

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 335

[Docket No. 1978N-036T]

RIN 0910-AC82

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule amending the final monograph (FM) 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 final rule is part of FDA's ongoing review of OTC drug products.

DATES: This rule is effective [*insert date 30 days after date of publication in the Federal Register*].

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. FDA published the proposed rule in the **Federal Register** of April 30, 1986 (51 FR 16138), as a tentative final monograph.

FDA discussed a travelers' diarrhea claim for bismuth subsalicylate in the final rule for OTC antidiarrheal drug products (68 FR 18869, April 17, 2003). Travelers' diarrhea is an acute diarrheal illness occurring among travelers, particularly those visiting developing countries where sanitation is suboptimal. Most 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.

FDA discussed the clinical data for this claim in section II, comment 3 of the final rule for OTC antidiarrheal drug products (68 FR 18869 at 18871). FDA has determined that the data support the use of bismuth subsalicylate in treating the symptoms of travelers' diarrhea. Accordingly, FDA is amending the FM to include an indication ["controls" or "relieves" "travelers' diarrhea"] for OTC antidiarrheal drug products containing bismuth subsalicylate identified in 21 CFR 335.10(a).

II. FDA's Conclusions on the Comment

In response to the proposal, FDA received one comment, which is on public display in the Division of Dockets Management (HFA-305), 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. The comment agreed completely with the proposal to amend the FM for OTC antidiarrheal drug products to include the additional indication for travelers' diarrhea for products containing bismuth subsalicylate. The comment encouraged FDA to expeditiously amend the FM so this indication can be used on appropriate OTC drug products.

FDA agrees with the comment and is providing that this final rule be effective 30 days after its date of publication.

III. FDA's Final Conclusions

FDA is amending the FM for OTC antidiarrheal drug products to make the following additions:

- Definitions in 21 CFR 335.3(c): "Travelers' diarrhea. A subset of diarrhea occurring in travelers that is most commonly caused by an infectious agent."
- Indications in 21 CFR 335.50(b)(1) for products containing bismuth subsalicylate: [select one of the following: "controls" or "relieves"] *** "travelers' diarrhea"]. If both "diarrhea" and "travelers' diarrhea" are selected, each shall be preceded by a bullet in accordance with 21 CFR 201.66(b)(4) and (d)(4) of this chapter and the heading "Uses" shall be used.

IV. Analysis of Impacts

FDA has examined the impacts of the final 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).

FDA concludes that this final rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. The final rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. As discussed in this section of the document, FDA has determined that this final rule will not have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for this final rule, because the final 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 final 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 FM. Adding this claim might result in additional product sales but, in any case, is completely optional. Thus, this final rule will not impose a significant

economic burden on affected entities. Therefore, FDA certifies that this final 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)).

V. Paperwork Reduction Act of 1995

FDA concludes that the labeling requirements 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 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(c)(2)).

VI. Environmental Impact

FDA 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.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the 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 concludes that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

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, 21 CFR part 335 is 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 “travelers’ diarrhea” are selected, each shall be preceded by a bullet in accordance with § 201.66(b)(4) and (d)(4) of this chapter and the heading “Uses” shall be used.

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Dated: May 3, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 04-????? Filed ??-??-04; 8:45 am]

BILLING CODE 4160-01-S