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 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 amending the tentative final monograph for over-the-counter (OTC) internal analgesic, antipyretic, and antirheumatic drug products. This proposal affects combinations of internal analgesic and antacid ingredients, specifically sodium bicarbonate used as an antacid active ingredient. As proposed, combination drug products intended to be dissolved in liquid prior to administration, such as powders and effervescent granules or tablets, would not be allowed to make a claim for "relief of overindulgence in food and drink" or a claim for "relief of hangover." FDA is issuing this notice of proposed rulemaking after receiving reports of gastric (stomach) rupture following ingestion of sodium bicarbonate to relieve gastrointestinal distress. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by April 4, 1994; written comments on the agency's economic impact determination by April 4, 1994. The agency is proposing that any final rule that may issue based on this proposal become effective 6 months after the date of publication in the Federal Register.

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

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:

I. Background

In the Federal Register of November 16, 1988 (53 FR 46204), the agency published the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products (internal analgesic tentative final monograph). This proposal permitted combinations of acetaminophen and any monograph antacid ingredient and combinations of aspirin and any monograph antacid ingredient (see proposed § 343.20(b)(1) and (b)(3) (53 FR 46204 at 46255)). As proposed in § 343.60(b)(2) and (b)(4), indications for these combination products included concurrent antacid and internal analgesic symptoms (53 FR 46258). In the same issue of the Federal Register (53 FR 46190), the agency proposed amendments to the final monograph for OTC antacid drug products so that the antacid and internal analgesic final monographs would be consistent. The agency proposed to revise § 331.15(b) (21 CFR 331.15(b)) to include antacid/acetaminophen and antacid/aspirin combinations as generally recognized as safe and effective. The agency also 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) should use the indications that were proposed in § 343.60(b)(2) and (b)(4) of the internal analgesic tentative final monograph.

In the Federal Register of October 1, 1982 (47 FR 43540), FDA published an advance notice of proposed rulemaking for OTC orally administered drug products for relief of symptoms associated with overindulgence in alcohol and food. The notice included a report prepared by the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (the Panel). The Panel had reviewed data on drug products containing antacid, analgesic, and stimulant ingredients in various combinations and recommended conditions for their safe and effective 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 classified two ingredients, bismuth subsalicylate and sodium citrate in solution, in Category I (generally recognized as safe and effective) for relief of symptoms of upset stomach due to overindulgence in food and drink.

In the tentative final monograph for OTC orally administered drug products for relief of symptoms associated with overindulgence in food and drink, published in the Federal Register of December 24, 1991 (56 FR 66742), the agency recognized that the overindulgence rulemaking significantly overlaps other OTC drug monographs, including antacid (21 CFR part 331), stimulant (21 CFR part 340), and internal analgesic (proposed 21 CFR part 343). To avoid unnecessary monograph duplication, the agency proposed to amend the final monographs for OTC antacid and stimulant drug products and to amend the tentative final monograph for OTC internal analgesic drug products to include conditions for relief of hangover symptoms. Similarly, the agency found that the Panel's recommended claim for relief of symptoms of upset stomach due to overindulgence in food and drink overlaps claims in the antacid monograph. Therefore, the agency proposed to amend the final monograph for OTC antacid drug products to include appropriate conditions for relief of the symptoms of upset stomach due to overindulgence in food and drink. In a proposed amendment of § 331.30 of the antacid final monograph (56 FR 66754 at 66756, December 24, 1991), the agency proposed to add a claim for the relief of upset stomach due to overindulgence in food and drink for all antacid ingredients, including sodium bicarbonate.

Likewise, in a proposed amendment to the internal analgesic tentative final monograph (56 FR 66762 at 66764, December 24, 1991), the agency proposed to include a claim for relief of symptoms of hangover and a claim for relief of symptoms of overindulgence in food and drink for internal analgesic/antacid combinations proposed in § 343.60(b)(2) and (b)(4). At that time, the agency was not aware of the number of reports of adverse effects associated with ingestion of sodium bicarbonate for the relief of gastrointestinal distress. These adverse effects include the possibility of stomach rupture and, in rare cases, death. The agency has identified several other problems that could occur when sodium bicarbonate is used as an OTC antacid. These include systemic metabolic alkalosis, occurrence of milk-alkali syndrome, increased sodium load for certain susceptible individuals, and the overall risk-to-benefit ratio of sodium bicarbonate as an OTC antacid drug product. Stomach rupture and additional agency concerns associated with sodium bicarbonate, the literature review, and the case reports that demonstrate these adverse effects are discussed elsewhere in this issue of the Federal Register in the proposed amendment to the antacid final monograph (part 331). Based on a

review of these reports of adverse effects, the agency is amending the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products so that it is consistent with proposed changes in the antacid final monograph.

II. The Agency's Proposal for Revised Labeling for Sodium Bicarbonate in OTC Internal Analgesic, Antipyretic, and Antirheumatic Combination Drug Products

The case reports have shown that the ingestion of sodium bicarbonate may cause gastric dilatation and rupture of the stomach, particularly if the stomach is overly full from food or drink. The reports indicate that this problem occurs with dosage forms intended to be dissolved in liquid before administration, such as powders or effervescent granules or tablets. Accordingly, the agency is proposing separate indications in § 343.60(b) for OTC internal analgesic/antacid combination drug products that either do or do not contain sodium bicarbonate as an active ingredient intended to be dissolved in liquid before administration. Products containing sodium bicarbonate intended to be dissolved in liquid before administration will not be allowed to include a claim for relief of overindulgence in food and drink or relief of hangover. Proposed labeling that specifically addresses warnings and directions for sodium bicarbonate appears in the amendment to the antacid final monograph, elsewhere in this issue of the Federal Register. A cross-reference to that labeling is proposed in the internal analgesic monograph.

The agency has examined the economic consequences of this proposed rulemaking and has determined that it does not require either a regulatory impact analysis, as specified in Executive Order 12866, or a regulatory flexibility analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96–354). This rulemaking for OTC internal analgesic/antacid combination drug products containing sodium bicarbonate as an antacid active ingredient is not expected to have an impact on small businesses. The final rule will impose direct one-time costs associated with changing product labels, but that cost is estimated to be less than $1 million. Also, there appears to be a limited number of products involved. Manufacturers will have 6 months after publication of the final rule in which to implement this relabeling. However, manufacturers of OTC internal analgesic/antacid combination drug products are encouraged to voluntarily implement this labeling as of the date of publication of this proposal, subject to the possibility that FDA may change the wording as a result of comments filed in response to this proposal. Because FDA is encouraging the proposed labeling changes to be used on a voluntary basis at this time, the agency advises that manufacturers will be given ample time after publication of the final rule to use up any labeling implemented in conformance with this proposal. The impact of the proposed rule, if implemented, appears to be minimal. Therefore, the agency concludes that the proposed rule is not a major rule as defined in Executive Order 12866. Further, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC internal analgesic/antacid combination drug products containing sodium bicarbonate as an antacid active ingredient. Types of impact may include, but are not limited to, costs associated with relabeling or repackaging. Comments regarding the impact of this rulemaking on OTC internal analgesic/antacid combination drug products should be accompanied by appropriate documentation. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

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 4, 1994, submit written comments on the proposed regulation and the agency's economic impact determination to the Dockets Management Branch (address above). Three copies of all comments are to be submitted, except that individuals may submit one copy. Comments should 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. Received comments 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

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 December 24, 1991 (56 FR 66762), be amended as follows:

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

1. The authority citation for 21 CFR part 343 is revised 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 343.60 is amended by revising paragraphs (b)(2) and (b)(4), by adding new paragraph (c)(2), by redesignating the heading in paragraph (d) introductory text as paragraph (d), by redesignating the text in existing paragraph (d) introductory text as paragraph (d)(1), by redesignating existing paragraphs (d)(1) and (d)(2) as paragraphs (d)(1)(i) and (d)(1)(ii), respectively, and by adding new paragraph (d)(2) to read as follows:

§ 343.60 Labeling of permitted combinations of active ingredients.

* * * * *

(b) * * *

(2) For permitted combinations identified in *§ 343.20(b)(1)*—(i) *All combinations except those containing sodium bicarbonate as an active ingredient in a dosage form intended to be dissolved in liquid before administration.* 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."))

(ii) *Any combination containing sodium bicarbonate as an active ingredient in a dosage form intended to be dissolved in liquid before administration.* 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 of the following, as appropriate: "this symptom" or "these symptoms.")) These products may not bear any claims

that relate to use for "overindulgence in food and drink" or "hangover."

* * * * *

(4) *For permitted combinations identified in § 343.20(b)(3)*—(i) *All combinations except those containing sodium bicarbonate as an active ingredient in a dosage form intended to be dissolved in liquid before administration.* 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.")]

(ii) *Any combination containing sodium bicarbonate as an active ingredient in a dosage form intended to be dissolved in liquid before administration.* 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 of the following, as appropriate: "this symptom" or "these symptoms")] 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.")] These products may not bear any claims that relate to use for "overindulgence in food and drink" or "hangover."

* * * * *

(c) * * *

(2) *For permitted combinations identified in § 343.20(b)(1) and (b)(3) containing sodium bicarbonate as an active ingredient in a dosage form intended to be dissolved in liquid before administration.* The warnings in § 331.30(c)(8) of this chapter should also be used.

(d) *Directions*—(1) 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:

* * * * *

(2) *For permitted combinations identified in § 343.20(b)(1) and (b)(3) containing sodium bicarbonate as an active ingredient in a dosage form intended to be dissolved in liquid before administration.* The directions in § 331.30(e)(1) of this chapter should also be used.

Dated: November 3, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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