DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 331

[Docket No. 88N-0327]

RIN 0905-AA06

Antacid Drug Products for Over-the-Counter Human Use; Proposed Amendment of Antacid Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that would amend the final monograph for over-the-counter (OTC) antacid drug products by deleting parts of the testing procedures in subpart C. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by November 22, 1993; written comments on the agency's economic impact determination by November 22, 1993. The agency is proposing that the final rule based on this proposal be effective 12 months after the date of its publication in the **Federal Register**.

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

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of June 4, 1974 (39 FR 19862), FDA issued a final monograph for OTC antacid drug products (21 CFR part 331) that included procedures for testing antacid drug products. In § 331.26 an acid neutralizing capacity test is described. When the final monograph was issued in 1974, the United States Pharmacopeia (U.S.P.) did not include an acid neutralizing capacity test. However, in 1980, an acid neutralizing capacity test was included in the U.S.P. (Ref. 1), and the test is substantially the same as that found in the final monograph for OTC antacid drug products.

In the July-August 1986 issue of the Pharmacopeial Forum (Ref. 2), the United States Pharmacopeial Convention (U.S.P.C.) proposed several revisions in the U.S.P. acid neutralizing capacity test that would increase the accuracy and utility of the test. The proposed revisions were implemented in the Fifth Supplement to the United States Pharmacopeia XXI/National Formulary XVI (U.S.P. XXI/N.F. XVI) (Ref. 3) and are contained in the current U.S.P. XXII/N.F. XVII (Ref. 4). Although the agency concurs in the revisions, the U.S.P. acid neutralizing capacity test is now different from the agency's antacid monograph testing procedures.

The acid neutralizing capacity test contained in the final monograph for OTC antacid drug products includes under § 331.26(b)(4) a procedure for a chewing gum dosage form. A testing procedure for this dosage form was included in the Seventh Supplement to U.S.P. XXI/N.F. XVI, which became official on May 15, 1988 (Ref. 5).

The antacid monograph also refers to the U.S.P. XVIII method of tablet disintegration, stating that a tablet intended for swallowing must disintegrate within 10 minutes using simulated gastric fluid test solution without enzymes rather than water as the immersion fluid. The agency is aware that for many antacid ingredients for which tablet monographs are included in the current U.S.P. XXII/N.F. XVII, there are differences between the FDA recommended disintegration test method and those included in current U.S.P. XXII/N.F. XVII monographs. For example, the U.S.P. XXII/N.F. XVII monograph for alumina, magnesia, and calcium carbonate tablets recommends a disintegration time of 45 minutes with water used as the immersion fluid (Ref. 6).

In contrast with the existing monograph testing procedures, the procedures in U.S.P. XXII/N.F. XVII include tests for powder and suspension dosage forms and for products having an acid neutralizing capacity greater than 25 milliequivalents (mEq) of acid, as well as a more detailed sample preparation procedure for capsule dosage forms. However, the U.S.P. XXII/N.F. XVII procedures do not include a "preliminary antacid test" (as contained in § 331.25 of the antacid monograph) or a procedure for the "determination of percent contribution of active ingredients" in a combination antacid drug product (as contained in § 331.21 of the antacid monograph). The agency does not consider the "preliminary antacid test" as essential to the determination of a product's acid neutralizing capacity. The monograph preliminary antacid test serves as a screening procedure to determine if a product merits the more exacting acid neutralizing capacity testing. The agency does not believe that a compendial procedure is needed for this purpose. In addition, manufacturers may elect to continue to use this "preliminary antacid test" as a screen even though it would no longer be included in the monograph.

To resolve the differences between current U.S.P. standards and the standards included in the FDA final monograph for OTC antacid drug products, the agency could amend its antacid monograph to be consistent with U.S.P. XXII/N.F. XVII. However, because U.S.P. XXII/N.F. XVII is the recognized official compendia for determining the identity, strength, quality, and purity of drugs, and also because the U.S.P. test is appropriate for determining the acid neutralizing capacity of OTC antacid drug products, the agency sees no reason at this time for retaining a different procedure in the FDA antacid drug products monograph. However, if in the future, the U.S.P.C. changes the methodology and FDA does not concur, it may be necessary to propose a different acid neutralizing capacity test for the final monograph for OTC antacid drug products. In that event, the agency will publish a notice in the **Federal Register** explaining its position and inviting comment.

As noted above, the U.S.P. XXII/N.F. XVII does not contain a procedure for the "determination of percent contribution of active ingredients." The antacid monograph (§ 331.10(a)) requires that each ingredient in an antacid drug product be included at a level that contributes at least 25 percent of the total acid neutralizing capacity of the product. Therefore, while the agency is proposing to delete the testing procedures from the antacid monograph and to refer to the U.S.P. XXII/N.F. XVII procedures for determination of the product's acid neutralizing capacity, it will retain § 331.21 ("determination of percent contribution of active ingredients") in the monograph (but redesignate it as § 331.20) so that a procedure will be available for making that determination. Further, new § 331.20 will be revised to refer to the U.S.P. XXII/N.F. XVII test procedure, rather than the procedure set forth in § 331.26, which is being deleted. In addition, new § 331.20 will be revised to incorporate more current language in U.S.P. XXII/N.F. XVII about wetting of the sample (Ref. 4).

Accordingly, the agency is proposing to remove the following sections from "Subpart C—Testing Procedures" in "Part 331—Antacid Products For Over-The-Counter (OTC) Human Use": §§ 331.20, 331.22, 331.23, 331.24, 331.25, and 331.26. Section 331.21 will be redesignated as § 331.20 and amended to refer to the U.S.P. XXII/N.F.

XVII test procedure in place of § 331.26, which is being removed. Section 331.29 ("test modifications") will be retained in case there is a need for any manufacturer to petition for a test modification. This section will be redesignated as § 331.21 and will be amended to reference the U.S.P. XXII/N.F. XVII test procedure. In addition, §§ 331.10(a) and 331.31(a)(1) are being amended by revising these sections to refer to U.S.P. XXII/N.F. XVII in place of § 331.26, which is being removed.

References

(1) "United States Pharmacopeia XX—National Formulary XV," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 912, 1980.

(2) "Acid-neutralizing Capacity—In Process Revision," Pharmacopeial Forum, 12:1605–1606, 1986.

(3) "United States Pharmacopeia XXI—National Formulary XVI," Supplement 5, United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 2461–2462, 1985.

(4) "United States Pharmacopeia XXII—National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 1528, 1989.

(5) "United States Pharmacopeia XXI—National Formulary XVI," Supplement 7, United States Pharmacopeial Convention, Inc., Rockville, MD, p. 2858, 1988.

(6) "United States Pharmacopeia XXII—National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 44 and 1577–1578, 1989.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC antacid drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96–354). That assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC antacid drug products is not expected to pose such an impact on small businesses because it simply deletes some testing procedures that have already been incorporated into the U.S.P./N.F. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC antacid drug products. Comments regarding the impact of this rulemaking on OTC antacid drug products should be accompanied by appropriate documentation.

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.

Interested persons may, on or before November 22, 1993, submit to the Dockets Management Branch (address above) written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before November 22, 1993. Three copies of all comments, objections, or requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests 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. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

List of Subjects in 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, it is proposed that 21 CFR part 331 be amended as follows:

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

1. 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).

2. Section 331.10 is amended by revising paragraph (a) to read as follows:

§ 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 XXII/National Formulary XVII. The method established in § 331.20 shall be used to determine the percent contribution of each antacid active ingredient.

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§ 331.20 [Removed]

3. Section 331.20 is removed from subpart C.

§ 331.21 [Redesignated as § 331.20]

4. Section 331.21 is redesignated as § 331.20 and revised to read as follows:

§ 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 XXII/National Formulary XVII, and calculate the percent contribution of the antacid active ingredient in the total product as follows:

Percent contribution = (Total mEq. Antacid Active Ingredient × 100) / (Total mEq. Antacid Product).

§ 331.22 [Removed]

5. Section 331.22 *Reagent standardization* is removed.

§ 331.23 [Removed]

6. Section 331.23 *Temperature standardization* is removed.

§ 331.24 [Removed]

7. Section 331.24 *Tablet disintegration test* is removed.

§ 331.25 [Removed]

8. Section 331.25 *Preliminary antacid test* is removed.

§ 331.26 [Removed]

9. Section 331.26 *Acid neutralizing capacity test* is removed.

§ 331.29 [Redesignated as § 331.21]

10. Section 331.29 is redesignated as § 331.21 and revised to read as follows:

§ 331.21 Test modifications.

The formulation or mode of administration of certain products may require a modification of the United States Pharmacopeia XXII/National Formulary XVII 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.

11. Section 331.80 is amended by revising paragraph (a)(1) to read as follows:

§ 331.80 Professional labeling.

(a) * * *

(1) Shall contain the neutralizing capacity of the product as calculated using the procedure set forth in United States Pharmacopeia XXII/National Formulary XVII 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.

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Dated: September 16, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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