DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 331

[Docket No. 85N–0049]

RIN 0905–AA06

Antacid Drug Products For Over-the-Counter Human Use; Amendment Of Antacid Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule to amend the final monograph for over-the-counter (OTC) antacid drug products to require that all antacid drug products contain the statement: "Drug Interaction Precaution: 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 or other health professional." FDA is issuing this final rule after considering public comments on the agency's proposed regulation and all new data and information 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: August 26, 1994.

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 that established conditions under which these products are generally recognized as safe and effective and not misbranded. Section 331.30(d)(1) (21 CFR 331.30(d)(1)) of the monograph currently requires that the labeling of OTC aluminum-containing antacid drug products include the following 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 also would have 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.

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. After evaluating the comments to the proposed amendment (44 FR 60328), the petition, and data in the literature indicating that antacids interact with a number of other drugs, in the Federal Register of July 30, 1986 (51 FR 27342), FDA proposed that a different drug interaction precaution be included in the labeling of all OTC antacid drug products, as follows: "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." Interested persons were invited to file written comments or objections by September 29, 1986.

In response to this notice of proposed rulemaking, seven professional associations, three manufacturers, three academic institutions, two pharmaceutical trade organizations, two pharmaceutical publications, and one individual submitted comments. Copies of the comments are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. 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.

I. The Agency's Conclusions on the Comments

1. Many comments requested that the wording of the proposed warning be revised to include the "pharmacist" as another health professional that consumers could check with about possible drug interactions. The comments mentioned several reasons for including pharmacists as a source of information and advice: their professional knowledge, ready availability, and willingness to provide advice without charging expensive professional fees. The comments contended that pharmacists have access to the patients' full medical profile and consumers are likely to purchase antacids from pharmacies. Two comments added that FDA has used similar language in the past.

The agency agrees that pharmacists' professional knowledge, ready availability, and willingness to provide advice make them an excellent source of information, particularly relating to drug interactions, for consumers taking both an OTC antacid and a prescription drug. In some cases, the pharmacist may have access to the consumer's complete medical profile and be able to offer medication counseling when a questionable situation arises.

The agency believes, however, that other health professionals, such as nurses and physician assistants, can also help consumers determine whether the prescription drug they are taking interacts with an antacid. Information about such interactions appears in references, such as the "Physicians' Desk Reference," that are available to these health professionals. In developing warning and drug interaction precaution statements for other OTC drug products, the agency has previously considered the most appropriate wording to designate who could provide consumers with information concerning OTC drugs. The agency determined that "health professional" is the preferred term, because this term does not restrict consumers from other available sources of information. (See, for example, the pregnancy-nursing warning for OTC drugs in 21 CFR 201.63 and the proposed drug interaction precaution for monoamine oxidase inhibitor drugs (57 FR 27658, 27662, and 27666 (June 19, 1992)).

Accordingly, in this final rule, the agency is revising the drug interaction precaution statement in § 331.30(d) to read as follows: "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 or other health professional."

2. Two comments contended that physicians and their staffs would be overburdened by patient inquiries regarding possible OTC antacid-prescription drug interactions, many of which may be "trivial, clinically insignificant, or nonexistent." Another comment stated that the warning language is so broad that it fails to distinguish between known interactions and merely conjectural ones. The comment considered the warning to be a public service message to remind patients to keep physicians apprised of all medications being consumed. The comment concluded that while this is a laudable goal, it is not a proper use of limited OTC drug labeling space.

The agency has determined that an antacid drug interaction precaution is necessary due to the large number of interactions that could occur between antacids and prescription drugs. Antacids can alter the rate of absorption, bioavailability, and/or renal elimination of a number of drugs (see discussion in comment 5). While the language in the precaution could be considered overly broad, the agency's goal is to alert consumers without resorting to a confusing and burdensome list of all known interactions.

The agency does not believe that physicians and their staffs will be overburdened as a result of the new precaution. Information regarding interactions of prescription drugs with other drugs (prescription or OTC) should be provided as part of the physician-patient consultation when prescription drugs are prescribed. However, in some instances, patients may not be taking an OTC antacid at the time a prescription drug is prescribed. Later, the patient may have a need for an OTC antacid. In these instances, the drug interaction precaution is intended to alert patients to check with their physician before taking the antacid. The agency believes that this process is an essential part of good health care, and that most physicians and their staffs would not consider such inquiries to be burdensome.

3. Four comments contended that if a drug interaction merits a warning, then the proper vehicle for the warning would be the approved labeling for the prescription drug in question. The comments argued that the information is best provided when the medication is prescribed by the physician as part of the physician-patient consultation. Two of the comments mentioned that information about possible drug interactions is also provided by the pharmacist at the time the prescription is filled.

The agency agrees that when clinically significant drug interactions occur, the labeling of the prescription drug in question is an appropriate place to state that information. However, the prescription labeling is not the only appropriate place where such information can be provided. Also, having this information in the OTC drug product labeling serves to remind patients who may have forgotten their physicians' or pharmacists' instructions and is intended to help prevent unnecessary drug interactions from occurring.

The agency's general policy is 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 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. However, in those cases where known drug interactions are not limited to specific drugs and involve numerous drugs or entire drug categories, the agency states the interaction information in terms of general drug categories. For example, if a significant number of prescription drugs are known to interact with an OTC drug, the drug interaction warning may need to be a general "prescription drug" warning rather than listing all of the possible prescription drugs likely to cause interactions.

In the case of antacid drug products, the interaction between aluminum, calcium, or magnesium antacids and tetracycline is the most frequently reported. However, as discussed in comment 5, data in the literature indicate that drugs in the entire class of antacids, due to pH-related and other mechanisms, interact with a number of other drugs (Refs. 1 through 8). Because it would be impossible to list every prescription drug that could possibly cause an interaction in the antacid product's labeling, the agency finds a general warning statement to be most appropriate for this situation.

References

(1) D'Arcy, P. F., and J. C. McElnay, "Drug-Antacid Interactions: Assessment of Clinical Importance," *Drug Intelligence and Clinical Pharmacy*, 21:607–617, 1987.

(2) "USP DI, Volume I, Drug Information for the Health Care Professional," 13th ed., United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 195–197, 1993.

(3) Hansten, P. D., and J. R. Horn, "Drug Interactions," 6th ed., Lea and Febiger, Philadelphia, pp. 225, 229, 250, and 348, 1987.

(4) "Drug Evaluations," 6th ed., American Medical Association, Chicago, p. 947, 1986.

(5) Garnett, W. R., "Antacid Products" in "Handbook of Nonprescription Drugs," 9th ed., American Pharmaceutical Association, Washington, pp. 270–274, 1990.

(6) Clark, W. G., D. C. Brater, and A. R. Johnson, "Goth's Medical Pharmacology," 12th ed., The C. V. Mosby Co., St. Louis, pp. 748–750, 1988.

(7) Brunton, L. L., "Agents for Control of Gastric Acidity and Treatment of Peptic Ulcers" in "The Pharmacological Basis of Therapeutics," 8th ed., edited by L. S. Goodman, and A. G. Gilman, Pergamon Press Co., Inc., New York, pp. 904–909, 1990.

(8) Shinn, A. F., and R. P. Shrewbury, "Evaluations of Drug Interactions," 3d ed., The C. V. Mosby Co., St. Louis, p. 399, 1985.

4. Two comments contended that the proposed warning is contrary to the statutory definition of OTC drugs in section 503(b)(1)(B) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 353(b)(1)(B) the intent of that definition which, according to one comment, "mandates nonprescription status for drug products which are deemed as safe for use without the supervision of a physician." These comments argued that a general drug interaction statement, as proposed, would "seek to impose a requirement of physician intervention before use if the patient is taking any concurrent prescription therapy."

The agency considers the drug interaction precaution statement to be consistent with section 503(b)(1)(B) of the act. That section states that certain drugs shall be dispensed only by prescription when certain conditions exist and the drug is not safe except when used under the supervision of a practitioner licensed by law to administer such drug. This section of the statute does not prohibit warnings and drug interaction precaution statements for OTC drug products. These warnings and precaution statements do not impose a requirement of physician intervention for all consumers, but serve to alert certain users of the product to consult a physician or other health professional for advice when certain situations exist (e.g., when taking a prescription drug product concurrently). Thus, the requirements are not at odds with the statute.

In other OTC drug rulemakings, the agency has included similar drug interaction precautions in the OTC drug products' labeling to alert consumers to consult a doctor before taking certain drugs concurrently. For example, the precaution, "Do not use this product if you are presently taking a prescription drug for high blood pressure or depression without first consulting your doctor," is currently required for OTC bronchodilator drug products (see 21 CFR 341.76(c)(4)) and OTC anorectal drug products (see 21 CFR 346.50(c)(7)(ii)). On June 19, 1992 (57 FR 27662), the agency proposed to revise the wording for the precaution for OTC bronchodilator drug products. Other examples include the warning, "Do not give this product to children who have a chronic pulmonary disease, shortness of breath, or who are taking other drugs unless directed by a doctor," for OTC antitussive drug products containing codeine labeled for children under 12 years of age (see 21 CFR 341.74(c)(4)(iii)) and the warning, "Avoid alcoholic beverages while taking

this product. Do not take this product if you are taking sedatives or tranquilizer, without first consulting your doctor," for OTC nighttime sleep-aid drug products containing diphenhydramine hydrochloride or diphenhydramine monocitrate (see 21 CFR 338.50(c)(4)).

5. Two comments contended that the proposed drug interaction warning is not supported by the medical/scientific literature. One comment stated that the articles referenced in the agency's proposal provide questionable support for the agency's position because they are largely review articles with citations to papers that are often anecdotal and out of date. The comment added that the articles contain broad generalizations about drug interactions without adequate discussion of clinical significance.The comment argued that unnecessary warnings dilute the significance and impact of such warnings that are needed for the safe use of the product by the consumer. The comment concluded that the warning is unnecessary.

The agency disagrees with the comments. The medical/scientific literature reviewed by the agency shows that the entire class of antacids can cause numerous drug interactions. In 1982, D'Arcy and McElnay identified the hazards of interactions with antacids as being largely confined to a relatively small group of drugs: tetracycline, phenytoin, digoxin, and chloroquine (Ref. 1). In 1987, the same authors reported newer evidence showing that additional interactions occurred between antacids and cimetidine, quinidine, nonsteroidal antiinflammatory drugs, and beta-adrenergic blocking drugs (Ref. 2). Other references published after the agency's proposal in 1986 include more reports of antacid interactions. For example, the "United States Pharmacopeial Dispensing Information" currently contains extensive interaction data, listing 35 specific interactions between antacids containing aluminum, calcium, magaldrate, magnesium, or sodium bicarbonate and frequently prescribed medications selected on the basis of their potential clinical significance (Ref. 3).

These reports in the literature show that antacids can interact with a wide range of primary drugs, and can adversely affect the efficacy of the primary medication. Interactions can occur by a number of mechanisms, some of which act concomitantly: for example, by altering gastric pH (giving rise to altered dissolution rate of drug formulation, changed drug ionization, and modified absorption patterns), by adsorption of drug onto the surface of the interactant, or through the formation of poorly soluble salts or complexes. Interactions with antacids may also involve kinetic changes, including changed gastric emptying rate and/or gastric motility.

Antacids may alter the rate of dissolution, absorption, biovailability, and renal elimination of a number of drugs. Numerous authors report that, through a combination of factors, many antacids decrease the bioavailability of cimetidine, ranitidine, nitrofurantoin, digoxin, ethambutol, some indomethacin, phenytoin, vitamin A, fluoride, and phosphate (Refs. 2 and 4 through 8). It has also been reported that antacids considerably reduce ketoconazole concentrations (Ref. 4). Antacids decrease the bioavailability of atenolol and propranolol and increase the bioavailability of metoprolol. Antacids also increase the dissolution and absorption of the acidic forms of sulfonamides and the rate of absorption of levodopa (Ref. 8). Concurrent antacid therapy with ferrous sulfate, isoniazid, or tetracycline has frequently been reported to decrease the bioavailability of these drugs in actual patients (Refs. 2, 3, and 9).

Concurrent administration of tetracycline with antacid products containing aluminum hydroxide or divalent ions (magnesium or calcium) significantly decreases the gastrointestinal absorption of the antibiotic, thereby lessening its therapeutic effect. Demeclocycline, methacycline, chlortetracycline, and oxytetracycline are other forms of tetracycline that, administered concurrently with an aluminum hydroxide antacid product, also form insoluble chelates (Ref. 9).

Aluminum hydroxide has been shown to interfere with the absorption or excretion of warfarin, while aluminum hydroxide in combination with magnesium hydroxide can increase the absorption of dicumarol (Refs. 5 and 6). Thiazide diuretics cause retention of calcium and may exacerbate hypercalcemia when calcium carbonate antacids are taken concurrently (Ref. 8).

Alkalinization of the urine affects renal clearance of drugs that are weak acids or bases. Concurrent antacid therapy increases the rate of elimination of salicylates and phenobarbital and decreases the elimination of amphetamine, ephedrine, mecamylamine, pseudoephedrine, and quinidine (Refs. 5 and 8).

Antacids containing aluminum delay gastric emptying, tending to slow the entry of drugs to the absorptive surface of the small intestine, thus resulting in a delayed absorption rate. In combination products, compounds that contain magnesium can partially block the effect of aluminum on gastric motility; therefore, the combination product's absorption rate will be less delayed as compared to that of an aluminum compound's. Magnesium trisilicate and aluminum compounds are notable for their ability to absorb drugs and to form insoluble complexes that are not absorbed (Ref. 8).

Based on information in the medical/scientific literature, the agency concludes that the drug interaction precaution statement is necessary not only for antacid drug products containing aluminum, but for all OTC antacid drug products. Section 331.30(d) of the antacid monograph is revised accordingly.

References

(1) D'Arcy, P. F., and J. C. McElnay, "Drug-Metal Ion Interactions in the Gut," in Sigel H., "Metal Ions in Biological Systems, Vol. 14," in "Inorganic Drugs in Deficiency and Disease," Marcel Dekker, New York, 1982:1–35.

(2) D'Arcy, P. F., and J. C. McElnay, "Drug-Antacid Interactions: Assessment of Clinical Importance," Drug Intelligence and Clinical Pharmacy, 21:607–617, 1987.

(3) "USP DI, Volume I, Drug Information for the Health Care Professional," 13th ed., United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 195–197, 1993.

(4) Hansten, P. D., and J. R. Horn, "Drug Interactions," 6th ed., Lea and Febiger, Philadelphia, pp. 225, 229, 250, and 348, 1987.

(5) "Drug Evaluations," 6th ed., American Medical Association, Chicago, p. 947, 1986.

(6) Garnett, W. R., "Antacid Products" in "Handbook of Nonprescription Drugs," 9th ed., American Pharmaceutical Association, Washington, pp. 270–274, 1990.

(7) Clark, W. G., D. C. Brater, and A. R. Johnson, "Goth's Medical Pharmacology," 12th ed., The C. V. Mosby Co., St. Louis, pp. 748–750, 1988.

(8) Brunton, L. L., "Agents for Control of Gastric Acidity and Treatment of Peptic Ulcers" in "The Pharmacological Basis of Therapeutics," 8th ed., edited by L. S. Goodman, and A. G. Gilman, Pergamon Press Co., Inc., New York, pp. 904–909, 1990.

(9) Shinn, A. F., and R. P. Shrewbury, "Evaluations of Drug Interactions," 3d ed., The C. V. Mosby Co., St. Louis, p. 399, 1985.

6. Two comments stated that this proposal for a general warning may be setting a precedent that could affect the labeling of many OTC drug products in other drug classes. One comment contended that such action after a rulemaking process has been completed represents a major deviation from the scope of a final monograph and usurps the dedicated efforts of many people who participated in that process. The other comment argued that, because the proposed change is of such a sweeping

nature, it should be made subject to a formal rulemaking proceeding in order to provide meaningful notice to all interested parties with opportunity for comment. The comment concluded that if the policy is not abandoned, it must be published as a freestanding proposed rule.

The agency does not consider this antacid drug interaction precaution to be a precedent setting matter that could affect the labeling of many other classes of OTC drug products. This particular drug interaction is a problem specific to OTC antacid drug products. While FDA has used general warnings that affect more than one class of OTC drugs, such as the general pregnancy and nursing warning in 21 CFR 201.63, this usage has been rather limited and there currently are no plans to expand the usage of general warnings on a broad basis. The agency will consider the need for such general warnings as circumstances arise.

In the current situation, the drug interaction precaution for OTC antacid drug products was initiated by a citizen petition (Ref. 1) after the rulemaking for OTC antacid drug products had been completed. Agency regulations in 21 CFR 330.10(a)(12) provide for the amendment of monographs in this manner. Further, the proposed change has been the subject of a proposed rule in a notice and comment rulemaking proceeding, and interested parties have had the opportunity to comment.

Reference

(1) CP, Docket No. 82P–0360, Dockets Management Branch.

7. One comment strongly urged the agency to finalize the proposed rule to amend the labeling requirements for OTC antacid drug products. The comment mentioned personal experience relating to an adverse interaction that occurred between an OTC antacid and a prescription drug. The comment stated that "physicians can not be relied upon to inform their patients of possible negative reactions to a combination of a prescription drug and OTC antacid drug," and "the general public has no other way of ascertaining the information easily."

This comment supports the need for having the drug interaction precaution statement in the labeling of OTC antacid drug products. The warning provides the general public guidance on how to seek information when a question arises as to drug use and should specifically benefit consumers who did not receive adequate instructions initially, who may have forgotten the original instructions regarding their prescription products, or who need to take an antacid after a prescription medication has been prescribed by a doctor. In the event that adequate information was not given initially, the warning alerts consumers to check with their physician or other health professional when taking an OTC antacid drug product with their prescription medication(s) and should result in specific guidance being given at the time of the subsequent inquiry.

II. Summary of Changes in the Final Monograph

After considering the comments received and warnings used for other OTC drug products (see comment 1), the agency has added the words or "other health professional" to the second sentence of the drug interaction precaution so that it now reads: "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 or other health professional." In addition, the agency is now requiring that this drug interaction precaution appear in the labeling of all OTC antacid drug products, not just antacid drug products containing aluminum. (See comment 5.) Section 331.30(d) of the antacid monograph is revised accordingly.

The agency is also adding new § 331.30(h) to provide that the word doctor may be substituted for the word physician in any of the labeling statements in § 331.30. No comments were received in response to this part of the proposal. This addition makes the antacid monograph consistent with other recently published monographs.

III. The Agency's Final Conclusions on a Revised Drug Interaction Precaution Statement for OTC Antacid Drug Products

The agency has determined that a drug interaction precaution is needed in the labeling of all OTC antacid drug products (not just those containing aluminum) because the medical/scientific literature identifies a number of interactions that can occur between OTC antacids and prescription drugs. The agency believes that this information represents good health care and will serve as a reminder to consumers who are using antacids to contact their physicians or other health professionals for medication counseling if they are taking a prescription drug.

As discussed in the proposal (51 FR 27342 at 27343), the agency advised that any final rule resulting from the proposal would be effective 12 months after its date of publication in the **Federal Register**. Therefore, on or after August 26, 1994, any OTC antacid drug product that is not in compliance with the final rule may not be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC antacid drug product subject to the rule that is 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.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (51 FR 27342 at 27343). 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 amendment of the monograph 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 amending the final monograph for OTC antacid drug products is not expected to pose such an impact on small businesses. This final rule will require minor relabeling of one statement in the labeling for all OTC antacid drug products. Manufacturers will have 1 year to implement this relabeling, and almost all manufacturers normally reorder labeling during that time span. 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 actions 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 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, 21 CFR part 331 is 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 331.30 is amended by revising paragraph (d) introductory text and by adding paragraph (h) to read as follows:

§ 331.30 Labeling of antacid products.

* * * * *

(d) Drug interaction precaution. The labeling of the product contains the following statements under the heading "Drug Interaction Precaution": "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 or other health professional."

* * * * *

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

Dated: August 19, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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