

of this document are due by July 16, 2003.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Mary S. Robinson or Gerald M. Rachanow, 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 § 330.10(a)(6) (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 (the panel), which evaluated these drug classes. The agency's proposed regulation for OTC antidiarrheal drug products was published in the **Federal Register** of April 30, 1986 (51 FR 16138), in the form of a TFM. In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency issued a final rule establishing that certain active ingredients, including some antidiarrheal active ingredients, in OTC drug products are not generally recognized as safe and effective or are misbranded. These antidiarrheal active ingredients are listed in § 310.545(a)(3) (21 CFR 310.545(a)(3)). This final rule adds nine ingredients to that section.

On or after the compliance dates established in this final rule (see **DATES** section) no OTC drug product that is subject to this final rule and that contains a nonmonograph condition may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application (NDA) or abbreviated new drug application. Further, any OTC drug product subject to this final rule that is repackaged or relabeled after the effective date of the final rule must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the conditions in this final monograph as soon as possible.

In the TFM (51 FR 16138 at 16148), the agency proposed monograph status for activated attapulgite, calcium polycarbophil, and polycarbophil. The agency has reevaluated the data for these ingredients and classified them as nonmonograph conditions (see section III of this document). Kaolin and bismuth subsalicylate were category III (see § 330.10(a)(6)(iii)) in the TFM. They are monograph conditions in this final rule.

In the **Federal Register** of March 17, 1999 (64 FR 13254), the agency established a standardized format and content for the labeling of all OTC drug products (see § 201.66 (21 CFR 201.66)). The labeling in this final monograph incorporates those requirements. The agency is specifically soliciting comments on the labeling for bismuth subsalicylate and kaolin. If the comments justify a change, the agency will propose to amend the final monograph accordingly at a later date.

All "OTC Volumes" cited throughout this document refer to information on public display in the Dockets Management Branch (see **ADDRESSES**).

II. The Agency's Conclusions on the Comments

(Comment 1) One comment requested the agency to increase the proposed dose for activated attapulgite (51 FR 16138 at 16149) from a maximum of 8.4 grams (g) per day to a maximum of 9 g per day for adults and children 12 years of age and over. The comment also recommended higher daily doses for children under 12 years old. The comment submitted three clinical studies to support these higher doses (Refs. 1, 2, and 3).

The agency has determined that the studies are insufficient to support an increase in the daily dose. The studies were neither designed nor analyzed to support the requested increase of the maximum daily dose. The data do not provide information as to the basis or need for an increased dose, do not establish a target population for such a dose, and do not directly compare the two dose levels in order to establish that the higher dose is as safe and provides any additional benefit. The agency's detailed comments and evaluation of the studies are on file in the Dockets Management Branch (Ref. 4). Moreover, based on a reevaluation of the studies submitted to support the effectiveness of attapulgite (51 FR 16138 at 16142), the agency concludes that additional effectiveness data are needed to support monograph status (see section III of this document).

(Comment 2) One comment submitted a safety study (Ref. 5) and two clinical

studies (Refs. 6 and 7) to support the use of bismuth subsalicylate for the prophylaxis of travelers' diarrhea.

The agency has determined that the data are insufficient to support use of bismuth subsalicylate for prophylaxis of travelers' diarrhea. The safety study (Ref. 5) evaluated a dose that was 50 percent higher and given for a time period that was 50 percent longer than planned for the travelers' diarrhea study, which was a 17-week, double-blind, parallel, randomized study conducted in 93 healthy, adult volunteers. One objective was to determine the blood levels and urinary excretion of bismuth resulting from long-term dosing. Average blood bismuth concentration, after 6 weeks of dosing, was significantly higher for the bismuth subsalicylate four times a day group than the two times a day group. Blood levels slowly decreased through a 9-week followup period. None of the subjects in either placebo group exhibited a detectable blood bismuth level.

One clinical study (Ref. 6) was a 14-day double-blind, randomized, placebo-controlled comparison of the prophylactic effects of two doses of bismuth subsalicylate on the incidence of travelers' diarrhea in 390 subjects traveling to destinations where the incidence of travelers' diarrhea was at least 20 percent. Depending upon the group assigned, subjects were given either 525 milligrams (mg) bismuth subsalicylate two times a day (low dose), 1,050 mg bismuth subsalicylate two times a day (high dose), or lactose placebo tablets two times a day.

The primary efficacy parameter was the incidence rate of travelers' diarrhea. The investigators concluded that both doses provide a statistically significant reduction in the occurrence of diarrhea. Additional analyses were done. In one analysis, the data were evaluated strictly according to the inclusion/exclusion criteria and the definition of diarrhea as stated in the protocol. Results indicated that the significant advantage of each dose regimen claimed in the original analyses was not maintained. A further (intent-to-treat) analysis was done using all subjects, *i.e.*, inclusion/exclusion criteria were ignored and all subjects were included. This evaluation also did not confirm the statistical advantage of each dose regimen claimed in the original analysis. In addition, this study is inadequate because there was a 47 percent rate of protocol violations and differences in definitions of diarrhea used (in the protocol and in the evaluable subjects) raise questions about the adequacy of the blinding of the study.