DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 335 and 369

[Docket No. 78N-036D]

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

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) antidiarrheal drug products (products that treat or control the symptoms of diarrhea) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal deals only with antidiarrheal drug products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by June 30, 1986. New data by April 30, 1987. Comments on the new data by June 30, 1987. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determination by August 28, 1986.

ADDRESS: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: 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 laxative, antidiarrheal, emetic, and antiemetic drug products, together with the recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. Interested persons were invited to submit comments by June 19, 1975. Reply comments in response to comments filed in the initial comment period could be submitted by July 19, 1975.

In a notice published in the **Federal Register** of March 21, 1980 (45 FR 18398), the agency advised that it had reopened the administrative record for OTC antidiarrheal drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch after the date the administrative record previously had officially closed. The agency concluded that any new data and information filed prior to March 21, 1980 should be available to the agency in developing a proposed regulation in the form of a tentative final monograph.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. Data and information received after the administrative record was reopened have also been put on display in the Dockets Management Branch. In response to the advance notice of proposed rulemaking, 19 drug manufacturers, 2 trade associations, and 1 State planning and budget office submitted comments on antidiarrheal drug products. Copies of the comments received are on public display in the Dockets Management Branch.

The advance notice of proposed rulemaking, which was published in the **Federal Register** on March 21, 1975 (40 FR 12902), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) to establish Part 335 (21 CFR Part 335) FDA states for the first time its position on the establishment of a monograph for OTC antidiarrheal drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC antidiarrheal drug products.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC antidiarrheal drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

The OTC procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register.** On or after that date, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph 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 monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC antidiarrheal drug products (published in the **Federal Register** of March 21, 1975; 40 FR 12902), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with xtension requests and related aperwork.

In addition, some products will have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be plemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of February 8, 1973 (38 FR 3614) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments

1. One comment objected to the Panel's recommendation that the quantity of each active ingredient be stated in OTC drug product labeling, on the grounds that section 502(e)(1)(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(e)(1)(A)) provides for quantitative ingredient labeling only for prescription drugs.

The agency agrees that other than for certain specifically named substances, the act currently requires quantitative ingredient labeling only for prescription drugs. The tentative final monograph does not require active ingredient labeling. However, the agency advises that the Panel's recommendation is consistent with that of the National Advisory Drug Committee, which advocates that all OTC drugs be labeled with a quantitative statement of the active ingredients. It is also consistent with the recommendation in 21 CFR 330.1(j) that the labeling of an OTC drug product contain the quantitative amount of each active ingredient, expressed in terms of the dosage unit stated in the directions for use.

Drug manufacturers who are members of The Proprietary Association, the trade association that represents approximately 85 OTC drug manufacturers who reportedly market between 90 and 95 percent of the volume of all OTC drug products sold in the United States, have been voluntarily including the quantities of active ingredients on OTC drug labels for a number of years (Ref. 1). The agency commends these voluntary efforts and urges all other OTC drug manufacturers to voluntarily label their products in accordance with The Proprietary Association's guidelines.

Reference

(1) "Proprietary Association Adopts Voluntary Disclosure of Inactive Ingredients," News Release, The Proprietary Association, Washington, DC, May 14, 1984, copy included in OTC Volume 09DTFM.

2. Several comments objected to the Panel's recommendation that all inactive ingredients be listed on the labeling, arguing that such a listing would be meaningless, confusing, and misleading to most consumers.

The agency advises that neither the March 21, 1975 advance notice of proposed rulemaking nor the monograph in this tentative final rule requires that all inactive ingredients be listed in OTC drug labeling. However, the agency agrees with the Panel that listing of inactive ingredients in OTC drug product labeling would be in the public interest. Consumers with known allergies or intolerances to certain ingredients would then be able to identify substances that they may wish to avoid.

The Proprietary Association recently announced that its member companies would voluntarily begin to list inactive ingredients in the labeling of OTC drug products under guidelines established by the Assoication (Ref. 1). The agency commends these voluntary efforts and urges all other OTC drug manufacturers to voluntarily label their products in accordance with The Proprietary Association's guidelines.

Reference

(1) "Proprietary Association Adopts Voluntary Disclosure of Inactive Ingredients," News Release, The Proprietary Association, Washington, DC, May 14, 1984, copy included in OTC Volume 09DTFM.

3. Two comments contended that FDA does not have the authority to establish substantive rules.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464) and in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated there. Subsequent court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F.2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).

4. Several comments urged a greater role for pharmacists in the sale of OTC drugs. One comment recommended that OTC drugs be available only through

pharmacies, and two suggested that any labeling which suggests consultation with a physician should mention a pharmacist as a viable alternative.

These issues were fully discussed in the preamble to the proposal to revise requirements for drug interaction warnings on OTC drug products (see the **Federal Register** of June 4, 1974 (39 FR 19880)). These views will not be restated here. However, the agency notes that § 330.1(g) (21 CFR 330.1(g)) requires that labeling for OTC drugs include a warning to seek professional assistance in case of accidental overdose. The pharmacist is one of the health professionals that a consumer might choose to consult.

5. One comment noted that on several pages of the Panel's recommended monograph the abbreviation "gm" is used for gram, yet 21 CFR 201.62(1) (formerly 21 CFR 1.102(d)) states that the only abbreviation which may be used for gram is "g."

The situation outlined in the comment was an editorial oversight. The OTC drug labeling regulations cited in the comment permit the use of "g" as the only abbreviation for gram. For clarity, metric units have been fully written out in this tentative final monograph.

6. One comment stated that the Panel's recommendations violate the objectives and philosophy of the OTC drug review and that the Panel failed to discharge its obligations by placing many long-established antidiarrheal ingredients and antidiarrheal combinations in Category III. Other comments contended that the Panel did not consider the extent-of-use and consumer-acceptance data or the professional opinion surveys of physicians and pharmacists submitted for products containing ingredients placed in Category III.

The agency believes that the Panel's recommendations for OTC antidiarrheal drug products are fully in accord with the objectives of the OTC drug review as stated in the applicable regulations (21 CFR Part 330). The Panel reviewed all of the data submitted for each antidiarrheal active ingredient, including marketing histories and information on the extent of use by consumers. In placing antidiarrheal ingredients or combinations in Category III, the Panel concluded that the available data were insufficient to permit classification in Category I or Category II at the time it reviewed those drugs. The agency has also evaluated these data, marketing histories, and information on extent of use, as well as more recent data and information, in reaching its conclusions in this tentative final monograph.

B. General Comments on Antidiarrheal Drug Products

7. One comment disagreed with the definition of "diarrhea" recommended by the Panel in § 335.3(a): "The abnormally frequent passage of watery stools, self-limiting (24 to 48 hours) usually with no identifiable cause." The comment argued that this definition is vague and does not provide any assistance for individuals interested in designing protocols and conducting tests for antidiarrheals. The comment added that evaluations of diarrhea are best determined by a subjective, case-by-case approach and that the definition of the condition should be related to the individual and his or her personal bowel habits, not to the "average" person. The comment proposed the following definition of diarrhea: "An increase in the frequency, fluidity, or volume of bowel movements, relative to the usual habit of each individual."

The agency agrees that the Panel's definition of diarrhea does not provide criteria for use in designing protocols or conducting clinical trials. Therefore, the definition of diarrhea in this tentative final monograph has been revised to read: "*Diarrhea.* A condition characterized by increased frequency of excretion of loose, watery stools (three or more daily) during a limited period (24 to 48 hours), usually with no identifiable cause." This revised definition suggests criteria, i.e., decreased frequency of excretion and/or improved consistency of stools, which can be used in designing clinical protocols to establish the effectiveness of an OTC antidiarrheal drug. In addition, the definition of antidiarrheal has been revised to read: "*Antidiarrheal.* A drug that can be shown by objective measurement to treat or control (stop) the symptoms of diarrhea." The agency believes that this emphasis on relief of symptoms more accurately reflects the expectations for an OTC antidiarrheal and is therefore helpful in designing testing protocols for OTC antidiarrheal drugs.

8. One comment suggested that the term "high fever" in the Panel's recommended warning in § 335.50(c)(1), "Do not use . . . in the presence of high fever" . . .," be clarified by stating a specific temperature, i.e., over 102° F (oral) or 103° F (rectal), in order to provide specific directions.

The agency believes that the use of the term "high fever" is inappropriate for inclusion in the warning. OTC antidiarrheal drug products are intended to be used for the treatment of acute nonspecific diarrhea that is not associated with fever (any temperature above 98.6 °F), because the presence of fever may be indicative of a serious condition that is not amenable to treatment with such products. Because consumers understand the term "fever" to mean any temperature over 98.6° F, there is no need to specify a specific temperature. Therefore, the agency is proposing in this tentative final monograph that the warning in § 335.50(c)(1) read as follows: "Do not use . . . in the presence of fever. . . ."

9. Two comments stated that the Panel's request that the mechanism of action for antidiarrheal ingredients be determined is unnecessary because, as the Panel recognized, there are many safe and effective ingredients whose precise mechanisms of action are unknown (40 FR 12934). One comment added that as long as a product can be shown to be safe and effective, there should be no requirement to demonstrate a precise mechanism of action.

The agency agrees that the precise mechanism of action of an antidiarrheal ingredient need not be demonstrated as long as there is sufficient evidence of safety and effectiveness for its intended use. However, development of such information is certainly encouraged.

10. One comment suggested that the Panel's use of the phrase "to increase the bulk of the stool" as an example of recommended labeling might be misleading when used in the context of antidiarrheal products, because that description is usually associated with laxatives.

The Panel used the phrase "to increase the bulk of the stool" only as an example and did not include it in the labeling requirements for antidiarrheal drug products in § 335.50(a) of its recommended monograph. However, the agency believes that antidiarrheal drug products should be clearly labeled to reflect their intended results because not all antidiarrheal active ingredients have the same effect. Some ingredients may actually control or stop diarrhea. Other ingredients may only improve the consistency of the bowel movement or reduce the number of bowel movements without actually affecting other factors contributing to the diarrheal process, such as increased water content and weight of stools or loss of electrolytes, bile salts, etc. There is no objection to the OTC marketing of antidiarrheal drug products that provide only symptomatic relief of diarrhea because providing symptomatic relief is the intent of these products. However, it is important that consumers be told which action the drug exerts. Therefore, the agency is recommending the following indications

for use for these drug products: (1) "For the treatment of diarrhea" or "Controls (stops) diarrhea"; (2) "Reduces the number of bowel movements in diarrhea"; (3) "Improves consistency of loose, watery bowel movements in diarrhea." One or more of these indications may be included in the labeling of OTC antidiarrheal drug products, depending on the results of studies conducted on the ingredient contained in the product. The agency also recognizes 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. The agency has no objection to including information of this type in the indications for OTC antidiarrheal drug products, provided that the results of studies conducted on the ingredients contained in the product support this inclusion. However, the agency does not believe that relief of symptoms that are secondary to diarrhea can be considered as primary indications for use of an OTC antidiarrheal drug product. Therefore, indications for relief of symptoms secondary to diarrhea will be allowed in the labeling of an OTC antidiarrheal drug product only when the product meets the criteria of one or more of the above three indications for OTC antidiarrheal drug products being proposed in this tentative final monograph. The tentative final monograph specified the allowable indications proposed for each ingredient included in the monograph.

C. Comments on Specific Antidiarrheal Active Ingredients

11. One comment asserted that the Panel's recommended pediatric dosage statement for polycarbophil, which provides a dosage for children 3 years of age and under, is in conflict with the Panel's general warning in § 335.50(c)(1), which limits the use of antidiarrheals to children 3 years of age and older unless directed by a physician. The comment urged that the general warning as applied to polycarbophil be revised to delete the phrase "or infants or children under 3 years unless directed by a physician."

The comment is correct that the Panel's recommended pediatric dosage statement for polycarbophil is in conflict with its general warning. The Panel's general warning is in accord with the agency's recommended warning in § 369.20 (21 CFR 369.20), which limits the use of antidiarrheal drug products to children 3 years of age and older, unless directed by a physician. The agency has, therefore, determined that pediatric doses of this ingredient for children under 3 years of age will not appear in the OTC drug labeling, but will be included only in professional labeling. Consumers will be instructed in the OTC drug labeling to consult a doctor for this dosage information.

12. Two comments contended that the studies cited by the Panel in support of the Category I classification of polycarbophil in the treatment of diarrhea do not meet the Panel's own criteria for establishing effectiveness. One of the comments added that the Panel had apparently applied a dual standard of classification in placing polycarbophil and the opiates in Category I although they have not been shown to be effective in double-blind studies for the list of objective parameters prescribed by the Panel for kaolin and pectin. The comment contended that there are no differences in the clinical endpoints which would account for this apparent dual standard for kaolin and pectin vis-a-vis polycarbophil and the opiates. A third comment defended the studies on polycarbophil as having been performed by well-qualified investigators whose findings were carefully documented and published in reputable medical journals. The comment contended that no other OTC antidiarrheal ingredient has been the subject of such competent and well-documented evaluation.

The agency has reviewed the studies cited by the Panel to support the Category I classification of polycarbophil (40 FR 12926). Although the comment is correct that the polycarbophil studies do not demonstrate that polycarbophil is effective for all the objective parameters listed by the Panel, the studies do provide objective evidence that polycarbophil is effective in improving consistency of watery bowel movements and in decreasing the frequency of bowel movements. As discussed in comment 10 above, the agency recognizes that not all OTC antidiarrheals have the same effect. The agency has no objection to the OTC marketing of products which relieve only certain symptoms of diarrhea provided the labeling of the product clearly indicates the expected action. Although there are similarities between the data for polycarbophil and the data for kaolin and pectin, as described in comment 23 below, the kaolin-pectin data have certain deficiencies that prevent conclusions from being drawn at this time. If those deficiencies are remedied, then kaolin and pectin may be placed in Category I. The agency believes that the Panel did not apply a dual standard in its classifications and concurs with the Panel's conclusions. As discussed in comment 20 below, because opiate ingredients may be marketed OTC only in combination in accordance with § 329.20(a)(1) and because no combinations of opiates with other ingredients are in Category I at this time, opiate ingredients are placed in Category III in this document.

13. Two comments questioned whether the calcium salt of polycarbophil should be included in the monograph, noting that two of the studies cited by the Panel in support of its Category I classification of polycarbophil involved calcium polycarbophil (40 FR 12926). A third comment submitted data elucidating the role of the calcium in calcium polycarbophil and supporting the safety and effectiveness of this ingredient (Ref. 1). The comments explained that inclusion of calcium polycarbophil in the monograph would permit the formulation of polycarbophil in liquid as well as solid dosage forms, because calcium polycarbophil is not hydrosorptive and can be used in a liquid medium.

Calcium polycarbophil is a simple salt of polycarbophil in which calcium has been substituted for the acidic hydrogen ions. Following ingestion, the calcium salt is converted to acidic polycarbophil when the calcium is replaced by hydrogen ions of the stomach acid. Polycarbophil is then made available to exert its maximal hydrosorptive effect during intestinal transit (Ref. 2). Because the calcium ion does not alter either the chemical or pharmacological effect of polycarbophil, calcium polycarbophil can be considered to be therapeutically identical to polycarbophil (Ref. 1). Therefore, the agency is proposing to include calcium polycarbophil in the tentative final monograph.

References

(1) Comment No. C00073, Docket No. 78N-036D, Dockets Management Branch.

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

14. One comment contended that polycarbophil, which is a hydrosorptive agent, might be contraindicated in treatment of diarrhea, especially in children, because of the danger that hydrosorption might heighten systemic electrolyte loss and dehydration. The comment further contended that the studies on which the Panel based its evaluation of polycarbophil did not adequately measure stool water content or electrolyte loss.

The comment submitted no data to support its contention that polycarbophil, as a hydrosorptive agent, might heighten systemic electrolyte loss and dehydration. However, because of the danger of rapid electrolyte imbalance and dehydration in infants and children as a result of diarrhea, the agency believes that no OTC antidiarrheal drug product should be used in children under the age of 3 years, or for more than 2 days in anyone over 3 years of age, except under the advice of a physician. Although the studies cited by the Panel did not adequately measure stool water content or electrolyte loss, no clinically significant side effects were reported either when polycarbophil was used in children for the treatment of acute nonspecific diarrhea (Refs. 1 and 2) or in adults for chronic constipation for up to 2 years (Ref. 3). Moreover, one of the studies cited by the Panel suggests that polycarbophil exhibits the capacity to decrease the abnormally rapid transit of the intestinal contents (Ref. 4). This would possibly allow for the increased absorption of water and electrolytes back into the systemic circulation. Therefore, the agency concludes that there is no basis for the contraindication of polycarbophil in treating symptoms of diarrhea.

References

(1) 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.

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

(3) Grossman, A.J., et al., "Polyacrylic Resin: Effective Hydrophilic Colloid for the Treatment of Constipation," *Journal of the American Geriatric Society*, 5:187–192, 1957.

(4) Winkelstein, A., "Effect of Calcium Polycarbophil (Carbofil®) Suspension on Gastrointestinal Transit Time," *Current Therapeutic Research*, 6:572–583, 1964.

15. One comment cited a clinical study submitted to the Panel in 1974 (Ref. 1) and submitted a new clinical study (Refs. 2, 3, and 4) in support of the effectiveness of attapulgite. The comment requested that attapulgite be reclassified from Category III to Category I for use as an OTC antidiarrheal.

The agency has evaluated all of the data and concludes that they are adequate to support the reclassification of attapulgite from Category III to Category I for use as an OTC antidiarrheal.

In the 1974 double-blind randomized placebo-controlled study, the effectiveness of tablets containing 600 milligrams (mg) attapulgite and 50 mg pectin was compared with placebo in subjects with acute gastroenteritis and diarrhea, characterized by abdominal pain and/or discomfort with watery bowel movements (Ref. 1). Four tablets were administered initially with four tablets to be taken after each diarrheal stool. Patients were given report forms to record frequency and consistency of stools as well as frequency of cramps and the duration and severity of pain.

This study was originally submitted to the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic and Antiemetic Drug Products, which concluded that the study showed the combination of attapulgite and pectin to be more effective than placebo. However, because there was no assessment of individual ingredients, the study cannot be used to demonstrate the effectiveness of attapulgite alone.

The newly submitted clinical study (Refs. 2, 3, and 4) is identical in format to the 1974 study (Ref. 1), except that it employed a dose of 2 tablets each containing 600 mg attapulgite alone versus placebo. Fifty patients were randomly assigned attapulgite or placebo at the initial visit. Results of the study indicated that the subjects of the active group had significantly fewer bowel movements, better stool consistency, and fewer cramps than the subjects of the placebo group ($p < .0001$). Based on the results of this study, the agency is proposing the following indications for this ingredient: (1) "Reduces the number of bowel movements in diarrhea," and (2) "Improves consistency of loose, watery bowel movements in diarrhea." The following indication may also be used in the labeling of attapulgite products: "Relieves cramps in diarrhea." As discussed in comment 10 above, this indication may be used in addition to one or both of the other indications but may not be used alone.

Although the 1974 study utilized a higher dosage of attapulgite, the agency believes that based on the Panel's recommendations, the results of the new study, and the dosages currently promoted on the marketed products submitted for evaluation, the use of attapulgite should be limited to the following oral dosage:

Adults and children 12 years of age and over: oral dosage is 1,200 mg after initial bowel movement, 1,200 mg after each subsequent bowel movement, not to exceed 8,400 mg in 24 hours. Children 6 to under 12 years of age: oral dosage is 600 mg after initial bowel movement, 600 mg after each subsequent bowel movement, not to exceed 4,200 mg in 24 hours. Children 3 to under 6 years of age: oral dosage is 300 mg after initial bowel movement, 300 mg after each subsequent bowel movement, not to exceed 2,100 mg in 24 hours.

The agency's detailed comments and evaluations on the data are on file with the Dockets Management Branch (Ref. 5).

References

(1) OTC Volume 090133, Docket No. 78N–036D, Dockets Management Branch.

(2) Comment No. SUP005, Docket No. 78N–036D, Dockets Management Branch.

(3) Comment No. AMD002, Docket No. 78N–036D, Dockets Management Branch.

(4) Comment No. SUP006, Docket No. 78N–036D, Dockets Management Branch.

(5) Letter from W.E. Gilbertson, FDA, to D.C. Oppenheimer, Pfizer Pharmaceuticals, ANS LET004, Docket No. 78N–036D, Dockets Management Branch.

16. One comment stated that it would be difficult or impossible to demonstrate the effectiveness of an antidiarrheal agent in vivo in humans by objective double-blind studies because of the self-limiting nature (24 to 48 hours) of acute nonspecific diarrhea. The comment added that, because of the difficulty in conducting clinical studies, evidence developed in double-blind, placebo-controlled primate studies using kaolin and pectin should be sufficient to establish the effectiveness of kaolin and pectin alone and in combination as antidiarrheal agents. The comment pointed out that FDA has endorsed other types of efficacy tests (e.g., an in vitro efficacy test in the monograph for OTC antacid drug products) in situations where human studies are difficult to perform.

This comment is incorrect. Adequate clinical studies in acute nonspecific diarrhea have been carried out in humans and have been submitted to the agency. (See comment 23 below.) Thus, there is no reason to rely solely on primate studies to reach conclusions about the effectiveness of an antidiarrheal drug in humans. The agency concludes that clinical studies in humans are required to establish the effectiveness of OTC antidiarrheal drugs.

17. One comment submitted a clinical study (Ref. 1) and detailed statistical analyses of that study (Refs. 2 and 3) in support of the effectiveness of bismuth subsalicylate. The comment requested that bismuth subsalicylate be reclassified from Category III to

Category I for use as an OTC antidiarrheal.

The agency has evaluated all of the data and concludes that they are insufficient to support the reclassification of bismuth subsalicylate from Category III to Category I for use as an OTC antidiarrheal.

In the clinical study submitted the effectiveness of bismuth subsalicylate was compared with placebo in the symptomatic treatment of diarrhea in a double-blind placebo-controlled study among students attending a Mexican University. The study was conducted in two sequential 48 hour phases. Students in Phase I were given a 30-milliliter (mL) dose of a bismuth subsalicylate preparation every ½ hour for eight doses for a total dose of 4.2 g, and students in Phase II were given twice this dose. The objective parameters assessed were frequency, consistency, weight, and water content of the stools. Results of the study indicate that frequency was the only objective parameter that improved after use of the drug. The data were analyzed for the periods 4 to 24 hours and 4 to 48 hours after initiation of the study. For the reasons stated below, the Phase II study will not be further evaluated.

Although no statistically significant difference was shown in the Phase I study for the 4 to 48 hour period, analysis of the data suggests that bismuth subsalicylate may reduce the number of bowel movements in diarrhea when compared to placebo for the time period 4 to 24 hours. However, because no formal protocol was submitted with the study, the agency is unable to determine whether the analyzes performed are consistent with the initial intended objectives of the study. The agency does not believe that it is appropriate to exclude the 0 to 4 hour data from the analysis or to focus on any particular time period, considering that the study was conducted over a 2-day period. The agency's detailed evaluation and comments on the data are on file in the Dockets Management Branch (Refs. 4 through 7).[1]

Although the Panel's report states that bismuth subsalicylate is safe for OTC use in amounts up to 8g (40 FR 12930), the agency believes, for the reasons stated below, that should bismuth subsalicylate be included in the final monograph its dosage should be limited to the following: Adults and children 14 years of age and over: oral dosage is 525 mg every ½ to 1 hour, not to exceed 4,200 mg in 24 hours. Children 10 to under 14 years of age: oral dosage is 350 mg every ½ to 1 hour, not to exceed 2,800 mg in 24 hours. Children 6 to under 10 years of age: oral dosage is 175 mg every ½ to 1 hour, not to exceed 1,400 mg in 24 hours. Children 3 to under 6 years of age: oral dosage is 87.5 every ½ to 1 hour, not to exceed 700 mg in 24 hours. Children under 3 years of age: consult a doctor.

Recent reports on the literature (Refs. 8 through 11) indicate that the salicylate moiety is readily absorbable from bismuth subsalicylate. For this reason, the agency believes the higher dose used in the Phase II study presents a potential for toxicity without a compensating therapeutic benefit. Although the amount of salicylate absorbed from the lower dose used in the Phase I study does not present a safety problem when bismuth subsalicylate is taken alone, the agency is concerned that if products containing this drug were taken with other salicylate-containing products, such as aspirin, the increased blood plasma salicylate concentration could result in adverse side effects. Additionally, the salicylate in bismuth subsalicylate is readily absorbable and salicylates are known to interact with certain other drugs, e.g., anticoagulants, uricosuric drugs. For these reasons, should bismuth subsalicylate be included in the final monograph, the agency will consider requiring the following warning in the monograph for all products containing bismuth subsalicylate: "This product contains salicylate. Do not take this product with other salicylate-containing products, such as aspirin, unless directed by a doctor. If you are taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout, or arthritis, do not take this product unless directed by a doctor." In addition, because bismuth-containing products cause the stools to darken in color and cause a temporary darkening of the tongue (Refs. 12, 13, and 14), the agency will also consider requiring that the following statement be included in the labeling of all products containing bismuth subsalicylate: "This product may cause the stool to darken or cause a temporary darkening of the tongue."

References

(1) Comment No. C00082, Docket No. 78N–036D, Dockets Management Branch.

(2) Comment No. C00074, Docket No. 78N–036D, Dockets Management Branch.

(3) Comment No. 0B052A, Docket No. 78N–036D, Dockets Management Branch.

(4) Letter from W.E. Gilbertson, FDA to S. Mercurio, Norwich Eaton Pharmaceuticals, LET003, Docket No. 78N–036D, Dockets Management Branch.

(5) Letter from W.E. Gilbertson, FDA to W.E. Cooley, Proctor and Gamble Co., LET008, Docket No. 78N–036D, Dockets Management Branch.

(6) Comment No. MM0005, Docket No. 78N–036D, Dockets Management Branch.

(7) Letter from W.E. Gilbertson, FDA to W.E. Cooley, Proctor and Gamble Co., LET009, Docket No. 78N–036D, Dockets Management Branch.

(8) Feldman, S., et al., "Absorption of Salicylate from a Bismuth Subsalicylate Antidiarrheal Preparation (Pepto-Bismol)," *Clinical Pharmacology and Therapeutics*, 27:252, 1980.

(9) Feldman, et al., "Salicylate Absorption From a Bismuth Subsalicylate Preparation," *Clinical Pharmacology and Therapeutics*, 29:788–792, 1981.

(10) Anonymous, "Salicylate in Pepto-Bismol," *The Medical Letter on Drugs and Therapeutics*, 22:63, 1980.

(11) Pickering, L.K., et al., "Absorption of Salicylate and Bismuth from a Bismuth Subsalicylate-Containing Compound (Pepto-Bismol)," *The Journal of Pediatrics*, 99:654–656, 1981.

(12) Bank, S., et al., "Gastro-Intestinal and Hepatic Diseases," *in* "Drug Treatment, Principles and Practice of Clinical Pharmacology and Therapeutics," 2nd Ed., edited by G.S. Avery, Adis Press, New York, pp. 703 and 1249, 1980.

(13) Weiss, G., and W.J. Serfontein, "The Efficacy of a Bismuth-Protein-Complex Compound in the Treatment of Gastric and Duodenal Ulcers," *South African Medical Journal*, 45:467–470, 1971.

(14) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," W.B. Saunders Co., Philadelphia, 1957.

18. One comment suggested that the entire paragraph dealing with bismuth subsalicylate labeling claims (40 FR 12931) should be stricken from the Panel's report because the Panel confused the use of a single ingredient for multiple symptoms and the use of multiple ingredients for multiple symptoms. The comment stated that although bismuth subsalicylate is used for treating symptoms of nausea, indigestion, upset stomach, and diarrhea, it is not necessary for a patient to suffer from more than one of these symptoms concurrently for bismuth subsalicylate to be used rationally.

The agency agrees that it is not necessary for a patient to suffer concurrently from more than one of the symptoms described above in order for bismuth subsalicylate to be used rationally. However, the use of bismuth subsalicylate as an antidiarrheal is the only claim discussed in this document. Claims for the treatment of other symptoms, such as nausea, indigestion, or upset stomach, may be included in labeling if the ingredient is proven

[1] Industry has responded to FDA's concern regarding the need for additional data and is in the process of conducting additional studies (Comment No. PR0002, Docket No. 78N–036D, Dockets Management Branch).

effective for each symptom in other rulemakings. The use of bismuth subsalicylate for the treatment of nausea was discussed in the tentative final monograph for OTC antiemetic drug products, published in the **Federal Register** of July 13, 1979 (44 FR 41064). Bismuth subsalicylate used for the treatment of upset stomach due to overindulgence in food and alcohol was reviewed by the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, in its advance notice of proposed rulemaking published in the **Federal Register** of October 1, 1982 (47 FR 43540).

19. One comment stated that the Panel's classification of a product containing *Lactobacillus acidophilus* and sodium carboxymethylcellulose as a combination was in error, noting that the initial submission to the Panel did not make it clear that the sodium carboxymethylcellulose acts as a pharmaceutical necessity by coating and matrixing the lactobacillus organisms to protect them from stomach acid and to transport them to the intestine.

The agency has reviewed the submission to the Panel and notes that sodium carboxymethylcellulose was listed along with *Lactobacillus acidophilus* as an ingredient in the product. Although the label did not specifically claim sodium carboxymethylcellulose as an active ingredient, the Panel assumed it was an active ingredient and reviewed it as such. Although the comment makes it clear that the sodium carboxymethylcellulose in the product is present as a pharmaceutical necessity, the Panel recognized that sodium carboxymethylcellulose can increase the viscosity of fluids and, therefore, might be rational for inclusion in antidiarrheal drug products. However, data were insufficient to establish effectiveness of this ingredient, and the Panel classified it in Category III. The agency concurs with the Panel's conclusions. While the agency has no objection to the use of sodium carboxymethylcellulose as an inactive ingredient in antidiarrheal drug products, the products should be labeled to avoid the appearance that sodium carboxymethylcellulose is an active ingredient.

20. One comment stated that the Panel's recommended monograph is not consistent with existing regulations (21 CFR 329.20(a)(1)) that require the presence of another nonnarcotic active ingredient in OTC drug preparations containing opiates. Another comment expressed the hope that opiates would remain in Category I despite the fact that regulations do not permit OTC marketing of these ingredients as single active ingredient products.

The Panel's recommended monograph is not inconsistent with existing regulations. Section 335.10(a)(2) of that monograph cites the requirements of § 329.20(a)(1), which states that pharmaceutical preparations containing not more than 100 mg of opium per 100 mL or per 100 g may be exempt from prescription status, *provided* that such preparations contain one or more nonnarcotic active medicinal ingredients in sufficient proportion to confer upon the preparation valuable medicinal qualities other than those possessed by the narcotic drug alone. Although the Panel placed opiate ingredients in Category I (for use in combination), the data were insufficient for the Panel to classify any combination of an opiate and other active ingredients in Category I. No new data on such combinations were submittted to the FDA, and the agency concurs with the Panel's Category III classification of these combinations. Therefore, opiate ingredients are placed in Category III in this document and are not included in the tentative final monograph. However, if data are received to support any such opiate-containing combination in accordance with § 329.20(a)(1), opiates will be included in the final monograph. (See comment 22 below.)

21. One comment suggested that the requirement stated in § 329.20(a), that a narcotic-containing product also contain one or more nonnarcotic active medicinal ingredients, is not consistent with the Panel's recommended limitation of antidiarrheal combination products to two active ingredients at 40 FR 12932. The Comment proposed that § 329.20(a) be changed to read, "Provided that the preparations * * * contain one additional (but no more than one) nonnarcotic active medicinal ingredient," etc.

As discussed in comment 27 below, an antidiarrheal combination drug product may contain two or more active ingredients so long as it meets the agency's combination policy. Therefore, the inconsistency has been resolved without any need to modify § 329.20(a).

22. Two comments stated that the Panel's placement of paregoric, which contains six ingredients, in Category I as a single active ingredient is inconsistent and not in keeping with the OTC drug review concept of an ingredient by ingredient review. Citing § 329.20(a), one comment stated that an active ingredient in paregoric in addition to opium must be recognized in order for paregoric to be exempt from prescription status. However, to do so would mean placing paregoric in Category II because the other ingredient would not have been reviewed by the Panel. In addition, the comment stated that camphor should be deleted from the paregoric formula because the alternate name "camphorated tincture of opium" for paregoric implies that camphor at one time was thought to be an active ingredient in the paregoric formula. Therefore, according to the Panel, camphor cannot now be claimed as an inactive ingredient without proper documentation. Also, if camphor is considered inactive, the labeling of paregoric as "comphorated tincture of opium" would be illegal because inactive ingredients must not be emphasized or identified as active ingredients in the labeling or in the advertisement of such products.

The agency acknowledges that the Panel placed "camphorated tincture of opium" in parentheses after paregoric in its recommended monograph. However, the name "comphorated tincture of opium" has not been included in the official compendia since 1960 (USP XVI), and "paregoric" is the official compendial name. Therefore, "comphorated tincture of opium" as an alternate name for paregoric is not allowed, and the comment's argument regarding emphasizing an inactive ingredient in the labeling is moot.

Paregoric is an official article in the USP XXI and is a formulation of six ingredients—powdered opium, anise oil, benzoic acid, camphor, diluted alcohol, and glycerin (Ref. 1). However, only the powered opium is considered to be active as an antidiarrheal. Although the other ingredients when combined with powdered opium constitute what is recognized as paregoric, they do not contribute to the antidiarrheal effect of the product and are considered to be inactive ingredients. Therefore, paregoric is considered to be a single active ingredient formulation and when used alone is a prescription item (See 37 FR 6734; April 4, 1972). Although the Panel listed paregoric, tincture of opium, and powdered opium as allowable sources of opium, the Panel did not provide specific dosages for each individual preparation, but instead based the dosage on the opium component (40 FR 12943). As discussed in comment 20 above, opiate ingredients are not being included in the tentative final monograph. However, should combinations containing an opiate and other active ingredients be included in the final monograph, manufacturers may market their products in the formulation of their choice using any of the

allowable sources of opium (i.e., paregoric, tincture of opium, or powdered opium) provided that the dosage is equivalent to the opium dosage provided in the monograph.

Reference

(1) "The United States Pharmacopeia XXI—National Formulary XVI," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 787–788, 1985.

D. Comments on Antidiarrheal Combinations

23. One comment submitted three new clinical studies and two literature references on the effectiveness of kaolin and pectin in fixed combination for the treatment of acute nonspecific diarrhea (Refs. 1 through 5). The comment requested reclassification of kaolin and pectin in combination from Category III to Category I for the treatment of acute nonspecific diarrhea.

After evaluating all of the available data, the agency concludes that they are insufficient to reclassify kaolin and pectin, alone or in combination, in Category I for the treatment of acute nonspecific diarrhea.

The study by Portnoy seems to indicate some possible benefit in terms of a greater number of formed stools and a smaller number of liquid stools from either the kaolin-pectin combination or pectin alone (Ref. 1). However, because no data were submitted on frequency and consistency of stools prior to accession and randomization or on admission, it is impossible to establish and assess the baseline comparability of the study groups or otherwise statistically evaluate the study.

A study of 61 outpatients in Guadalajara, Mexico, showed virtually no difference in soft-stool frequency between the kaolin-pectin combination and placebo (Ref. 2). The study had relatively few patients (61 in 7 treatment groups) and cannot provide a definitive answer on effectiveness of kaolin and pectin either alone or in combination.

The third study, the United States multicenter study, is a double-blind, randomized, placebo-controlled study of a kaolin-pectin suspension in the treatment of acute nonspecific diarrhea (Ref. 3). The study showed a marginal increase in the frequency of formed stools and improved consistency of stools with the kaolin-pectin suspension compared to placebo, but showed no effect for these ingredients on overall stool frequency. In addition, the study failed to evaluate the ingredients kaolin and pectin separately; therefore, the study cannot be used to demonstrate that each ingredient makes a contribution to the claimed effect of the product.

The two literature references (Refs. 4 and 5) mentioned the use of the kaolin-pectin combination among other ingredients in the treatment of diarrhea, but they contained no specific information that would establish the effectiveness of the combination.

The agency's detailed comments and evaluations on the data are on file with the Dockets Management Branch (Ref. 6).[2]

References

(1) Portnoy, B.L. et al., "Antidiarrheal Agents in the Treatment of Acute Diarrhea in Children," *Journal of the American Medical Association,* 236:844–846, 1976.

(2) DuPont, H.L., "Comparison of the Effectiveness of Kaopectate Concentrate, Kaolin, Pectin, Lomotin® and Placebo in the Treatment of Non-Specific Diarrhea," unpublished study in Comment No. OB0064, Docket No. 78N–036D, Dockets Management Branch.

(3) Study #295 and 295A in Comment OBOO64, RPT, SUP004, and AMD004, Docket No. 78N–036D, Dockets Management Branch.

(4) DuPont, H.L., "Enterpathogenic Organisms—New Etiologic Agents and Concepts of Disease," *Medical Clinics of North America,* 62:945–960, 1978.

(5) DuPont, H.L., "Interventions in Diarrheas of Infants and Young Children," *Journal of the American Veterinary Medical Association,* 173:649–653, 1978.

(6) Letter from W.E. Gilbertson, FDA, to G.H. Ishler, The Upjohn Company, ANS LET002, Docket No. 78N–036D, Dockets Management Branch.

24. One comment requested reclassification of pectin as an antidiarrheal adjunct in a product in which it is used in combination with tincture of opium, which the Panel recommended as a Category I active ingredient. The comment contended that even though the Panel concluded that the effectiveness data are insufficient to classify pectin and a Category I antidiarrheal, it is a useful adjunct which used in combination with an ingredient such as tincure of opium. The comment cited a number of literature articles in support of its request (Ref. 1).

The General Guidelines of OTC Drug Combination Products (Ref. 2) state that an ingredient claimed to be a pharmacological adjuvant will be considered an active ingredient, and that such an ingredient may be included in addition to one or more principal active ingredients only if it meets the combination policy in all respects. None of the articles offers data to demonstrate that pectin makes a contribution to the product, a requirement of the OTC drug combination policy as specified in § 330.10(a)(4)(iv). Therefore, the combination will remain in Category III.

References

(1) Comment No. C00039, Docket No. 78N–036D, Dockets Management Branch.

(2) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D–0322, Dockets Management Branch.

25. Two comments suggested that morphine and codeine be considered as ingredients in Category I combination antidiarrheal drug products. One comment pointed out that the antidiarrheal action of opium is attributable to its morphine content and that the other ingredients in opium contribute insignificantly to any therapeutic effect. The second comment noted that, similar to morphine, codeine exhibits inhibitive effects on the small intestine and colon, but with fewer side effects (Ref. 1). The comment suggested that an antidiarrheal drug product combining codeine with another active ingredient, possibly kaolin, would be effective and safe for OTC use.

The agency is aware of the constipating effects of both morphine and codeine. However, no data on any drug product used for the treatment of acute, nonspecific diarrhea, containing either morphine or codeine, have been submitted to the Panel or the agency for review. Therefore, neither morphine nor codeine is included in the monograph at this time.

Reference

(1) Miller, J.W., and H.H. Anderson, "The Effect of N-Demethylation on Certain Pharmacologic Actions of Morphine, Codeine, and Meperidine in the Mouse," *Journal of Pharmacology and Experimental Therapeutics,* 112:191–196, 1954.

26. Two comments requested that a combination of polycarbophil and powdered opium, USP be classified in Category I. The comments pointed out that, although both ingredients were recommended as Category I as single ingredients, the Panel did not make any provision for combining them. The comments stated that such a combination is therapeutically rational because the powdered opium acts to inhibit the motility of the intestine and through this action prolongs the transit time of polycarbophil; the prolonged transit time would allow the polycarbophil to exert its maximum hydrosorptive effect.

The agency's General Guidelines for OTC Drug Combination Products (Ref. 1)

[2] Industry has responded to FDA's concern regarding the need for additional data and is in the process of conducting additional studies (Comment No. LET006, Docket No. 78N–036D, Dockets Management Branch).

permit combining two Category I active ingredients from the same therapeutic category that have different mechanisms of action if the combination meets the OTC combination policy in all respects and the combination is on a benefit-risk basis equal to or better than each of the active ingredients used alone at its therapeutic dose. However, no data to support the comment's rationale for the combination of polycarbophil and powdered opium, USP have been submitted to the Panel or to the agency. Data demonstrating the combination to be generally recognized as safe and effective must be submitted in order for it to be included in the monograph.

Reference

(1) "Food and Drug Administration General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D–0322, Dockets Management Branch.

27. Several comments objected to the Panel's Category II classification of all combination products containing more than two active ingredients. The comments contended that the Panel presented no scientific data to support limiting a product to two active ingredients. Others objected to this limit as being unnecessarily restrictive, arbitrary, and not in agreement with the OTC combination policy set forth in § 330.10(a)(4)(iv). One comment urged that combination products that contain more than two active ingredients, but do not contain a Category II ingredient, be reclassified as Category III so that they might be tested for safety and effectiveness.

The agency agrees with the comments that a fixed limit need not be set on the number of active ingredients an antidiarrheal drug product may contain. However, adequate justification must be presented for the inclusion of each active ingredient in a combination product. Both the General Guidelines for OTC Drug Combination Products (Ref. 1) and the regulations at § 330.10(a)(4)(iv) provide that an OTC drug product may combine two or more safe and effective active ingredients provided the product meets the combination policy in all respects.

Three of the combinations that the Panel placed in Category II are combinations of three active ingredients. Each of the ingredients was placed by the Panel in Category I or Category III as a single ingredient. The combinations are activated attapulgite, pectin, and hydrated alumina powder; kaolin, hydrated alumina powder, and pectin; and paregoric, pectin, and kaolin. The Panel determined that the ingredients in these products are safe, but concluded that adequate data were lacking to establish their effectiveness. The agency believes it reasonable to move these three combination products, which contain no Category II ingredients, from Category II to Category III. The revised procedures for classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730), provide for the submission of new data and information for up to 12 months after publication of a tentative final monograph to support any condition excluded from the proposal.

Reference

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978 Docket No. 78D–0322, Dockets Management Branch.

28. One comment noted that, although the Panel's report discussed criteria for antidiarrheal combinations, no provision was made in the recommended monograph for antidiarrheal combinations. The comment recommended that a new subsection for combinations of active antidiarrheal ingredients be established in the monograph.

The intended purpose of an OTC drug monograph is to set forth those specific conditions under which drugs that are subject to the monograph are generally recognized as safe and effective for OTC use and not misbranded. The Panel did not include any antidiarrheal combinations in its monograph because the data were insufficient for any of the combinations that were reviewed to be generally recognized as safe and effective. At this time, the agency concurs with the Panel's decision. Should data establishing the safety and effectiveness of any antidiarrheal combination be received in the comment and new data periods following publication of this tentative final monograph, the agency will state the conditions for such combination product(s) in the final monograph.

E. Comments on Data Pertinent to Antidiarrheal Ingredient Evaluation

29. Several comments objected to the Panel's recommended testing guidelines at 40 FR 12933 for establishing the safety and effectiveness of antidiarrheal ingredients. The comments contended that the testing guidelines do not provide adequate time to complete the required testing; the guidelines for antidiarrheals were apparently taken virtually verbatim from a similar provision for laxatives appearing elsewhere in the panel's report, and there is no basis for this apparent incorporation by reference; the guidelines do not adequately describe what test should be conducted or which data should be developed in order to move Category III ingredients to Category I; under the guidelines, manufacturers would not be allowed to use other well-controlled and well-designed studies to obtain necessary data; and many of the testing procedures listed in the guidelines require long-term use of antidiarrheal drug products to obtain the complete data required, thus contradicting the Panel's warning against use of antidiarrheal drug products for more than 2 days.

The agency has not addressed specific testing guidelines in this document. In revising the OTC drug review procedures relating to Category III, published in the **Federal Register** of September 29, 1981 (46 FR 47730), the agency advised that tentative final and final monographs will not include recommended testing guidelines for conditions that industry wishes to upgrade to monograph status. Instead, the agency will meet with industry representatives at their request to discuss testing protocols. The revised prodecures also state the time in which test data must be submitted for consideration in developing the final monograph. (See also part II. paragraph A. 2. below—*Testing of Category II and Category III conditions.*)

II. The Agency's Tentative Adoption of the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and has proposed the recategorization of attapulgite from Category III to Category I and opiate ingredients (in combination) from Category I and Category III for use as OTC antidiarrheal active ingredients. As a convenience to the reader, the following list is included as a summary of the categorization of antidiarrheal active ingredients recommended by the Panel and the proposed categorization by the agency.

Antidiarrheal active ingredients	Panel	Agency
Alumina powder, hydrated	III	III
Atropine sulfate	III	III
Attapulgite, activated	III	I
Bismuth subnitrate	III	III
Bismuth subsalicylate	III	III
Calcium carbonate precipitated	III	III
Calcium hydroxide	III	III
Calcium polycarbophil	N.C.[1]	I
Charcoal, activated	III	III
Glycine[2]	II	II
Homatropine methylbromide	III	III
Hyoscyamine sulfate	III	III

Antidiarrheal active ingredients	Panel	Agency
[1]Kaolin	III	III
Lactobacillus acidophilus	III	III
Lactobacillus bulgaricus	III	III
Opiate ingredients (for use in combination): [2]		
Opium power	I	III
Opium, tincture of	I	III
Paregoric	I	III
Pectin	III	III
Phenyl salicylate (salo)	III	III
Polycarbophil	I	I
Potassium carbonate	II	II
Rhubarb fluidextract	II	II
Scopolamine hydrobromide	II	II
Sodium carboxymethylcellulose	III	III
Zinc phenolsulfonate	III	III

[1] Not classified by Panel.
[2] Although "aminoacetic acid" was the name designated by the Panel for this ingredient, "glycine" is the official title for this ingredient in the "USAN and the USP dictionary of drug names, 1985."

2. *Testing of Category II and Category III conditions.* The agency's position regarding the Panel's testing guidelines is discussed in comment 29 above. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any antidiarrheal ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes in the Panel's Recommendations

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency follows.

1. Because of the number of changes that have been made, as summarized below, many of the section and paragraph numbers have been redesignated in this tentative final monograph. In addition, Subpart D has been redesignated as Subpart C, and the labeling sections are placed under Subpart C.

2. The following changes have been made to conform to the format and Content of other recent OTC drug tentative final monographs:

a. A "statement of identity" section has been added and identifies the product as an antidiarrheal.

b. The dosage information for each active ingredient has been moved to the directions section for the respective antidiarrheal ingredient.

c. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulation will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option.

3. The definitions for antidiarrheal and diarrhea have been revised. (See comment 7 above.)

4. The phrase "high fever" has been replaced with the word "fever" in the general warning for OTC antidiarrheals in § 335.50(c)(1). (See comment 8 above.)

5. The agency recognized that not all OTC antidiarrheals have the same effect and believes that consumers should be aware of the intended results from the use of the products. The agency has proposed expanded indications for use in the tentative final monograph accordingly. (See comment 10 above.)

6. The pediatric dosage for children 3 years of age and under for polycarbophil is proposed in the tentative final monograph under professional labeling only. (See comment 11 above.)

7. The agency has reclassified activated attapulgite from Category III to Category I. (See comment 15 above.)

8. Should bismuth subsalicylate be included in the final monograph, the agency will consider proposing that the directions for use be revised and additional warnings be included in the labeling. (See comment 17 above.)

9. In accordance with § 329.20(a)(1) opiate ingredients may be marketed for OTC use in combination only. Because no data have been submitted to support combinations of opiates and other active ingredients, opiates will not be included in the tentative final monograph. (See comment 20 above.)

10. The Panel recommended in its report that Category I antidiarrheal combination drug products be limited to two Category I active ingredients. The agency has determined that an OTC antidiarrheal drug product may combine two or more safe and effective active ingredients in accordance with the provisions set forth in § 330.10(a)(4)(iv) and the agency's General Guidelines for OTC Drug Combination Products. (See comment 27 above.)

11. The agency has revised the dosage for polycarbophil in the monograph to reflect the dosage used in studies submitted for evaluation. This dosage is also the same as that currently promoted on marketed products.

12. The sodium, potassium, and magnesium warnings have been deleted from the monograph because none of the active antidiarrheal drugs in the monograph contain these ingredients.

The agency proposes to revoke the existing warning statement in § 369.20 for diarrhea preparations at the time that this monograph becomes effective.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that not one of these rules, including this proposed rule for OTC antidiarrheal drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Public Law 96–354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC antidiarrheal drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC antidiarrheal drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC antidiarrheal drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on antidiarrheal drug products, a period of

120 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined that under 21 CFR 25.24(c)(6) (April 26, 1985; 50 FR 16636) 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.

Exclusivity of Labeling

In the **Federal Register** of April 22, 1985 (50 FR 15810) the agency proposed to change its "exclusivity" policy for the labeling of OTC drug products that has existed during the course of the OTC drug review. Under this policy, the agency has maintained that the terms that may be used in an OTC drug product's labeling are limited to those terms included in a final OTC drug monograph.

The proposed rule would establish three alternatives for stating the indications for use in OTC drug labeling while all other aspects of OTC drug labeling (i.e., statement of identity, warnings, and directions for use) would continue to be subject to the existing exclusivity policy. The proposed rule for OTC antidiarrheal drug products included in this document incorporates the exclusivity proposal by providing for the use of other truthful or nonmisleading statements in the product's labeling to describe the indications for use. After considering all comments submitted on the proposed revision to the exclusivity policy, the agency will announce its final decision on this matter in a future issue of the **Federal Register**. The final rule for OTC antidiarrheal drug products will incorporate the final decision on exclusivity of labeling.

Interested persons may, on or before June 30, 1986, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before August 28, 1986. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

Interested persons, on or before April 30, 1987, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before June 30, 1987. These dates are consistent with the time and periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on June 30, 1987. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects

21 CFR Part 335

Over-the-counter drugs, Antidiarrheal drug products.

21 CFR Part 369

Over-the-counter drugs, Warning and caution statements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act and under 21 CFR 5.11, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended as follows:

PART 335—ANTIDIARRHEAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. By adding new Part 335, to read as follows:

Subpart A—General Provisions

Subpart B—Active Ingredients

Subpart C—Labeling

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); 5 U.S.C. 553; 21 CFR 5.11.

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.

(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 excretion 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 of the following when used within the dosage limits established for each ingredient in § 335.50(d):

(a) Attapulgite, activated.

(b) Calcium polycarbophil.

(c) Polycarbophil.

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 products as an "antidiarrheal."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in this paragraph, as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed below, may also be used, as provided in § 330.1(c)(2), subject to the provisions of section 502 of 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 attapulgite, activated, identified in § 335.10(a).* (i) "Reduces the number of bowel movements in diarrhea."

(ii) "Improves consistency of loose, watery bowel movements in diarrhea."

(iii) "Relieves cramps in diarrhea." This indication is permitted only in addition to one or both of the indications identified in § 335.50(b)(1)(i) or (ii).

(2) *For products containing calcium polycarbophil or polycarbophil identified in § 335.10 (b) or (c).* (i) "Reduces the number of bowel movements in diarrhea."

(ii) "Improves consistency of loose, watery bowel movements in diarrhea."

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

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

(1) *For products containing attapulgite, activated identified in § 335.10(a).* Adults and children 12 years of age and over: oral dosage is 1,200 milligrams after initial bowel movement, 1,200 milligrams after each subsequent bowel movement, not to exceed 8,400 milligrams in 24 hours. Children 6 to under 12 years of age: oral dosage is 600 milligrams after initial bowel movement, 600 milligrams after each subsequent bowel movement, not to exceed 4,200 milligrams in 24 hours. Children 3 to under 6 years of age: oral dosage is 300 milligrams after initial bowel movement, 300 milligrams after each subsequent bowel movement, not to exceed 2,100 milligrams in 24 hours. Children under 3 years of age: consult a doctor.

(2) *For products containing calcium polycarbophil or polycarbophil identified in § 335.10 (b) or (c).* Dosages are based on the polycarbophil equivalent. Adults and children 12 years of age and over: oral daily dosage is 1 gram 4 times a day or 2 grams 3 times a day or as needed, not to exceed 6 grams in 24 hours. Children 6 to under 12 years of age: oral daily dosage is 0.5 to 1 gram 3 times a day or as needed, not to exceed 3 grams in 24 hours. Children 3 to under 6 years of age: oral daily dosage is 0.33 to 0.5 grams 3 times a day or as needed, not to exceed 1.5 grams in 24 hours. Children under 3 years of age: consult a doctor.

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

§ 335.80 Professional labeling.

The labeling provided to health professionals (but not to the general public) may contain the following additional dosage information for products containing the active ingredient identified below:

For products containing calcium polycarbophil or polycarbophil identified in § 335.10 (b) or (c). Dosages are based on the polycarbophil equivalent. Children under 3 years of age: oral daily dosage is 166.6 milligrams to 333.3 milligrams 3 times a day or as needed, not to exceed 1 gram in 24 hours.

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

2. The authority citation for Part 369 continues to read as follows:

Authority: Secs. 502, 503, 506, 507, 701, 52 Stat. 1050 as amended, 1052 as amended, 53 Stat. 854, 55 Stat. 851, 59 Stat. 463 as amended, 52 Stat. 1055 as amended (21 U.S.C. 352, 353, 356, 357, 371); 21 CFR 5.11.

3. In § 369.20 *Drugs; recommended warning and caution statements,* by removing the entry for "Diarrhea Preparations."

Frank E. Young,

Commissioner of Food and Drugs.

Dated: April 1, 1986.

Otis R. Bowen,

Secretary of Health and Human Services.

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