DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 79N-0176]

Stomach Acidifier Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that any stomach acidifier drug product for over-the-counter (OTC) human use is not generally recognized as safe and effective, is misbranded, and is subject to regulatory action unless it has an approved new drug application (NDA). Stomach acidifiers are drugs that add hydrochloric acid to the stomach. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final rule, and all new data and information on stomach acidifier drug products that have come to the agency's attention. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: February 17, 1989.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of October 19, 1979 (44 FR 60316), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking that would classify OTC stomach acidifier drug products as not generally recognized as safe and effective and as being misbranded and would declare these products to be new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)). The notice was based on the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by January 17, 1980. Reply comments in response to comments filed in the initial comment period could be submitted by February 18, 1980.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final rule for OTC stomach acidifier drug products was published in the **Federal Register** of January 15, 1985 (50 FR 2184). Interested persons were invited to file by May 15, 1985, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by May 15, 1985. New data could have been submitted until January 15, 1986, and comments on the new data until March 17, 1986. Final agency action occurs with the publication of this final rule on OTC stomach acidifier drug products.

The OTC drug procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA is no longer using the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

As discussed in the proposed regulation for OTC stomach acidifier drug products (50 FR 2184), the agency advised that the conditions under which the drug products that are subject to this rule are not generally recognized as safe and effective and are misbranded (nonmonograph conditions) would be effective 6 months after the date of publication of the final rule in the **Federal Register**. Therefore, on or after February 17, 1989, no OTC drug products that are subject to this final rule may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved NDA.

In response to the proposed rule on OTC stomach acidifier drug products, eight consumers submitted comments. No requests for oral hearing before the Commissioner were received. Copies of the comments received are on public display in the Dockets Management Branch. Any additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179) or to additional information that has come to the agency's attention since publication of the notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

Six comments agreed with the agency's proposal that stomach acidifiers as a class of drugs are not generally recognized as safe and effective and are misbranded. Two comments objected to the removal of stomach acidifiers from the OTC market and presented testimonials that these drug products had provided relief from symptoms such as fainting, digestive distress, and improper "assimulation of minerals." Both comments noted that these products had been prescribed by a physician. One comment added that switching these products from OTC to prescription status would be both unncessary, inconvenient, and an added expense.

The agency acknowledges that betaine hydrochloride, glutamic acid hydrochloride, and dilute hydrochloric acid have been traditionally prescribed for use in the conditions of achlorhydria and hypochlorhydria. However, the agency is not aware of any data nor have any been submitted to demonstrate that the administration of any of these ingredients has any therapeutic value in either condition. Moreover, as discussed in the notice of proposed rulemaking for OTC stomach acidifier drug products (50 FR 2185), recent evaluations of hydrochloric acid therapy in recognized pharmacology texts conclude that there are no established indications for hydrochloric acid use. Therefore, the agency concludes that any ingredient recommended for OTC stomach acidifier use cannot be generally recognized as safe and effective.

In reference to the comment's statement on an OTC to prescription switch, it should be noted that removal

of stomach acidifier drug products from the OTC market does not mean that these products will then be made available for prescription use. Because no stomach acidifier has been shown to be safe and effective in treating achlorhydria and hypochlorhydria, neither OTC nor prescription marketing will be permitted unless a stomach acidifier drug product is the subject of an approved NDA. Currently, no stomach acidifier drug product is the subject of an approved NDA.

II. The Agency's Final Conclusions on OTC Stomach Acidifier Drug Products

The agency has determined that no stomach acidifier active ingredient has been found to be generally recognized as safe and effective and not misbranded for use in treating achlorhydria and hypochlorhydria. Therefore, all stomach acidifier ingredients, including betaine hydrochloride, glutamic acid hydrochloride, diluted hydrochloric acid, and pepsin, which were reviewed by the Panel, are considered nonmonograph ingredients and misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352) and are new drugs under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved NDA under section 505 of the act (21 U.S.C. 355) and Part 314 of the regulations (21 CFR Part 314) is required for marketing. Any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule that is not in compliance with the regulation is subject to regulatory action.

Consideration of glutamic acid hydrochloride as an ingredient in digestive aid drug products was transferred to this rulemaking (see 53 FR 2711). Accordingly, this final rule constitutes final agency action for this ingredient as an OTC stomach acidifier in both rulemakings.

The agency has examined the economic consequences of this final rule 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 final rule for OTC stomach acidifier 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 stomach acidifier drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

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 in 21 CFR Part 310

Administrative practice and procedure, Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations is amended to read as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR Part 310 continues to read as follows:

Authority: Secs. 501, 502, 503, 505, 701, 704, 705, 52 Stat. 1049–1053 as amended, 52 Stat. 1055–1056 as amended, 67 Stat. 477 as amended, 52 Stat. 1057–1058 (21 U.S.C. 351, 352, 353, 355, 371, 374, 375); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

2. Section 310.540 is added to Subpart E to read as follows.

§ 310.540 Drug products containing active ingredients offered over-the-counter (OTC) for use as stomach acidifiers.

(a) Betaine hydrochloride, glutamic acid hydrochloride, diluted hydrochloric acid, and pepsin have been present as ingredients in over-the-counter (OTC) drug products for use as stomach acidifiers. Because of the lack of adequate data to establish the effectiveness of these or any other ingredients for use in treating achlorhydria and hypochlorhydria, and because such conditions are asymptomatic, any OTC drug product containing ingredients offered for use as a stomach acidifier cannot be considered generally recognized as safe and effective.

(b) Any OTC drug product that is labeled, represented, or promoted for use as a stomach acidifier is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act, for which an approved new drug application under section 505 of the act and Part 314 of this chapter is required for marketing. In the absence of an approved new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted as a stomach acidifier for OTC use is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in Part 312 of this chapter.

(d) After the effective date of the final regulation, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

Dated: July 1, 1988.

Frank E. Young,

Commissioner of Food and Drugs.

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