

§ 335.80—professional labeling, because of the lack of adequate studies to support the safety and effectiveness of the monograph ingredients in children of any age.

The OTC drug product labeling format has changed since the TFM was published. Under the current format, the word “fever” follows the subheading “Ask a doctor before use if you have.” The phrase “Do not use for more than 2 days” is now included after the subheading “Stop use and ask a doctor if” as “[bullet] diarrhea lasts more than 2 days.” Because this information is now in the final monograph, the agency is removing the warning statement for “DIARRHEA PREPARATIONS” in § 369.20 (21 CFR 369.20).

(Comment 15) One comment noted the agency’s statement that the following labeling might be required for bismuth subsalicylate: “This product may cause the stool to darken or cause a temporary darkening of the tongue” (51 FR 16138 at 16143). Although agreeing in principle, the comment stated that it should appear as a notation and not as a warning because this effect is temporary and harmless. The comment suggested the labeling read as follows: “This product may cause a temporary, but harmless, darkening of the stool and tongue.”

The agency agrees in part. Under the new OTC drug labeling format, this statement appears under the “Warnings” subheading “When using this product” as “a temporary, but harmless, darkening of the stool and/or tongue may occur”.

III. Summary of Significant Changes From the Proposed Rule

The agency has reclassified activated attapulgite from proposed category I to a nonmonograph condition in § 310.545(a)(3) because of insufficient effectiveness data. On April 9, 1993, the committees discussed the continued marketing of products containing attapulgite (Ref. 31). They reviewed effectiveness studies (Refs. 33 through 36) cited in the TFM (51 FR 16138 at 16142) and reviewed two studies (Refs. 37 and 38) not previously considered. The committees determined that the data were not sufficient to support the effectiveness of activated attapulgite for antidiarrheal use. One study (Ref. 33) was not implemented according to its protocol and adequate data were not collected or recorded in the individual patient report forms. Thus, the results were not considered interpretable. The committees questioned the method of collection and reporting of data, and the amount of lactose in the placebo used in another study (Refs. 35, 36, and 37). The

results were considered questionable because lactose can cause diarrhea in individuals with lactase deficiency. The committees concluded that replication of the study results by an independent investigator was needed.

The two new studies (Refs. 37 and 38) were active treatment-controlled, comparing attapulgite with loperamide. The authors of one study (Ref. 37) stated that the results of this bicentric, randomized, parallel-group, comparative study showed that attapulgite was as effective as loperamide in stopping diarrhea. They concluded that attapulgite offers the safety of a nonsystemic adsorbent while providing efficacy equivalent to that of loperamide, a systemic antiperistaltic drug. However, the committees determined that, because of the absence of a placebo control, the authors’ conclusions indicated a value judgment and no conclusions of efficacy could be determined from the study. The results of the other study (Ref. 38), a randomized, parallel, open-label study, suggested that loperamide, the active treatment-control, was better than attapulgite. Because no placebo control was used, the committees felt that no decision could be made as to the effectiveness of attapulgite in stopping diarrhea.

While acknowledging that FDA’s “Guidelines for the Clinical Evaluation of Antidiarrheal Drugs” (Ref. 39) indicate that a reference drug of proven efficacy may be used, the committees stated that improvement could be shown with any drug because the duration of symptoms of acute nonspecific diarrhea is 2 days. Therefore, it was the committees’ consensus that placebo-controlled studies were needed to establish the effectiveness of attapulgite.

FDA notified the OTC drug manufacturers association by correspondence dated September 14, 1993, of the agency’s intent to classify attapulgite as a nonmonograph condition (Ref. 40). The agency requested interested parties to submit any additional data on these ingredients in the form of a petition to reopen the administrative record. FDA placed this correspondence in the public docket, but has not received any additional data or other comments in response to its request. Thus, based on the above analysis and the recommendation of the committees, FDA has classified this ingredient as a nonmonograph condition in this final rule.

The agency has reclassified bismuth subsalicylate from category III to a monograph condition in § 335.10(a) (see section II, comment 3 of this document)

and included specific labeling in § 335.50(b)(1), (b)(3)(ii), (c)(2), and (d)(2) for products containing bismuth subsalicylate (see section II, comments 3, 4, 5, and 15 of this document).

The agency has reclassified calcium polycarbophil and polycarbophil from proposed category I to a nonmonograph condition in § 310.545(a)(3) because of insufficient effectiveness data. On April 9, 1993, the committees discussed the continued marketing of OTC antidiarrheal drug products containing attapulgite, kaolin, and pectin (Ref. 31). Based on the effectiveness issues the committees raised, the agency rereviewed the data cited in the TFM (51 FR 16138 at 16141 to 16142) and determined that the existing data do not support the OTC use of calcium polycarbophil and polycarbophil for acute nonspecific diarrhea (Refs. 40 and 41). Only two of the studies relied on by the panel (40 FR 12926) and the agency (51 FR 16138 at 16141) to support monograph status involved subjects with acute nonspecific diarrhea (Refs. 42 and 43). These studies were conducted in a population in which the majority (88 to 92 percent) of subjects enrolled were less than 5 years old. No placebo controls were used and the comparative drug (kaolin-pectin suspension) had not been shown to be effective at the time of the trial. There was no indication of duration of diarrhea preceding treatment or relationship to onset of relief, and the randomization scheme was unequal and unclear. The agency does not believe that these data can be extrapolated to an adult population.

The other studies previously cited in support of polycarbophil included an uncontrolled study (Ref. 44) on the effectiveness of polycarbophil for the relief of constipation, a condition not covered in this monograph. Two other studies (Refs. 45 and 46) are inadequate because chronic diarrhea was considered, the patient selection criteria were not defined, and concomitant medications were unknown.

Therefore, the agency has classified calcium polycarbophil and polycarbophil as nonmonograph conditions. Placebo-controlled studies are needed to establish their effectiveness. FDA notified the OTC drug manufacturers association by correspondence dated May 5, 1994, of the agency’s intent to classify calcium polycarbophil and polycarbophil as nonmonograph conditions (Ref. 41). FDA requested interested parties to submit any additional data concerning these ingredients to the agency. FDA placed this correspondence in the public docket, but has not received any