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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 335

[Docket No. 78N–036T]

RIN 0910–AA01

Antidiarrheal Drug Products for Over-the-Counter Human Use; Proposed Amendment of Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a proposed rule that would amend the final monograph for over-the-counter (OTC) antidiarrheal drug products to include relief of travelers' diarrhea as an indication for products containing bismuth subsalicylate. Travelers' diarrhea occurs in travelers and is most commonly caused by an infectious agent. This proposal is part of FDA's ongoing review of OTC drug products.

DATES: Submit written or electronic comments by [*insert date 90 days after date of publication in the* **Federal Register**]; written or electronic comments on the agency's economic impact determination by [*insert date 90 days after date of publication in the* **Federal Register**]. Please see section VIII of this document for the effective date of any final rule that may publish based on this proposal.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061,

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Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments.

FOR FURTHER INFORMATION CONTACT: Mary S. Robinson, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2222.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of March 21, 1975 (40 FR 12902), FDA published under 21 CFR 330.10(a)(6) an advance notice of proposed rulemaking to establish a monograph for OTC antidiarrheal drug products, together with the recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products, which evaluated these drug classes. The proposed rule was published in the **Federal Register** of April 30, 1986 (51 FR 16138), as a tentative final monograph.

In response to the proposed rule, one manufacturer requested a travelers' diarrhea claim for bismuth subsalicylate (Ref. 1). Travelers' diarrhea is an acute diarrheal illness occurring among travelers, particularly those visiting developing countries where sanitation is suboptimal. Virtually all cases of travelers' diarrhea are caused by infectious agents, acquired through the ingestion of fecally contaminated food and/or water. Bacterial pathogens account for the great majority of episodes. Overall, one of the most common etiologic agents in travelers' diarrhea are enterotoxigenic *Escherichia coli*, which are responsible for 50 to 75 percent of episodes in certain areas of the world. Other recognized enteropathogens can be isolated from most of the remainder of cases, but with great regional differences in prevalence. Viruses

(rotavirus, Norwalk-like virus) and protozoa (amebas, Giardia) are collectively responsible for fewer than 10 percent of cases of travelers' diarrhea (Ref. 2).

The clinical data for this claim are discussed in section II, comment 3 of the final rule for OTC antidiarrheal drug products, published elsewhere in this issue of the **Federal Register**. The agency has tentatively determined that the data support the use of bismuth subsalicylate in treating the symptoms of travelers' diarrhea. Accordingly, the agency is proposing to amend the final monograph to include "relieves travelers' diarrhea" as a monograph indication for OTC antidiarrheal drug products containing bismuth subsalicylate identified in § 335.10(a).

II. Summary of the Agency's Proposal for Travelers' Diarrhea

The agency proposes to add the following definition in § 335.3(c): "*Travelers' diarrhea.* A subset of diarrhea occurring in travelers that is most commonly caused by an infectious agent." The agency is also proposing to add the following labeling indication in § 335.50(b)(1) for products containing bismuth subsalicylate: "[* * * "controls" or "relieves"] [* * * "travelers' diarrhea"] * * *." Products may not be labeled with this claim until the monograph amendment process is completed and the agency publishes a final rule in a future issue of the **Federal Register**.

III. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory

approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

The agency tentatively concludes that this proposed rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. The proposed rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. The Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for this proposed rule, because the proposed rule is not expected to result in any 1-year expenditure that would exceed $100 million adjusted for inflation. The current inflation adjusted statutory threshold is about $110 million.

The purpose of this proposed rule is to provide an additional (optional) claim for OTC antidiarrheal drug products containing bismuth subsalicylate. Manufacturers can add this claim to their labeling when ordering new product labeling to be in compliance with the OTC antidiarrheal drug products final monograph. Adding this claim might result in additional product sales but, in any case, is completely optional. Thus, this proposed rule will not impose

a significant economic burden on affected entities. Therefore, the agency certifies that this proposed rule will not have a significant economic impact on a substantial number of small entities. No further analysis is required under the Regulatory Flexibility Act (5 U.S.C. 605(b)).

The agency invites public comment regarding any substantial or significant economic impact that this proposed rule would have on OTC antidiarrheal drug products. Types of impact may include, but are not limited to, costs associated with relabeling or repackaging. Comments regarding the impact of this proposed rule should be accompanied by appropriate documentation. A period of 90 days from the date of publication of this proposed rule in the **Federal Register** will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this proposed rule in the preamble to the final rule.

IV. Paperwork Reduction Act of 1995

FDA tentatively concludes that the labeling requirements proposed in this document are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the proposed labeling statements are a "public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(a)).

V. Environmental Impact

The agency has determined under 21 CFR 25.31(a) 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.

VI. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement has not been prepared.

VII. Request For Comments

Interested persons may submit written or electronic comments regarding this proposal and on the agency's economic impact determination to the Dockets Management Branch (see **ADDRESSES**) by (see **DATES**). Three copies of all written comments are to be submitted, except individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

VIII. Proposed Effective Date

The agency is proposing that any final rule that may issue based on this proposal become effective 30 days after its date of publication in the **Federal Register**.

IX. References

The following references are on display in the Dockets Management Branch (see **ADDRESSES**) under Docket No. 78N–036D and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comments No. SUP 8, SUP 13, SUP 14, LET 21, LET 23, PR 3, and MT 2.

2. Wilson, J. D. et al., editors, *Harrison's Principles of Internal Medicine*, 12th ed., McGraw-Hill, Inc., New York, NY, pp. 523–524, 1991.

List of Subjects in 21 CFR Part 335

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 335 be amended as follows:

PART 335—ANTIDIARRHEAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 335 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

2. Section 335.3 is amended by adding paragraph (c) to read as follows:

§ 335.3 Definitions.

* * * * *

(c) *Travelers' diarrhea.* A subset of diarrhea occurring in travelers that is most commonly caused by an infectious agent.

3. Section 335.50 is amended by revising paragraph (b)(1) to read as follows:

§ 335.50 Labeling of antidiarrheal drug products.

* * * * *

(b) * * *

(1) *For products containing bismuth subsalicylate identified in § 335.10(a).* The labeling states [select one of the following: "controls" or "relieves"] [select one or both of the following: "diarrhea" or "travelers' diarrhea"]. If both "diarrhea" and "traveler's diarrhea" are selected, each shall be preceded by

a bullet in accordance with § 201.66(b)(4) of this chapter and the heading "Uses" shall be used.

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Dated: 3/31/03
March 31, 2003.

Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. 03–????? Filed ??–??–03; 8:45 am]

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