms for sodium in the labeling of foods is based on the sodium content "per serving" rather than on a "maximum daily intake," physicians usually monitor a patient's total daily sodium intake, not how much is consumed at each meal. When physicians instruct people to maintain a low-sodium diet, the physicians and individuals determine what foods to avoid to keep the daily sodium intake at an acceptable level. If an antacid is needed, total daily sodium intake can be reduced by using a calcium antacid rather than a sodium antacid.

The agency acknowledges that the basis for the descriptive terms for sodium labeling of OTC drug products is not the same as for food labeling. Nonetheless, the agency considers the two to be consistent. In general, the amount of sodium derived from a given OTC drug in 1 day is limited to the amount contained in the labeled maximum daily dosage, while that derived from a given food is often the amount of sodium in a single daily serving. Therefore, in this final rule for OTC drug product labeling the agency is providing for the voluntary use of descriptive terms for sodium that are based on the labeled maximum daily dose. (See also section II.E., comment 15 of this document.)

3. One comment expressed concern that descriptive terms based on sodium content using rounded-off numbers could be different from descriptive terms based on sodium content using actual numbers. The comment stated that potential compliance problems could arise if an FDA inspector examined the label of an affected product, multiplied the rounded-off, approximated sodium content number by the maximum recommended daily dose, and arrived at a number that did not fall within the range that correlates to the descriptive term on the label. The comment contended that calculations for descriptive terms should be done using actual sodium content numbers. The comment suggested that if discrepancies between actual and rounded-off numbers occur, reasonable documentation showing the method of calculation using the actual sodium content numbers should be accepted as sufficient to resolve the matter.

Another comment supported the first comment's position on the rounding-off rules. The comment mentioned the sodium content labeling regulation for food in § 101.9(g)(5) (21 CFR 101.9(g)(5)), which states: "A food with a label declaration of calories, sugars, total fat, saturated fat, cholesterol, or sodium shall be deemed to be misbranded under section 403(a) of the act if the nutrient content of the composite is greater than 20 percent in excess of the value for that nutrient declared on the label." This regulation, referred to as the "120 percent rule," provides an upper limit to the amount that sodium content may vary in food, above which a product would be deemed misbranded. The comment suggested that such a rule for the upper limit of variation for sodium labeling for OTC drugs, without an accompanying lower limit, would be reasonable because manufacturers will tend to declare as low a sodium content as is reasonable for the product. The comment contended that applying the "120 percent rule" to sodium labeling of OTC drugs would alleviate many of the compliance issues associated with providing a sodium content on the label that is different from the actual sodium content.

The agency has reconsidered the "rounding-off" provision and concludes that rounding-off could result in potential discrepancies between the actual and apparent sodium content, and may lead to consumer confusion. For instance, if the actual sodium content of a product is 8 mg per dosage unit and the product is to be taken four times daily, the labeled maximum daily dose is 32 mg. Because the sodium content is less than 35 mg (per labeled maximum daily dose), the term "very low sodium" could be used. However, if the actual dosage unit (8 mg) is rounded-off to 10 mg, the apparent labeled maximum daily dose for that product would be 40 mg and the descriptive term would be "low sodium."

Food labeling regulations provide for rounding-off the sodium content to the nearest 5 or 10 mg sodium per serving. Because most food products contain naturally occurring sodium, at least in small amounts, some variation in sodium content is expected. On the other hand, most OTC drug products are manufactured and the amount of sodium in products can be strictly controlled. Thus, the sodium content of OTC drug products is expected to be less variable than that of foods. The agency concludes that the sodium content of OTC drug products can readily be disclosed in mg per dosage unit, without rounding-off. As a result, the agency considers the "120 percent rule" provided for in § 101.9(g) of the food regulations unnecessary for OTC drug products. Therefore, the agency is revising proposed § 201.64(b) in this final rule (21 CFR 201.64(b)) to eliminate the 5 mg and 10 mg rounding-off provision. The final rule requires that the sodium content be rounded-off to the nearest whole number, whatever the content per dosage unit.

B. Comments on the Scope of Sodium Labeling

4. Three comments disagreed with the agency's "across-the-board" sodium warning requirement for OTC drugs, stating that this method ignores the OTC drug review's category-by-category mechanism for considering warnings. One comment added that if a warning statement is required, the agency should consider the product's pharmacologic class, its use patterns, and the currently required labeling of particular active ingredients. Another comment contended that sodium warnings should only be required where a need has been shown for a particular category of OTC drugs.

FDA disagrees with the comments, which provided no scientific basis for their concerns. Although the agency generally considers OTC drug labeling on a category-by-category basis, FDA has required certain "across-the-board" labeling during the course of the OTC drug review, such as the pregnancy-nursing warning in § 201.63 (21 CFR 201.63). Thus, an "across the board" approach is consistent with past agency regulatory actions. FDA has determined that a certain level (140 mg) of sodium

may present a potential safety problem, regardless of the source of the sodium. Therefore, the agency sees no reason to consider the warning on a category-by-category basis, which would result in a lack of uniformity in product labeling until the agency's evaluation of each drug category is completed. The agency's "across-the-board" approach to sodium labeling is not based on various drug categories; it is based on sodium being present in any OTC drug product.

5. Two comments agreed with the proposal to include both active and inactive ingredients when labeling/calculating total sodium content in an OTC drug product. One comment added that all recommended diluents should also be included in the sodium content labeling.

FDA appreciates the comments' concurrence. Including all sources of sodium in the total sodium content labeling enables consumers to determine the total amount of sodium consumed, regardless of the source. Diluents in OTC drug products are inactive ingredients and would be covered by this rulemaking. Under § 201.64(b) of this final rule, the agency is requiring the sodium content labeling of OTC drug products to include both active and inactive ingredients, which would include any diluents used in these products.

6. Several comments contended that the scope of covered products should be limited to products intended for ingestion rather than orally administered products. The comments argued that "orally administered" OTC drug products include dentifrices and mouthwashes that are not ingested, but rather expectorated. The comments pointed out any absorption of sodium from these products is minuscule.

The agency agrees that certain OTC drug products, such as dentifrices and mouthwashes, although orally administered, need not be covered by this rulemaking. These products are not intended to be ingested by the user, and the agency does not have sufficient information on the absorption of sodium when these products are used to warrant a labeling requirement at this time. However, orally administered gum or lozenge forms of OTC drug products intended for either partial or complete ingestion are covered by this rule. Therefore, in this final rule the agency is changing the language in § 201.64(a), (c), and (d) from "orally administered OTC drug products" to "OTC drug products intended for oral ingestion," and is adding the following sentence to § 201.64(a): "OTC drug products intended for oral ingestion include gum and lozenge dosage forms, but do not include dentifrices, mouthwashes, or mouth rinses."

The agency notes that some OTC laxative and vaginal drug products intended for rectal or vaginal administration can contain very high levels of sodium from both active and inactive ingredients. Significant amounts of some of these products may be absorbed. At this time, the agency does not have sufficient information on the absorption of sodium from these products to warrant a labeling requirement.

The agency is seeking comments from interested individuals on whether this final rule should be amended to include sodium content labeling for OTC rectal laxative, vaginal, dentifrice, mouthwash, and mouth rinse drug products. Comments should be sent to the Dockets Management Branch (address above) by July 22, 1996.

7. Two comments suggested requiring sodium content labeling for prescription drugs as well as OTC drug products. The comments stated that this information was important for the elderly and for patients receiving more than one drug product. One comment added that physicians treating patients on sodium restricted diets need to be aware of the amount of sodium in prescription products.

The agency agrees that sodium content labeling of prescription drugs would be beneficial. This information would be helpful to physicians, pharmacists, and consumers so they can make informed decisions. However, prescription drug labeling is outside the scope of this rulemaking for OTC drug products. Currently, the agency is actively considering the comments' recommendation for prescription drug labeling and is appraising whether the problem can best be dealt with via a regulation, guidance document, or another approach. At this time, the agency encourages sodium content labeling of prescription drugs on a voluntary basis.

C. Comments on Sodium Content Labeling

8. One comment recommended that any level of sodium in OTC drug products be listed on the label to enable consumers to make their own decision as to what is an insignificant amount of sodium in relation to their diet. Another comment suggested that the minimum level of sodium requiring labeling be increased from greater than 5 mg per maximum recommended dose to greater than 70 mg per maximum recommended daily dose. The comment mentioned that data generated by the Food and Nutrient Board indicate that 4,000 to 5,800 mg sodium are consumed per capita per day. Therefore, the sodium consumed in medications provides only a minimal amount and does not pose the same potential risk as food. The comment reasoned that 70 mg is only 5 percent of the Food and Nutrient Board's recommended daily intake of 1.4 grams (g) sodium for people on sodium restricted diets. The comment contended that this amount of sodium would not pose a risk to consumers on a low-sodium diet because 70 mg does not contribute a significant amount to their daily intake.

The agency has considered the comments' suggestions and has decided to use 5 mg of sodium per maximum recommended dose as the basis for including sodium content in the labeling of OTC drug products. As discussed in section II.E., comment 13 of this document, the agency considers a sodium level below 5 mg per dose to be physiologically insignificant. Thus, the agency is not requiring any labeling if the amount of sodium in the product is below 5 mg.

The agency considers a 5 mg maximum recommended dose standard a reasonable approach, based in part on experience with OTC antacid drug product labeling. Although the agency believes a 70 mg labeled maximum daily dose standard is not unreasonable, a 5 mg maximum labeled dose is consistent with the antacid monograph, which has been in effect since 1974. As discussed in the proposed rule, the existing requirement for OTC antacid drug products in § 331.30(f) (21 CFR 331.30(f)) provides that the labeling include sodium content per dosage unit if it contains 5 mg or more. This labeling requirement for OTC antacids has been in effect for over 20 years, and consumers are familiar with that approach. The sodium labeling requirements in this final rule, based on sodium content per dose, are similar to those in the antacid monograph.

The 5 mg approach will also result in more informative labeling than the 70 mg approach, because more products will be labeled with sodium content. More than 14 doses per day of a product containing less than 5 mg sodium per dose would be required to exceed 70 mg sodium per labeled maximum daily dose. Almost all OTC drug products are not taken that often. Thus, more products will likely require sodium content labeling based on 5 mg per dose than would result using 70 mg per labeled maximum daily dose as the basis. (See also section I.E., comment 13. of this document)

9. Three comments endorsed the agency's proposal to express the sodium

content of an OTC drug product in mg per dosage unit. The first comment suggested that those monographs now stating sodium labeling in milliequivalents (mEq) could be amended to mg. The comment stated that sodium declaration is more useful when provided in terms of dosage units (such as a teaspoonful or a tablet) than in terms of the recommended dosage amount, because the recommended dosage amount can vary. The second comment considered the option of having the sodium content declaration based on the recommended daily dose, but rejected that option because studies have shown that consumers frequently take more than the recommended daily dosage for OTC drug products. The third comment stated that the sodium content declaration should include the total sodium in both mg and mEq per dosage unit, average daily intake, and maximum recommended daily intake, if applicable.

The agency appreciates the comments' endorsements of the requirement that sodium content be listed in mg per dosage unit. The agency does not believe that listing some or all of the options (e.g., in both mg and mEq per dosage unit, per average daily intake, and per maximum daily intake) would be useful, because these multiple numbers would tend to confuse consumers and would unnecessarily clutter the label. Further, the agency believes consumers are more familiar with the term "mg" as used in food labeling than the term "mEq." Therefore, in this final rule the agency is using only mg per dosage unit for declaring the sodium content of OTC drug products.

As one comment noted, other OTC drug monographs address sodium labeling. These monographs will be amended to delete specific sodium labeling requirements so that the sodium labeling of all OTC drug products will appear in a single regulation. In the proposed rule for sodium labeling, the agency proposed to delete the existing requirements for OTC antacid drug products that appear in § 331.30(c)(5) and (f) (56 FR 19224 to 19225). The agency is finalizing that in this final rule. The sodium labeling requirements proposed in § 334.50(b)(5) and (b)(8) of the tentative final monograph for OTC laxative drug products (50 FR 2124 at 2153, January 15, 1985) and proposed in § 343.50(c)(1)(viii)(A) and (c)(1)(viii)(B) and § 343.50(c)(2)(viii)(A) and (c)(2)(viii)(B) of the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products (53 FR 46204 at 46256 to 46257, November 16, 1988) will be deleted when the final monographs for those drug classes are issued in a future issue of the **Federal Register**.

10. One comment requested that the agency require sodium content information to be presented in a predetermined place on the OTC drug product label, such as the ingredients list. The comment gave an example of a product containing a level of sodium requiring a warning while, at the same time, its label prominently displayed "75% less sodium than (a comparable product)" under active ingredients. The actual sodium content was listed at the end of a long paragraph of warnings and would make the product off-limits to an individual on a sodium-restricted diet. The comment contended that such labeling could potentially mislead consumers.

FDA agrees that the sodium content of an OTC drug product should be expressed at a specific location on the product label. By designating a specific location, consumers can find the sodium content of the product more quickly and with less confusion because the information will appear in the same location in the labeling of all orally ingested OTC drug products. The agency believes the most logical place for the sodium content labeling is at the end of the ingredients section. Further, the sodium content should be listed on a separate line after the heading 'Sodium Content' so that it is easily recognized by the consumer. Accordingly, the agency is amending proposed § 201.64(b) in this final rule to add a sentence that states: "The sodium content per dosage unit shall be listed on a separate line after the heading 'Sodium Content' as the last statement in the ingredients section."

11. One comment suggested that product labeling state a recommended safe range of sodium intake to provide consumers with a baseline for the control of sodium consumption.

The comment's request for labeling to advise consumers of a safe level of sodium is impractical because different medical and physiological problems require different levels of sodium restriction. Consumers should consult with physicians or other health professionals to determine the optimum levels of sodium consumption for their particular conditions. Thus, FDA is not requiring that the labeling state a recommended safe range of sodium intake at this time.

D. Comments on Sodium Warning Labeling

12. Two comments contended that the agency's proposal to include a sodium warning in the labeling of OTC drug products when the maximum recommended daily dose contains more than 140 mg of sodium is inconsistent with the labeling of foods, which does not require warnings at any level. The comments questioned the choice of 140 mg per maximum recommended daily dose as the level that triggers the sodium warning. The comments argued that the warning may unnecessarily confuse or alarm consumers. The first comment contended that the choice of 140 mg is completely arbitrary and questioned its scientific relevance. The comment stated that there is no evidence that consumers derive a significant percentage of sodium intake from OTC drug products.

The second comment stated that 140 mg of sodium is markedly lower than the level required to effect an increase in blood pressure. Asserting that OTC drugs are intended for short term use, the comment said intermittent use of such products will not affect the long-term benefit of a low-sodium diet because the resulting increase in blood pressure is rapidly reversed upon discontinuation of the product. The comment contended that the sodium warning, if required, should be based on "per dose" or "per dosage unit," rather than "maximum recommended daily dose," because a single dose more closely resembles a single serving, the unit used for food labeling. The comment also contended that the readability of the label will be compromised as the label becomes more cluttered, and that additional warnings of questionable value will only reduce the impact of other warnings on the label.

Noting that the sodium warning represents a familiar cautionary signal for consumers, a third comment stated that sodium-containing drugs could contribute a significant percentage of the daily sodium intake for some individuals. The comment mentioned that 1,000 mg of sodium per day is common for sodium restricted diets and that 140 mg of sodium represents 14 percent of the daily allowance for such diets. Several comments argued that sodium warnings should be considered on a case-by-case basis. (See section II.B., comment 4 of this document.)

FDA is establishing, where possible, uniformity in labeling between foods and OTC drug products. FDA recognizes that OTC drug products containing greater than 140 mg of sodium require a warning, while foods do not require a warning at any level of sodium. The labeling requirements for drugs need to be somewhat different from those for foods because of the differences in

consumption patterns. (See section II.A., comment 2 of this document.) The agency considers the labeling approach in this final rule appropriate, even though it is not the same as that for foods in all respects.

The choice of 140 mg as the level of sodium above which a warning should be required is not, as one comment contended, completely arbitrary. In a survey conducted by the agency and discussed in the final rule for declaration of sodium content and label claims for foods on the basis of sodium content (49 FR 15510 at 15519, April 18, 1984), it was found that over 50 percent of the foods surveyed contained less than 140 mg of sodium per serving. Thus, the agency determined that a substantial portion of the food supply is eligible to bear the "low sodium" descriptive term. By establishing 140 mg as an upper limit for the term "low sodium" for OTC drug products and requiring a warning for products containing sodium above that level, consumers can more easily monitor their total daily sodium intake. Requiring a warning for products below the 140 mg level could be confusing to consumers because some products containing the term "low-sodium" could, at the same time, contain the warning. FDA believes that a warning requirement for OTC drug products that contain more than 140 mg sodium would not unnecessarily confuse or alarm consumers, as two comments suggested. As another comment stated, the sodium warning represents a familiar cautionary signal for consumers. The agency concludes that the warning requirement will be welcomed by those who want to monitor their sodium intake.

The agency considers a numeric value that can be readily converted from mg to mEq useful for dietary planning, because physicians and dietitians sometimes calculate sodium in mEq rather than mg when prescribing sodium restrictions (49 FR 15510 at 15519). One mEq of sodium is equivalent to 23 mg. Thus, the 140 mg sodium level is approximately 6 mEq, allowing for easy calculation. The comments did not provide any evidence that warnings based on some other level of sodium would be more informative or useful to consumers than the 140 mg level proposed by the agency.

The agency agrees with one comment's contention that an OTC drug containing 140 mg of sodium is well below the level needed to affect blood pressure. However, it is the total amount of sodium consumed from all sources, both foods and drugs, that must be considered. As one comment pointed out, 140 mg represents 14 percent of a common (1,000 mg) sodium-restricted diet. The agency considers the level of sodium found in some OTC drug products, such as antacids, to be significant for people on low- sodium diets, especially if the drug product is taken in multiple daily doses as most antacids are. While many consumers do not derive significant amounts of sodium from OTC drug products, many others do. The agency concludes that it is important to provide information to those consumers who can be adversely affected by the sodium content of OTC drug products.

The agency disagrees with one comment's suggestion that the warning, if required, should be based on "per dose," rather than on "maximum recommended daily dose." Drug products are often taken in multiple doses in 1 day, while many different foods are more likely to be consumed only once a day. Thus, by equating one serving of food to one dose of drug, the intake per day for a drug would be a multiple of the amount in one dose, while the intake per day for a food may be only the amount found in a single serving of food. Because low-sodium diets are based on the total amount of sodium consumed in 1 day, the agency believes it is appropriate to base the sodium warning threshold on the labeled maximum daily dose.

The agency shares the comment's concern about readability of the label and avoiding unnecessary clutter. However, the agency considers a warning for OTC drug products containing appreciable amounts of sodium important to alert those consumers who wish or need to minimize their sodium intake. Therefore, in this final rule the agency is providing for a mandatory warning for all OTC drug products intended for oral ingestion containing more than 140 mg sodium per labeled maximum daily dose.

E. Comments on Use of Descriptive Terms in Sodium Labeling

13. One comment supported the intent of the sodium labeling proposal, but asserted that the term "sodium free" should be prohibited on drugs containing any sodium. The comment stated that labeling should be reliable and not mislead consumers as to the sodium content of OTC drug products. The comment contended that most consumers expect products labeled as "sodium free" to contain no sodium, but this would not be true if "sodium free" products were allowed to contain up to less than 5 mg of sodium. The comment mentioned health concerns about high blood pressure related to sodium, and argued that inaccurate labeling adversely impacts consumer purchasing decisions. The comment acknowledged that agency regulations for food allow products with less than 5 mg of sodium per serving to be labeled as "sodium free." The comment requested that the existing food regulations and the proposed OTC drug regulations be modified to prohibit the use of the term "sodium free" on food and drug products containing any sodium.

The agency has considered the comment's request and concludes that the term "sodium free" should only be used for products containing "0 mg" sodium, as defined in this final rule. Thus, the level of sodium in OTC drug products for which the term "sodium free" proposed in § 201.64(d) may be used is being changed from "less than 5 milligrams per maximum recommended daily dose" to "0 milligrams per labeled maximum daily dose" in this final rule. The agency's basis for the term "sodium free" in the proposed rule for sodium labeling of OTC drug products (56 FR 19222 at 19223) was based on the sodium labeling regulation for foods in § 101.61(b)(1)(i) (21 CFR 101.61(b)(1)(i)), which provides for the voluntary use of "sodium free" in the labeling of foods containing less than 5 mg sodium per serving. Most foods naturally contain at least trace amounts of sodium and the amount of sodium in a given food can vary. The agency concluded that the 5 mg sodium level for food is, practically speaking, a nonsignificant amount of dietary sodium.

However, in contrast to foods in which sodium may occur naturally, the amount of sodium in OTC drug products can be controlled during the manufacturing process. With today's analytical methodology, sodium can be accurately measured in parts per million. Thus, the agency believes consumers expect labels of drug products to accurately and reliably convey the level of ingredients in the product. While there may be no need to inform consumers of minute amounts of sodium (e.g., this final rule requires sodium content labeling only for those products containing 5 or more mg sodium per recommended dose), there is also no reason to label a product as "sodium free" when, in fact, it contains more than "0 mg" of sodium, as defined in this final rule.

In § 201.64(b) of this final rule, sodium content labeling is rounded-off to the nearest whole number as mg per dosage unit. Thus, a product containing less than 0.5 mg sodium per dosage unit could be labeled as "0 mg" sodium and

a product containing more than 0.5 mg and less than 1.5 mg sodium could be labeled as "1 mg" sodium. The agency believes that the term "sodium free" should not be used in the labeling of OTC drug products except for those products that contain "0 mg" sodium per labeled maximum daily dose. Thus, a product containing 0.4 mg sodium per tablet or teaspoon (rounded-off to 0) with labeling to take one tablet or teaspoon daily may use the descriptive term "sodium free" in its labeling. However, when the recommended dose in an OTC drug monograph provides for more than one dosage unit per day, e.g., the directions advise to take one or two tablets (or teaspoons) or to take two tablets (or teaspoons), the same product containing 0.4 mg sodium (rounded-off to 0) per tablet or teaspoon could not use the term "sodium free" because the labeled maximum dose contains 0.8 mg (rounded-off to 1). The labeling set forth in this final rule also eliminates the possibility that products labeled "sodium free" will at the same time be labeled with a sodium content greater than "0 mg," a potential basis for consumer confusion.

Similarly, the agency determined that the term "alcohol free" may not be used in the labeling of OTC drug products that contain any alcohol (see the **Federal Register** of March 13, 1995, 60 FR 13590). In § 328.50(e) (21 CFR 328.50(e)) the agency requires: "For a product to state in its labeling that it is 'alcohol free,' it must contain no alcohol (0 percent)."

Therefore, in this final rule, the agency is providing under § 201.64(d) for the voluntary use of the term "sodium free" if the amount of sodium in the labeled maximum daily dose is "0 mg." The agency recognizes that this position differs from that for nutrition labeling for foods, but believes that, for OTC drug product labeling, it is more appropriate. Any request to change the existing "sodium free" labeling for food products in § 101.61(b)(1)(i) should be made in a citizen petition, in accord with § 10.30 (21 CFR 10.30).

14. One comment recommended a relative print size limit on descriptive terms for sodium content to ensure that the primary emphasis of the OTC drug product label remains on the medical indication of the product. The comment stated that a consumer's foremost reason for purchasing an OTC drug product should be based on its medical indication, not on its sodium content.

FDA agrees with the comment that a relative print size limit on descriptive terms would be useful to help ensure that consumers are not distracted from the medical purpose of the product. The food regulations (21 CFR 103.13(f)) provide that a nutrient content claim shall be in a type size no larger than two times the statement of identity and shall not be unduly prominent in type style compared to the statement of identity. The agency believes that a related approach should also be used for OTC drug products.

The agency does not believe that the print size of the descriptive terms for sodium labeling for OTC drug products should be any larger than the print size of the statement of identity. Allowing larger print size (e.g., two times the size of that for the statement of identity, as for nutrient claims) could result in label clutter or misplaced emphasis. OTC drug products are generally marketed in smaller packages than foods and, thus, have less label space available than food products. Accordingly, the agency is adding in § 201.64(h) of this final rule the following statement:

The terms "sodium free," "very low sodium," and "low sodium" shall be in print size and style no larger than the product's statement of identity and shall not be unduly prominent in print size or style compared to the statement of identity.

15. One comment stated that descriptive terms in sodium labeling of OTC drug products will help improve consumer understanding of the message, and that the terms must be in simple language for lay persons to understand. Another comment contended that voluntary descriptive terms are unnecessary, often confusing, and potentially misleading. The comment suggested the proposed terms "sodium free," "very low sodium," and "low sodium" could translate into "healthy" and thereby become misleading. Further, the comment questioned using these descriptive terms in conjunction with the required warning, arguing that an inconsistent jump occurs from 140 mg (maximum daily dosage as "low sodium") to 141 mg (maximum daily dosage requiring a warning). The comment concluded that these two diverse measurements would prime the consumer for confusion.

The agency believes the voluntary descriptive terms "sodium free," "very low sodium," and "low sodium" are simple for consumers to understand. The terms are not intended to convey the exact level of sodium in a product, only an approximation. The comment did not provide any evidence that consumers might misinterpret these terms as meaning "healthy," specifically as they relate to OTC drug product labeling. The agency recognizes that the jump for the maximum daily dose from 140 mg, representing "low sodium," to 141 mg, requiring a warning, is not ideal. However, many standards have a set criterion, above or below which some action is triggered. The agency concludes there is no evidence to believe that these preset levels will lead to consumer confusion. (See also section II.A., comment 2 of this document.)

F. Comments on the Sodium-Hypertension Relationship

16. One comment considered it inappropriate for the agency to adopt regulations that address only sodium intake without reference to the anion (chloride). The comment urged that FDA regulations reflect the "emerging learning that the chloride ion is a necessary causative element in salt-induced hypertension." The comment referenced 16 studies (Ref. 1) to show that both the sodium and chloride ions play roles in inducing hypertension in some persons, and that other sodium salts do not induce hypertension.

The comment stated that a report by the National Academy of Sciences/National Research Council (Ref. 2) on diet and health correlated dietary "salt" or "sodium chloride," rather than "sodium," with hypertension. The comment added that recent medical surveys reflect the growing understanding that both the sodium and the chloride ions play roles in causing salt-sensitive hypertension. For example, the comment cited the Yearbook of Medicine (Ref. 3) as stating that "it remains to be established that any commonly ingested sodium salt other than sodium chloride can increase blood pressure in patients with salt-sensitive essential hypertension."

A second comment also contended that the effects of sodium on blood pressure are limited to sodium in the form of sodium chloride. The comment provided literature references (Ref. 4) suggesting that when the accompanying anion was other than chloride, sodium intake did not affect blood pressure. The comment mentioned that sodium in drug products is usually present as the benzoate, phosphate, or citrate salt, and contended that there is no clear evidence that the sodium content of the drug presents a hazard sufficient to deem the proposed warning appropriate.

One comment, which approved of sodium content labeling but was opposed to the warning, mentioned a submission made in response to FDA's request for scientific data and information to determine if a scientific basis exists for health claims relating to sodium and hypertension (Ref. 5). In that submission, the comment concluded that there are no well-

documented scientific data supporting a clear relationship between dietary sodium and hypertension applicable to the general public. The comment claimed that recent scientific evidence shows that a reduced sodium diet does not reduce the risk of hypertension in healthy individuals, but that it may contribute to heart disease and additional health risks. The comment concluded that appropriate scientific evidence does not exist to support any general health claims based on a relationship between sodium and hypertension.

The comment subsequently provided current articles and reviews on the salt-blood pressure relationship (Ref. 6). The comment emphasized one article (Ref. 7) that addressed the question of whether and how sodium chloride intake influences blood pressure. The authors stated that past literature was interpreted as "demonstrating a strong relationship between salt intake and blood pressure, a substantial benefit to all hypertensive persons of reduced salt intake, and a relatively low risk to society of promulgating this policy." Based on more recent studies, the authors suggested that only a portion (30 to 40 percent) of adults are salt (sodium chloride) sensitive and that salt sensitivity is linked to other cations and anions in the diet (e.g., adequate potassium and calcium intake may protect against salt sensitivity). The comment contended that because of new and mounting evidence that low-sodium diets may present some risk to individuals who are not salt-sensitive hypertensives, FDA should not require the sodium warning. Although opposed to the warning, the comment agreed that some individuals need to monitor their sodium intake.

The agency agrees with the comments that the sodium ion is not the only influence on hypertension. The question of whether or not the chloride ion is necessary for sodium to increase blood pressure is an academic issue. Even if chloride or another ion in addition to sodium is necessary to elevate blood pressure, hypertension is not the sole reason for this rulemaking. There are other conditions for which physicians recommend low-sodium diets. For instance, sodium bicarbonate reportedly exacerbates congestive heart failure. While sodium chloride is the primary source of sodium in the general population, sodium bicarbonate and other sodium-containing ingredients can account for a considerable amount of sodium in OTC drug products. Sodium labeling is not aimed specifically at patients with hypertension, but is intended to benefit all people who need or wish to monitor their sodium intake for whatever reason. The comments made no mention of the effect of sodium on any aspects of health other than hypertension.

This rulemaking does not state a causal relationship between sodium and hypertension, but rather provides for sodium content labeling and recommends that individuals on a low-sodium diet consult a physician if daily doses of greater than 140 mg sodium are to be ingested. This final rule provides that the labeling of OTC drug products include the total sodium content (including both active and inactive ingredients). It is reasonable for consumers on low-sodium diets to consult with their physician before taking OTC drug products with a high sodium content. The physician can put the variables into perspective and decide whether specific OTC drug products should be used. Alternative products containing less or no sodium may be available.

The agency has previously considered the relationship of sodium and hypertension and agrees that this is a complex subject that deserves more study. The agency recognizes that there are differences of opinion on this subject. Nonetheless, in a final rule on food labeling (health claims and labeling statements; sodium and hypertension), the agency stated "based on the totality of the scientific evidence, there is significant agreement among qualified experts that diets high in sodium are associated with high blood pressure" (58 FR 2820 at 2822, January 6, 1993). The agency stated that some studies indicate that sodium chloride and other sodium salts have distinct effects on blood pressure (58 FR 2829). Sodium chloride is the major source of sodium in foods and most studies investigating the effect of sodium on hypertension have involved either increasing or decreasing sodium chloride intake. The agency acknowledged that if it is true that sodium chloride, and not sodium, is implicated in high blood pressure, products containing other sources of sodium may be incorrectly considered to promote high blood pressure. The agency allowed the optional term "salt" to be used in addition to "sodium" in health claims in food labeling. However, the agency noted there is not significant scientific agreement that only sodium chloride affects blood pressure (58 FR 2829). Therefore, the basis for health claims relating to hypertension in that final rule was sodium content, not sodium chloride content.

FDA recognizes that not all individuals need to or should reduce their sodium intake. Sodium consumed from OTC drug products alone may, for most individuals, be insignificant and may not cause a significant increase in blood pressure. However, OTC drug products are not a consumer's sole source of sodium. All sources of sodium must be taken into account when monitoring daily intake. Even though, as one comment suggested, some individuals may need counseling from physicians or dietitians in order to maintain a strict low-sodium diet, the agency considers the sodium warning for OTC drug products helpful even for those individuals. This rulemaking does not recommend specific levels of sodium intake for the general population or for individuals h specific conditions. However, for those who need or want to monitor their sodium intake, the agency concludes that sodium content and warning labeling for OTC drug products is useful.

References

(1) Comment No. C00017, Docket No. 90N–0309, Dockets Management Branch.

(2) Committee on Diet and Health, National Academy of Sciences/National Research Council (U.S.), Diet and Health: Implications for Reducing Chronic Disease Risk, National Academy Press, Washington, 1989.

(3) D. E. Rogers et al., editors, Yearbook of Medicine, Yearbook Medical Publishers, Inc., Chicago, pp 589–590, 1989.

(4) Comment No. C00014, Docket No. 90N–0309, Dockets Management Branch.

(5) Comment No. C00007, Docket No. 91N–0095, Dockets Management Branch.

(6) Comment No. SUP 1, Docket No. 90N–0309, Dockets Management Branch.

(7) Muntzel, M., and T. Drueke, "A Comprehensive Review of the Salt and Blood Pressure Relationship," American Journal of Hypertension, 5:1S–42S, 1992.

III. Summary of Significant Changes from the Proposed Rule

1. In this final rule, the agency is revising § 201.64(b) to eliminate the 5-mg rounding-off provision. The final rule requires that the sodium content be rounded-off to the nearest whole number, whatever the content, per dosage unit. (See section II.A., comment no. 3 of this document.)

2. The agency is changing the language in § 201.64(a) and (c) through (f) from "orally administered OTC drug products" to "OTC drug products intended for oral ingestion," and is adding the following sentence to § 201.64(a): "OTC drug products intended for oral ingestion include gum and lozenge dosage forms, but do not include dentifrices, mouthwashes, or mouth rinses." (See section II.B., comment no. 6 of this document.)

3. The agency is adding the following in § 201.64(b): "The sodium content per

dosage unit shall be listed on a separate line after the heading 'Sodium Content' as the last statement in the ingredients section." (See section II.C., comment no. 10 of this document.)

4. Proposed § 201.64(d) provided for the voluntary use of the term "sodium free" for products containing "less than 5 milligrams" of sodium in the maximum recommended daily dose. This final rule allows for the use of the term "sodium free" only for those products containing "0 mg" of sodium in the labeled maximum daily dose. The agency is revising the example in proposed § 201.64(d) to clarify the basis for use of descriptive terms, taking into account the rounding-off provision for the sodium content in mg per dosage unit to the nearest whole number. (See section II.A., comment no. 3; section II.E., comment no. 13; and part III.1 of this document.)

5. The agency has added a provision in § 201.64(h) of this final rule limiting the print size and style of the "sodium free," "very low sodium," and "low sodium" terms to no larger than and not unduly prominent in comparison to the product's statement of identity. (See section II.E., comment no. 14 of this document.)

IV. The Agency's Final Conclusions on Sodium Labeling

FDA believes that the public interest in and the public health consequences of sodium intake have produced a need for more informative and consistent sodium content labeling information on drugs and foods. This is true for individuals with hypertension, heart failure, or other conditions who must monitor their sodium intake.

To establish uniform content declarations, warnings, and descriptive terms for sodium in foods and OTC drug products, the agency is implementing the following requirements for OTC drug products intended for oral ingestion: (1) The product must have a sodium content declaration if it contains five mg or more of sodium per single labeled dose (which may involve one or more dosage units, e.g., tablets, teaspoons). (2) The product must bear a sodium warning if it contains more than 140 mg (about 6 mEq) of sodium in the labeled maximum daily dose. This warning states: "Do not use this product if you are on a sodium-restricted diet unless directed by a doctor." (3) Manufacturers may use the following descriptive terms for sodium content: "Sodium-free" for products containing 0 mg sodium in the labeled maximum daily dose; "very low sodium" for products containing 35 mg or less; and "low sodium" for products containing 140 mg or less. The requirement for a sodium content declaration is based on the number of mg of sodium in one dose, while the requirement for a warning statement and the use of the optional descriptive terms are based on the number of mg of sodium in the labeled maximum daily dose.

Because consumers and health professionals are accustomed to computing sodium intake in mg (49 FR 15510 at 15530), and to provide for uniformity in the declaration of sodium content labeling for foods and OTC drug products intended for oral ingestion, the term "milligrams" or the abbreviation "mg" is used to designate the sodium content of OTC drug products. The total sodium content (including both active and inactive ingredients), in mg per dosage unit, should be rounded-off to the nearest whole number. If the single recommended dose (one or more dosage units) of the product contains 5 mg or more of sodium, a declaration of sodium content expressed in mg per single dosage unit (e.g., tablet, teaspoon) is required to be listed on a separate line after the heading "Sodium Content" as the last statement in the ingredients section.

The new sodium labeling requirements apply to all OTC drugs intended for oral ingestion, whether marketed under an OTC drug monograph, an approved application, or no application. The existing requirements relating to sodium labeling in § 331.30(c)(5) and (f) of the final monograph for OTC antacid drug products are being deleted. The proposed sodium labeling requirements being considered 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**.

V. Analysis of Impacts

An analysis of the costs and benefits of this regulation, conducted under Executive Order 12291 was discussed in the proposed rule (56 FR 19222 at 19225). No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking. Executive Order 12291 has been superseded by Executive Order 12866.

FDA has examined the impacts of the final 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 final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final 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. With this final rule, one-time label modification costs associated with changing product labels will 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 this final 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 sodium. The monograph for those products has been in effect since 1974 and these products currently bear sodium labeling. For these products, the labeling change will involve a slight change in wording, resulting only in a minor cost to have a labeling revision printed. In almost all cases, manufacturers can routinely revise labeling at the next printing so that minimal costs should be incurred. Manufacturers will have up to 12 months after publication of this final rule in the **Federal Register** to revise their product labeling. FDA anticipates that most antacid drug products would undergo a label printing within a 12-month period. Because these OTC antacid drug products already bear sodium labeling warnings, the agency may extend the time period beyond 12 months, if necessary, upon request, for the revised wording to be implemented.

Other OTC drug products (i.e., laxatives and internal analgesics) having a few sodium-containing active ingredients affected by this final rule previously were not required to bear sodium labeling. These products will need to have new labels printed to incorporate the sodium labeling. These products must also have new labeling printed in the future when the final monographs for OTC laxative and internal analgesic drug products are published. This again involves one-time label modification costs. For products undergoing such labeling changes, the incremental costs attributable to this rule for sodium labeling will be

negligible. A limited number of OTC laxative and internal analgesic drug products contain sodium-containing active ingredients. Tentative final monographs with sodium labeling requirements for these products have been published, and no adverse comments concerning economic impacts have been received in response to the proposals. The agency is not aware of any significant number of other OTC drug products that will be affected due to the sodium content of inactive ingredients. Use of the descriptive terms for sodium set forth in this rulemaking is voluntary. Therefore, any implementation of these terms could be done by a manufacturer at any time that new labeling is ordered. The agency finds that the cost of adding one of these descriptive terms to the product's labeling will be negligible. Accordingly, the agency certifies that the final 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.

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 warning statement and the sodium terms 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 sodium content per dosage unit is product formulation information that manufacturers have on hand as part of their usual and customary business practice.

VII. 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.

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, title 21 of the Code of Federal Regulations is 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 § 201.64 is added to subpart C to read as follows:

§ 201.64 Sodium labeling.

(a) The labeling of over-the-counter (OTC) drug products intended for oral ingestion shall contain the sodium content per dosage unit (e.g., tablet, teaspoonful) if the sodium 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 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. The sodium content shall be rounded-off to the nearest whole number. The sodium content per dosage unit shall be listed on a separate line after the heading "Sodium 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 sodium present in the labeled maximum daily dose of the product is more than 140 milligrams: "Do not use this product if you are on a sodium-restricted diet unless directed by a doctor."

(d) The term "sodium free" may be used in the labeling of OTC drug products intended for oral ingestion if the amount of sodium in the labeled maximum daily dose is 0 milligram. For example, a product containing 0.4 (rounded-off to zero (0)) milligram sodium per tablet with directions to take one tablet daily may use the term "sodium free" in its labeling. However, when the recommended dose provides for taking more than one dosage unit per day, e.g., take one or two tablets, or take two tablets, the same product containing 0.4 milligram sodium per tablet shall not use the term "sodium free" because the labeled maximum daily dose contains 0.8 milligram sodium.

(e) The term "very low sodium" may be used in the labeling of OTC drug products intended for oral ingestion if the amount of sodium in the labeled maximum daily dose is 35 milligrams or less.

(f) The term "low sodium" may be used in the labeling of OTC drug products intended for oral ingestion if the amount of sodium in the labeled maximum daily dose is 140 milligrams or less.

(g) The term "salt" is not synonymous with the term sodium and shall not be used interchangeably or substituted for the term "sodium."

(h) The terms "sodium free," "very low sodium," and "low sodium" shall be in print size and style no larger than the product's statement of identity and shall not be unduly prominent in print size or style compared to the statement of identity.

(i) 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 April 22, 1997, 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

3. 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]

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

Dated: March 30, 1996.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 96–9735 Filed 4–19–96; 8:45 am]

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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 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-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, hypercalcemia, 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 hypermagnesemia 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 hypermagnesemia 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, 1975), 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 Concensus 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, miligrams 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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