

limit of bismuth subsalicylate recommended by the panel (40 FR 12902 at 12930). The comment stated that 4.2 g per day is equivalent to 1.59 g per day salicylate, which is only about one-half of the maximum daily salicylate dosage limit recommended by the OTC Internal Analgesic Panel (42 FR 35346 at 35358, July 8, 1977).<sup>1</sup> The comment stated that it is essential that the maximum allowable dose be based on total salicylate consumption because some bismuth subsalicylate products may also contain other salicylates as excipients. Thus, the maximum daily dose should be limited by the equivalents of salicylate ingested, and that formulated products should contain a total of no more than 3.04 g of salicylate per day. The comment stated that the bismuth subsalicylate level should be established by the lowest clinically effective dose.

Based on clinical studies submitted (see section II, comment 3 of this document), bismuth subsalicylate for antidiarrheal use has been shown to be effective at a dose of 4.2 g per day. Thus, there is no rationale for increasing the daily dosage to up to 8 g. The agency is aware that products may contain other salicylates as excipients (formulation aids). Inactive ingredients must meet the requirements of § 330.1(e) (21 CFR 330.1(e)), *i.e.*, be safe and not interfere with the effectiveness or testing of the product. There is no basis at this time to place a restriction on the use of other salicylates as inactive ingredients. However, manufacturers would be prudent to use nonsalicylate inactive ingredients when bismuth subsalicylate is the active ingredient. The agency will consider a restriction should the need arise.

(Comment 6) One comment submitted a report (Ref. 17) from a Scientific Advisory Group (SAG) that evaluated pediatric dosing for bismuth subsalicylate. The SAG reviewed three studies (Refs. 18, 19, and 20) and marketing and epidemiological data. The SAG report concluded that: (1) The clinical data support the safety and effectiveness of bismuth subsalicylate to treat diarrhea in children between 3 and 12 years of age, (2) currently recommended dose regimens to treat diarrhea in children 6 to 12 years of age, based on the effective adult dose of bismuth subsalicylate, are rational and supportable. However, increasing the currently marketed labeled dose for

children 3 to 6 years old is recommended, (3) no additional clinical studies are required to treat acute diarrhea in children 3 to 12 years old, and (4) bismuth subsalicylate labeling should include a warning to maintain adequate fluid intake when treating diarrhea in young children.

Based on the SAG's recommendations, the comment requested an age range and dosage schedule different from that included in the TFM. The comment stated that its age ranges were intended to be consistent with the age ranges specified in pediatric dose schedule C of the advance notice of proposed rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products (42 FR 35346 at 35368). The comment explained that age groupings in that monograph were determined on the basis of body surface area, which, according to the Internal Analgesic Panel, is the most accurate parameter to use in calculating salicylate dosage. The SAG stated that the pediatric dosages on currently marketed bismuth subsalicylate containing products are rational for children ages 6 to 9 and 9 to 12 years of age. Employing extrapolations based on age (Young's rule), body-weight, and body-surface area from an effective adult dose, the SAG recommended an increase in the dose for children 3 to 6 years of age from the currently-labeled dose of 87 mg to 131 mg.

The agency has reviewed the SAG report, which discusses three controlled studies (Refs. 18, 19, and 20) in infants and children (8 weeks to under 5 years) with chronic or acute diarrhea. However, only one subject was above 3 years of age. The comment contended these studies were sufficient evidence to show effectiveness in childhood diarrhea at various doses. The doses of bismuth subsalicylate used were: (1) Gryboski study (chronic diarrhea) (Ref. 18): 44 mg every 4 hours for 7 days for infants from 8 weeks to 2 years of age (mean 5.7 mg/kilogram (kg)) and 88 mg every 4 hours for 7 days for children 2 to 6 years of age (only 1 subject in this study was above 3 years of age, 5.5 mg/kg); (2) Soriano-Brucker et al. study (Ref. 19): 20 mg/kg five times a day for 5 days, and (3) Figueroa et al. study (Ref. 20): 20 mg/kg and 30 mg/kg five times a day for 5 days. Because these studies did not include children 3 to under 12 years of age, the agency has no basis to conclude from these studies that the ingredient will be effective for these age groups. The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 21).

Another comment included the results of a double-blind, placebo controlled study of bismuth subsalicylate in children 3 to 6 years of age with acute diarrhea (Ref. 22). The study involved children from 13 clinical centers located in Central and South America and the United States. Subjects were randomized to receive 131 mg bismuth subsalicylate or matching placebo every 30 minutes for a total of eight doses per day for 2 consecutive days. Observations were recorded in a diary over a 5-day period. Subjects were eligible if they had diarrhea of less than 48 hours in duration. Efficacy parameters included duration of diarrhea (primary variable), stool consistency and frequency (secondary variables). A total of 291 patients were included in the final analysis. The study demonstrated that subjects receiving bismuth subsalicylate showed a statistically significant shorter duration of diarrhea versus placebo when evaluated at 72 hours (LR (likelihood ratio)  $p=0.009$ ) and 120 hours (LR  $p=0.001$ ), but statistical significance was not shown at 48 hours (LR  $p=0.228$ ). The  $p$ -values were calculated via the likelihood ratio test for comparing equality of survival curves. The comment stated that the shorter observation period of 48 hours contained more censored observation times and hence had less statistical power to detect the treatment effect than that at 72 hours.

The agency considers it reasonable to expect efficacy to be shown at 120-hours due to the self-limited nature of nonspecific diarrhea. However, failure to demonstrate a statistically significant effect at 48-hours is a cause for concern in the pediatric population due to the danger that dehydration poses to this age group. Analysis of the secondary variables, stool consistency and frequency, revealed that while subjects treated with bismuth subsalicylate as compared to those treated with placebo had a statistically significant increase in the number of formed stools at the 36 to 48 hour time interval, they only demonstrated a trend towards a decrease in the frequency of unformed stools (defined as soft or watery bowel movements) and never achieved statistical significance for the entire duration (120 hours) of the study.

The study was well designed to demonstrate the product's effectiveness as an antidiarrheal agent. On review, the majority of the reported protocol violations (*i.e.*, randomization out of sequence, discrepancy in stool analysis, use of acetaminophen, study duration, and the filling out of the study diary cards) realistically should not have

<sup>1</sup>The panel's recommended maximum daily dosage for sodium salicylate was 4 g. Sodium salicylate contains approximately 14 percent sodium and 86 percent salicylate. Four g of sodium salicylate contains approximately 3.4 g of salicylate.