DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

21 CFR Part 340

[Docket No. 75N-244U]

RIN 0905-AA06

Stimulant 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 to amend the final monograph for over-the-counter (OTC) stimulant drug products to include conditions for the relief of symptoms associated with hangover. 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, 1992. 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 20857.

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 February 29, 1988 (53 FR 6100), FDA issued a final monograph for OTC stimulant drug products (21 CFR part 340). This monograph did not contain any provision for combination drug products containing stimulant and nonstimulant active ingredients.

In the **Federal Register** of October 1, 1982 (47 FR 43540), the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (the Panel) reviewed data on drug products containing antacid, analgesic, and stimulant active ingredients in various combinations and recommended conditions for their safe and effective use in its report on orally administered drug products for the relief of symptoms associated with overindulgence in alcohol and food. That Panel concluded that combinations of Category I ingredients from the following pharmacologic groups were safe and effective for use in the relief of the symptoms of hangover: (1) Antacid and analgesic, (2) antacid and stimulant, (3) analgesic and stimulant, and (4) antacid, analgesic, and stimulant.

In the tentative final monograph for OTC drug products for the relief of symptoms associated with overindulgence in food and drink, published elsewhere in this issue of the **Federal Register**, FDA states for the first time its position on the establishment of a monograph for these drug products. In formulating its proposals on conditions for marketing combination products containing antacid, analgesic, and stimulant ingredients for the relief of symptoms associated with hangover and/or overindulgence in food and drink, the agency recognized that rulemaking significantly overlaps other rulemakings in the OTC drug review. For example, the Panel's recommendations on OTC drug products for the relief of hangover symptoms include a combination of ingredients already classified as Category I in the OTC antacid rulemaking (21 CFR part 331), the OTC stimulant rulemaking (21 CFR part 340), and the pending OTC internal analgesic, antipyretic, and antirheumatic rulemaking (21 CFR part 343), proposed in the **Federal Register** of November 16, 1988 (53 FR 46204). Therefore, the agency decided not to further consider ingredients for the relief of hangover symptoms in the overindulgence tentative final monograph and decided instead to amend the internal analgesic, antipyretic, and antirheumatic tentative final monograph, the antacid final monograph, and the stimulant final monograph to include a claim for the relief of symptoms of hangover for combinations of ingredients from these drug categories.

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) 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.

The agency believes that labeling specific to stimulant/internal analgesic combinations need only appear in one monograph, with an appropriate cross-reference in the other monograph. In this notice, the agency is proposing to add § 340.20 to the stimulant monograph to allow for the combination of caffeine, the stimulant active ingredient, with an internal analgesic ingredient. Such combinations are also being proposed in § 343.20(b)(5) of the internal analgesic monograph (21 CFR 343.20(b)(5)).

While the Miscellaneous Internal Panel recommended that any Category I stimulant ingredient could be combined with any Category I internal analgesic ingredient, the agency is not aware of a marketing history for combination products other than those containing a stimulant with acetaminophen or aspirin. Internal analgesic/stimulant combinations for the treatment of hangover are therefore being limited to the internal analgesic ingredients listed in § 343.10 (a) and (b)(1) only, i.e., acetaminophen and aspirin.

The agency is further proposing to add § 340.60 to provide for the labeling of combination drug products. For combinations containing a stimulant ingredient with an internal analgesic ingredient as provided for in § 340.20, the following indication should be used in addition to the appropriate indication related to the internal analgesic component "Helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness associated with a hangover." Indications for such combinations are proposed in § 343.60(b)(6). In addition, § 340.60(c), the agency is proposing that the following warning be used for combination products containing a stimulant ingredient combined with any internal analgesic ingredient "For occasional use only. Do not use for more than 2 days for a hangover unless directed by a doctor. Not intended for use as a substitute for sleep. If fatigue or drowsiness persists or continues to recur, consult a doctor." This warning should be used instead of the warnings in §§ 340.50(c)(2) and 343.50(c)(1).

Because of the interrelationship of this amendment to the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products, the agency does not intend to finalize this amendment until the comments to the internal analgesic, antipyretic, and antirheumatic tentative final monograph 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, 142:107–113, 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 not one of these rules, including this proposed rule for OTC stimulant 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 stimulant 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 stimulant drug products. Comments regarding the impact of this rulemaking on OTC stimulant 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 Dockets 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 340

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 340 be amended as follows:

PART 340—STIMULANT DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 340 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. New § 340.20 is added to subpart B to read as follows:

§ 340.20 Permitted combinations of active ingredients.

The following combinations are permitted provided each active ingredient is present within the established dosage limits and the products is labeled in accordance with § 340.60.

(a) *Combinations containing a stimulant active ingredient and an internal analgesic active ingredient.* (See § 343.20(b)(5) of this chapter.)

(b) [Reserved]

3. New § 340.60 is added to Subpart C to read as follows:

§ 340.60 Labeling of permitted combinations of active ingredients.

Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable over-the-counter (OTC) drug monographs. For a combination drug product that does not have an established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs.

(b) *Indications.* The labeling of the product states, under the heading "Indications," the indication(s) for each ingredient in the combination, as established in the indications sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph. 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 act 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.

(1) *For permitted combinations containing a stimulant and an internal analgesic active ingredient identified in § 340.20(a).* The indications in § 343.60(b)(6) of this chapter should be used.

(2) [Reserved]

(c) *Warnings.* The labeling of the product states, under the heading "Warnings," the warning(s) for each ingredient in the combination, as established in the warnings sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph.

For permitted combinations containing any stimulant ingredient identified in § 340.20. The following warning should be used instead of the warnings in § § 340.50(c)(2) and 343.50(c)(1) of this chapter: "For occasional use only. Do not use for more than 2 days for a hangover unless directed by a doctor. Not intended for use as a substitute for sleep. If fatigue or drowsiness persists or continues to recur, consult a" (select one of the following: "physician" or "doctor").

(2) [Reserved]

(d) *Directions.* The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph. When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product:

(1) May not contain any dosage that exceeds those established for any individual ingredient in the applicable OTC drug monograph(s), and

(2) May not provide for use by any age group lower than the highest minimum age limit establish for any individual ingredient.

Dated: November 1, 1991.

Michael R. Taylor,

Deputy Commissioner for Policy.

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