

individual adverse drug experience reports (FDA Form 3500A or equivalent) along with a summary of all serious adverse drug experiences and expected or frequently reported side effects for the condition. Individual reports that are not in English must be translated to English in accordance with §10.20(c)(2) of this chapter.

(g) *Administrative procedures.* The agency may use an advisory review panel to evaluate the safety and effectiveness data in accord with the provisions of §330.10(a)(3). Alternatively, the agency may evaluate the data in conjunction with the advisory review panel or on its own without using an advisory review panel. The agency will use the safety, effectiveness, and labeling standards in §330.10(a)(4)(i) through (a)(4)(vi) in evaluating the data.

(1) If the agency uses an advisory review panel to evaluate the data, the panel may submit its recommendations in its official minutes of meeting(s) or by a report under the provisions of §330.10(a)(5).

(2) The agency may act on an advisory review panel's recommendations using the procedures in §§330.10(a)(2) and 330.10(a)(6) through (a)(10).

(3) If the condition is initially determined to be generally recognized as safe and effective for OTC use in the United States, the agency will propose to include it in an appropriate OTC drug monograph(s), either by amending an existing monograph(s) or establishing a new monograph(s), if necessary.

(4) If the condition is initially determined not to be generally recognized as safe and effective for OTC use in the United States, the agency will inform the sponsor and other interested parties who have submitted data of its determination by letter, a copy of which will be placed on public display in the docket established in the Dockets Management Branch. The agency will publish a notice of proposed rulemaking to include the condition in §310.502 of this chapter.

(5) Interested parties will have an opportunity to submit comments and new data. The agency will subsequently publish a final rule (or reproposal if necessary) in the FEDERAL REGISTER.

(h) *Marketing.* A condition submitted under this section for consideration in the OTC drug monograph system may be marketed in accordance with an applicable final OTC drug monograph(s) only after the agency determines that the condition is generally recognized as safe and effective and includes it in the appropriate OTC drug final monograph(s), and the condition complies with paragraph (i) of this section. When an OTC drug monograph has not been finalized and finalization is not imminent, after the agency has evaluated the comments to a proposed rule to include a new condition in a tentative final monograph as generally recognized as safe and effective and the agency has not changed its position as a result of the comments, and the condition complies with paragraph (i) of this section, the agency may publish a notice of enforcement policy that allows marketing to begin pending completion of the final monograph subject to the risk that the agency may, prior to or in the final monograph, adopt a different position that could require re-labeling, recall, or other regulatory action.

(i) *Compendial monograph.* Any active ingredient or botanical drug substance included in a final OTC drug monograph or the subject of an enforcement notice described in paragraph (h) of this section must be recognized in an official USP–NF drug monograph that sets forth its standards of identity, strength, quality, and purity. Sponsors must include an official or proposed compendial monograph as part of the safety and effectiveness data submission listed in §330.10(a)(2) under item VII of the outline entitled “OTC DRUG REVIEW INFORMATION.”

[67 FR 3074, Jan. 23, 2002]

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

### Subpart A—General Provisions

Sec.  
331.1 Scope.

### Subpart B—Active Ingredients

331.10 Antacid active ingredients.  
331.11 Listing of specific active ingredients.

331.15 Combination with nonantacid active ingredients.

**Subpart C—Testing Procedures**

331.20 Determination of percent contribution of active ingredients.

331.21 Test Modifications.

**Subpart D—Labeling**

331.30 Labeling of antacid products.

331.80 Professional labeling.

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

SOURCE: 39 FR 19874, June 4, 1974, unless otherwise noted.

**Subpart A—General Provisions**

**§ 331.1 Scope.**

An over-the-counter antacid product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

**Subpart B—Active Ingredients**

**§ 331.10 Antacid active ingredients.**

(a) The active antacid ingredients of the product consist of one or more of the ingredients permitted in § 331.11 within any maximum daily dosage limit established, each ingredient is included at a level that contributes at least 25 percent of the total acid neutralizing capacity of the product, and the finished product contains at least 5 meq of acid neutralizing capacity as measured by the procedure provided in the United States Pharmacopeia 23/National Formulary 18. The method established in § 331.20 shall be used to determine the percent contribution of each antacid active ingredient.

(b) This section does not apply to an antacid ingredient specifically added as a corrective to prevent a laxative or constipating effect.

[39 FR 19874, June 4, 1974, as amended at 61 FR 4822, Feb. 8, 1996]

**§ 331.11 Listing of specific active ingredients.**

(a) Aluminum-containing active ingredients:

- (1) Basic aluminum carbonate gel.

- (2) Aluminum hydroxide (or as aluminum hydroxide-hexitol stabilized polymer, aluminum hydroxide-magnesium carbonate codried gel, aluminum hydroxide-magnesium trisilicate codried gel, aluminum-hydroxide sucrose powder hydrated).

- (3) Dihydroxyaluminum aminoacetate and dihydroxyaluminum aminoacetic acid.

- (4) Aluminum phosphate gel when used as part of an antacid combination product and contributing at least 25 percent of the total acid neutralizing capacity; maximum daily dosage limit is 8 grams.

- (5) Dihydroxyaluminum sodium carbonate.

- (b) Bicarbonate-containing active ingredients: Bicarbonate ion; maximum daily dosage limit 200 mEq. for persons up to 60 years old and 100 mEq. for persons 60 years or older.

- (c) Bismuth-containing active ingredients:

- (1) Bismuth aluminate.
- (2) Bismuth carbonate.
- (3) Bismuth subcarbonate.
- (4) Bismuth subgallate.
- (5) Bismuth subnitrate.

- (d) Calcium-containing active ingredients: Calcium, as carbonate or phosphate; maximum daily dosage limit 160 mEq. calcium (e.g., 8 grams calcium carbonate).

- (e) Citrate-containing active ingredients: Citrate ion, as citric acid or salt; maximum daily dosage limit 8 grams.

- (f) Glycine (aminoacetic acid).

- (g) Magnesium-containing active ingredients:

- (1) Hydrate magnesium aluminate activated sulfate.
- (2) Magaldrate.
- (3) Magnesium aluminosilicates.
- (4) Magnesium carbonate.
- (5) Magnesium glycinate.
- (6) Magnesium hydroxide.
- (7) Magnesium oxide.
- (8) Magnesium trisilicate.
- (h) Milk solids, dried.

- (i) Phosphate-containing active ingredients:

- (1) Aluminum phosphate; maximum daily dosage limit 8 grams.
- (2) Mono or dibasic calcium salt; maximum daily dosage limit 2 grams.
- (3) Tricalcium phosphate; maximum daily dosage limit 24 grams.

## § 331.15

(j) Potassium-containing active ingredients:

(1) Potassium bicarbonate (or carbonate when used as a component of an effervescent preparation); maximum daily dosage limit 200 mEq. of bicarbonate ion for persons up to 60 years old and 100 mEq. of bicarbonate ion for persons 60 years or older.

(2) Sodium potassium tartrate.

(k) Sodium-containing active ingredients:

(1) Sodium bicarbonate (or carbonate when used as a component of an effervescent preparation); maximum daily dosage limit 200 mEq. of sodium for persons up to 60 years old and 100 mEq. of sodium for persons 60 years or older, and 200 mEq. of bicarbonate ion for persons up to 60 years old and 100 mEq. of bicarbonate ion for persons 60 years or older. That part of the warning required by § 330.1(g), which states, "Keep this and all drugs out of the reach of children" is not required on a product which contains only sodium bicarbonate powder and which is intended primarily for other than drug uses.

(2) Sodium potassium tartrate.

(1) Silicates:

(1) Magnesium aluminosilicates.

(2) Magnesium trisilicate.

(m) Tartrate-containing active ingredients. Tartaric acid or its salts; maximum daily dosage limit 200 mEq. (15 grams) of tartrate.

[39 FR 19874, June 4, 1974, as amended at 51 FR 27763, Aug. 1, 1986; 55 FR 19859, May 11, 1990]

### § 331.15 Combination with nonantacid active ingredients.

(a) An antacid may contain any generally recognized as safe and effective nonantacid laxative ingredient to correct for constipation caused by the antacid. No labeling claim of the laxative effect may be used for such a product.

(b) An antacid may contain any generally recognized as safe and effective analgesic ingredient(s), if it is indicated for use solely for the concurrent symptoms involved, e.g., headache and acid indigestion, and is marketed in a form intended for ingestion as a solution.

(c) An antacid may contain any generally recognized as safe and effective antifatulent ingredient if it is indi-

## 21 CFR Ch. I (4-1-02 Edition)

cated for use solely for the concurrent symptoms of gas associated with heartburn, sour stomach or acid indigestion.

### Subpart C—Testing Procedures

#### § 331.20 Determination of percent contribution of active ingredients.

To determine the percent contribution of an antacid active ingredient, place an accurately weighed amount of the antacid active ingredient equal to the amount present in a unit dose of the product into a 250-milliliter (mL) beaker. If wetting is desired, add not more than 5 mL of alcohol (neutralized to an apparent pH of 3.5), and mix to wet the sample thoroughly. Add 70 mL of water, and mix on a magnetic stirrer at 300±30 r.p.m. for 1 minute. Analyze the acid neutralizing capacity of the sample according to the procedure provided in the United States Pharmacopeia 23/National Formulary 18 and calculate the percent contribution of the antacid active ingredient in the total product as follows:

Percent contribution = (Total mEq. Antacid Active Ingredient x100)/(Total mEq. Antacid Product).

[61 FR 4823, Feb. 8, 1996]

#### § 331.21 Test modifications.

The formulation or mode of administration of certain products may require a modification of the United States Pharmacopeia 23/National Formulary 18 acid neutralizing capacity test. Any proposed modification and the data to support it shall be submitted as a petition under the rules established in § 10.30 of this chapter. All information submitted will be subject to the disclosure rules in part 20 of this chapter.

[61 FR 4823, Feb. 8, 1996]

### Subpart D—Labeling

#### § 331.30 Labeling of antacid products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antacid."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: "For the relief of" (optional, any or all of the following:) "heartburn," "sour stomach,"

and/or “acid indigestion” (which may be followed by the optional statement:) “and upset stomach associated with” (optional, as appropriate) “this symptom” or “these symptoms.” Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in §330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(c) *Warnings.* The labeling of the product contains the following warnings, under the heading “Warnings”, which may be combined but not rearranged to eliminate duplicative words or phrases if the resulting warning is clear and understandable:

(1) “Do not take more than (maximum recommended daily dosage, broken down by age groups if appropriate, expressed in units such as tablets or teaspoonfuls) 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.”

(2) For products which cause constipation in 5 percent or more of persons who take the maximum recommended dosage: “May cause constipation.”

(3) For products which cause laxation in 5 percent or more of persons who take the maximum recommended dosage: “May have laxative effect.”

(4) For products containing more than 50 mEq. of magnesium in the recommended daily dosage: “Do not use this product except under the advice and supervision of a physician if you have kidney disease.”

(5) For products containing more than 25 mEq. potassium in the maximum recommended daily dose: “Do not use this product except under the advice and supervision of a physician if you have kidney disease.”

(6) For products containing more than 5 gm per day lactose in a maximum daily dosage: “Do not use this product except under advice and super-

vision of a physician if you are allergic to milk or milk products.”

(d) *Drug interaction precaution.* The labeling of the product contains the following statement “Ask a doctor or pharmacist before use if you are [bullet]<sup>1</sup> presently taking a prescription drug. Antacids may interact with certain prescription drugs.”

(e) *Directions for use.* The labeling of the product contains the recommended dosage, under the heading “Directions”, per time interval (e.g., every 4 hours) or time period (e.g., 4 times a day) broken down by age groups if appropriate, followed by “or as directed by a physician.”

(f) *Exemption from the general accidental overdose warning.* The labeling for antacid drug products containing the active ingredients identified in §331.11(a), (b), and (d) through (m); permitted combinations of these ingredients provided for in §331.10; and any of these ingredients or combinations of these ingredients in combination with simethicone (identified in §332.10 of this chapter and provided for in §331.15(c)), are exempt from the requirement in §330.1(g) of this chapter that the labeling bear the general warning statement “In case of accidental overdose, seek professional assistance or contact a poison control center immediately.” With the exception of sodium bicarbonate powder products identified in §331.11(k)(1), the labeling must continue to bear the first part of the general warning in §330.1(g) of this chapter, which states, “Keep this and all drugs out of the reach of children.”

(g) [Reserved]

(h) The word “doctor” may be substituted for the word “physician” in any of the labeling statements in this section.

[39 FR 19874, June 4, 1974, as amended at 47 FR 38484, Aug. 31, 1982; 51 FR 16266, May 1, 1986; 51 FR 27763, Aug. 1, 1986; 52 FR 7830, Mar. 13, 1987; 55 FR 11581, Mar. 29, 1990; 58 FR 45208, Aug. 26, 1993; 59 FR 60556, Nov. 25, 1994; 61 FR 17806, Apr. 22, 1996; 64 FR 13295, Mar. 17, 1999]

<sup>1</sup> See §201.66(b)(4) of this chapter.

**§ 331.80**

**21 CFR Ch. I (4-1-02 Edition)**

**§ 331.80 Professional labeling.**

(a) The labeling of the product provided to health professionals (but not to the general public):

(1) Shall contain the neutralizing capacity of the product as calculated using the procedure set forth in United States Pharmacopeia 23/National Formulary 18 expressed in terms of the dosage recommended per minimum time interval or, if the labeling recommends more than one dosage, in terms of the minimum dosage recommended per minimum time interval.

(2) May contain an indication for the symptomatic relief of hyperacidity associated with the diagnosis of peptic ulcer, gastritis, peptic esophagitis, gastric hyperacidity, and hiatal hernia.

(3) *For products containing basic aluminum carbonate gel identified in § 331.11(a)(1)—Indication.* “For the treatment, control, or management of hyperphosphatemia, or for use with a low phosphate diet to prevent formation of phosphate urinary stones, through the reduction of phosphates in the serum and urine.”

(4) *For products containing aluminum identified in § 331.11(a)—Warnings.* (i) Prolonged use of aluminum-containing antacids in patients with renal failure may result in or worsen dialysis osteomalacia. Elevated tissue aluminum levels contribute to the development of the dialysis encephalopathy and osteomalacia syndromes. Small amounts of aluminum are absorbed from the gastrointestinal tract and renal excretion of aluminum is impaired in renal failure. Aluminum is not well removed by dialysis because it is bound to albumin and transferrin, which do not cross dialysis membranes. As a result, aluminum is deposited in bone, and dialysis osteomalacia may develop when large amounts of aluminum are ingested orally by patients with impaired renal function.

(ii) Aluminum forms insoluble complexes with phosphate in the gastrointestinal tract, thus decreasing phosphate absorption. Prolonged use of aluminum-containing antacids by normophosphatemic patients may result in hypophosphatemia if phosphate intake is not adequate. In its more severe forms, hypophosphatemia can lead to

anorexia, malaise, muscle weakness, and osteomalacia.

(b) Professional labeling for an antacid-antiflatulent combination may contain the information allowed for health professionals for antacids and antiflatulents.

[39 FR 19874, June 4, 1974. Redesignated and amended at 55 FR 19859, May 11, 1990]

**PART 332—ANTIFLATULENT PRODUCTS FOR OVER-THE-COUNTER HUMAN USE**

**Subpart A—General Provisions**

Sec.

332.1 Scope.

332.3 Definitions.

**Subpart B—Active Ingredients**

332.10 Antiflatulent active ingredients.

332.15 Combination with non-antiflatulent active ingredients.

**Subpart C—Labeling**

332.30 Labeling of antiflatulent products.

332.31 Professional labeling.

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

SOURCE: 39 FR 19877, June 4, 1974, unless otherwise noted.

**Subpart A General Provisions**

**§ 332.1 Scope.**

An over-the-counter antiflatulent product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

**§ 332.3 Definitions.**

As used in this part:

*Antigas.* A term that may be used interchangeably with the term anti-flatulent. Neither term should be considered as describing the mechanism of action of the active ingredient contained in the product.

[61 FR 8838, Mar. 5, 1996]