

21 CFR PART 332**[DOCKET NO. 87N-0053]****RIN 0910-AA01****Antiflatulent Drug Products for Over-the-Counter Human use; Amendment of Monograph****AGENCY:** Food and Drug Administration, HHS.**ACTION:** Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule amending the monograph for over-the-counter (OTC) antiflatulent drug products by adding a statement of identity section to conform to the format of other OTC drug final monographs and by revising the indications to include additional descriptive terms, and by adding a definition for the term "antigas." FDA is issuing this final rule after considering public comments on the agency's proposed regulation and all new data and information on OTC antiflatulent 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.

DATES: Effective March 5, 1997; written comments by June 3, 1996.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-105), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2304.

SUPPLEMENTARY INFORMATION:**I. Background**

In the Federal Register of June 4, 1974 (39 FR 19862), FDA issued a final monograph for OTC antiflatulent drug products (21 CFR part 332) that established conditions under which these drug products are generally recognized as safe and effective and not misbranded.

In the Federal Register of January 29, 1988 (53 FR 2716), the agency published a proposed amendment of the monograph for OTC antiflatulent drug products to add a statement of identity section to conform to the format of other OTC drug final monographs and to revise the indications for use to include additional descriptive terms describing the symptoms that are commonly referred to as "gas." The proposed statement of identity was "antiflatulent," "antigas," or "antiflatulent (antigas)." FDA issued that proposal after considering the report and recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products

(the Miscellaneous Internal Panel) and public comments on the advance notice of proposed rulemaking for OTC digestive aid drug products (47 FR 454, January 5, 1982), that was based on those recommendations. Interested persons were invited to submit comments, objections, or requests for oral hearing by March 29, 1988.

In the Federal Register of April 19, 1988 (53 FR 12778 and 12779), the agency extended the comment period from March 29, 1988, until May 27, 1988, to allow adequate time for one manufacturer to fully evaluate information it had received from the agency and to prepare comments to the notices of proposed rulemaking for OTC antiflatulent drug products and OTC digestive aid drug products.

In response to the proposed monograph amendment, three drug manufacturers and three physicians submitted comments. One comment requested an oral hearing before the Commissioner of Food and Drugs. That request concerned the inclusion of activated charcoal in the OTC antiflatulent monograph if the ingredient was found to be Category I in the OTC digestive aid monograph. The agency addressed the hearing request in comment 1 of the final rule for OTC digestive aid drug products (58 FR 54450 at 54451, October 21, 1993), and concluded that activated charcoal will not be included in either monograph, and a hearing is not necessary. Copies of the comments and the hearing request received are on public display in the Dockets Management Branch (H.A.-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23 Rockville, MD 20857, and may be seen between 9 a.m. and 4 p.m., Monday through Friday. 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.

In proceeding with this final rule, the agency has considered all comments, objections, and the request for oral hearing. A summary of the comments and the new data with FDA's responses to them follows.

II. Summary of the Comments Received

1. One comment agreed with the agency's use of the term "antigas" as interchangeable with "antiflatulent." The comment expressed concern, however, that the agency was prohibiting other terminology, e.g., "antigas formulation relieves gas trapped in the intestine" or "for gas pain." The comment stated that the basis for the agency's labeling restriction appeared to be recommendations of the

Miscellaneous Internal Panel (47 FR 454), which were at variance with the findings of the Advisory Review Panel on OTC Antacid Drug Products (38 FR 8714, April 5, 1973) (the Antacid Panel) that recognized the cause of "bloating," "pressure," and "fullness" as being the result of gas. The comment cited the Antacid Panel's recommended indication "alleviate or relieve the symptoms of gas" for simethicone-containing products as support for its position that excess gas causes discomfort. The comment also cited the double-blind, placebo-controlled clinical study by McDonald, O'Leary, and Stratton (Ref. 1) as demonstrating that dosing with simethicone results in a reduction of gastrointestinal foam. Finally, the comment stated that terms such as "relieves gas trapped in the intestine," "for gas pain," and "relieves the symptoms of gas" should not be prohibited under the antiflatulent final monograph because consumers use these terms. The comment referred, specifically, to the consumer survey discussed in the proposed amendment (53 FR 2716) and indicated that the terms "bloating," "pressure," "stuffed feeling," and "fullness" are very meaningful to and used by consumers to describe "gas." The comment concluded by stating it is unclear whether the existing indication in § 332.30(a), "to alleviate or relieve the symptoms of gas," is still permitted because the proposal appears to omit this indication.

The agency is no longer including the indication "to alleviate or relieve the symptoms of gas" in the antiflatulent monograph. As explained in the proposal to amend the antiflatulent monograph (53 FR 2716), the agency modified the wording of this indication to ("alleviates" or "relieves") "the symptoms referred to as gas." The agency also recognized that consumers use the terms "bloating, pressure, fullness," "or" "stuffed feeling" "to refer to gas and provided an additional indication statement that includes these terms: ("alleviates" or "relieves") ("bloating, pressure, fullness, or stuffed feeling) commonly referred to as gas."

The agency disagrees with the comment's statement that the Antacid Panel recognized the cause of "bloating," "pressure," and "fullness" as being the result of gas. The Antacid Panel stated that claims or indications such as "full feeling" or "gas" encourage the user to draw conclusions as to the cause of such symptoms, "a conclusion that even the medical profession is incapable of drawing at this time," and placed claims such as "full feeling" or "gas" in Category III (38

FR 8714 at 8722 to 8723). Further, while these symptoms describe discomfort, as noted by the Antacid Panel, the Panel did not include "pain" as one of the symptoms of gas (38 FR 8722 to 8723).

In the proposal to amend the antifatulent monograph, the agency also stated that phrases such as "antigas formulation relieves gas trapped in the intestine" and "for gas pain" would be considered inappropriate (53 FR 2716). The agency reviewed the study by McDonald, O'Leary, and Stratton (Ref. 1), cited by the comment, which discusses the effectiveness of simethicone in eliminating foam and bubbles that may obscure the visual field in peroral endoscopy. According to the study results, simethicone is effective as a defoaming agent, but the study does not define the term "bubbles" or explain the source of the foam or bubbles that obscure the visual field. Without knowing whether the bubbles are derived from gas or air, the study cannot support the phrases "relieves gas trapped in the intestine" and "for gas pain."

In the advance notice of proposed rulemaking for OTC digestive aid drug products (47 FR 454), the Miscellaneous Internal Panel discussed at length the question of whether excessive gas is the causative agent of distress in the upper gastrointestinal tract and concluded that data were insufficient to make this assumption. In the tentative final monograph for OTC digestive aid drug products (53 FR 2706, January 29, 1988), the agency acknowledged that the word "gas" is commonly used by consumers. Therefore, the agency had no objection to use of the word "gas" in the labeling of OTC digestive aid drug products, provided there was no implication that the presence of gas, in the literal sense of excess gas bubbles in the gastrointestinal tract, is the cause of the symptoms. The agency discussed the consumer survey mentioned by the comment and agreed that a number of terms were commonly used by consumers in describing what is commonly, if not accurately, referred to as "gas" (53 FR 2706 at 2710). However, the terms did not include "gas pain."

Based on all of the data evaluated to date, the agency finds the claims "antigas formulation relieves gas trapped in the intestine" and "for gas pain" inappropriate for OTC antifatulent drug products. The agency concludes that the general term "antigas" is appropriate when used for the indications provided in the monograph, e.g., "relieves the symptoms referred to as gas." However, the agency acknowledges that the term could be interpreted by some as the

mechanism of action for these products. While this is not supported scientifically, the agency concludes that this term is understood by consumers and is an appropriate statement of identity for these products.

The agency is adding the following definition for the term "antigas" in the monograph: "Antigas is a term that may be used interchangeably with the term antifatulent. Neither term should be considered as describing the mechanism of action of the active ingredient contained in the product." This definition appears in new § 332.3 of the final monograph.

Reference

(1) McDonald, G. B., R. O'Leary, and C. Stratton, "Pre-Endoscopic Use of Oral Simethicone," *Gastrointestinal Endoscopy*, 24:283, 1978.

2. Three comments, submitting to both the OTC antifatulent and digestive aid drug products rulemakings, contended that activated charcoal was solely an antifatulent drug and did not belong in the digestive aid drug products rulemaking. Another comment expressed concern that activated charcoal was not included as a monograph ingredient in the 1988 proposal to amend the final monograph for OTC antifatulent drug products. The comments cited studies (Refs. 1 through 5) in the literature to support monograph status for activated charcoal. One comment mentioned that physicians who use charcoal to treat lower intestinal gas symptoms indicate that charcoal is effective under certain circumstances. The comment referred to studies by Jain et al. (not cited), as well as its own studies (not submitted), as evidence that activated charcoal decreased intestinal gas and relieved associated symptoms. The comment argued that the need for additional studies and ongoing research should not deter the availability or use of activated charcoal for excessive gas and related symptoms for which it is reasonably expected to be effective. The comment felt charcoal was not approved because it had a stigma as "an old remedy," which is difficult to overcome.

Two advisory review panels (Antacid (38 FR 8714) and Miscellaneous Internal (47 FR 454)) evaluated charcoal for antifatulent and digestive aid use. Both panels concluded that more data were needed to establish effectiveness for these uses.

Subsequently, after the comments were submitted, the agency received additional data, including studies done by one comment and by Jain et al. (referenced by the comment). The agency discussed these studies and the

references provided by the comments in the final rule for OTC digestive aid drug products (58 FR 54450 at 54451). The agency found the data insufficient to support the effectiveness of activated charcoal as a digestive aid or as an antifatulent (58 FR 54453). No new data have been provided to the agency.

The agency has never attached a "stigma" to a drug because it has been in the marketplace for many years. The agency has proposed a number of very old ingredients (e.g., aspirin, bran, cascara, and psyllium) as monograph ingredients. The data that have been provided have not been adequate to include activated charcoal in a monograph for use as an antifatulent. Manufacturers have the option to petition the agency to amend the antifatulent monograph in the future should additional data become available to support the effectiveness of activated charcoal as an antifatulent.

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) 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.

(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) Vargo, D., L. Ozick, and M. H. Floch, "The Effect of Activated Charcoal on Dietary Carbohydrate Fermentation" *American Journal of Gastroenterology*, (abst.), 82:950, 1987.

3. Three manufacturers submitted protocols to study the effectiveness of activated charcoal in decreasing gastrointestinal distress. One manufacturer did not pursue studies after 1989.

The agency met with representatives of the other two manufacturers (Ref. 1) to discuss their study protocols. Both manufacturers submitted revised protocols in response to the agency's comments. The agency provided written comments on only one of the protocols (Ref. 2) because one manufacturer indicated that it intended to begin its study and that no further review by the agency was necessary.

Subsequently, one manufacturer informed FDA that it had decided not to pursue studies (Ref. 3). The other manufacturer (Ref. 4) has not submitted

any study results to date. In the absence of new data, the agency concludes there is no basis to include activated charcoal in the OTC antifatulent drug products monograph at this time. Manufacturers have the option to petition the agency to amend the antifatulent monograph in the future should additional data become available to support the effectiveness of activated charcoal as an antifatulent.

References

(1) Memorandum of Meeting between FDA representatives and representatives from Kramer Laboratories and Requa, Inc., coded MM4, Docket No. 81N-0106, Dockets Management Branch.

(2) Letter from W. E. Gilbertson, FDA, to J. Geils, Requa, Inc., dated July 22, 1994, coded LET 20, Docket No. 81N-0106, Dockets Management Branch.

(3) Memorandum of Telephone Conversation between M. Barach, of Akin, Gump, Strauss, Hauer & Feld on behalf of Kramer Laboratories, and B. Ryland, FDA, coded MT3, Docket No. 81N-0106, Dockets Management Branch.

(4) Memorandum of Telephone Conversation between B. Marlin, Requa Consultant, and B. Ryland, FDA, coded MT4, Docket No. 81N-0106, Dockets Management Branch.

III. The Agency's Final Conclusions

The agency has carefully evaluated the comments' proposals and concludes that the terms "antigas" and "antifatulent" are interchangeable. The agency is providing manufacturers the option of using either term or both as the statement of identity for their products. Although "antigas" is now the preferable term, the agency is also allowing "antifatulent."

In respect to the one comment's concern that activated charcoal is not a monograph ingredient, the agency points out that manufacturers of products containing this ingredient have had over 20 years to provide sufficient data to support claims for activated charcoal as an antifatulent and have failed to do so. Accordingly, simethicone remains the only antifatulent monograph ingredient.

Interested persons may, on or before June 3, 1996, submit to the Dockets Management Branch (address above) written comments on these warnings. Comments should be identified with the docket number found in brackets in the heading of this document. Three copies of all comments are to be submitted, except that individuals may submit one copy. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

IV. Analysis of Impacts

No comments regarding the economic impact of this rulemaking were received. FDA has examined the final rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory action as defined by the Executive Order and, thus, is not subject to review under the Executive Order. This final rule provides for minor labeling revisions that can be implemented at very little cost by manufacturers at the next printing of labels. The agency is providing 12 months for these revisions to be made and, thus, believes that this rule will have no significant economic impact. Accordingly, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

V. Paperwork Reduction Act of 1995

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

VI. Environmental Impact

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 332

Labeling, Over-the-counter drugs. Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 332 is amended as follows:

PART 332—ANTIFLATULENT PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 332 is revised to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

2. New § 332.3 is added to Subpart A to read as follows:

Subpart A—General Provisions

§ 332.3 Definitions.

As used in this part:

Antigas. A term that may be used interchangeably with the term antifatulent. Neither term should be considered as describing the mechanism of action of the active ingredient contained in the product.

3. Subpart D consisting of §§ 332.30 and 332.31 is redesignated as Subpart C; and § 332.30 is amended by revising the section heading; by redesignating paragraphs (a), (b), and (c) as paragraphs (b), (c), and (d), respectively; by adding new paragraph (a); and by revising newly redesignated paragraph (b) to read as follows:

Subpart—Labeling

§ 332.30 Labeling of antifatulent drug products.

(a) Statement of identity. The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antifatulent,"

"antigas," or "antifatulent (antigas)."

(b) Indications. The labeling of the product states, under the heading "Indications," one or more of the phrases listed in this paragraph (b), as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) (Select one of the following: "Alleviates or Relieves") "the symptoms referred to as gas."

(2) (Select one of the following: "Alleviates" or "Relieves") (select one or more of the following: "bloating," "pressure," "fullness," or "stuffed feeling") "commonly referred to as gas."

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Dated: February 23, 1996.

William K. Hubbard,

Associate Commissioner for Policy

Coordination.

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