DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 331

[Docket No. 85N-0049]

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

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

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 to require that all antacid drug products contain the statement "Antacids may interact with certain prescription drugs. If you are presently taking a prescription drug, do not take this product without checking with your physician." FDA is issuing this notice of proposed rulemaking after considering public comments to a prior proposal (see the Federal Register of October 19, 1979; 44 FR 60328) and a citizen petition (Docket No. 82P-0360/CP) that requested additional labeling information to be included on OTC antacid drug products. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATE: Written comments or objections by September 29, 1986.

ADDRESS: Written comments or objections 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 (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

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). Under § 331.30(d)(1), the labeling of OTC aluminum-containing antacid drug products is required to contain the drug interaction precaution "Do not take this product if you are presently taking a prescription antibiotic drug containing any form of tetracycline." In the Federal Register of October 19, 1979 (44 FR 60328), the agency proposed to amend the antacid monograph to require that this drug interaction precaution also be included on the labeling of antacid drug products containing calcium or magnesium. The proposed amendment would have also required the following additional statement as part of the drug interaction precaution: "If you are not sure whether or not you are taking a tetracycline product, contact your physician or pharmacist." Interested persons were invited to file written comments to the proposed amendment on or before December 18, 1979.

In response to the notice of proposed rulemaking, five manufacturers, one trade association, one citizen's group, and one pharmaceutical association submitted comments. A number of the comments questioned the necessity and desirability of the second statement of the proposed warning. One comment questioned FDA's general policy with respect to OTC drug-prescription drug interaction precaution statements, in particular whether such statements should appear in prescription labeling rather than OTC drug labeling. Another comment urged that the proposed warning be limited to instances involving concurrent (simultaneous) ingestion of the antacids and tetracycline. One comment concurred with the proposed warning, but suggested the FDA consider expanding the warning to include prescription drug products other than tetracycline, or broadening it to include other products containing aluminum, calcium, or magnesium. Copies of the comments received are on public display in the Dockets Management Branch.

On November 15, 1982, FDA received a petition (Docket No. 82P-0360/CP) requesting, among other things, that the labeling of OTC antacid drug products include a precaution concerning the interaction between antacids and the prescription drug digoxin. In a letter dated August 23, 1983, the agency responded to the petition and stated that FDA would initiate the necessary action to implement the petitioner's request with respect to the drug interaction precaution.

After considering the comments to the October 19, 1979 proposed rule (44 FR 60328) and the petition received on November 15, 1982 (Docket No. 82P-0360/CP), the agency believes it is necessary to clarify its policy with respect to drug interaction precaution statements in the labeling of OTC drug products.

The agency's general approach to drug interaction labeling on OTC drug products was discussed in the Federal Register of June 4, 1974 (39 FR 19880). In the interest of providing fully informative labeling to the consumer, the agency stated "that the proper way to handle possible drug interactions is to require that the labeling [of OTC drug products] include a separate section headed 'Drug Interaction Precautions,' stating the specific or general interaction problem involved with that particular OTC drug. . . . The same format will be used for other specific drug interactions found to exist in other monographs. Where known drug interactions exist but are not limited to a specific drug, the precaution statement shall be phrased in terms of general drug categories. . . ." The agency has been operating under this general policy since it was stated in the June 4, 1974 Federal Register.

However, in light of the comments made to the October 19, 1979 proposed rule, the agency believes it is necessary to expand its policy as follows:

1. In general, the agency believes that when an interaction between a prescription drug and an OTC drug is significant enough to be included in the approved labeling of the prescription drug product, a similar corresponding warning should be included in the labeling of the OTC drug product.

This general policy may not apply when the known prescription-OTC drug interaction cited in the prescription drug labeling affects only a limited portion of the total population taking the prescription drug. For example, the labeling for the prescription drug dexamethasone includes a statement advising that aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. Conceivably, only a small subset of the population taking dexamethasone would have a hypoprothrombinemic condition and, therefore, the label warning may not be necessary on OTC aspirin-containing drug products.

2. Consistent with the June 4, 1974 Federal Register statements, in those cases where the known interactions are not limited to specific drugs and involve numerous drugs or entire drug categories, the statement would be phrased in terms of general drug categories. For example, if a significant number of prescription drugs are known to interact with an OTC drug, the interaction warning may need to be a general "prescription drug" warning rather than a listing of all possible prescription drugs likely to cause interactions.

3. Where interactions are known to exist between OTC drug products and are recognized as being significant, all of the OTC drug products involved should include the drug interaction precaution.

In the case of antacid drug products, the interaction between aluminum, calcium, or magnesium antacids and tetracycline is the most frequently reported. However, the agency is aware

of data in the literature indicating that the entire class of antacides, due to pH-related and other mechanisms, interacts with a number of other drugs (Refs. 1 through 6). Many of the interactions result from elevation of the pH of the stomach contents produced by the antacids, which may in turn affect the rate of absorption of a number of drugs. In some cases the interaction may be beneficial, i.e., the drug may be absorbed faster and get to the site of action quicker. For example, the rate of absorption of salicylates, indomethacin, naproxen, pseudoephedrine, sulfadiazine, and levodopa is increased by elevated gastric pH.

In other cases, the rate of absorption may be delayed, thereby reducing efficacy of the drug. For example, the efficacy of tetracycline, digoxin, phenytoin, chlorpromazine, and isoniazid is reduced because of reduced absorption of the drugs. Aluminum hydroxide delays gastric emptying, thereby slowing the rate of absorption of indomethacin, dicumarol, isoniazid, barbiturates, and some benzodiazepines. In addition, aluminum hydroxide can adsorb and decrease the bioavailability of propranolol, antimuscarinic drugs, digoxin, tetracyclines, chlorpromazine, and sulfadiazine. Likewise, magnesium trisilicate interferes with the bioavailability of digoxin, certain benzodiazepines, phenothiazines, and antimuscarinic drugs. Antacids that increase urinary pH can delay the elimination and elevate the blood levels of quinidine and amphetamines.

Because of the number of significant interactions that can occur between antacids and prescription drugs, the agency is proposing the following drug interaction precaution for inclusion in the labeling of all OTC antacid drug products: "Antacids may interact with certain prescription drugs. If you are presently taking a prescription drug, do not take this product without checking with your physician." This statement would replace the current drug interaction precaution statement required by 21 CFR 331.30(d)(1). The statement proposed here would also replace the wording proposed in the Federal Register of October 19, 1979 (44 FR 60328). Elsewhere in this issue of the Federal Register, the agency is withdrawing the proposed rule of October 19, 1979.

In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This document proposes that that option be added to the final monograph for OTC antacid drug products.

References

(1) "Evaluation of Drug Interactions," 2d Ed., American Pharmaceutical Association, Washington, 1976.

(2) Hurwitz, A., "Antacid Therapy and Drug Kinetics," *Clinical Pharmacokinetics*, 2:269–280, 1977.

(3) Romankiewicz, J.A., "Effects of Antacids on Gastrointestinal Absorption of Drugs," *Primary Care*, 3:537–550, 1976.

(4) Harvey, S.C., "Gastrict Antacids and Digestants" *in* "The Pharmacological Basis of Therapeutics," 6th Ed., edited by L.S. Goodman, A. Gilman, and A.G. Gilman, Macmillan Publishing Co., Inc., New York, pp. 988–991, 1980.

(5) Garnett, W.R., "Antacid Products" *in* "Handbook of Nonprescription Drugs," 7th Ed., American Pharmaceutical Association, Washington, pp. 34–37, 1982.

(6) Hartshorn, E.A., "Drug Interactions Update 1982," American Society of Hospital Pharmacists, Bethesda, MD, 1983.

Because this proposal relates only to warnings for OTC antacid drug products, the changes in the "exclusivity" policy that were recently published in the Federal Register of May 1, 1986 (51 FR 16258) do not apply to this document.

The agency advises that any final rule resulting from this proposed rule will be effective 12 months after its date of publication in the Federal Register. On or after that date, OTC drug products that are not in compliance may not be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved new drug application (NDA). Further, any OTC drug products subject to the rule that are repackaged or relabeled after the effective date of the rule must be in compliance with the rule regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the rule at the earliest possible date.

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. 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) (April 26, 1985; 50 FR 16636) 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 September 29, 1986, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments or objections. Three copies of all comments or objections are to be submitted, except that individuals may submit one copy. Comments and objections 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 and objections may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 331

OTC drugs, Antacid drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the

Administrative Procedure Act, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 331 as follows:

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

1. The authority citation for Part 331 continues to read as follows:

Authority: 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); 5 U.S.C. 553; 21 CFR 5.11.

2. In § 331.30 by revising paragraph (d) and adding new paragraph (h) to read as follows:

§ 331.30 Labeling of antacid products.

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(d) *Drug interaction precautions.* The labeling of the product contains the following statement under the heading "Drug Interaction Precautions":
"Antacids may interact with certain prescription drugs. If you are presently taking a prescription drug, do not take this product without checking with your physician."

* * * * *

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

Dated: May 3, 1986.

Frank E. Young,

Commissioner of Food and Drugs.

[FR Doc. 86–17038 Filed 7–29–86; 8:45 am]

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21 CFR Part 331

[Docket No. 79N–0152]

Antacid Drug Products for Over-the-Counter Human Use; Withdrawal of Proposed Rule

AGENCY: Food and Drug Administration.

ACTION: Withdrawal of proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing a proposed rule that would have required over-the-counter (OTC) antacid drug products containing calcium and magnesium to contain a precautionary statement. Elsewhere in this issue of the **Federal Register**, FDA is proposing a revised drug interaction precaution for all OTC antacid drug products. That proposal supersedes the proposal being withdrawn.

EFFECTIVE DATE: July 30, 1986.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (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 60328), FDA published a proposal to amend the monograph for OTC antacid drug products (21 CFR Part 331) to require a tetracycline drug interaction precaution statement on the labeling of calcium- and magnesium-containing OTC antacid drug products. The statement previously had been required only for aluminum-containing OTC antacid drug products. Elsewhere in this issue of the **Federal Register**, the agency is proposing an amendment to the monograph for OTC antacid drug products to require a prescription drug interaction precaution for all OTC antacid drug products. The new proposal supersedes the October 19, 1979 proposal, which is being withdrawn.

List of Subjects in 21 CFR Part 331

OTC drugs; Antacid 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)), under 21 CFR 5.11, and under 21 CFR 10.40(c), the proposed rule published in the **Federal Register** of October 19, 1979 (44 FR 60328) is withdrawn effective July 30, 1986.

Dated: May 3, 1986.

Frank E. Young,

Commissioner of Food and Drugs.

[FR Doc. 86–17039 Filed 7–29–86; 8:45 a.m.]

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