DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 343

[Docket No. 77N-094U]

RIN 0905-AA06

Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Proposed Amendment to the Tentative Final 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 tentative final monograph for over-the-counter (OTC) internal analgesic, antipyretic, and antirheumatic drug products to include conditions for the relief of upset stomach associated with overindulgence in food and drink and 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 hearings 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 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 November 16, 1988 (53 FR 46204), FDA issued a tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products (21 CFR Part 343). That proposal included conditions for marketing combination drug products containing internal analgesic and antacid ingredients. The agency proposed that (1) acetaminophen may be combined with any antacid ingredient(s) and may be labeled only for concurrent symptoms, and (2) aspirin may be combined with any antacid ingredient(s) when marketed in a form intended for ingestion as a solution and may be labeled for concurrent symptoms as well as analgesic indications alone. (See proposed § 343.20(b) (1) and (3) at 53 FR 46204 at 46255.)

As part of the rulemaking for orally administered drug products for relief of symptoms associated with overindulgence in alcohol and food for OTC human use, published 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 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 could be combined with any Category I internal analgesic ingredient and be labeled for the relief of symptoms of upset stomach associated with overindulgence in the combination of alcohol and food. 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).

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 OTC 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 from 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 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 has 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. Similarly, combination drug products containing internal analgesic, antacid, and stimulant ingredients are also irrational. 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, plus an internal analgesic.

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. A number of internal analgesic/antacid combinations were proposed in the internal analgesic tentative final monograph. (See § 343.20(b) (1) and (3) (53 FR 46204 at 46255).) Concurrently, in the same issue of the **Federal Register** (November 16, 1988, 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 (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 add new § 343.20(b)(5) to allow for internal analgesic and stimulant combination drug products. 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 aspirin or acetaminophen. 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.

This notice also amends the labeling for internal analgesic/antacid combinations proposed in § 343.60 (b)(2) and (b)(4) of the OTC internal analgesic, antipyretic, and antirheumatic tentative final monograph to include a claim for relief or symptoms of hangover and a claim for relief of symptoms of overindulgence in food and drink. Because of the interrelationship of this amendment to the internal analgesic, antipyretic, and antirheumatic tentative final monograph and to other proposals included elsewhere in this issue of the **Federal Register** to amended the final monograph for OTC antacid 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 these proposals have been fully evaluated.

In this notice, the agency is also proposing to add new § 343.60(c)(1) containing the following warning for internal analgesic/antacid combination products labeled for the relief of symptoms of hangover, "Do not use for more than 2 days for a hangover unless directed by a doctor." This warning is being added because, although hangover is generally an acute self-limiting condition, the symptom complex can be experienced for periods of several days, either as a result of excessive and physically harmful consumption of alcoholic beverages or as a result of the consumption of alcohol aggravating some other disease or condition. If symptoms persist for more than 2 days, the individual should seek medical guidance and not continue to rely on a hangover remedy for symptomatic relief.

The agency is further proposing to revise the labeling directions for combination drug products in § 343.60(d), by modifying the last sentence as follows:

* * * 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 established for any individual ingredient.

This change is being made to make these labeling directions for combination drug products consistent with other recently proposed OTC drug monographs.

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 no one of these rules, including this proposed rule for OTC internal analgesic, antipyretic, and

antirheumatic 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 internal analgesic, antipyretic, and antirheumatic 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 internal analgesic, antipyretic, and antirheumatic drug products. Comments regarding the impact of this rulemaking on OTC internal analgesic, antipyretic, and antirheumatic 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 343

Internal analgesic drug products, 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 343, as proposed in the **Federal** Register of November 16, 1988 (53 FR 46204), be amended as follows:

PART 343—INTERNAL ANALGESIC, ANTIPYRETIC, AND ANTIRHEUMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation in 21 CFR part 343 is revised to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

2. Section 343.20 is amended by adding new paragraph (b)(5) to read as follows:

§ 343.20 Permitted combinations of active ingredients.

* * * * *

(b) * * *

(5) *Internal analgesic and stimulant combinations.* Any internal analgesic ingredient identified in § 343.10 (a) or (b)(1) of this chapter may be combined with any stimulant ingredient identified in § 340.10 of this chapter provided the product bears labeling indications in accordance with § 343.60(b)(6).

3. Section 343.60 is amended by revising paragraphs (b)(2), (b)(4), (c), and (d), and by adding new paragraph (b)(6) to read as follows:

§ 343.60 Labeling of permitted combinations of active ingredients.

* * * * *

(b) * * *

(2) *For permitted combinations identified in § 343.20(b)(1).* The indications are the following: "For the temporary relief of minor aches and pains with" (select one or more of the following: "heartburn," "sour stomach," or "acid indigestion") (which may be followed by: "and upset stomach associated with" (select one or more of the following, as appropriate: "this symptom," "these symptoms," "hangover," or "overindulgence in food and drink.")]

* * * * *

(4) *For permitted combinations identified in § 343.20(b)(3).* The indications are the following: "For the temporary relief of minor aches and pains with" (select one or more of the following: "heartburn," "sour stomach," or "acid indigestion") [which may be followed by "and upset stomach associated with" (select one or more of the following, as appropriate: "this symptom," "these symptoms," "hangover," or "overindulgence in food and drink")] and "Also may be used for the temporary relief of minor aches and pains alone" [which may be followed by one or more of the following: ("such as associated with" (select one or more of the following: "a cold," "the common cold," "sore throat," "headache," "toothache," "muscular aches," "backache," "the premenstrual and menstrual periods" (which may be followed by "(dysmenorrhea)"), or "premenstrual and menstrual cramps" (which may be followed by: "(dysmenorrhea)")), ("and for the minor pain from arthritis"), and ("and to reduce fever.")]

* * * * *

(6) *For permitted combinations identified in § 343.20(b)(5).* The indications are the following: "For the temporary relief of minor aches and pain associated with a hangover. Helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness associated with a hangover."

* * * * *

(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.

(1) *For permitted combinations identified in § 343.20 (b)(1) and (b)(3) when labeled for the relief of the symptoms of hangover.* "Do not use for more than 2 days for a hangover unless directed by a 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 established for any individual ingredient.

Dated: November 1, 1991.

Michael R. Taylor,

Deputy Commissioner for Policy.

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