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#### List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 201 is amended as follows:

#### PART 201—LABELING

■ 1. The authority citation for 21 CFR part 201 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

■ 2. Section 201.314 is amended by revising paragraphs (h)(1) and (h)(4) to read as follows:

#### § 201.314 Labeling of drug preparations containing salicylates.

\* \* \* \* \*

(h)(1) The labeling of orally or rectally administered over-the-counter drug products containing aspirin or nonaspirin salicylates as active ingredients subject to this paragraph is required to prominently bear the following warning: "Reye's syndrome [subheading in bold type]: Children and teenagers who have or are recovering from chicken pox or flu-like symptoms should not use this product. When using this product, if changes in behavior with nausea and vomiting occur, consult a doctor because these symptoms could be an early sign of Reye's syndrome, a rare but serious illness."

\* \* \* \* \*

(4) Any product subject to paragraphs (h)(1), (h)(2), and (h)(3) of this section that is not labeled as required by these paragraphs and that is initially introduced or initially delivered for introduction into interstate commerce after the following dates is misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

(i) Compliance by October 18, 2004, for OTC drug products containing aspirin and nonaspirin salicylates as an active ingredient and marketed under a new drug application or abbreviated new drug application.

(ii) Compliance by April 19, 2004, for OTC antidiarrheal and overindulgence drug products that contain bismuth subsalicylate as an active ingredient and have annual sales greater than \$25,000.

(iii) Compliance by April 18, 2005, for OTC antidiarrheal and overindulgence drug products that contain bismuth subsalicylate as an active ingredient and have annual sales less than \$25,000.

(iv) Compliance dates for all other OTC drug products containing aspirin and nonaspirin salicylates as an active ingredient and marketed under an OTC drug monograph (for internal analgesic,

antipyretic, and antirheumatic drug products, or for menstrual drug products) will be established when the final monographs for those products are published in a future issue of the **Federal Register**. In the interim, these products should continue to be labeled with the previous Reye's syndrome warning that appears in paragraph (h)(1) of this section.

Dated: March 31, 2003.

**Jeffrey Shuren,**

*Assistant Commissioner for Policy.*

[FR Doc. 03–9382 Filed 4–16–03; 8:45 am]

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#### DEPARTMENT OF HEALTH AND HUMAN SERVICES

#### Food and Drug Administration

#### 21 CFR Parts 310, 335, and 369

[Docket No. 78N–036D]

RIN 0910–AA01

#### Antidiarrheal Drug Products for Over-the-Counter Human Use; Final Monograph

**AGENCY:** Food and Drug Administration.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) antidiarrheal drug products (to control the symptoms of diarrhea) are generally recognized as safe and effective and not misbranded. This final rule is part of FDA's ongoing review of OTC drug products. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph (TFM), and all new data and information on OTC antidiarrheal drug products that have come to the agency's attention. Also, this final rule amends the regulation that lists nonmonograph active ingredients by adding those OTC antidiarrheal active ingredients that have been found to be not generally recognized as safe and effective.

**DATES:** *Effective Date:* This rule is effective April 19, 2004.

*Compliance Dates:* The compliance date for products with annual sales less than \$25,000 is April 18, 2005. The compliance date for all other OTC antidiarrheal drug products is April 19, 2004.

*Comment Date:* Comments on specific labeling items discussed in section IX of the **SUPPLEMENTARY INFORMATION** section

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.

The other clinical study (Ref. 7) was a 21-day, double-blind, randomized, placebo-controlled clinical study comparing two dose levels of bismuth subsalicylate in the prevention of travelers' diarrhea. Subjects were randomly assigned bismuth subsalicylate either 1.05 g per day (262.5 mg four times a day) (low dose), 2.1 g per day (525 mg four times a day) (high dose), or 7.15 g lactose (two placebo tablets four times a day). Additional analyses were also done. In the original analysis, the difference in diarrheal incidence rate from placebo was only statistically significant for the high-dose regimen. Supplemental comparisons done only for subjects who completed all 21 days of the study or who contracted diarrhea ("four or more unformed stools in a 24-hour period") were consistent with the primary efficacy comparisons. The investigators concluded that 525 mg bismuth subsalicylate four times a day provides a statistically significant reduction in the occurrence of diarrhea for up to 3 weeks and that 262.5 mg four times a day provides a marginal benefit that could be considered in the range of the minimum effective dose. However, this significant reduction in the incidence of diarrhea was not discernible when the data from both analyses were evaluated. Similarly, when the effects of the "high" and "low" bismuth subsalicylate dose were compared, no significant difference in the incidence of diarrhea was detected.

Only the second clinical study (Ref. 7) showed that bismuth subsalicylate tablets in a dosage of 525 mg four times a day may be effective in the prevention of travelers' diarrhea. However, an additional double-blind, randomized, placebo-controlled study by another independent investigator is needed to substantiate the study findings. The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 8).

The agency is concerned about the benefit-to-risk ratio associated with prophylactic use for several weeks for acute diarrhea, which itself is usually self-limiting, lasting only from 24 to 72 hours. Although there have been no reported cases of bismuth encephalopathy associated with the dosage and time period usually recommended for OTC use, the safety of prophylactic use for 3 weeks to persons traveling to high-risk diarrhea areas is not well documented. Thus, any future study of effectiveness should also include an evaluation of tinnitus and other subtle and mild central nervous system symptomatology, such as vertigo, gait disturbances, etc. An

evaluation of bismuth pharmacokinetics during the period of use would also be desirable.

(Comment 3) One comment submitted four clinical studies (Refs. 9 through 14) to support the use of bismuth subsalicylate for the treatment of diarrhea for the three labeling indications discussed in the proposal (51 FR 16138 at 16140 to 16141). The comment also requested that a travelers' diarrhea claim for bismuth subsalicylate be included in the final monograph.

The agency has determined that these studies (DuPont, Steffen-DuPont, Steffen, and Gryboski) support the use of bismuth subsalicylate to treat the symptoms of acute nonspecific diarrhea and, tentatively, travelers' diarrhea. The DuPont and Steffen-DuPont studies were double-blind, randomized, parallel group trials comparing the efficacy of bismuth subsalicylate with placebo for the treatment of acute, nonspecific diarrhea. The DuPont study (Ref. 10) involved 112 students from the United States enrolled at universities in Mexico and who were suffering from diarrhea. The subjects received placebo or bismuth subsalicylate at a dose of 525 mg per 30 milliliter (mL) solution every half hour up to a maximum of eight doses (4.2 g) per day for 2 days. The students were given diary cards on which to record the time of passage of each stool, the stool consistency, the severity of any associated symptoms, and the times and amounts of medication ingested. Diary cards were maintained for 72 hours (the 48-hour treatment period and the ensuing 24 hours). Diarrhea was defined as one or more symptoms of enteric infection (e.g., fever, abdominal discomfort, urgency, nausea) plus either three or more unformed stools in an 8-hour period or four or more such stools in a 24-hour period.

The primary effectiveness measures were reduction in the duration of diarrhea, improvement in stool consistency, and reduction of stool frequency. Results significantly favoring bismuth subsalicylate were obtained for all parameters of effectiveness. Half of the subjects who took bismuth subsalicylate experienced total relief by 27 hours. Additionally, 78 percent of the subjects treated with bismuth subsalicylate had total relief of diarrhea and all associated symptoms at the end of the 72-hour period compared with 50 percent of the placebo-treated subjects. The mean percentage of total firm stools among subjects treated with bismuth subsalicylate was numerically greater than for the placebo-treated subjects at all time intervals, and significantly greater for the first 24 hours after

treatment (36.6 percent versus 8.6 percent,  $p < 0.01$ ). Stool frequency data also showed that the number of unformed stools was numerically lower for all time intervals after the first 12 hours for the bismuth subsalicylate subjects compared to the placebo subjects. However, only the 12- to 24-hour interval showed statistical significance ( $p = 0.04$ ). Subjects global assessment of relief was 92 percent for those who received bismuth subsalicylate compared to 73 percent for those who received placebo on day 1 ( $p = 0.032$ ) and 98 percent versus 86 percent on day 2 ( $p = 0.059$ ). The physician's global ratings showed relief in 84 percent of subjects treated with bismuth subsalicylate and 58 percent of placebo subjects ( $p < 0.01$ ).

The Steffen-DuPont study (Ref. 10) included 130 Swiss nationals traveling in West Africa. It had essentially the same design as the DuPont study except that diarrhea was defined as one or more watery stools (pourable) or one or more pasty stools (do not retain shape). Subjects were given bismuth subsalicylate 1.05 g every hour up to a maximum of four doses (4.2 g) per day for 2 days, or placebo. Results indicated that 69 percent of subjects treated with bismuth subsalicylate had relief after 48 hours compared to 40.6 percent for placebo subjects. Stool consistency was numerically higher for subjects treated with bismuth subsalicylate than subjects who received placebo. Subject's global assessments of relief was 76 percent for those who received bismuth subsalicylate and 72 percent for those who received placebo on day 1 ( $p = 0.76$ ). On day 2, a significantly greater percentage of subjects treated with bismuth subsalicylate reported relief (89 percent) compared to placebo subjects (73 percent),  $p = 0.02$ .

A subgroup analysis on subjects identified as having entry criteria (three or more unformed stools before entry) similar to subjects in the Dupont study allowed for direct comparisons of these two studies. The analysis confirmed a significant effect for bismuth subsalicylate over placebo.

The Gryboski study (Refs. 9 and 10) was a double-blind, placebo-controlled, parallel clinical trial, conducted for 7 days, that involved 29 infants and children (age range 2 to 70 months) with chronic diarrhea, defined as a change in the consistency of the stool to watery or soft (mushy) and of greater than 2 weeks duration. A bismuth subsalicylate suspension containing 525 mg/30 mL was given based on age as follows: 6 weeks to 2 years, 2.5 mL; 2 to 6 years, 10 mL. The results indicated that bismuth subsalicylate significantly

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

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.

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

possesses any antidiarrheal properties and, thus, it should be regarded as an inactive ingredient. Likewise, the panel concluded that there was no evidence to permit classification of rhubarb fluidextract as an antidiarrheal (40 FR 12902 at 12926). No data were subsequently submitted to support these ingredients as active ingredients. Therefore, in the TFM (51 FR 16138 at 16146 to 16147), the agency placed rhubarb fluidextract and potassium carbonate singly and in combination in category II. No additional data have been submitted, and rhubarb fluidextract and potassium carbonate are nonmonograph active ingredients in this final rule.

The agency is not aware of rhubarb fluidextract or potassium carbonate being included as inactive ingredients in any OTC antidiarrheal drug products. Rhubarb garden root and rhubarb root are listed in 21 CFR 172.510 as flavors only in alcoholic beverages. Potassium carbonate is listed in 21 CFR 184.1619 as a substance affirmed as generally recognized as safe that may be added directly to human food. These ingredients would need to meet the criteria in § 330.1(e) to be acceptable inactive ingredients in products marketed under an OTC drug monograph.

(Comment 11) One comment submitted 6 clinical studies (Ref. 29) to support the use of kaolin and pectin in a "fixed" combination of 45 parts kaolin to 1 part pectin for the proposed labeling indications to treat diarrhea (51 FR 16138 at 16140 to 16141).

The agency has determined that these studies are insufficient to demonstrate that the "fixed" combination is effective. However, studies 295 and 303 demonstrate that kaolin alone, but not pectin, is effective. While only these studies are summarized in this document, the agency's detailed comments and evaluations of all the studies are on file in the Dockets Management Branch (Refs. 30 and 31). Kaolin (26.2 g) and/or pectin (583 mg) as single ingredients, or in combination, were administered in a 3 ounce (oz) dose in all six studies.

In study 303, acute nonspecific diarrhea was defined as the passage of three or more watery or mixed stools in 24 hours. In this 33-center study, the subjects were randomized as follows: 125 to receive kaolin and pectin in combination, 126 to receive kaolin, 133 to receive pectin, and 124 to receive placebo. Each subject received an initial 3-oz dose of study medication, followed by a 3-oz dose every 6 hours or after each bowel movement, whichever was more frequent (not to exceed 10 doses

per 24 hours), for a 48-hour period or until diarrhea ended. From a total of 508 subjects, 414 were evaluable for effectiveness for both the first and second days of treatment.

The results indicated reasonable statistical evidence that stool consistency is improved by kaolin and pectin in combination and kaolin alone. However, this study did not provide sufficient statistical evidence that kaolin and pectin as a "fixed" combination is superior to kaolin in terms of improving stool consistency on day 2 of treatment. There was no statistical evidence that pectin is effective in improving stool consistency.

Treatment with both kaolin and pectin in combination and kaolin alone reduced the average elapsed time from first drug dose to either last liquid (watery or mixed) stool or first formed stool by 5 to 7 hours ( $p < 0.01$ ) in comparison to placebo during the 48-hour treatment period. The duration of diarrhea was the time from the first dose to the first formed stool, which was 37 hours with kaolin and pectin in combination and 43 hours with placebo, a 6 hour difference over the 48-hour duration of treatment. Neither kaolin and pectin in combination nor kaolin alone was superior to placebo in reducing the number of stools passed in the 48-hour treatment period.

Study 295 was a multicenter, double-blind, randomized study comparing the effectiveness of the combination with placebo to treat acute nonspecific diarrhea, which was defined as the passage of three or more liquid stools in the 24 hours immediately preceding entry into the study. The study had 213 subjects (109 received drug, 104 received placebo) who were instructed to take one 3-oz dose of medication after each bowel movement or at 6 hour intervals in the absence of a bowel movement, for a period of 48 hours or until diarrhea ended, not to exceed 10 doses in 24 hours. The subjects recorded on a diary card the date and hour of each bowel movement and the character of the stool.

The results showed improvement in the consistency of the stool in the drug group on day 2 of treatment. A statistically significant greater proportion of subjects receiving the combination had formed stools on day 2 (kaolin-pectin 51/81, 63 percent compared to placebo 30/75, 40 percent,  $p < 0.005$ ). The mean time to the first formed stool was 35 hours with kaolin and pectin in combination and 41 hours with placebo ( $p = 0.002$ ). The difference in the mean number of watery stools (kaolin-pectin 0.13, placebo 0.57) was 0.44 of a stool, and the difference in the

mean number of formed stools (kaolin-pectin 0.97, placebo 0.52) was 0.45 of a stool. No statistical significance was demonstrated for frequency of bowel movements on day 1 and day 2. Numerically, the placebo group had a slightly larger mean stool frequency at baseline, which was taken 24 hours prior to entrance into the study (6.65 for drug and 7.67 for placebo), but there was little difference in the mean number of bowel movements between the two treatment groups on day 1 (3.78 for drug and 3.37 for placebo) and day 2 (2.02 for drug and 2.01 for placebo). The agency concludes that the combination resulted in a statistically significant improvement in the mean time to the first formed stool and in the consistency of the stool on day 2 of treatment.

In study 303, the improvement in stool consistency appeared to be due to the kaolin component whereas pectin seemed to perform similar to placebo. Thus, the improvement in stool consistency in study 295 appeared to be due entirely to kaolin alone. Therefore, the results indicate that kaolin alone improves stool consistency in a 24- to 48-hour period. Likewise, study 303 also showed that the combination and kaolin alone significantly reduced the duration from first drug doses to either first normal (formed) stool or last loose (watery or mixed) stool ( $p < 0.05$ ) by 5 to 7 hours (compared to placebo) during the 48-hour treatment period. Study 295 also showed that the combination significantly reduced the duration from first dose to first normal stool ( $p < 0.005$ ) by 7 hours.

The agency concludes that the evidence is not sufficient to show that kaolin and pectin in combination are better than kaolin alone. However, study 303 provides reasonable statistical evidence that kaolin as a single ingredient is likely to improve stool consistency in subjects with acute nonspecific diarrhea in 24 to 48 hours. Data from this and other studies have shown that pectin has no effect. Although study 295 involved a comparison of the combination only against placebo, rather than against the single ingredients, the study supports kaolin as the active ingredient in the combination product.

On April 9, 1993, the Nonprescription Drugs Advisory Committee and the Gastrointestinal Drugs Advisory Committee (the committees) met to discuss OTC antidiarrheal drug products containing attapulgit, kaolin, and pectin (Ref. 31). The committees evaluated studies 295 and 303 and determined that the data were sufficient to support the effectiveness of kaolin as a single ingredient, recommending that

products be labeled to state the results they provide and the timeframe in which they occur. Therefore, the agency is including the following indication for kaolin in this final monograph: "Helps firm stools within 24 to 48 hours" (see section III of this document).

Kaolin is an adsorbent that can interfere with the gastrointestinal absorption of a number of oral medications, including some antibiotics, digitalis glycosides, and theophylline, resulting in decreased therapeutic effectiveness. The interaction might be avoided if kaolin is given at least 3 hours before or after taking any oral medication. Therefore, the agency is requiring a specific drug interaction precaution statement for products containing kaolin: "Ask a doctor or pharmacist before use if you are taking any other drugs. Try to use at least 3 hours before or after taking any other drugs."

The committees also noted that the available data did not address the safety and effectiveness of kaolin in children and recommended that the ingredient should not be administered to children under 12 years of age without the specific recommendations of a doctor. Further, the agency is concerned about use in children because they may have a greater potential for fluid loss and electrolyte imbalance due to diarrhea and antidiarrheal products that only improve stool consistency may mask the extent of fluid loss. Dehydration due to diarrhea in children can occur early in the disease process and may have serious consequences, such as circulatory collapse and renal failure (Ref. 32). Kaolin improves stool consistency in 24 to 48 hours. However, current information is insufficient to show whether it also reduces fluid and electrolyte loss. None of the studies demonstrated the effectiveness of kaolin in children under 12 years of age. As noted in the TFM (51 FR 16138 at 16145), one study on the use of kaolin and pectin in children 3 to 11 years old indicated some possible benefit for a greater number of formed stools and a smaller number of liquid stools from either the kaolin-pectin combination or pectin alone. However, because of the lack of sufficient information, it could not be adequately evaluated. The agency concludes that the available information is insufficient to include monograph directions for kaolin for children 3 to under 12 years of age. Adequate data from a double-blind, placebo-controlled study in pediatric subjects with acute nonspecific diarrhea is needed to support the safety and effectiveness of kaolin for use in this age group.

Based on the studies evaluated, the dosage for kaolin in this final monograph is: Adults and children 12 years of age and over: oral dosage is 26.2 g after each loose stool. Continue to take every 6 hours until stool is firm but not more than 2 days. Do not exceed 262 g in 24 hours. Children under 12 years of age: ask a doctor.

(Comment 12) One comment contended that the proposed labeling indications are too detailed and technical and, thus, will not be understood by persons of low comprehension. The comment argued that many users of OTC drug products have little education and take these products on their own without the direction of a physician, clinician, nurse, or pharmacist. To simplify the labeling for persons of low comprehension, the comment suggested that the statement of identity be "for diarrhea" instead of "antidiarrheal." The comment also suggested that the indication "Reduces the number of bowel movements in diarrhea" be changed to "Decreases bowel movements" or "Reduces bowel movements."

The agency agrees. Section 335.50(a) in this final rule gives manufacturers the option of using either "antidiarrheal" or "for diarrhea" as the statement of identity for these products. The agency modified the indication to "reduces number of bowel movements" and included it as an additional optional claim for products containing bismuth subsalicylate (see section III this document).

(Comment 13) One comment stated that there was a contradiction in the indications proposed in § 335.50(b) (51 FR 16138 at 16149). The comment noted that the agency stated that it was recommending that the indications "For the treatment of diarrhea" or "Controls (stops) diarrhea" be used in the labeling of OTC antidiarrheal drug products, but these indications were not included in the proposed monograph (51 FR 16138 at 16140 to 16141). The comment also suggested that "relieves pain in diarrhea" be a monograph indication. The comment stated that these indications are good, simple, and understandable and should be adopted by the agency.

The comment is correct that the indications "For the treatment of diarrhea" or "Controls (stops) diarrhea" were not included in the TFM. In comment 10 of the TFM (51 FR 16138 at 16140 to 16141), the agency stated that one or more of the following indications could be used depending upon the results of studies conducted on the ingredient contained in the

product: (1) "For the treatment of diarrhea" or "Controls (stops) diarrhea"; (2) "Reduces the number of bowel movements in diarrhea"; and (3) "Improves consistency of loose, watery bowel movements in diarrhea." Based on the data on attapulgit, calcium polycarbophil, and polycarbophil evaluated in the TFM, only the second and third indications were proposed at that time.

The agency would not object to use of the indication "relieves pain in diarrhea," provided studies support this claim. In the TFM (51 FR 16138 at 16141), the agency stated that there are other symptoms that are secondary to diarrhea, such as abdominal pain or cramps, and that some antidiarrheal ingredients may also act to relieve these symptoms. However, adequate supporting data have not been submitted to date.

(Comment 14) One comment requested revisions in the warning proposed in § 335.50(c), which stated: "Do not use for more than 2 days, or in the presence of fever, or in children under 3 years of age unless directed by a doctor." The comment recommended: "If diarrhea continues for more than 2 days or is accompanied by a fever, consult your doctor." The comment stated that the agency's proposed wording inappropriately suggests that consumers should be concerned about safety of the product if it is used for more than 2 days or in the presence of fever. The comment contended that its revision would alert consumers to the serious conditions that may be indicated by prolonged diarrhea or diarrhea accompanied by fever and would emphasize the need for medical attention because of the disease condition, not because of drug use, as might be inferred from the agency's proposed warning. The comment also recommended deletion of the part of the proposed warning regarding use in children under 3 years of age because it is redundant with information that appears in the directions section. The comment explained that the directions proposed in § 335.50(d) advise that these products should not be used in children under 3 years of age without consulting a doctor and the professional labeling proposed in § 335.80 provides health professionals information about using these products in children under 3 years of age.

The agency agrees that the information about use in children is repetitious and could be deleted. The directions in § 335.50(d) in this final monograph advise to "ask a doctor" for children under 12 years of age. The final monograph does not include proposed

§ 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

additional data or other comments in response to its request. New relevant data can be submitted in accordance with §§ 330.10(a)(12) and 10.30.

For products containing bismuth subsalicylate, a required indication is included in § 335.50(b)(1) as follows: "The labeling states [select one of the following: "controls" or "relieves"] "diarrhea". Additional indications" in § 335.50(b)(3)(ii) \* \* \* include one or both of the following \* \* \*: "[bullet] reduces number of bowel movements" "[bullet] helps firm stool". The indication "Relieves pain in diarrhea" has not been included because of insufficient data to support such a claim (see section II, comment 12 of this document).

The agency is including in new § 335.50(b)(2) the following indication for kaolin: "helps firm stool within 24 to 48 hours" (see section II, comment 11 of this document).

The agency has revised the warnings included in the TFM (see section II, comments 4, 14, and 15 of this document).

Because the potential for fluid loss and electrolyte imbalance due to diarrhea may have serious consequences, the agency is adding an additional direction in § 335.50(d)(1): "The labeling states '[bullet] drink plenty of clear fluids to help prevent dehydration caused by diarrhea.'"

#### IV. The Agency's Final Conclusions

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC antidiarrheal drug products are generally recognized as safe and effective and not misbranded. Any drug product labeled, represented, or promoted for uses as an OTC antidiarrheal drug product that contains any of the ingredients listed in § 310.545(a)(3)(i) or (a)(3)(ii) or that is not in conformance with the monograph (to be codified at 21 CFR part 335) may be considered a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)) and misbranded under section 502 of the act (21 U.S.C. 352). Such a product cannot be marketed for antidiarrheal use unless it is the subject of an approved application under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations (21 CFR part 314). An appropriate citizen petition to amend the monograph may also be submitted in accordance with §§ 10.30 and 330.10(a)(12)(i). Any OTC antidiarrheal drug product initially introduced or initially delivered for introduction into interstate commerce after the compliance dates of the final

rule for § 310.545(a)(3)(i) or this final rule that is not in compliance with the regulations is subject to regulatory action.

The agency is revoking the existing warning statement in § 369.20 for diarrhea preparations at the time that this monograph becomes effective. That warning is superseded by the requirements of the final monograph.

Mandating warnings in an OTC drug monograph does not require a finding that any or all of the OTC drug products covered by the monograph actually caused an adverse event, and FDA does not so find. Nor does FDA's requirement of warnings repudiate the prior OTC drug monographs and monograph rulemakings under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that warnings are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the act. This judgment balances the benefits of these drug products against their potential risks (see 21 CFR 330.10(a)).

FDA's decision to act in this instance need not meet the standard of proof required to prevail in a private tort action (*Glastetter v. Novartis Pharmaceuticals, Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)). To mandate warnings, or take similar regulatory action, FDA need not show, nor do we allege, actual causation. For an expanded discussion of case law supporting FDA's authority to require such warnings, see Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use, a final rule that published in the **Federal Register** of December 6, 2002 (67 FR 72555).

#### V. Analysis of Impacts

An analysis of the costs and benefits of this regulation, conducted under Executive Order 12291, was discussed in the TFM for OTC antidiarrheal drug products (51 FR 16138 at 16147). (Executive Order 12291 was revoked by Executive Order 12866.) The agency certified that under the Regulatory Flexibility Act the proposed rule would not have a significant economic impact on a substantial number of small entities. No comments were received on the economic impact of this rulemaking.

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits

of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation). The proposed rule that has led to the development of this final rule was published on April 30, 1986, before the Unfunded Mandates Reform Act of 1995 was enacted. The agency explains in this final rule that the final rule will not result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million.

The agency concludes that this final rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. The final rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of costs and benefits for this final rule, because the final rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation. The current inflation adjusted statutory threshold is about \$110 million.

The purpose of this final rule is to establish allowable monograph ingredients and labeling under which OTC antidiarrheal drug products are generally recognized as safe and effective. The agency has identified 45 manufacturers currently marketing 383 OTC antidiarrheal drug products containing bismuth subsalicylate (334), attapulgite (32), kaolin and pectin (13), polycarbophil (2), and calcium polycarbophil (2). This final rule will result in the reformulation or removal of about 50 products containing activated attapulgite, calcium polycarbophil, polycarbophil, and pectin. These products may be reformulated to contain bismuth subsalicylate or kaolin. The agency is unaware of any current marketing of bismuth subnitrate,

calcium hydroxide, charcoal (activated), potassium carbonate, or rhubarb fluidextract for antidiarrheal use.

The cost to reformulate a product will vary greatly depending on the nature of the change in formulation, the product, the process, and the size of the firm. Some of the manufacturers of the 50 products containing nonmonograph active ingredients may elect not to reformulate (*i.e.*, they may elect to discontinue marketing of the product). For those products that need reformulation, the cost can be significant. Because of the other monograph active ingredients available for reformulation, no manufacturer should need to change its dosage form; however, it will have to redo the validation (product, process, new supplier), conduct stability tests, and change master production records in order to ensure compliance with current good manufacturing practice. (See section 501(a)(1)(B) of the act (21 U.S.C. 351(a)(1)(B) and parts 210 and 211 (21 CFR parts 210 and 211).) The agency estimates the cost of reformulation to range from \$100,000 to \$500,000 per product. Therefore, if all 50 products are reformulated, the midpoint of the cost estimate implies total costs of \$15 million. However, the agency believes the total costs will be much smaller because not all manufacturers will elect to reformulate and some may choose to discontinue a product line if sales are too low to justify the added cost and/or they also produce substitute products that do not require reformulation. Manufacturers may also elect to purchase reformulated products from another manufacturer and then be a distributor of that product.

Because these products must be manufactured in compliance with the pharmaceutical current good manufacturing practices (parts 210 and 211), all firms would have the necessary skills and personnel to perform these tasks either in-house or by contractual arrangement. The final rule does not require any new reporting or recordkeeping activities. No additional professional skills are needed.

This final rule establishes the monograph for OTC antidiarrheal drug products and will require relabeling of all products covered by the monograph. Estimates of relabeling costs for the type of changes required by this rule vary greatly and range from \$500 to \$15,000 per stockkeeping unit (SKU) (individual products, packages, and sizes) depending on whether the products are nationally branded or private label. The agency assumes the same weighted average cost to relabel (*i.e.*, \$3,600 per SKU) that it estimated for the final rule

requiring uniform label formats of OTC drug products (64 FR 13254 at 13279 to 13281). Assuming 350 to 400 affected OTC SKUs in the marketplace, total one-time costs of relabeling would be \$1.26 to 1.44 million. Because frequent labeling redesigns are a recognized cost of doing business in the OTC drug industry, these costs may be less. Manufacturers that make voluntary market-driven changes to their labeling during the implementation period can implement the regulatory requirements for a nominal cost.

This final rule may have an economic impact on some small entities. The agency's drug listing system indicates that about 350 to 400 products will need to be relabeled, and that this relabeling will be prepared by about 45 manufacturers, most of which are private label or contract manufacturers. Based on the Small Business Administration's determination that a small firm in this industry has fewer than 750 employees, roughly 70 percent of the firms are considered small. The economic impact on any particular firm is very difficult to measure, because it will vary with the type and number of products affected, the number of SKUs per product, and the ability to coordinate these label changes with those required for other purposes. For example, assuming average industry costs, a small company that had 5 products with 3 SKUs each for a total of 15 SKUs would experience a one-time cost of \$54,000. A small private label manufacturer with the same product line and 10 customers per SKU, for a total of 150 SKUs, would experience a one-time cost of \$540,000. If one or more products needed to be reformulated, the costs would increase by \$100,000 to \$500,000 per formulation.

Some of these relabeling costs will be mitigated because the agency is allowing 12 months for manufacturers to implement the required labeling revisions for all products containing antidiarrheal active ingredients. Products with annual sales less than \$25,000 have 12 additional months. Therefore, many of the labeling revisions may be done in the normal course of business. Among the steps the agency is taking to minimize the impact on small entities are: (1) Providing enough time for implementation to enable entities to use up existing labeling stock, and (2) allowing the labeling changes required by this final monograph to be implemented concurrently with the labeling changes required by the new OTC drug labeling format final rule. The agency believes that these actions provide substantial

flexibility and reductions in cost for small entities.

The agency considered but rejected several labeling alternatives: (1) A shorter or longer implementation period, and (2) an exemption from coverage for small entities. While the agency believes that consumers would benefit from having this new labeling in place as soon as possible, the agency also acknowledges that coordination of the labeling changes resulting from implementation of the new OTC "drug facts" labeling and the antidiarrheal final rule may significantly reduce the costs of this final rule. A longer time period would unnecessarily delay the benefit of new labeling and revised formulations, where applicable, to consumers who self-medicate with these OTC antidiarrheal drug products. The agency rejected an exemption for small entities because the new labeling and revised formulations, where applicable, are also needed by consumers who purchase products marketed by those entities. However, a longer compliance date (24 months) is being provided for products with annual sales less than \$25,000.

This analysis shows that the agency has undertaken important steps to reduce the burden to small entities. This economic analysis, together with other relevant sections of this document, serves as the agency's final regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

## VI. Paperwork Reduction Act of 1995

FDA concludes that the labeling requirements in this document are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the labeling statements are a "public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

## VII. Environmental Impact

The agency has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## VIII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not

contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

## IX. Request for Comments

This final monograph establishes labeling for OTC antidiarrheal drug products containing bismuth subsalicylate and kaolin. The warnings for products containing bismuth subsalicylate in § 335.50(c)(2) include: (1) The Reye's syndrome warning in § 201.314(h), (2) "Allergy alert: Contains salicylate. Do not take if you are [bullet] allergic to salicylates (including aspirin), [bullet] taking other salicylate products," (3) "Do not use if you have [bullet] an ulcer [bullet] a bleeding problem," (4) "Ask a doctor or pharmacist before use if you are taking any drug for [bullet] anticoagulation (thinning the blood) [bullet] diabetes [bullet] gout [bullet] arthritis," (5) "When using this product a temporary, but harmless, darkening of the stool and/or tongue may occur," and (6) "Stop use and ask a doctor if [bullet] symptoms get worse [bullet] ringing in the ears or loss of hearing occurs [bullet] diarrhea lasts more than 2 days".

These warnings for products containing kaolin in § 335.50(c)(3) include: (1) "Ask a doctor or pharmacist before use if you are taking any other drugs. Try to use at least 3 hours before or after taking any other drugs," and (2) "Stop use and ask a doctor if [bullet] symptoms get worse [bullet] diarrhea lasts more than 2 days".

In addition, products containing either ingredient must state: (1) "Do not use if you have [bullet] bloody or black stool," and (2) "Ask a doctor before use if you have [bullet] fever [bullet] mucus in the stool". The agency notes that fever and use for more than 2 days were included in the "Do not use" warning proposed in § 335.50(c) of the TFM (51 FR 16138 at 16149).

The indications in this final rule are similar to those discussed in the TFM, and the directions in this final rule are based on the studies discussed in this document. While interested persons may comment on any portions of the labeling in this final rule, the agency would like to receive specific comments primarily on the warnings labeling in § 335.50(c).

This final rule also includes labeling requirements for products that meet the criteria established in § 201.66(d)(10) (see § 335.50(e)). This reduced labeling results from the modified labeling format for OTC drug products in § 201.66(d)(10), which did not exist when the TFM was published. Interested persons may also comment on this labeling.

The agency is particularly interested in receiving comments on the specific labeling requirements discussed in this section of this document. Comments should be identified with the docket number found in brackets in the heading of this document. Three copies of all written comments are to be submitted. Individuals submitting written comments or anyone submitting electronic comments may submit one copy. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. If the comments justify a change in labeling, the agency will propose to amend the final monograph accordingly at a later date.

## X. References

The following references are on display in the Dockets Management Branch (see ADDRESSES) under Docket No. 78N-036D and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. C85.
2. Comment No. C92.
3. Comment No. SUP12.
4. Letter from W. E. Gilbertson, FDA, to A. R. Giaquinto, Schering-Plough Corp., coded LET20.
5. Study IB-101, Comment No. CP2.
6. Steffen Study, Protocol PB-103, Comments No. CP2 and SUP10.
7. DuPont Study, Protocol PB-114, Comments No. CP2 and SUP10.
8. Letter from W. E. Gilbertson, FDA, to P. Sinnott, The Procter and Gamble Co., coded LET26.
9. Comment No. SUP8.
10. Comment No. SUP13.
11. Comment No. LET23.
12. Comment No. LET24.
13. Comment No. PR3.
14. Comment No. SUP14.
15. Comment No. TR1, pp. 43-46.
16. Letter from W. E. Gilbertson, FDA, to P. Sinnott, The Procter and Gamble Co., coded LET27.
17. Comment No. C94.
18. Gryboski, J. D. et al., "Bismuth Subsalicylate in the Treatment of Chronic Diarrhea in Childhood," *American Journal of Gastroenterology*, 80:871, 1985.
19. Soriano-Brucker, H. et al., "Bismuth Subsalicylate in the Treatment of Acute Diarrhea in Children: A Clinical Study," *Pediatrics*, 87:18-27, 1991.
20. Figueroa, D. et al., "Bismuth Subsalicylate Reduces Volume and Duration of Watery Diarrhea in Young Peruvian

Children," *Thirty-First Interscience Conference on Antimicrobial Agents and Chemotherapy*, Chicago, IL, Prog. Abstr. 31:224 (Abstr. No. 754), 1991.

21. Letter from W. E. Gilbertson, FDA, to P. Sinnott, The Procter and Gamble Co., coded LET29.

22. Comment No. PR8.

23. Comment No. CP3.

24. Comment No. SUP11.

25. Comment No. PR4.

26. Comment No. LET25.

27. Comment No. C89.

28. OTC Vol. 090005.

29. Comment No. SUP09.

30. Letter from W. E. Gilbertson, FDA, to G. H. Ishler, The Upjohn Co., coded LET2.

31. Comment No. MM8.

32. *The United States Pharmacopeia Dispensing Information*, 20th ed., Vol. I, United States Pharmacopeia Convention, Inc., Rockville, MD, pp. 1869-1870, 1999.

33. OTC Vol. 090133.

34. Comment No. SUP5.

35. Comment No. AMD2.

36. Comment No. SUP6.

37. De Sola Pool, N. et al., "A Comparison of Nonsystemic and Systemic Antidiarrheal Agents in the Treatment of Acute Nonspecific Diarrhea in Adults," *Today's Therapeutic Trends*, 52:31-38, 1987.

38. DuPont, H. L. et al., "A Randomized, Open-Label Comparison of Nonprescription Loperamide and Attapulgite in the Symptomatic Treatment of Acute Diarrhea," *The American Journal of Medicine*, 88 supp. 6A:20-23, 1990.

39. Food and Drug Administration, "Guidelines for the Clinical Evaluation of Antidiarrheal Drugs," September 1977, in OTC Vol. 09DFM.

40. Letter from W. E. Gilbertson, FDA, to R. W. Soller, Nonprescription Drug Manufacturers Association, coded LET34.

41. Letter from W. E. Gilbertson, FDA, to R. W. Soller, Nonprescription Drug Manufacturers Association, coded LET39.

42. Rutledge, M. L. et al., "Clinical Comparison of Calcium Polycarbophil and Kaolin-Pectin Suspensions in the Treatment of Acute Childhood Diarrhea," *Current Therapeutic Research*, 23:443-447, 1978.

43. Rutledge, M. L. et al., "Calcium Polycarbophil in Acute Childhood Diarrhea," *Clinical Pediatrics*, 2:61-63, 1963.

44. Grossman, A. J., R. C. Batterman, and P. Leifer, "Polyacrylic Resin: Effective Hydrophilic Colloid for the Treatment of Constipation," *Journal of the American Geriatric Society*, 5:187-192, 1957.

45. Roth, J. L. A., "Effects of Polycarbophil as Enteral Hydrosorbent in Diarrhea," *American Journal of Digestive Diseases*, 5:965-971, 1960.

46. Pimparker, B. D. et al., "Effect of Polycarbophil on Diarrhea and Constipation," *Gastroenterology*, 40:397-404, 1961.

## List of Subjects

### 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

## 21 CFR Part 335

Labeling, Over-the-counter drugs.

## 21 CFR Part 369

Labeling, Medical devices, Over-the-counter drugs.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR chapter I is amended as follows:

**PART 310—NEW DRUGS**

■ 1. The authority citation for 21 CFR part 310 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

■ 2. Section 310.545 is amended by adding paragraph (a)(3)(i) heading, paragraphs (a)(3)(ii) and (d)(17), and by revising paragraph (d)(1) to read as follows:

**§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.**

(a) \* \* \*

(3) *Antidiarrheal drug products*—(i) *Approved as of May 7, 1991.*

\* \* \* \* \*

(ii) *Approved as of April 19, 2004; April 18, 2005, for products with annual sales less than \$25,000.*

Attapulgit, activated

Bismuth subnitrate

Calcium hydroxide

Calcium polycarbophil

Charcoal (activated)

Pectin

Polycarbophil

Potassium carbonate

Rhubarb fluidextract

\* \* \* \* \*

(d) \* \* \*

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(2)(i), (a)(3)(i), (a)(4), (a)(6)(i)(A), (a)(6)(ii)(A), (a)(7) (except as covered by paragraph (d)(3) of this section), (a)(8)(i), (a)(10)(i) through (a)(10)(iii), (a)(12)(i) through (a)(12)(iv)(A), (a)(14) through (a)(15)(i), and (a)(16) through (a)(18)(i)(A) of this section.

\* \* \* \* \*

(17) April 19, 2004, for products subject to paragraph (a)(3)(ii) of this section. April 18, 2005, for products with annual sales less than \$25,000.

\* \* \* \* \*

■ 3. Part 335 is added to read as follows:

**PART 335—ANTIDIARRHEAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE****Subpart A—General Provisions**

335.1 Scope.

335.3 Definitions.

**Subpart B—Active Ingredients**

335.10 Antidiarrheal active ingredients.

**Subpart C—Labeling**

335.50 Labeling of antidiarrheal drug products.

**Authority:** 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

**Subpart A—General Provisions****§ 335.1 Scope.**

(a) An over-the-counter antidiarrheal drug product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this part and each general condition established in § 330.1 of this chapter.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21 unless otherwise noted.

**§ 335.3 Definitions.**

As used in this part:

(a) *Antidiarrheal*. A drug that can be shown by objective measurement to treat or control (stop) the symptoms of diarrhea.

(b) *Diarrhea*. A condition characterized by increased frequency of loose, watery stools (three or more daily) during a limited period (24 to 48 hours), usually with no identifiable cause.

**Subpart B—Active Ingredients****§ 335.10 Antidiarrheal active ingredients.**

The active ingredient of the product consists of any one of the following when used within the dosage limits established for each ingredient in § 335.50(d):

(a) Bismuth subsalicylate.

(b) Kaolin.

**Subpart C—Labeling****§ 335.50 Labeling of antidiarrheal drug products.**

(a) *Statement of identity*. The labeling of the product contains the established name of the drug, if any, and identifies the product either as an “antidiarrheal” or “for diarrhea.”

(b) *Indications*. The labeling of the product states, under the heading “Use,” one or more of the phrases listed in this paragraph (b), as appropriate. Other truthful and nonmisleading statements, describing only the

indications for use that have been established and listed in this paragraph (b) may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For products containing bismuth subsalicylate identified in § 335.10(a)*. The labeling states [select one of the following: “controls” or “relieves”] “diarrhea”.

(2) *For products containing kaolin identified in § 335.10(b)*. The labeling states “helps firm stool within 24 to 48 hours”.

(3) *Additional indications*—(i) When any additional indications are used, the heading “Uses” shall be used and each listed use shall be preceded by a bullet in accord with § 201.66(b)(4) of this chapter.

(ii) In addition to the indication in paragraph (b)(1) of this section, one or both of the following may be used for products containing bismuth subsalicylate in § 335.10(a): “[bullet] reduces number of bowel movements” “[bullet] helps firm stool”.

(c) *Warnings*. The labeling of the product contains the following warnings under the heading “Warnings”:

(1) *For products containing any ingredient identified in § 335.10*. (i) “Do not use if you have [bullet] bloody or black stool”.

(ii) “Ask a doctor before use if you have [bullet] fever [bullet] mucus in the stool”.

(2) *For products containing bismuth subsalicylate identified in § 335.10(a)*.

(i) The following shall appear in accordance with § 201.66(c)(5)(ii) of this chapter.

(A) The Reye’s syndrome warning in § 201.314(h) of this chapter.

(B) “Allergy alert: Contains salicylate. Do not take if you are [bullet] allergic to salicylates (including aspirin), [bullet] taking other salicylate products”.

(ii) “Do not use if you have [bullet] an ulcer [bullet] a bleeding problem”.

(iii) “Ask a doctor or pharmacist before use if you are taking any drug for [bullet] anticoagulation (thinning the blood) [bullet] diabetes [bullet] gout [bullet] arthritis”.

(iv) “When using this product a temporary, but harmless, darkening of the stool and/or tongue may occur”.

(v) “Stop use and ask a doctor if [bullet] symptoms get worse [bullet] ringing in the ears or loss of hearing

occurs [bullet] diarrhea lasts more than 2 days”.

(3) *For products containing kaolin identified in § 335.10(b).* (i) “Ask a doctor or pharmacist before use if you are taking any other drugs. Try to use at least 3 hours before or after taking any other drugs.”

(ii) “Stop use and ask a doctor if [bullet] symptoms get worse [bullet] diarrhea lasts more than 2 days”.

(d) *Directions.* The labeling of the product contains the following information under the heading “Directions”:

(1) *For products containing any ingredient identified in § 335.10.* The labeling states “[bullet] drink plenty of clear fluids to help prevent dehydration caused by diarrhea”.

(2) *For products containing bismuth subsalicylate identified in § 335.10(a).* The labeling states “[bullet] adults and children 12 years and over:” 525 milligrams “every 1/2 to 1 hour, or” 1,050 milligrams “every hour as needed [bullet] do not exceed” 4,200 milligrams “in 24 hours [bullet] use until diarrhea stops but not more than 2 days [bullet] children under 12 years: ask a doctor”.

(3) *For products containing kaolin identified in § 335.10(b).* The labeling states “[bullet] adults and children 12 years and over:” 26.2 grams “after each loose stool [bullet] continue to take every 6 hours until stool is firm but not more than 2 days [bullet] do not exceed” [262 grams] “in 24 hours [bullet] children under 12 years of age: ask a doctor”.

(e) *Products that meet the criteria established in § 201.66(d)(10) of this chapter.* The information described in § 201.66(c) of this chapter shall be printed in accordance with the following specifications.

(1) The labeling shall meet the requirements of § 201.66(c) of this chapter except that the information in § 201.66(c)(3) of this chapter may be omitted, and the information in § 201.66(c)(5) and (c)(6) of this chapter may be presented as follows:

(i) The words “Contains salicylate.” may be omitted from the warning in § 335.50(c)(2)(i)(B).

(ii) The subheading “When using this product” in § 335.50(c)(2)(iv) may be omitted.

(iii) The words “continue to” may be omitted from the directions in § 335.50(d)(3).

(2) The labeling shall be printed in accordance with the requirements of § 201.66(d) of this chapter except that any requirements related to § 201.66(c)(3) of this chapter and the bullet in the warning in § 335.50(c)(1)(i) may be omitted.

## **PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE**

■ 4. The authority citation for 21 CFR part 369 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 371.

### **§ 369.20 [Amended]**

5. Section 369.20 *Drugs; recommended warning and caution statements* is amended by removing the entry for “DIARRHEA PREPARATIONS.”

Dated: March 31, 2003.

**Jeffrey Shuren,**

*Assistant Commissioner for Policy.*

[FR Doc. 03–9380 Filed 4–16–03; 8:45 am]

**BILLING CODE 4160–01–S**

## **DEPARTMENT OF HEALTH AND HUMAN SERVICES**

### **Food and Drug Administration**

#### **21 CFR Part 520**

#### **Oral Dosage Form New Animal Drugs; Deracoxib**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of a supplemental new animal drug application (NADA) filed by Novartis Animal Health US, Inc. The supplemental NADA provides for the veterinary prescription use of deracoxib tablets in dogs for the control of pain and inflammation associated with osteoarthritis.

**DATES:** This rule is effective April 17, 2003.

**FOR FURTHER INFORMATION CONTACT:** Melanie R. Berson, Center for Veterinary Medicine (HFV–110), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–827–7543, e-mail: mberson@cvm.fda.gov.

**SUPPLEMENTARY INFORMATION:** Novartis Animal Health US, Inc., 3200 Northline Ave., suite 300, Greensboro, NC 27408, filed a supplement to NADA 141–203 that provides for the veterinary prescription use of DERAMAXX (deracoxib) Chewable Tablets for the control of pain and inflammation associated with osteoarthritis. The supplemental NADA is approved as of February 11, 2003, and 21 CFR 520.538 is amended to reflect the approval. The

basis of approval is discussed in the freedom of information summary.

In accordance with the freedom of information provisions of 21 CFR part 20 and 21 CFR 514.11(e)(2)(ii), a summary of safety and effectiveness data and information submitted to support approval of this application may be seen in the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, between 9 a.m. and 4 p.m., Monday through Friday.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(c)(2)(F)(iii)), this supplemental approval qualifies for 3 years of marketing exclusivity beginning February 11, 2003.

The agency has determined under 21 CFR 25.33(d)(1) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

This rule does not meet the definition of “rule” in 5 U.S.C. 804(3)(A) because it is a rule of “particular applicability.” Therefore, it is not subject to the congressional review requirements in 5 U.S.C. 801–808.

#### **List of Subjects in 21 CFR Part 520**

Animal drugs.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to the Center for Veterinary Medicine, 21 CFR part 520 is amended as follows:

#### **PART 520—ORAL DOSAGE FORM NEW ANIMAL DRUGS**

■ 1. The authority citation for 21 CFR part 520 continues to read as follows:

**Authority:** 21 U.S.C. 360b.

■ 2. Section 520.538 is amended by revising paragraphs (d)(1) and (d)(2) to read as follows:

#### **§ 520.538 Deracoxib.**

\* \* \* \* \*

(d) \* \* \* (1) *Amount.* Administer orally as needed, as a single daily dose based on body weight.

(i) 1 to 2 mg/kilograms (kg) (0.45 to 0.91 mg/pound (lb), for use as in paragraph (d)(2)(i) of this section.

(ii) 3 to 4 mg/kg (1.4 to 1.8 mg/lb) for up to 7 days, for use as in paragraph (d)(2)(ii) of this section.

(2) *Indications for use.* (i) For the control of pain and inflammation associated with osteoarthritis.