

improved stool consistency and decreased stool frequency ( $p < 0.05$ ). However, because of the small sample size and because only one child was more than 3 years of age, this study alone cannot be used to establish dosages for infants and children.

In the Steffen study (Refs. 9 and 10), 2,580 people traveling to various third world countries were randomly assigned in a double-blind manner to bismuth subsalicylate (or 1 of 5 other active drugs) or 1 of 6 respective placebos. Treatment for diarrhea began immediately after the onset of symptoms. The study results, for 530 evaluable subjects, indicated that the cure rates for subjects treated with bismuth subsalicylate were 62 percent by the end of day 1 and 76 percent by the end of day 2,  $p = 0.002$  (Ref. 10). These rates were significantly greater than those in the placebo group (40 percent day 1, 55 percent day 2). While this study is supportive, the agency cannot consider it a critical study to support effectiveness for bismuth subsalicylate for several reasons: (1) The study did not provide baseline data, (2) the study did not contain objective measures of stool frequency and consistency, and (3) the raw data were not available to the agency for review.

In summary, the Dupont and the Steffen-Dupont studies support the monograph status of bismuth subsalicylate for OTC antidiarrheal use. Each study confirms the results of the other because of the similar design. The Steffen study is supportive. The Gryboski study, although well-controlled and supportive of bismuth subsalicylate, does not provide adequate information on dosing regimens for children under 12 years of age (see section II, comment 6 of this document).

The dosage for bismuth subsalicylate is: Adults and children 12 years of age and over: oral dose is 525 mg every 1/2 to 1 hour, or 1,050 mg every hour as needed, not to exceed 4,200 mg in 24 hours. Children under 12 years of age: ask a doctor.

Because almost 50 percent of persons traveling from an industrialized to an underdeveloped country experience diarrhea, this target population was used in the clinical studies. The primary etiology of diarrhea in the United States is nonbacterial, while diarrhea occurring in foreign countries is primarily bacterial. Thus, the agency needed to consider whether studies on travelers' diarrhea (a subset of diarrhea) in foreign countries could be extrapolated to acute nonspecific diarrhea in the United States (Ref. 15).

On July 26, 1991, the agency's Gastrointestinal Drugs Advisory

Committee considered this question by evaluating the pathogens identified in the restudy stool samples in the Dupont and Steffen studies. The most common pathogen was *Escherichia coli* enterotoxin. The committee also considered the Gryboski study, in which the entry criteria included subjects with no evidence of parasitic or bacterial infection, and the Soriano study (Ref. 15), an additional study (not submitted by the comment) that was conducted in hospitalized children with acute diarrhea and focused on subjects infected with Rotavirus. The Soriano study showed that bismuth subsalicylate is superior to placebo and is also effective in subjects with diarrhea when the primary etiology is viral. The committee concluded that the studies support the use of bismuth subsalicylate in treating the symptoms of acute nonspecific and travelers' diarrhea.

In the TFM (51 FR 16138 at 16149), the agency proposed the following indications in § 335.50(b): (i) "Reduces the number of bowel movements in diarrhea," (ii) "Improves consistency of loose, watery bowel movements in diarrhea" and (iii) "Relieves cramps in diarrhea." The agency also stated (see comment 10, 51 FR 16138 at 16140 to 16141) that the indications "For the treatment of diarrhea" or "Controls (stops) diarrhea" could also be used depending on the results of studies conducted on the ingredients present in a product, but these indications were not included in proposed § 335.50(b) (also, see section II, comment 13 of this document). The agency concludes that the data support monograph status for these claims for bismuth subsalicylate with the exception of "relieves cramps in diarrhea." The data support the term "controls" or "relieves" rather than the absolute cessation of diarrhea inferred in the term "stops." Therefore, the agency is using the claim "controls" or "relieves" "diarrhea" as the primary indication in this final monograph. To further simplify labeling, the agency had revised the other claims, which are optional, to "reduces number of bowel movements" and "helps firm stool" (see new § 335.50(b)(1)).

FDA tentatively concludes that the data also support use for "travelers' diarrhea." Elsewhere in this issue of the **Federal Register**, the agency is proposing to amend the final monograph to include that indication. However, that indication may not appear in product labeling until the amendment is final. The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 16).

(Comment 4) One comment disagreed with an agency recommendation (Ref. 16) that the Reye's syndrome warning for products containing bismuth subsalicylate read: "WARNING: Children and teenagers who have or are recovering from chicken pox or flu should NOT use this medicine to treat vomiting or diarrhea. If vomiting or diarrhea is present, consult a doctor because this could be an early sign of Reye syndrome, a rare but serious illness." The comment contended that this reference to diarrhea should not be included because, unlike vomiting, diarrhea is not a recognized early warning symptom of Reye's syndrome. The comment added that this warning would be incorrect and confusing to consumers and that there is no scientific data linking Reye's syndrome to bismuth subsalicylate. One comment added that the following Reye's syndrome warning it voluntarily uses in its labeling is adequate for bismuth subsalicylate: "WARNING: Children and teenagers who have or are recovering from chicken pox or flu should not use this medicine to treat nausea or vomiting. If nausea or vomiting is present, consult a doctor because this could be an early sign of Reye Syndrome, a rare but serious illness."

FDA issued the Reye's syndrome warning in 21 CFR 201.314(h) at the time when scientific research was focused primarily on the association of Reye's syndrome and aspirin rather than nonaspirin salicylates. That warning is limited to aspirin and reads:

"WARNING: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye's syndrome, a rare but serious illness reported to be associated with aspirin."

In the **Federal Register** of May 5, 1993 (58 FR 26886), the agency proposed a Reye's syndrome warning for OTC overindulgence drug products containing bismuth subsalicylate. In a technical amendment published in the **Federal Register** of January 3, 2000 (65 FR 7), the agency corrected the word "Reye" to "Reye's." Elsewhere in this issue of the **Federal Register**, the agency is finalizing the May 5, 1993, proposal, requiring the Reye's syndrome warning for all OTC drug products that contain bismuth subsalicylate.

(Comment 5) One comment disagreed with the agency's proposal (51 FR 16138 at 16143, see comment 17) that the maximum adult daily dose of bismuth subsalicylate be limited to 4.2 g because of the potential of salicylate toxicity. The comment argued that this limitation is contrary to the up to 8 g per 1 day