DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 81N–0106]

RIN 0905–AA06

Digestive Aid Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that activated charcoal and certain other digestive aid ingredients for over-the-counter (OTC) human use are not generally recognized as safe and effective and are misbranded. 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, and all new data and information on OTC digestive aid drug products that have come to the agency's attention. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: April 21, 1994.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–295–8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of January 5, 1982 (47 FR 454), 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 digestive aid drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by April 5, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by May 5, 1982.

In a document that published in the **Federal Register** on March 30, 1982 (47 FR 13385), the agency advised that it had extended the comment period until June 4, 1982, and the reply comment period to July 5, 1982, on the advance notice of proposed rulemaking for OTC digestive aid drug products to allow for consideration of additional data and information.

In accordance with § 330.10(a)(10), the data and information considered by the Panel, after deletion of a small amount of trade secret information, were placed on display in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC digestive aid drug products was published in the **Federal Register** of January 29, 1988 (53 FR 2706). Interested persons were invited to file by March 29, 1988, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by May 31, 1988. New data could have been submitted until January 30, 1989, and comments on the new data until March 29, 1989.

In a document that published in the **Federal Register** on April 19, 1988 (53 FR 12779), the agency advised that it had extended the comment period until May 27, 1988, to allow adequate time for one manufacturer to fully evaluate information it had recently received from the agency and to prepare comments to the notice of proposed rulemaking.

In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency published a final rule establishing that certain active ingredients that had been under consideration in a number of OTC drug rulemaking proceedings were not generally recognized as safe and effective. That final rule was effective on May 7, 1991, and included in § 310.545(a)(8) (21 CFR 310.545(a)(8)) 21 ingredients that had been under consideration as part of this rulemaking for OTC digestive aid drug products.

In the **Federal Register** of May 10, 1993 (58 FR 27636), the agency published a final rule establishing that certain additional active ingredients that had been under consideration in a number of OTC drug rulemaking proceedings were not generally recognized as safe and effective. That final rule is effective on November 10, 1993, and included in § 310.545(a)(8)(ii) 83 additional ingredients that had been under consideration as part of this rulemaking for OTC digestive aid drug products.

After these two final rules were published, only two ingredients remained to be evaluated in this rulemaking: Activated charcoal and lactase enzyme. The agency's action in this document completes the OTC digestive aids rulemaking with respect to activated charcoal. In this final rule, the agency is adding new paragraph (a)(8)(iii) to § 310.545 to establish that activated charcoal is not generally recognized as safe and effective and is misbranded when present in OTC digestive aid drug products. The agency will publish its final decision on the status of lactase enzyme in OTC digestive aid drug products in a future issue of the **Federal Register**.

The agency stated in the tentative final monograph (53 FR 2706 at 2709) that at that time no submissions had been made to the agency regarding lactase enzyme products, nor was the agency aware of any specific data that would establish general recognition of safety and effectiveness for this ingredient. The agency acknowledged that lactase enzyme is contained in a number of marketed products and is promoted for use as a digestive aid for persons who are intolerant to lactose-containing foods. Although lactase deficiency can be controlled by ingestion of a lactose-free diet, the agency stated that lactase enzyme products could be potentially useful for those persons who do not wish to avoid lactose in their diets. Therefore, the agency invited interested persons to submit specific data and information regarding the use of lactase enzyme products.

In response to the proposed rule, two manufacturers submitted the results of several new studies to demonstrate the effectiveness of lactase enzyme derived from *Aspergillus oryzae* and *A. niger*. The agency is currently reviewing these studies and is awaiting additional information from both manufacturers. Accordingly, in order to complete this rulemaking with regard to all other conditions except lactase enzyme, the agency is not addressing the data submitted on lactase enzyme at this time. Those data will be addressed as soon as the agency's review is completed. If the data support the safety and effectiveness of lactase enzyme, the agency will propose to establish a monograph for OTC digestive aid drug products at that time. Appropriate labeling will be proposed based on the results of the studies being evaluated. In the interim, products containing lactase enzyme may remain in the marketplace and are not subject to this final rule.

In the tentative final monograph for OTC digestive aid drug products (53 FR 2706), the agency did not propose any active ingredient as generally recognized as safe and effective and not misbranded. However, the agency proposed monograph labeling in the

event that data were submitted that resulted in the upgrading of any ingredient to monograph status. In this final rule, no active ingredient has been determined to be generally recognized as safe and effective for use in OTC digestive aid drug products. As noted above, the monograph status of lactase enzyme is still under evaluation. Therefore, proposed subpart D of part 357 (21 CFR part 357) for OTC digestive aid drug products is being held in abeyance until the agency's review of lactase enzyme is completed.

This final rule declares OTC digestive aid drug products containing the active ingredient activated charcoal to be new drugs under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 321(p)), for which an application or abbreviated application (hereinafter called application) approved under section 505 of the Act (21 U.S.C. 355) and 21 CFR part 314 is required for marketing. In the absence of an approved application, products containing activated charcoal for this use also would be misbranded under section 502 of the Act (21 U.S.C. 352). In appropriate circumstances, a citizen petition to establish a monograph may be submitted under § 10.30 (21 CFR 10.30) in lieu of an application.

The OTC drug procedural regulations (§ 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 does not 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. In place of Category I, the term "monograph conditions" is used; in place of Categories II or III, the term "nonmonograph conditions" is used.

In the proposed rule for OTC digestive aid drug products (53 FR 2706), the agency advised that it would provide a period of 12 months after the date of publication of the final monograph in the **Federal Register** for relabeling and reformulation of digestive aid drug products to be in compliance with the monograph. Although data and information were submitted on activated charcoal in response to the proposed rule, they were not sufficient to support monograph conditions, and no monograph is being established at this time. Therefore, digestive aid drug products that are subject to this rule are not generally recognized as safe and effective and are misbranded (nonmonograph conditions). In the advance notice of proposed rulemaking (47 FR 454 at 455), the agency advised that conditions for OTC digestive aid drug products that are not generally recognized as safe and effective and are misbranded would be effective 6 months after the date of publication of a final rule in the **Federal Register**. Because no OTC drug monograph is being established for this class of drug products, the agency is adopting this 6-month effective date for the nonmonograph conditions in this final rule. This 6-month effective date is also consistent with the effective dates for the other digestive aid active ingredients included in § 310.545(a)(8). Therefore, on or after April 21, 1994, no OTC drug products that are subject to this final rule may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved application.

In response to the proposed rule on OTC digestive aid drug products, two drug manufacturers and three physicians submitted comments on activated charcoal, and four drug manufacturers submitted comments on lactase enzyme. A request for an oral hearing before the Commissioner of Food and Drugs was received on one issue. Copies of the comments and the hearing request received are on public display in the Dockets Management Branch (address above). Any additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

The hearing request is discussed in comment 1. (see section I.A. of this document). In proceeding with this final rule, the agency has considered all objections, requests for oral hearing, and the changes in the procedural regulations. A summary of the comments and the new data with FDA's responses to them follows.

I. The Agency's Conclusions on the Comments

A. Comments on Activated Charcoal

1. Two comments submitted data (Refs. 1 through 6) to support the use of activated charcoal for the treatment of intestinal distress related to gas. The comments requested that activated charcoal be included in either the monograph for OTC antiflatulent or OTC digestive aid drug products. One comment requested an oral hearing regarding inclusion of activated charcoal in the OTC antiflatulent monograph if it was found to be a Category I ingredient in the OTC digestive aid monograph. Two other comments argued that activated charcoal was an antiflatulent ingredient and objected to its inclusion in the OTC digestive aid monograph.

The agency has reviewed the data and concludes that they are insufficient to support the use of activated charcoal for the treatment of intestinal distress related to gas. Accordingly, activated charcoal will not be included in either monograph, and a hearing is not necessary.

Jain et al. (Ref. 1) conducted a randomized, placebo-controlled, double-blind, crossover study in which the effect of activated charcoal in reducing gas in the lower intestinal tract was evaluated by measuring breath hydrogen levels. Sixty-nine healthy adults in India and 30 in the United States participated in the study. Serial end-expiratory breath samples were collected at 30-minute intervals from each subject for 4½ hours. A dose of 1,040 milligrams (mg) of activated charcoal or placebo was administered after the first sample was collected and again 1 hour later. Lactulose, the substrate used to produce hydrogen in the colon, was administered ½ hour after the first dose. Symptoms of bloating, abdominal cramps, and diarrhea were recorded for 4 hours. The investigators reported that activated charcoal compared to placebo significantly ($p < 0.05$) reduced breath hydrogen levels and provided symptomatic relief (reduced symptoms of bloating, abdominal cramps, and diarrhea). One design problem with this study was that activated charcoal was given before the lactulose (the substance used to produce the hydrogen).

In a triple-crossover, double-blind, placebo-controlled study (Ref. 2), Jain et al. evaluated the effects of activated charcoal, placebo, and simethicone in reducing gas in the colon as measured by breath hydrogen levels in 10 healthy subjects. Results were provided for nine subjects; one subject was excluded due to failure to produce hydrogen gas. The study design was similar to that used in the first Jain et al. study (Ref. 1), except that 8 ounces (oz) of baked beans were used as the gas-producing substrate and serial breath samples were collected at 30-minute intervals for 7 hours. The beans were eaten 30 minutes after the first doses of either activated charcoal, simethicone, or placebo. Simethicone was administered at a dose of 80 mg and

activated charcoal at 1,040 mg, with repeat doses given after 1 hour. The investigators reported that only activated charcoal significantly ($p < 0.05$) reduced breath hydrogen levels and reduced abdominal symptoms (bloating and abdominal discomfort).

In a placebo-controlled, crossover study (Ref. 3), Vargo, Ozick, and Floch evaluated the effect of activated charcoal on breath hydrogen levels in 12 subjects after a bean meal using a design and dosage similar to the Jain studies. A statistically significant reduction ($p < 0.05$) in breath hydrogen levels was found only at the 7-hour (420-minute) collection period. Further, this study only measured breath hydrogen; symptoms of gas were not evaluated.

Hall, Thompson, and Strother (Ref. 4) evaluated the effects of activated charcoal on breath hydrogen levels and the number of flatus events in a randomized, double-blind, placebo-controlled, crossover study. Baseline data were collected on the number of times flatus was passed each hour for 7 hours following administration of a normal meal (containing no known gas-forming items). Each of the 13 subjects in this part of the study also had a bean meal on two separate occasions (with a period of at least 2 days between bean meals) and recorded flatus events after each bean meal. The subjects received either 582 mg of activated charcoal or placebo administered immediately after the bean meal and 2 hours later. In an additional test to determine the effectiveness of a smaller dose, seven subjects were given 388 mg of activated charcoal only at 2 hours after the meal. In the breath hydrogen portion of the study, 10 subjects were fed a normal meal and 10 subjects were fed a bean meal. The subjects fed the normal meal were not treated. The subjects receiving the bean meal were treated with either 582 mg of activated charcoal or placebo immediately after the meal and every 30 minutes thereafter for a total of five doses (2,910 mg of activated charcoal).

The mean number of flatus events per subject was almost three following the normal meal and 14.5 following the bean meal. When the bean meal was followed by activated charcoal, the mean number of flatus events decreased to less than three ($p < 0.001$ compared to placebo). In the additional study involving 388 mg of activated charcoal, the mean number of flatus events during the first 3 hours after the meal was greater compared to the subjects who received 582 mg. However, there was no significant difference between the two groups in the number of flatus events during the last 4 hours of observation. The authors explained this lack of difference on normal transit time to the colon (2 to 3 hours) and stated that once activated charcoal reaches the colon, the lower dose is also effective in reducing flatus events. In the breath hydrogen portion of the study, the mean breath hydrogen concentrations were similar for 4 hours following the normal meal and the bean meal followed by placebo. Thereafter, the concentrations increased threefold for the next 4 hours. Concentrations following the bean meal and activated charcoal remained low throughout the study and after the 4th hour were significantly different ($p < 0.001$) compared to the bean meal-placebo group.

In another study (Ref. 5), Potter et al. used in vitro and in vivo methods to evaluate the ability of activated charcoal to reduce intestinal gas production. The in vivo evaluation involved a double-blind study that measured breath hydrogen levels and flatus events of 10 healthy subjects. Each subject was studied on four occasions, twice with placebo and twice with activated charcoal. Subjects were fed a bean meal followed by 1,000 mg of activated charcoal or placebo. Doses were repeated every 30 minutes for a total of four doses. Breath hydrogen levels were obtained at time zero and every hour for 9 hours. Subjects also recorded the number of times they passed flatus. The investigators reported no significant differences in breath hydrogen levels or the number of flatus events between the treatment and placebo groups. The investigators concluded that activated charcoal does not reduce the volume of bowel gas.

Riggs (Ref. 6) reported the results of a study involving a pretest and test meal. Fifty-three subjects ate a gas-producing pretest meal and took two placebo capsules upon onset of symptoms. Subjects were dropped from the study if they did not develop symptoms within 1 hour or if they developed symptoms but responded to the placebo medication. Subsequently, 42 subjects were given a test meal (identical to the pretest meal). At the onset of symptoms, subjects were randomized to receive activated charcoal or placebo in a blinded fashion. One subject was dropped for not having symptoms after consuming the test meal. Twenty-one subjects received activated charcoal, and 20 subjects received placebo. Every 30 minutes the subject could take an additional dose, up to a maximum of four doses. The subjects rated the degree of overall symptom relief as none, poor, fair, good, or excellent. Riggs reported that 71 percent of the subjects who took activated charcoal rated their relief (of pain and/or cramping and overall symptom relief) "as good to excellent," as compared to only 35 percent who took placebo. Riggs noted, however, that several factors (the time to complete relief, the percentage of subjects with complete relief within 2 hours, and the duration of flatulence) did not demonstrate a statistically significant difference. Riggs stated that these factors did show a "trend" favoring activated charcoal, particularly when only those subjects that had a significant history of symptoms were considered.

The agency concludes that these studies do not provide sufficient evidence to establish that activated charcoal can be generally recognized as safe and effective for use as an OTC antiflatulent or digestive aid. The majority of the studies (Refs. 1 through 5) are not presented in sufficient detail for an indepth agency review. The statistical significance of the findings cannot be verified because of the absence of individual subject data, which have never been provided. Further, the subjects used were inappropriate in most studies. The agency considers it necessary that studies be conducted in a population where all subjects have the condition in question, rather than relying entirely on volunteers in which the condition may or may not occur. Riggs (Ref. 6) was the only investigator that used subjects with a history of meal-induced gastrointestinal discomfort. Although Riggs used the correct type of subjects, the sample size was too small to demonstrate a clinically important difference.

Regarding this sample size, the comment stated that a sample size of 21 subjects in each group provides 90-percent power for detecting a clinically important difference. However, the agency maintains that to obtain a 90-percent power at a 0.05 level (two-sided), the sample size should be approximately 80 subjects per group. If the number were doubled as a precaution, as stated in the protocol, the final sample size would be 160 subjects per group. The study included 21 subjects in the activated charcoal group and 20 subjects in the placebo group.

The study (without invoking considerations of interim analyses and multiple comparisons) was negative for its primary prestated endpoints. While numerically these results are in the right direction, the study was too small to be definitive. Issues such as interim analyses, multiple comparisons, and unspecified subsetting must be considered. With those considerations, the findings in the Riggs study at best might help plan additional studies;

however, they do not change the outcome of this negative trial.

Finally, additional data are needed to establish the dosage range, dosage interval, or dosage duration. In addition, data would be needed to establish whether subsequent dosing is needed because colon gas will eventually dissipate without treatment. Because the submitted data are inadequate to establish the effectiveness of activated charcoal for the relief of symptoms of intestinal distress related to gas, activated charcoal is not a monograph ingredient.

The agency's detailed comments and evaluation of the above data are on file in the Dockets Management Branch (Refs. 7, 8, and 9).

References

(1) Jain, N.K. et al., "Efficacy of Activated Charcoal in Reducing Intestinal Gas: A Double-Blind Clinical Trial," *American Journal of Gastroenterology*, 81:532–535, 1986.

(2) Jain, N.K., V.P. Patel, and C. Pitchumoni, "Activated Charcoal, Simethicone, and Intestinal Gas: A Double-Blind Study," *Annals of Internal Medicine*, 105:61–62, 1986.

(3) Vargo, D., L. Ozick, and M.H. Floch, "The Effect of Activated Charcoal on Breath H_2 Concentration in Subjects With Low and High Baseline H_2 Production," Comment No. CP1, Docket No. 81N–0106, Dockets Management Branch.

(4) Hall, R.G., H. Thompson, and A. Strother, "Effects of Orally Administered Activated Charcoal on Intestinal Gas," *The American College of Gastroenterology*, 75:192–196, 1981.

(5) Potter, T., C. Ellis, and M. Levitt, "Activated Charcoal: In Vivo and In Vitro Studies of Effect on Gas Formation," *Gastroenterology*, 88:620–624, 1985.

(6) Riggs, M.W., "Activated Charcoal Study, Final Report," copy included in Comment No. CP2, Docket No. 81N–0106, Dockets Management Branch.

(7) Letter from W.E. Gilbertson, FDA, to J. Geils, Requa, Inc., Coded LET1, Docket No. 81N–0106, Dockets Management Branch.

(8) Letter from W.E. Gilbertson, FDA, to J. L. Geils, Requa Inc., Coded LET5, Docket No. 81N–0106, Dockets Management Branch.

(9) Letter from W.E. Gilbertson, FDA, to W.R. Weaver, Gulf Bio-Systems, Inc., Coded ANS1, Docket No. 81N–0106, Dockets Management Branch.

2. Two comments stated that activated charcoal could be placed in either the digestive aid monograph or the antiflatulent monograph because the indications for ingredients covered by both monographs are strikingly similar. One of the comments stated that there is very little difference between the indications proposed in the digestive aid tentative final monograph (i.e., "for relief of symptoms of gastrointestinal distress such as * * * fullness, pressure, bloating, or stuffed feeling," (optional: "commonly referred to as gas,") (optional: "pain," and/or "cramping,") "which occur(s) after eating,") (53 FR 2706 at 2713)) and the indications proposed in the amendment to the antiflatulent final monograph (i.e., "alleviates" or "relieves" * * * "bloating," "pressure," "fullness," or "stuffed feeling" "commonly referred to as gas," (53 FR 2716 at 2717)). The comment stated that the only apparent difference is that the digestive aid indication associates the symptoms of gas with the consumption of food, whereas the antiflatulent indication does not. The comment contended that this approach does not make scientific sense because the symptoms of gaseousness are almost always associated with the ingestion of a symptom-provoking meal. The comment argued that consumers will become confused because antiflatulent drug products are able to use the term "antigas" and digestive aid products cannot, even though "antigas" may be the best term to describe the symptomatic relief provided by activated charcoal. The comment requested that FDA allow the term "antigas" as an alternative statement of identity to "digestive aid" because "antigas" is the most accurate and recognizable term describing the symptomatic relief provided by activated charcoal.

The agency has considered activated charcoal in both the antiflatulent and the digestive aid drug products rulemakings. The data submitted to both rulemakings were found to be insufficient to classify activated charcoal as a monograph ingredient for either of these uses. Accordingly, because activated charcoal is not being included in either monograph, the agency does not need to address the statement of identity for this ingredient. Should activated charcoal achieve monograph status in the future, the agency will address its statement of identity at that time.

B. Comments on Testing Digestive Aid Ingredients

3. Two comments stated that FDA should provide clinical protocol design criteria appropriate for OTC digestive aid drug products. The first comment stated that the agency had greatly modified the approach recommended by the Panel for the digestive aid drug category. The comment was concerned that the agency had not published alternative guidelines to clarify how a sponsor should go about investigations to obtain Category I labeling claims.

The second comment stated that if the agency wanted to be helpful in this area it should clearly articulate protocol standards and criteria that can be commented upon, revised if necessary, and then followed. The comment expressed dissatisfaction with certain testing criteria provided at the March 8, 1988, meeting (Ref. 1). The comment felt that the criteria were not applicable to OTC drug products designed to provide symptomatic relief for self-limiting conditions, but rather were applicable to "new drugs" designed to treat serious, chronic, and organic disease. The comment stated that the public and the industry are unaware, as a whole, of what testing criteria are or are not acceptable. The comment argued that if the agency does not know or cannot articulate what label claims it will permit or the protocol criteria it would require to gain Category I status as a digestive aid, it is quite clearly preventing the industry from ever achieving this goal. The comment requested that the agency waive its general policy of not publishing testing guidelines in tentative final monographs and officially state and notify the public, through a written guideline in a revision to the digestive aid tentative final monograph, as to its proposed protocol design criteria to obtain Category I status for OTC digestive aid ingredients.

The Panel provided fairly extensive testing guidelines in its report on OTC digestive aid drug products (47 FR 454 at 485 through 486). The Panel recognized that a generally accepted protocol for the testing of drug products used for the treatment of symptoms of intestinal distress was not available. Further, because of the several categories of drugs marketed for the relief of these symptoms and the different mechanisms of these drugs, the Panel realized that it was unlikely that a single protocol, which would be appropriate for all of these drugs, could be developed. The Panel did not attempt to produce such a protocol. However, the Panel believed that there were important issues that must be considered to ensure proper evaluation of these drugs, and it developed guidelines to aid investigators in designing effectiveness tests. The Panel suggested that deviations from these guidelines be discussed with the appropriate FDA personnel prior to initiation of a study.

The agency did not address testing guidelines in its proposed rule on OTC digestive aid drug products (53 FR 2706 at 2712) and is not providing specific testing guidelines in this document. In revising the OTC drug review

procedures relating to Category III ingredients, published in the **Federal Register** of September 29, 1981 (46 FR 47730), the agency announced its policy that tentative final and final monographs will not include recommended testing guidelines for conditions that industry wishes to upgrade to monograph status. In the same issue of the **Federal Register** (46 FR 47740), the agency published a policy statement concerning the submission and review of protocols to evaluate an ingredient or condition in the OTC drug review. The agency has stated that it will meet with manufacturers, at their request, to discuss protocols and other testing issues involving conditions that industry is interested in upgrading and to advise industry on the adequacy of proposed testing protocols.

The March 8, 1988, meeting (Ref. 1) referred to by the comment involved a discussion of clinical data submitted to establish the effectiveness of an ingredient for OTC digestive aid or antiflatulent use. The agency's view was that the data were insufficient to justify the dosage range, interval, or duration and the indications requested by the comment. The meeting included a discussion of the patient population to be used in any future studies. The data from the studies and the agency's minutes of this meeting are included as part of the public administrative file for this rulemaking and can be obtained by any interested manufacturer who wishes to ascertain the agency's views. Based on this open public record and the agency's willingness to review testing protocols, the agency sees no need to develop protocol design criteria through notice and comment rulemaking.

Reference

(1) Comment No. MM1, Docket No. 81N–0106, Dockets Management Branch.

C. Comments on Labeling

3. Several comments discussed proposed labeling for OTC digestive aid drug products. Because no active ingredients have been classified as a monograph condition in this final rule for OTC digestive aid drug products, the agency is not addressing the comments' requests at this time. In the future, should a monograph be established for this class of OTC drug products, the agency will consider labeling recommendations, such as those made by the comments, at that time.

II. The Agency's Final Conclusions on OTC Digestive Aid Drug Products

At this time, the agency has determined that no active ingredient has been found to be generally recognized as safe and effective and not misbranded for use as an OTC digestive aid.

In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency published a final rule establishing that 21 active ingredients for OTC digestive aid use were not generally recognized as safe and effective. That final rule was effective on May 7, 1991, and listed 21 ingredients in § 310.545(a)(8) (currently designated as § 310.545(a)(8)(i)). In the **Federal Register** of May 10, 1993 (58 FR 27636), the agency published a final rule establishing that 83 additional active ingredients for OTC digestive aid use were not generally recognized as safe and effective. That final rule is effective on November 10, 1993, and lists the 83 ingredients in paragraph (a)(8)(ii). In this final rule, the agency is adding new paragraph (a)(8)(iii) to § 310.545 to include activated charcoal. This final rule expands the list of nonmonograph ingredients and establishes that any OTC digestive aid drug product containing activated charcoal is not generally recognized as safe and effective. Therefore, activated charcoal, when labeled, represented, or promoted for OTC use as a digestive aid, is considered nonmonograph and misbranded under section 502 of the act and is a new drug under section 201(p) of the act, for which an approved application under section 505 of the act and 21 CFR part 314 of the regulations is required for marketing. In appropriate circumstances, a citizen petition to establish a monograph may be submitted under § 10.30 in lieu of an application. In conclusion, any OTC digestive aid drug product containing any of the 105 ingredients listed in § 310.545(a)(8) that is initially introduced or initially delivered for introduction into interstate commerce after the applicable effective date in this paragraph is subject to regulatory action.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (53 FR 2706 at 2713). The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published 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 no one of these rules, including this final rule for OTC digestive aid drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 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 digestive aid drug products is not expected to pose such an impact on small businesses. As noted above, two earlier final rules established that a total of 104 active ingredients used in OTC digestive aid drug products were nonmonograph ingredients. This final rule covers one additional ingredient: Activated charcoal. The agency is aware of only a few products that contain this for OTC digestive aid use. Based on the limited number of affected products, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

The agency has determined under 21 CFR 25.24(c)(6) 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.

List of Subjects in 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, 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 310 is amended as follows:

PART 310—NEW DRUGS

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

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 376); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. Section 310.545 is amended by adding paragraph (a)(8)(iii); by adding and reserving paragraphs (d)(16) through (d)(20); by adding paragraph (d)(21); and by revising the introductory text of paragraph (d) to read as follows:

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

(a) * * *

(8) * * *

(iii) Charcoal, activated

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(21) of this section.

* * * * *

(21) April 21, 1994, for products subject to paragraph (a)(8)(iii) of this section.

Dated: September 3, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 93-25841 Filed 10-20-93; 8:45 am]

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