DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 331

[Docket No. 88N-003U]

RIN 0905-AA06

Antacid Drug Products for Over-the-Counter Human Use; Proposed Amendment to the 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 to include conditions for the relief of upset stomach associated with overindulgence in food and drink. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and public comments on the advance notice of proposed rulemaking for orally administered drug products for relief of symptoms associated with overindulgence in alcohol and food for OTC human use that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by April 22, 1992. New data by December 24, 1992. Comments on the new data by February 24, 1993. Written comments on the agency's economic impact determination by April 22, 1992.

ADDRESSES: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, room 1-23, 12420 Parklawn Dr., Rockville, MD 30857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-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). Section 331.15(b) (21 CFR 331.15(b)) of the monograph provides for the combination of antacid and analgesic ingredients. In the **Federal Register** of August 31, 1982 (47 FR 38481), the agency concluded that antacid drug products may be labeled for relief of upset stomach associated with heartburn, sour stomach, and acid indigestion, and amended the monograph to include this claim in § 331.30(b). The agency recognized that "upset stomach" is a general term used by consumers to describe clusters of symptoms (47 FR 38481 at 38482). The agency also noted that terms such as "heartburn" may be used by consumers to describe gastrointestinal distress resulting from other causes such as overindulgence in food and drink. However, the agency stated that as of August 31, 1982. antacids have not been shown to relieve components of the upset stomach syndrome other than those for which labeling has been specified in the antacid monograph (47 FR 38481 at 38483).

Subsequent to the publication of the final rule for OTC antacid drug products and the amendment of the antacid monograph described above, the agency published the advanced notice of proposed rulemaking for orally administered drug products for relief of symptoms associated with overindulgence in alcohol and food for OTC human use (October 1, 1982, 47 FR 43540). In that notice, the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (the Panel) reviewed data on drug products containing antacid, analgesic, and stimulant ingredients in various combinations and recommended conditions for their safe and effective OTC use. The Panel concluded that the following combinations of Category I ingredients were safe and effective for use in relief of the symptoms of hangover: (1) Antacids and analgesics, (2) antacids and stimulants, (3) analgesics and stimulants and (4) antacids, analgesics, and stimulants. The Panel also recommended that the antacid ingredient sodium citrate in solution was safe and effective for use in the relief of upset stomach associated with overindulgence in the combination of alcohol and food. In addition, the Panel recommended that sodium citrate in solution for this use could be combined with any Category I internal analgesic ingredient in 21 CFR Part 343 (proposed in the **Federal Register** of November 16, 1988 53 FR 46204). The Panel added that if the product contains aspirin (as identified in Part 343), the finished product must meet the acid neutralizing requirements of § 331.10 of the antacid monograph (21 CFR 331.10).

The agency notes, however, that in recommending combination products to treat hangover symptoms, the Panel failed to adequately consider that caffeine stimulates gastric secretion of hydrochloric acid (Refs. 1 through 7). The ability of caffeine to significantly increase hydrochloric acid secretion is mentioned in standard medical reference textbooks (Refs. 1 and 2) and was reported by Roth and Ivy (Ref. 7) as early as 1944. McArthur, Hogan, and Isenberg (Ref. 3) undertook a study to determine the effect of nine commonly ingested beverages on gastric acid secretion in humans. Six healthy subjects were each studied on 11 separate days and in random order. Test substances were 3 types of soda water, 3 different brands of instant coffee, tea, milk, and beer. The control was water. The results were considered significantly different for each beverage versus the control ($p<0.05$). The authors stated that this study indicates that each of the beverages tested is a potent stimulus of gastric acid secretion regardless of its caffeine content. Studies by Cohen and Booth (Ref. 4) likewise demonstrated that Caffeine stimulates gastric acid secretion and reduces the competence of the lower esophageal sphincter in healthy subjects. Noting that caffeine is a potent stimulant of gastric secretion in man, Roth and Ivy (Ref. 7) conducted experiments to determine the synergistic effect of caffeine upon alcohol. They observed that the gastric secretory response to the combined action of alcohol plus caffeine was an average of 65.9 percent greater than the response produced when alcohol and caffeine were given separately. Further, the response to the combination of alcohol and caffeine was prolonged, lasting approximately 70 minutes longer than that of the individual ingredients.

The Advisory Review panel on OTC Sedative, Tranquilizer, and Sleep-aid Drug Products (Sleep-aid Panel) noted in its advance notice of proposed rulemaking for OTC nighttime sleep-aid, daytime sedative, and stimulant drug products (December 8, 1975, 40 FR 57292 at 57324 to 57325) that caffeine stimulates gastric secretion in man. While that Panel stated that normal doses of caffeine (i.e., 100 milligrams) did not seem to cause irritation of the gastrointestinal tract, the agency notes that the target population considered by that Panel in its assessment of the safety and effectiveness of caffeine as an OTC stimulant did not specifically include individuals that already had some degree of stomach or gastrointestinal irritation or upset due to overindulgence in alcohol and/or food. Further, the Sleep-aid Panel did not give any consideration to the safety of caffeine in

patients with already high levels of stomach acid.

In view of caffeine's documented effect in stimulating gastric secretions, the agency does not believe that combination products containing both caffeine, which stimulates hydrochloric acid secretion, and an antacid, which reduces the concentration of hydrochloric acid and treats the symptoms associated with high levels of hydrochloric acid, are rational. Therefore, the agency is reversing the Panel's Category I recommendation and is placing in Category II all combination products for the treatment of hangover that contain both an antacid ingredient and caffeine, a stimulant ingredient. The agency is not aware of any marketed OTC drug combination products, other than hangover remedies, that contain both stimulant and antacid ingredients.

In the tentative final monograph for OTC orally administered drug products for relief of symptoms associated with overindulgence in food and drink, published elsewhere in this issue of the **Federal Register**, FDA states its position on the establishment of a monograph for these drug products. Recognizing that there was considerable overlap in claims included in certain other rulemakings and the rulemaking for drug products for relief of symptoms associated with overindulgence in food and drink and with hangover, the agency determined that those claims should be included in the appropriate monographs for antacid, internal analgesic, and stimulant drug products. The agency recognizes that combination products may be intended for use by a specific target population, such as consumers who are suffering from a hangover or overindulgence in food and drink. The agency believes that the labeling for such combination products should reflect the principal intended use(s) of the product (e.g., pain reliever, antacid, stimulant). Such labeling should be consistent with the approved indications for the active ingredients, but would not be required to contain all of the indications.

The agency believes that labeling specific to internal analgesic/antacid or internal analgesic/stimulant combinations need only appear in one monograph, with an appropriate cross-reference in the other monograph. The agency previously proposed a number of internal analgesic/antacid combinations in the internal analgesic tentative final monograph. (See § 343.20 (b)(1) and (b)(3) (November 16, 1988, 53 FR 46204 at 46255)). Concurrently, in the same issue of the **Federal Register** (53 FR 46190), the agency proposed to amend the final monograph for OTC antacid drug products to revise § 331.15(b) to include the combinations that were proposed in § 343.20 (b)(1) and (b)(3) of the internal analgesic tentative final monograph. Likewise, the agency proposed to add a new § 331.60 (entitled "*Labeling of permitted combinations of active ingredients*") to reflect that the new combinations included in § 331.15 (b)(1) and (b)(2) should use the indications proposed in § 343.60 (b)(2) and (b)(4), respectively, of the internal analgesic tentative final monograph.

In this current notice, the agency is proposing to amend the final monograph for OTC antacid drug products to add a claim for relief of upset stomach due to overindulgence in food and drink. The agency does not need to propose any amendment to the final monograph to address the Panel's recommendation concerning sodium citrate in solution for use in the relief of upset stomach associated with overindulgence in the combination of alcohol and food because citrate-containing active ingredients are already included in § 331.11(e) of the antacid monograph.

FDA has previously amended the final monograph for OTC antacid drug products to permit the labeling for these products to include a claim for the relief of upset stomach associated with heartburn, sour stomach, and/or acid indigestion (47 FR 38481). This amendment was based on data (that were discussed in the September 21, 1979, proposal to amend the antacid monograph (44 FR 54731 at 54732)) which demonstrated that the term "upset stomach" is often used by consumers to describe the symptoms "acid indigestion," "sour stomach," and "heartburn." The agency also recognized that a cluster of symptoms referred to as "upset stomach" may be caused by overindulgence in food and drink, but this use was not considered in the August 31, 1982, amendment to the antacid final monograph. At that time, the agency concluded that a symptom described simply as "upset stomach" would not be used as an indication for OTC antacid drug products because it had not been specifically demonstrated to be associated with gastric hyperacidity (47 FR 38481 at 38482). In reaching that conclusion, the agency failed to note that the Advisory Review Panel on OTC Antacid Drug Products (Antacid Panel) had pointed out that evidence of the association between hyperacidity and the Category I antacid indications "heartburn," "sour stomach," and "acid indigestion," is "far from conclusive" (April 5, 1973, 38 FR 8714 at 8720).

Because of a recognized association between upset stomach and overindulgence in food and drink, the agency stated that it had referred further consideration of this issue to the Miscellaneous Internal panel for review (47 FR 38481 at 38483). That Panel reviewed data on only one antacid ingredient (sodium citrate in solution) for overindulgence claims and concluded that the ingredient was effective in relieving "upset stomach" due to overindulgence in the combination of food and drink (47 FR 43540 at 43549 and 43550).

Based on the Miscellaneous Internal Panel's review, the data discussed in the September 21, 1979, proposal to amend the antacid monograph (47 FR 38481), and the Antacid Panel's conclusion regarding hyperacidity (38 FR 8714 at 8722), the agency believes that consumers perceive the term "upset stomach" to refer to a variety of symptoms properly treated with antacids, including symptoms of heartburn, sour stomach, and "upset stomach" symptoms which may be due to overindulgence in food and drink.

Based on the above findings, the agency is proposing to amend the indications in § 331.30(b) of the final monograph for OTC antacid drug products to provide that the phrase "and upset stomach associated with" may be followed by the phrase "overindulgence in food and drink." Because the Miscellaneous Internal Panel also recommended an antacid/analgesic combination for the relief of symptoms of overindulgence in food and drink, the agency is proposing to include this same option in the OTC internal analgesic tentative final monograph, published elsewhere in this issue of the **Federal Register**. Because of the interrelationship of this amendment to the antacid final monograph and to other proposals published elsewhere in this issue of the **Federal Register** to amend the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products and the final monograph for OTC stimulant drug products, the agency does not intend to finalize this amendment until the comments to all of the proposals have been fully evaluated.

References

(1) Rall, T. W., "Drugs Used in the Treatment of Asthma," in "The Pharmacological Basis of Therapeutics," 8th ed., edited by A. G. Gilman, et al., Pergamon Press, New York, p. 623, 1990.

(2) Ivey, K. J., and J. L. A. Roth, "Drug and Chemical-Induced Injuries of the Stomach," Chapter 64 in "Bockus Gastroenterology," 4th

ed., Edited by J. E. Berk, W. B. Saunders Co., Philadelphia, pp. 975 and 995, 1985.

(3) McArthur, K., D. Hogan, and J. I. Isenberg, "Relative Stimulatory Effects of Commonly Ingested Beverages on Gastric Acid Secretion in Humans," Gastroenterology, 83:199–203, 1982.

(4) Cohen, S., and G. H. Booth, Jr., "Gastric Acid Secretion and Lower-Esophageal-Sphincter Pressure in Response to Coffee and Caffeine," The New England Journal of Medicine, 293:897–899, 1975.

(5) Friedman, G. D., A. B. Siegelaub, and C. C. Seltzer, "Cigarettes, Alcohol, Coffee and Peptic Ulcer," The New England Journal of Medicine, 290:469–473, 1974.

(6) Debas, H. T., et al, "Caffeine-Stimulated Acid and Pepsin Secretion: Dose-Response Studies," Scandinavian Journal of Gastroenterology, 6:453–457, 1971.

(7) Roth, J. A., and A. C. Ivy, "The Synergistic Effect of Caffeine Upon Histamine in Relation to Gastric Secretion," American Journal of Physiology, 142:107–133, 1944.

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) 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 April 22, 1992, submit to the Docket Management Branch (address above), 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

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 to read 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 (b) to read as follows:

§ 331.30 Labeling of antacid products.

* * * * *

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: "For the relief of" (select any or all of the following: "heartburn," "sour stomach," and/or "acid indigestion") (which may be followed by the statement: "and upset stomach associated with" (select one or more of the following, as appropriate "this symptom," "these symptoms," or "overindulgence in food and drink.")) Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

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Dated: November 1, 1991.

Michael R. Taylor,

Deputy Commissioner for Policy.

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