appropriate regulatory action will commence immediately and will not await publication of a final monograph. Marketing of such a product with a formulation or labeling not in accord with a proposed monograph or tentative final monograph also may result in regulatory action against the product, the marketer, or both.

(c) An OTC drug product that contains: (1) An active ingredient limited, on or after May 11, 1972, to prescription use for the indication and route of administration under consideration by an OTC advisory review panel, and not thereafter exempted from such limitation pursuant to §310.200 of this chapter, or

(2) An active ingredient at a dosage level higher than that available in any OTC drug product on December 4, 1975, which ingredient and/or dosage level is classified by the panel in category II (conditions subject to §330.10(a)(6)(ii)), may be marketed only after:

(i) The Center for Drug Evaluation and Research or the Commissioner tentatively determines that the ingredient is generally recognized as safe and effective, and the Commissioner states by notice in the FEDERAL REGISTER (separately or as part of another document) that marketing under specified conditions will be permitted;

(ii) The ingredient is determined by the Commissioner to be generally recognized as safe and effective and is included in the appropriate published OTC drug final monograph; or

(iii) A new drug application for the product has been approved.

(d) An OTC drug product that contains: (1) An active ingredient limited, on or after May 11, 1972, to prescription use for the indication and route of administration under consideration by an OTC advisory review panel, and not thereafter exempted from such limitation pursuant to §310.200 of this chapter, or

(2) An active ingredient at a dosage level higher than that available in any OTC drug product on December 4, 1975, which ingredient and/or dosage level is classified by the panel in category III (conditions subject to §330.10(a)(6)(iii)), may be marketed only after:

(i) The Center for Drug Evaluation and Research or the Commissioner tentatively determines that the ingredient is generally recognized as safe and effective, and the Commissioner states by notice in the FEDERAL REGISTER (separately or as part of another document) that marketing under specified conditions will be permitted;

(ii) The ingredient is determined by the Commissioner to be generally recognized as safe and effective and is included in the appropriate published OTC drug final monograph; or

(iii) A new drug application for the product has been approved.

(e) This section applies only to conditions under consideration as part of the OTC drug review initiated on May 11, 1972, and evaluated under the procedures set forth in §330.10. Section 330.14(h) applies to the marketing of all conditions under consideration and evaluated using the criteria and procedures set forth in §330.14.

[41 FR 32582, Aug. 4, 1976, as amended at 47 FR 17739, Apr. 23, 1982; 50 FR 8996, Mar. 6, 1985; 55 FR 11581, Mar. 29, 1990; 67 FR 3074, Jan. 23, 2002]

§330.14 Additional criteria and procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded.

(a) *Introduction.* This section sets forth additional criteria and procedures by which over the counter (OTC) drugs initially marketed in the United States after the OTC drug review began in 1972 and OTC drugs without any U.S. marketing experience can be considered in the OTC drug monograph system. This section also addresses conditions regulated as a cosmetic or dietary supplement in a foreign country that would be regulated as OTC drugs in the United States. For purposes of this section, ''condition'' means an active ingredient or botanical drug substance (or a combination of active ingredients or botanical drug substances), dosage form, dosage strength, or route of administration, marketed for a specific OTC use, except as excluded in paragraph (b)(2) of this section. For purposes of this part, ''botanical drug substance'' means a drug substance derived from one or more plants, algae, or macroscopic fungi, but does not include a highly purified or

chemically modified substance derived from such a source.

(b) *Criteria.* To be considered for inclusion in the OTC drug monograph system, the condition must meet the following criteria:

(1) The condition must be marketed for OTC purchase by consumers. If the condition is marketed in another country in a class of OTC drug products that may be sold only in a pharmacy, with or without the personal involvement of a pharmacist, it must be established that this marketing restriction does not indicate safety concerns about the condition's toxicity or other potentiality for harmful effect, the method of its use, or the collateral measures necessary to its use.

(2) The condition must have been marketed OTC for a minimum of 5 continuous years in the same country and in sufficient quantity, as determined in paragraphs (c)(2)(ii), (c)(2)(iii), and (c)(2)(iv) of this section. Depending on the condition's extent of marketing in only one country with 5 continuous years of marketing, marketing in more than one country may be necessary.

(c) *Time and extent application.* Certain information must be provided when requesting that a condition subject to this section be considered for inclusion in the OTC drug monograph system. The following information must be provided in the format of a time and extent application (TEA):

(1) Basic information about the condition that includes a description of the active ingredient(s) or botanical drug substance(s), pharmacologic class(es), intended OTC use(s), OTC strength(s) and dosage form(s), route(s) of administration, directions for use, and the applicable existing OTC drug monograph(s) under which the condition would be marketed or the request and rationale for creation of a new OTC drug monograph(s).

(i) A detailed chemical description of the active ingredient(s) that includes a full description of the drug substance, including its physical and chemical characteristics, the method of synthesis (or isolation) and purification of the drug substance, and any specifications and analytical methods necessary to ensure the identity, strength, quality, and purity of the drug substance.

(ii) For a botanical drug substance(s), a detailed description of the botanical ingredient (including proper identification of the plant, plant part(s), alga, or macroscopic fungus used; a certificate of authenticity; and information on the grower/supplier, growing conditions, harvest location and harvest time); a qualitative description (including the name, appearance, physical/chemical properties, chemical constituents, active constituent(s) (if known), and biological activity (if known)); a quantitative description of the chemical constituents, including the active constituent(s) or other chemical marker(s) (if known and measurable); the type of manufacturing process (e.g., aqueous extraction, pulverization); and information on any further processing of the botanical substance (e.g., addition of excipients or blending).

(iii) Reference to the current edition of the U.S. Pharmacopeia (USP)–National Formulary (NF) or foreign compendiums may help satisfy the requirements in this section.

(2) A list of all countries in which the condition has been marketed. Include the following information for each country. (For a condition that has been marketed OTC in 5 or more countries with a minimum of 5 continuous years of marketing in at least one country, the sponsor may submit information in accordance with paragraph (c)(4) of this section):

(i) How the condition has been marketed (e.g., OTC general sales direct-to-consumer; sold only in a pharmacy, with or without the personal involvement of a pharmacist; dietary supplement; or cosmetic). If the condition has been marketed as a nonprescription pharmacy-only product, establish that this marketing restriction does not indicate safety concerns about its toxicity or other potentiality for harmful effect, the method of its use, or the collateral measures necessary to its use.

(ii) The cumulative total number of dosage units (e.g., tablets, capsules, ounces) sold for each dosage form of the condition. Manufacturers or suppliers of OTC active ingredients may provide dosage unit information as the total weight of active ingredient sold. List the various package sizes for each dosage form in which the condition is

marketed OTC. Provide an estimate of the minimum number of potential consumer exposures to the condition using one of the following calculations:

(A) Divide the total number of dosage units sold by the number of dosage units in the largest package size marketed, or

(B) Divide the total weight of the active ingredient sold by the total weight of the active ingredient in the largest package size marketed.

(iii) A description of the population demographics (percentage of various racial/ethnic groups) and the source(s) from which this information has been compiled, to ensure that the condition's use(s) can be reasonably extrapolated to the U.S. population.

(iv) If the use pattern (*i.e.*, how often it is to be used (according to the label) and for how long) varies between countries based on the condition's packaging and labeling, or changes in use pattern have occurred over time in one or more countries, describe the use pattern for each country and explain why there are differences or changes.

(v) A description of the country's system for identifying adverse drug experiences, especially those found in OTC marketing experience, including method of collection if applicable.

(3) A statement of how long the condition has been marketed in each country and how long the current product labeling has been in use, accompanied by a copy of the current product labeling. All labeling that is not in English must be translated to English in accordance with §10.20(c)(2) of this chapter. State whether the current product labeling has or has not been authorized, accepted, or approved by a regulatory body in each country where the condition is marketed.

(4) For a condition that has been marketed OTC in five or more countries with a minimum of 5 continuous years of marketing in at least one country, the sponsor may select at least five of these countries from which to submit information in accord with paragraphs (c)(2)(i) through (c)(2)(iv) of this section. Selected countries must include the country with a minimum of 5 continuous years of OTC marketing, countries that have the longest duration of marketing, and countries having the most support for extent of marketing, *i.e.*, a large volume of sales with cultural diversity among users of the product. If the condition meets these criteria in countries listed in section 802(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act, some of these countries should be included among the five selected. Sponsors should provide information from more than five countries if they believe that it is needed to support eligibility. Sponsors should explain the basis for the countries selected in the TEA.

(5) A list of all countries where the condition is marketed only as a prescription drug and the reasons why its marketing is restricted to prescription in these countries.

(6) A list of all countries in which the condition has been withdrawn from marketing or in which an application for OTC marketing approval has been denied. Include the reasons for such withdrawal or application denial.

(7) The information requested in paragraphs (c)(2), (c)(2)(i) through (c)(2)(iv), and (c)(3) of this section must be provided in a table format. The labeling required by paragraph (c)(3) of this section must be attached to the table.

(8) For OTC drugs that have been marketed for more than 5 years in the United States under a new drug application, the information requested in paragraphs (c)(2)(i), (c)(2)(iii), (c)(2)(v), (c)(3), and (c)(5) of this section need not be provided.

(d) *Submission of information; confidentiality.* The sponsor must submit three copies of the TEA to the Central Document Room, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. The Food and Drug Administration will handle the TEA as confidential until such time as a decision is made on the eligibility of the condition for consideration in the OTC drug monograph system. If the condition is found eligible, the TEA will be placed on public display in the Division of Dockets Management after deletion of information deemed confidential under 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j). Sponsors must identify information that is considered confidential under these statutory provisions. If the condition is not found eligible, the TEA will not be

placed on public display, but a letter from the agency to the sponsor stating why the condition was not found acceptable will be placed on public display in the Division of Dockets Management.

(e) *Notice of eligibility.* If the condition is found eligible, the agency will publish a notice of eligibility in the FEDERAL REGISTER and provide the sponsor and other interested parties an opportunity to submit data to demonstrate safety and effectiveness. When the notice of eligibility is published, the agency will place the TEA on public display in the Division of Dockets Management.

(f) *Request for data and views.* The notice of eligibility shall request interested persons to submit published and unpublished data to demonstrate the safety and effectiveness of the condition for its intended OTC use(s). These data shall be submitted to a docket established in the Division of Dockets Management and shall be publicly available for viewing at that office, except data deemed confidential under 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j). Data considered confidential under these provisions must be clearly identified. Any proposed compendial standards for the condition shall not be considered confidential. The safety and effectiveness submissions shall include the following:

(1) All data and information listed in § 330.10(a)(2) under the outline ''OTC Drug Review Information,'' items III through VII.

(2) All serious adverse drug experiences as defined in §§ 310.305 and 314.80 of this chapter, from each country where the condition has been or is currently marketed as a prescription drug or as an OTC drug or product. Provide 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 Division of Dockets Management. 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 relabeling, 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

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331.1 Scope.

Subpart B—Active Ingredients

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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.