DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 357

[Docket No. 82N-0166]

RIN 0905-AA06

Orally Administered Drug Products for Relief of Symptoms Associated With Overindulgence in Food and Drink 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 proposing to amend the tentative final monograph for over-the-counter (OTC) orally administered drug products for relief of symptoms associated with overindulgence in food and drink to include a Reye syndrome warning for OTC drug products containing bismuth subsalicylate. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments or objections by July 6, 1993; written comments on the agency's economic impact determination by July 6, 1993.

ADDRESSES: Written comments or objections 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, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of October 1, 1982 (47 FR 43540), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC orally administered drug products for relief of symptoms associated with overindulgence in alcohol and food, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in these drug products. Interested persons were invited to submit comments by December 30, 1982. Reply comments in response to comments filed in the initial comment period could have been submitted by January 31, 1983.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC orally administered drug products for relief of symptoms associated with overindulgence in food and drink was published in the **Federal Register** of December 24, 1991 (56 FR 66742). Interested persons were invited to file by April 22, 1992, written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs. Interested persons were also invited to submit new data by December 24, 1992, and to submit comments on the new data by February 24, 1993.

Final agency action on this class of drugs will occur with the publication at a future date of a final rule for orally administered drug products for relief of symptoms associated with overindulgence in food and drink. The proposal included in this notice will be addressed in that final rule.

Since publication of the tentative final monograph for OTC drug products for relief of symptoms associated with overindulgence in food and drink, FDA has considered the need for a Reye syndrome warning for OTC drug products that contain bismuth subsalicylate. FDA is aware that a manufacturer of a major OTC drug product that contains bismuth subsalicylate has voluntarily included a Reye syndrome warning on its labeling (Ref. 1).

FDA promulgated the existing Reye syndrome warning for OTC drug products containing aspirin in § 201.314(h) (21 CFR 201.314(h)) at a time when scientific research was focused primarily on the association of Reye syndrome and aspirin rather than the broader category of drug products containing nonaspirin salicylates; thus, the warning was limited to aspirin. The warning in § 201.314(h)(1), currently required for all oral and rectal OTC drug products containing aspirin, states: "WARNING: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye syndrome, a rare but serious illness reported to be associated with aspirin."

While cases of Reye syndrome are rare, the agency is aware of one fatality from Reye syndrome reported to be associated with the use of bismuth subsalicylate (Ref. 2). The death, which occurred in January 1989, involved a 6-year-old child who reportedly developed Reye syndrome following the administration of the label-recommended dosage of an OTC bismuth subsalicylate product for the treatment of flu-like symptoms, diarrhea, and nausea.

Aspirin is de-acetylated in the gut, blood, and liver to salicylic acid and the major plasma component after ingestion of aspirin is salicylate, the ionized form of salicylic acid (Ref. 3). Similarly, bismuth subsalicylate is chemically transformed throughout the gastrointestinal tract and nearly all of the resultant salicylate is systemically available (Refs. 4 and 5). Because higher serum salicylate levels in children with Reye syndrome than in the general population have been found during outbreaks of this disease (Ref. 6) and the mechanism of toxicity is unknown, the agency believes the aspirin association with Reye syndrome may be applicable to other salicylate products as well. The agency's decision on this matter will be discussed in a future issue of the **Federal Register**. However, irrespective of this final determination on the Reye syndrome warning for all drug products containing nonaspirin salicylates, the agency is proposing a Reye syndrome warning for OTC drug monograph products that contain bismuth subsalicylate.

Therefore, the agency is proposing to amend § 357.950 (21 CFR 357.950) by redesignating paragraphs (c)(1) through (c)(4) as paragraphs (c)(2) through (c)(5) and by adding new paragraph (c)(1) to include a Reye syndrome warning for all OTC overindulgence drug products that contain bismuth subsalicylate. Proposed § 357.950(c)(1)(i) and (c)(1)(ii) read as follows:

(i) "Children and teenagers who have or are recovering from chicken pox, flu symptoms, or flu should NOT use this product. If nausea, vomiting, or fever occur, consult a doctor because these symptoms could be an early sign of Reye syndrome, a rare but serious illness."

(ii) This warning statement shall appear on the immediate container labeling. In cases where the immediate container is not the retail package, the retail package also must bear the warning statement. In addition, the warning statement shall appear on any labeling that contains warnings and, in such cases, the warning statement shall be the first warning statement under the heading "Warnings".

The proposed Reye syndrome warning for products containing bismuth subsalicylate differs from the existing warning in § 201.314(h)(1) for oral and rectal drug products containing aspirin. The first sentence of this proposed warning states that "Children and teenagers who have or are recovering from chicken pox, flu symptoms, or flu should NOT use this product," whereas the warning for aspirin states that "Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor * * *." Reye syndrome most

commonly occurs following influenza, chicken pox, and several other common viral infections. As symptoms of the viral illness begin to diminish or clear, the dramatic symptoms of Reye syndrome, i.e., intractable vomiting, lethargy, or delirium, begin (Ref. 7). Thus, the agency believes that it is important that aspirin and bismuth subsalicylate not be given to children and teenagers when flu symptoms are present as well as when symptoms are absent and the child seems to be recovering from the illness. Therefore, the agency believes that the wording used in this proposal, i.e., "who have or are recovering from chicken pox, flu symptoms, or flu," is more informative than the wording currently used in the aspirin warning.

The proposed Reye syndrome warning also differs from the existing warning because it contains a second sentence that includes the terms "nausea, vomiting, or fever." On July 26, 1991, the Gastrointestinal Drugs Advisory Committee reviewed data on the use of bismuth subsalicylate for the relief of acute diarrhea and travelers' diarrhea. The Committee reviewed a Reye syndrome warning currently voluntarily included on a major OTC drug product containing bismuth subsalicylate. That warning stated: "WARNING: Children and teenagers who have or are recovering from chicken pox or flu should not use this medicine to treat nausea or vomiting. If nausea or vomiting is present, consult a doctor because this could be an early sign of Reye Syndrome, a rare but serious illness." The Committee felt that bismuth subsalicylate containing products should have a stronger warning regarding Reye syndrome because of concern that with approval of the drug as a treatment for diarrhea, there could be wider use of the product in children who might have a viral illness. A Reye syndrome warning for bismuth subsalicylate used as an antidiarrheal will be discussed in the rulemaking for OTC antidiarrheal drug products in a future issue of the **Federal Register**.

The agency has evaluated the warning and the Committee's recommendations and determined that the first sentence of the warning could be shortened and achieve the same effect. The agency also concludes that an additional sentence stating the early recognizable symptoms of Reye syndrome, i.e., nausea, vomiting, and fever, is important information that should be included as part of the warning. Therefore, the agency is proposing that the second sentence of the Reye syndrome warning reads as follows: "If nausea, vomiting, or fever occur, consult a doctor because these symptoms could be an early sign of Reye syndrome, a rare but serious illness." The agency is inviting comment on the Reye syndrome warning proposed for bismuth subsalicylate containing drug products for relief of overindulgence in food and drink. The agency is also considering the appropriateness of revising the current Reye Syndrome warning for oral and rectal OTC drug products containing aspirin in § 201.314(h)(1) to be similar to the language being proposed in this document. Based on the comments received, in a future issue of the **Federal Register**, the agency may propose to revise the current Reye syndrome warning in § 201.314(h)(1).

References

(1) Copy of Labeling for Pepto-Bismol, in OTC Vol. 17LAM, Docket No. 82N–0166, Dockets Management Branch.

(2) Adverse Drug Reaction Report, in OTC Vol. 17LAM, Docket No. 82N–0166, Dockets Management Branch.

(3) Shearn, M. A., "Nonsteroidal Anti-inflammatory Agents; Nonopiate Analgesics; Drugs Used in Gout," in "Basic and Clinical Pharmacology," 2nd ed., edited by B. G. Katzung, Lange Medical Publications, Los Altos, CA, pp. 400–403, 1984.

(4) DuPont, H. L., "Bismuth Subsalicylate In the Treatment and Prevention of Diarrheal Disease," *Drug Intelligence and Clinical Pharmacy*, 21:687–693, 1987.

(5) Pickering, L. K., et al., "Absorption of Salicylate and Bismuth from a Bismuth Subsalicylate-Containing Compound (Pepto-Bismol)," *The Journal of Pediatrics*, 99:654–656, 1981.

(6) Isselbacher, K. J., and D. K. Podolsky, "Infiltrative and Metabolic Diseases Affecting the Liver" in "Harrison's Principles of Internal Medicine," 12th Ed., edited by J. D. Wilson, et al., McGraw-Hill, Inc., New York, p. 1353, 1991.

(7) Wolinsky, J. S., "Reye Syndrome," in "Cecil Textbook of Medicine," 19th Ed., edited by J. B. Wyngaarden, et al., W. B. Saunders Co., Philadelphia, pp. 2194–2195, 1992.

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 overindulgence 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 overindulgence drug products is not expected to pose such an impact on small businesses. The final rule will require some relabeling for all OTC overindulgence drug products containing bismuth subsalicylate; however, such relabeling should be a one time nominal cost. Manufacturers will have 1 year after publication of the final rule to implement this relabeling, and the cost to do so per product label is considered minimal. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

Because the tentative final monograph did not include a Reye syndrome warning, the agency is providing a 60-day period for comments. The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC overindulgence drug products. 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 orally administered drug products for relief of symptoms associated with overindulgence in food and drink 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 July 6, 1993, submit written comments or objections on the proposed regulation to the Dockets Management Branch (address above). Written comments on the agency's economic impact determination may be submitted on or before July 6, 1993. 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. 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 357

Labeling, Over-the-counter drugs, Reporting and recordkeeping requirements.

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 357 (as proposed in the **Federal Register** of December 24, 1991 (56 FR 66742)), be amended as follows:

PART 357—MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 357 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 357.950 is amended by redesignating paragraphs (c)(1) through (c)(4) as paragraphs (c)(2) through (c)(5) and by adding new paragraph (c)(1) to read as follows:

§ 357.950 Labeling of drug products for the relief of symptoms of upset stomach due to overindulgence in food and drink.

* * * * *

(c) * * *

(1)(i) "Children and teenagers who have or are recovering from chicken pox, flu symptoms, or flu should NOT use this product. If nausea, vomiting, or fever occur, consult a doctor because these symptoms could be an early sign of Reye syndrome, a rare but serious illness."

(ii) This warning statement shall appear on the immediate container labeling. In cases where the immediate container is not the retail package, the retail package also must bear the warning statement. In addition, the warning statement shall appear on any labeling that contains warnings and, in such cases, the warning statement shall be the first warning statement under the heading "Warnings".

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Dated: February 3, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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