DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 331 and 332

[Docket No. 75N-0357]

Antacid Drug Products and Antiflatulent Drug Products for Over-the-Counter Human Use; Proposed Amendment to the Monographs

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the over-the-counter (OTC) monographs for antacid drug products and antiflatulent drug products by adding new sections that will exempt certain antacid, antiflatulent, and antacid/antiflatulent combination drug products from that part of the accidental overdose warning required by § 330.1(g) (21 CFR 330.1(g)) that states, "In case of accidental overdose, seek professional assistance or contact a poison control center immediately." The exemption from the warning above is being provided because certain antacid and antiflatulent active ingredients contained in OTC drug products have been determined to have a low potential for acute toxicity resulting from accidental ingestion.

DATES: Written comments by June 12, 1984. Written comments on the agency's economic impact determination by August 13, 1984.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics National Center for Drugs and Biologics) (HFN-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: Under 21 CFR 330.1(g), the following general warning statements are required on all orally administered OTC drug products: "Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately."

Section 330.1(g) also states that FDA will grant an exemption from these general warnings where appropriate upon petition.

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) and a final monograph for OTC antiflatulent drug products (21 CFR Part 332) that established conditions under which these products are generally recognized as safe and effective and not misbranded. At that time, FDA exempted sodium bicarbonate powder from the general accidental overdose warning required by § 330.1(g) (39 FR 19867).

Since the publication of the antacid final monograph, a number of firms have petitioned for an exemption from the general overdose warning on the labeling of specific antacid, antiflatulent, and antacid/antiflatulent combination drug products. The firms assert that the antacid and antiflatulent ingredients covered by the petitions have a low potential for acute toxicity from accidental overdose. In support of these requests, the firms provided safety data in the form of acute toxicity studies that demonstrate that antacid ingredients have low potential for acute oral toxicity. Also, the firms cited bulletins from the National Clearing House for Poison Control Centers that show that no significant adverse effects from acute overdose have been reported for the various antacid ingredients. Several of the petitions also provided data demonstrating the safety of various antacid ingredients in combination with the antiflatulent ingredient simethicone.

Based on the data provided, FDA has granted each of these petitioners an exemption from the overdose portion of the general warning, i.e., "In case of accidental overdose, seek professional assistance or contact a poison control center immediately." Labeling must continue to contain the first part of the warning, which states, "Keep this and all drugs out of the reach of children." Copies of the petitions and FDA's response are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above).

The National Association of Pharmaceutical Manufacturers, by letters dated February 21, 1980 and July 10, 1981, has requested "that such an exemption should not be limited to those manufacturers who petition for such an exemption, but that the exemption should be published in the **Federal Register** and be applicable to all comparable products." The agency has considered this request and agrees that it is unnecessarily burdensome to require separate petitions for exemption from this warning from each manufacturer for every antacid product. FDA has granted petitions for certain ingredients within every class of antacid ingredients listed in the monograph, e.g., aluminum-containing ingredients, calcium-containing ingredients, silicates, etc., except for glycine and bismuth-containing ingredients for which no petitions were received.

In the case of glycine and bismuth-containing compounds, the agency has reviewed several sources regarding their toxicity (Refs. 1, 2, and 3). The data available for glycine indicate that acute toxicity from this naturally occurring amino acid would be highly unlikely. The National Institute for Occupational Safety and Health (Ref. 1) states that the lowest intravenous lethal does of glycine in cats is 3.0 grams/kilogram. The Advisory Review Panel on OTC Antacid Drug Products (Ref. 2) noted that glycine is rapidly metabolized and is practically nontoxic even with high blood levels produced by intravenous injection. The Panel did not find it necessary to impose a specific dosage limitation. Therefore, the agency believes that glycine, identified in § 331.11(f) of the antacid monograph, also may be exempted from the general overdose warning and is proposing such an exemption in this document.

Regarding bismuth-containing compounds, Gosselin et al. (Ref. 3) considered the oral toxicity of bismuth salts to be low because they are poorly absorbed. However, Gosselin et al. note that methemoglobinemia has been reported from bismuth subnitrate ingestion, especially in infants. The agency is not aware of other data pertinent to the toxicity of the bismuth compounds. The agency believes that the toxicity data for bismuth compounds are insufficient to warrant an exemption from the accidental overdose warning at this time. However, the agency invites comment and data regarding the toxicity of bismuth products.

With the exception of bismuth-containing ingredients, the agency believes that all other antacid and antiflatulent ingredients have low potential for acute toxicity and, therefore, antacid/antiflatulent products containing these ingredients should be exempted from the accidental overdose warning. FDA is proposing to add new §§ 331.30(g) and 332.30(c) that will exempt antacid drug products identified in § 331.11 (a), (b), and (d) through (m) and antiflatulent drug products indentified in § 332.10 or any allowable combination of these ingredients to be exempt from the general overdose warning requirement in § 330.1(g). Products containing these ingredients must continue to contain the first part of the warning, which states, "Keep this and all drugs out of the reach of children." Only products containing

bismuth, identified in § 331.11(c), must continue to bear the entire warning in § 330.1(g).

In conjunction with this action, it is also proposed that Part 331 be amended in § 331.11(k)(1) by deleting the last sentence of that paragraph, which states, "The warning required by § 330.1(g) concerning overdoses is not required on a product containing only sodium bicarbonate powder." This amendment will eliminate duplication of regulatory language concerning exemptions from § 330.1(g).

The agency proposes that this proposed rulemaking be effective upon publication of the final rule. However, manufacturers of OTC antacid drug products may adopt the labeling changes proposed in this document as of the date of publication of this proposal, subject to the possibility that FDA may change its position as a result of comments filed in response to this proposal.

References

(1) Lewis, R. J. and R. L. Fatken, editors, "Registry of Toxic Effects of Chemical Substances," 1979 Ed., Volume I, National Institute for Occupational Safety and Health, Cincinnati, p. 718, 1980.

(2) The Advisory Review Panel on OTC Antacid Drug Products, "Antacid Drug Products Proposed Rulemaking," **Federal Register**, April 5, 1973 (38 FR 8718).

(3) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products. Acute Poisoning," 4th Ed., The Williams and Wilkins Co., Baltimore, p. 93, 1976.

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 and antiflatulent 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 and antiflatulent drug product is not expected to pose such an impact on small businesses. 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 and antiflatulent drug products. Comments regarding the impact of this rulemaking on OTC antacid and antiflatulent drug products should be accompanied by appropriate documentation. A period of 120 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.

The agency has determined that under 21 CFR 25.24(d)(9) (proposed in the **Federal Register** of December 11, 1979; 44 FR 71742) this proposal is of a type that does not individually or comulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects

21 CFR Part 331

Labeling; OTC drugs, Antacid drug products.

21 CFR Part 332

Labeling, OTC drugs, Antiflatulent drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under 21 CFR 5.11, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Parts 331 and 332 as follows:

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

1. In Part 331:

§ 331.11 [Amended]

a. Section 331.11 *Listing of specific active ingredients* is amended in paragraph (k)(1) by removing the last sentence, which reads "The warning required by § 330.1(g) concerning overdoses is not required on a product containing only sodium bicarbonate powder."

b. Section 331.30 is amended by adding new paragraph (g) to read as follows:

§ 331.30 Labeling of antacid products.

* * * * *

(g) *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 permitted 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." 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."

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

2. In Part 332, § 332.30 is amended by adding new paragraph (c) to read as follows:

§ 332.30 Labeling of antiflatulent products.

* * * * *

(c) *Exemption from the general accidental overdose warning.* The labeling for antiflatulent drug products containing simethicone identified in § 332.10 and antacid/antiflatulent combination drug products provided for in § 332.15, containing the active ingredients identified in § 331.11 (a), (b), and (d) through (m) of this chapter 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." 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."

Interested persons may, on or before June 12, 1984, submit written comments to the Dockets Management Branch

(HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857. Written comments on the agency's economic impact determination may be submitted on or before August 13, 1984. 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. Comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: March 19, 1984.

Mark Novitch,

Acting Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

[FR Doc. 84–9904 Filed 4–12–84; 8:45 am]

BILLING CODE 4160–01–M