

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