

negatively impacted on the study's results. The size of the doses of bismuth subsalicylate used in this trial may have been subtherapeutic (hence the lack of a demonstrable treatment effect) since they were extrapolated from doses that have been shown to be effective in adult populations for the indication that was studied in this trial. Since bismuth subsalicylate's proposed antidiarrheal efficacy stems from various mechanisms (anti-infective, absorbent, and antisecretory) that work locally in the gastrointestinal tract, the product may not have had adequate time or surface area to work effectively in the pediatric subjects tested.

The agency concludes that another double-blind, placebo-controlled study in pediatric subjects with acute nonspecific diarrhea is needed to support the use of bismuth subsalicylate for OTC antidiarrheal use in children under 12 years of age. The agency recommends dose ranging studies using pharmacokinetic modeling to determine the doses to be used in the next trial. Accordingly, labeling for use in children 3 to under 12 years of age is not included in the monograph at this time.

(Comment 7) Two comments stated that it is generally recognized that the therapeutic value in bismuth salts is dependent on the percentage of bismuth oxide. One comment discussed two products (one containing bismuth subsalicylate and the other containing bismuth subnitrate) and stated that the dosage of the bismuth subnitrate product provides 16.75 percent more bismuth oxide than the bismuth subsalicylate product. The second comment stated that bismuth subgallate contains 9.35 mg/mL (52 to 57 percent) of bismuth oxide, bismuth subnitrate contains 75.84 mg/mL (not less than 79 percent) of bismuth oxide, and bismuth subsalicylate contains 11.20 mg/mL (62 to 66 percent) of bismuth oxide. The comment contended that bismuth subsalicylate at the recommended dosage is under dosed in effectiveness and concluded that bismuth subnitrate should be placed in category I. Another comment discussed the dose of bismuth subnitrate.

The comments did not submit any data to establish the exact mechanism of action of bismuth oxide in treating/relieving diarrhea. Bismuth subgallate, bismuth subnitrate, and bismuth subsalicylate, although chemically similar, are not chemically identical and, therefore, may not exert the same intended action. No clinical data have been submitted to show that these other bismuth compounds are acceptable for OTC antidiarrheal use. Additionally, no data have been submitted to show that

bismuth subsalicylate and bismuth subnitrate are therapeutically equivalent or that bismuth subnitrate is as effective, or more effective, than bismuth subsalicylate for use as an OTC antidiarrheal drug product. Therefore, the agency concludes that there is no basis to include bismuth subgallate or bismuth subnitrate in this final monograph.

(Comment 8) One comment submitted a clinical study (Refs. 23, 24, and 25) and requested that activated charcoal (at a dose of 1,040 mg after each bowel movement (up to 8,320 mg per day)) be reclassified from category III to category I and included in the final monograph.

The agency has determined that the data are inadequate to support effectiveness. The prospective, randomized, double-blind study (Ref. 23) was conducted at a single center where 51 subjects having nonspecific gastroenteritis with diarrhea, with or without associated abdominal cramps, completed the study. The data showed weak trends on diarrhea-related endpoints and a somewhat stronger trend on the global endpoint. There was no statistical significance for any of the three measures of outcome: (1) The patients' "global" (subjective) evaluation of treatment effectiveness, (2) the time from initiation of treatment until the last unformed stool, and (3) the time from initiation of treatment until the last cramp was reported. Because there are no well-controlled studies showing effectiveness, most likely two independently-conducted, placebo-controlled clinical trials will be needed to confirm the effectiveness of activated charcoal for antidiarrheal use. The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 26).

(Comment 9) One comment requested that a product containing a combination of bismuth subnitrate and calcium hydroxide be reclassified from category III to category I. The comment stated that the product has been sold in the United States since 1900 and in Mexico since 1923 for OTC antidiarrheal use with no reports of consumer injury and contended that controlled studies are unnecessary because of the many years of usage without reported adverse side effects and the vast amount of material in the scientific literature. The comment explained that bismuth subnitrate has been used as an antidiarrheal for over 200 years and that calcium hydroxide, an antacid and astringent, extends the shelf life of the product by neutralizing the acid residue that leaches from the bismuth subnitrate into the supernatant liquid over a long-standing period. The

comment provided selected extracts from reference textbooks (Ref. 27).

The panel classified bismuth subnitrate in category III because of insufficient effectiveness data and stated that it should not be used in infants under 2 years of age because of the risk of methemoglobinemia (40 FR 12902 at 12930). The panel placed calcium hydroxide in category III and stated that, although it is claimed useful for its antacid and buffering qualities, there is no evidence of effectiveness as an antidiarrheal (40 FR 12902 at 12930). The panel also stated that the combination of an antidiarrheal and an antacid is not rational concurrent therapy for a significant portion of the population and classified it as category II (40 FR 12902 at 12927 and 12930). The panel was also unable to find evidence to demonstrate that astringent properties for calcium hydroxide confer effectiveness in diarrhea (40 FR 12902 at 12929 to 12930).

While the absence of reported adverse reactions or historical use may be used as corroborative data, they cannot generally be considered as proof of safety or effectiveness (*see* § 330.10(a)(4)(i) and (a)(4)(ii)). New relevant data can be submitted in an NDA (*see* 21 CFR part 314) or a petition to amend the final monograph (*see* §§ 330.10(a)(12) and 10.30 (21 CFR 10.30)).

(Comment 10) Two comments requested the agency to designate rhubarb fluidextract and potassium carbonate as inactive ingredients instead of category II active ingredients in products that also included bismuth subnitrate and calcium hydroxide as active ingredients. The comments stated that rhubarb fluidextract is a necessary flavoring and coloring agent, while potassium carbonate causes the rhubarb fluidextract to go into solution. The comments added that the Panel was of the opinion that the potassium carbonate should be listed as an inactive ingredient (40 FR 12902 at 12926).

Based on data the manufacturer submitted, the panel reviewed rhubarb fluidextract and potassium carbonate as single active antidiarrheal ingredients (40 FR 12902 at 12926) as well as in combination with bismuth subnitrate and calcium hydroxide (40 FR 12902 at 12932). The manufacturer claimed that the rhubarb fluidextract is an astringent and that the potassium carbonate has some antacid value in the formulation (Ref. 28). The panel concluded that evidence was lacking to support effectiveness and placed the ingredients singly and in combination in category II. The panel stated that it found no evidence that potassium carbonate