

additional data or other comments in response to its request. New relevant data can be submitted in accordance with §§ 330.10(a)(12) and 10.30.

For products containing bismuth subsalicylate, a required indication is included in § 335.50(b)(1) as follows: "The labeling states [select one of the following: "controls" or "relieves"] "diarrhea". Additional indications" in § 335.50(b)(3)(ii) \* \* \* include one or both of the following \* \* \*: "[bullet] reduces number of bowel movements" "[bullet] helps firm stool". The indication "Relieves pain in diarrhea" has not been included because of insufficient data to support such a claim (see section II, comment 12 of this document).

The agency is including in new § 335.50(b)(2) the following indication for kaolin: "helps firm stool within 24 to 48 hours" (see section II, comment 11 of this document).

The agency has revised the warnings included in the TFM (see section II, comments 4, 14, and 15 of this document).

Because the potential for fluid loss and electrolyte imbalance due to diarrhea may have serious consequences, the agency is adding an additional direction in § 335.50(d)(1): "The labeling states '[bullet] drink plenty of clear fluids to help prevent dehydration caused by diarrhea.'"

#### IV. The Agency's Final Conclusions

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC antidiarrheal drug products are generally recognized as safe and effective and not misbranded. Any drug product labeled, represented, or promoted for uses as an OTC antidiarrheal drug product that contains any of the ingredients listed in § 310.545(a)(3)(i) or (a)(3)(ii) or that is not in conformance with the monograph (to be codified at 21 CFR part 335) may be considered a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)) and misbranded under section 502 of the act (21 U.S.C. 352). Such a product cannot be marketed for antidiarrheal use unless it is the subject of an approved application under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations (21 CFR part 314). An appropriate citizen petition to amend the monograph may also be submitted in accordance with §§ 10.30 and 330.10(a)(12)(i). Any OTC antidiarrheal drug product initially introduced or initially delivered for introduction into interstate commerce after the compliance dates of the final

rule for § 310.545(a)(3)(i) or this final rule that is not in compliance with the regulations is subject to regulatory action.

The agency is revoking the existing warning statement in § 369.20 for diarrhea preparations at the time that this monograph becomes effective. That warning is superseded by the requirements of the final monograph.

Mandating warnings in an OTC drug monograph does not require a finding that any or all of the OTC drug products covered by the monograph actually caused an adverse event, and FDA does not so find. Nor does FDA's requirement of warnings repudiate the prior OTC drug monographs and monograph rulemakings under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that warnings are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the act. This judgment balances the benefits of these drug products against their potential risks (see 21 CFR 330.10(a)).

FDA's decision to act in this instance need not meet the standard of proof required to prevail in a private tort action (*Glastetter v. Novartis Pharmaceuticals, Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)). To mandate warnings, or take similar regulatory action, FDA need not show, nor do we allege, actual causation. For an expanded discussion of case law supporting FDA's authority to require such warnings, see Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use, a final rule that published in the **Federal Register** of December 6, 2002 (67 FR 72555).

#### V. Analysis of Impacts

An analysis of the costs and benefits of this regulation, conducted under Executive Order 12291, was discussed in the TFM for OTC antidiarrheal drug products (51 FR 16138 at 16147). (Executive Order 12291 was revoked by Executive Order 12866.) The agency certified that under the Regulatory Flexibility Act the proposed rule would not have a significant economic impact on a substantial number of small entities. No comments were received on the economic impact of this rulemaking.

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). The proposed rule that has led to the development of this final rule was published on April 30, 1986, before the Unfunded Mandates Reform Act of 1995 was enacted. The agency explains in this final rule that the final rule will not 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.

The agency 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. The Unfunded Mandates Reform Act of 1995 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 establish allowable monograph ingredients and labeling under which OTC antidiarrheal drug products are generally recognized as safe and effective. The agency has identified 45 manufacturers currently marketing 383 OTC antidiarrheal drug products containing bismuth subsalicylate (334), attapulgite (32), kaolin and pectin (13), polycarbophil (2), and calcium polycarbophil (2). This final rule will result in the reformulation or removal of about 50 products containing activated attapulgite, calcium polycarbophil, polycarbophil, and pectin. These products may be reformulated to contain bismuth subsalicylate or kaolin. The agency is unaware of any current marketing of bismuth subnitrate,