DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 357

[Docket No. 81N-0106]

Digestive Aid 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) digestive aid drug products 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 Miscellaneous Internal Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal 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 March 29, 1988. New data by January 30, 1989.

Comments on the new data by March 29, 1989. Written comments on the agency's economic impact determination by May 31, 1988.

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 Drug Evaluation and Research (HFN-210), 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 (Miscellaneous Internal 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 notice published in the Federal Register of 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)(1), 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.

In response to the advance notice of proposed rulemaking, one physician, seven drug manufacturers, one research firm, and one trade association submitted comments. Copies of the comments received are on public display in the Dockets Management Branch.

In order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10), the present document is designated as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) to establish Subpart D of Part 357 (21 CFR Part 357, Subpart D), FDA states for the first time its position on the establishment of a monograph for OTC digestive aid drug products. Final agency action on this matter will occur with the publication at a future date of a final rule for OTC digestive aid drug products.

This proposal constitutes FDA's tentative conclusions on OTC digestive aid drug products based on the agency's independent evaluation of the Panel's report and the comments received. 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.

In reviewing the Panel's recommendations on OTC digestive aid drug products, the agency recognizes that there is significant overlap between the rulemaking on OTC digestive aid drug products and other rulemakings in the OTC drug review. A number of ingredients reviewed as digestive aids were also reviewed for similar claims in other rulemakings. For example, glutamic acid hydrochloride was reviewed in the rulemaking for OTC stomach acidifier drug products and the pancreatic enzymes, pancreatin and pancrelipase, were reviewed in the rulemaking for OTC exocrine pancreatic insufficiency drug products. (See the Federal Register of October 19, 1979 (44 FR 60316); December 21, 1979 (44 FR 75666); January 15, 1985 (50 FR 2184); and November 8, 1985 (50 FR 46594), respectively.) Simethicone was evaluated for use in relieving the symptoms of gas in the rulemaking for OTC antiflatulent drug products. (See 21 CFR Part 332.) A number of the ingredients reviewed as digestive aids are antacid ingredients that are included in the rulemaking for OTC antacid drug products as well as the rulemaking for OTC drug products for relief of symptoms associated with overindulgence in alcohol and food. (See 21 CFR Part 331 and the Federal Register of October 1, 1982 (47 FR 43540), respectively.) In addition, the claims for many of these ingredients in the other rulemakings are very similar to those in the digestive aid rulemaking, i.e., to relieve symptoms of gastrointestinal distress (e.g., heartburn, sour stomach, acid indigestion, gas, upset stomach, etc.).

Therefore, in proceeding with the development of this tentative final monograph on OTC digestive aid drug products, the agency has decided to limit the digestive aid rulemaking to those ingredients and labeling claims that have not been adequately covered by other rulemakings on OTC drug products. For further discussion, see comment 4 below.

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 digestive aid drug products (published in the Federal Register of January 5, 1982 (47 FR 454)), the agency suggested that the conditions included in the monograph (Category I) be effective 6 months after the date of publication of the final monograph in the Federal Register. 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 6 months 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 extension requests and related paperwork.

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.

If the agency determines that any labeling for a condition included in the final monograph should be implemented sooner than the 12-month effective date, 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.

In the event that no new data are submitted to the agency during the allotted 12-month new data period or if submitted data are not sufficient to establish "monograph conditions" for OTC digestive aid drug products, the final rule will declare there products 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 applications approved under section 505 of the act (21 U.S.C. 355) and 21 CFR 314 are required for marketing. Such rule will also declare that in the absence of an approval application, these products would be misbranded under section 502 of the act (21 U.S.C. 352). The rule will then be incorporated into 21 CFR Part 310, Subpart E—Requirements for Specific New Drugs or Devices, instead of into an OTC drug monograph in Part 357.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notices published in the Federal Register of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179) 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

General Comments

1. One comment contented that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comment referred to statements on this issue submitted earlier to other OTC drug rulemaking proceedings.

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 9 of the preamble to the tentative final monograph for OTC 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 Manfacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd* 637 F.2d 887 (2d Cir. 1981).

2. One comment contended that FDA lacks the statutory authority to prescribe exclusive lists of terms from which indications for OTC drug use must be drawn, thus prohibiting alternative OTC labeling terminology that is truthful, accurate, not misleading, and intelligible to the consumer. The comment stated that existing statutory provisions (15 U.S.C. 1453(a)), and sections 508 and 502(e) of the fact (21 U.S.C. 358 and 352(e)) do not grant FDA the authority to legislate the exact wording of OTC drug claims to the exclusion of other equally accurate and truthful claims. The comment further contended that section 502(c) of the act (21 U.S.C. 352(c)) may in fact be violated by manufacturers if some of the terms being prescribed by OTC review panels are adopted because the act requires that label information be in such terms as to render it likely to be read and understood by consumers under ordinary conditions of purchase and use.

In the Federal Register of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indicating for use of OTC drug products. Under the final rule, the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a

boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All required OTC drug labeling other than indications for use (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under an OTC drug monograph where exact language has been established and identified by quotation marks in an applicable monograph or other regulation, e.g., 21 CFR 201.63 or 330.1(g). The proposed rule in this document is subject to the final rule revising the labeling policy.

3. One comment disagreed with the Panel's recommendation that inactive ingredients be listed on the label. The comment argued that a list of inactive ingredients would be meaningless to all but a few consumers and that such a list might overemphasize the importance of the inactive ingredients, obscure more meaningful information such as warnings or directions for use, and be more confusing than helpful. The comment also stated that if the quantity of the inactive ingredients had to be listed there would be an additional problem of changing the labels whenever the quantity of an inactive ingredient is changed.

The act specifies the requirements for ingredient labeling of OTC drug products. Section 502(e) of the act (21 U.S.C. 352(e)) requires that all active ingredients and certain other ingredients, whether included as active or inactive, be disclosed on the label. The act also limits the requirement for stating quantity of ingredients in OTC drug products to those specifically mentioned in section 502(e). Although the act does not require the disclosure of all inactive ingredients in the labeling of OTC drug products, the agency agrees with the Panel that listing of inactive ingredients in OTC drug product labeling would be useful information for some consumers. Consumers with known allergies or intolerance to certain ingredients would then be able to identify substances that they may wish to avoid.

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, has announced that its member companies would voluntarily begin to list inactive ingredients in the labeling of OTC drug products under guidelines established by the association (Ref. 1). Under another voluntary program begun in 1974, the member companies of The Proprietary Association have been including the quantities of active ingredients on OTC drug labels. The agency is not at this time proposing to require the listing of inactive ingredients in OTC drug product labeling. However, the agency commends these voluntary efforts and urges all other OTC drug manufacturers to similarly label their products.

Reference

(1) "Proprietary Association Adopts Disclosure of Inactive Ingredients," News Release, The Proprietary Association, Washington, DC, May 14, 1984, copy included in OTC Volume 17GTFM.

4. Several comments disagreed with the Panel's recommendations to divide digestive aid drug products into two categories, that is, (1) products for immediate postprandial upper abdominal distress (IPPUAD) and (2) products for intestinal distress—with the distinguishing feature between the two categories being the time to onset of symptoms. The comments pointed out that the symptoms of bloating, distention, fullness, and pressure are the same for both categories. The comments stated that patients do not differentiate symptoms on the basis of time relationships and, therefore, establishing a time-based differentiation of symptoms has no logical basis. One comment argued that adopting the Panel's recommendations would create a "phantom" category of products that the consuming public could not understand. Most comments recommended that the concept of IPPUAD be abolished, and several suggested that the digestive aid monograph be expanded to encompass all abdominal and intestinal distress claims, whether due to food-related or other causes, e.g., stress, travel, or changes in the environment.

The Panel reviewed digestive aid drug products as those products which were claimed to alleviate symptoms in the stomach as well as the intestines following the ingestion of food. In reviewing these products, the Panel decided to classify them into the following two groups: (1) Those that treat symptoms that occur within 30 minutes after ingestion of food (immediate postprandial upper abdominal distress drug products) and (2) those that treat symptoms that occur from 30 minutes to several hours after ingestion of food (intestinal distress drug products). As one comment pointed out, the symptom complex of bloating, distention, fullness, and pressure was common to both classifications.

After reviewing the available data and information, the agency agrees with the comments that the distinction between IPPUAD and intestinal distress, with the distinguishing feature being the time to onset of symptoms, is one that will have little meaning to consumers. In addition, historically, this distinction has not been made in the labeling of digestive aid drug products. Further, the agency notes that the Miscellaneous Internal Panel also reviewed drug products for relieving symptoms of overindulgence in food and drink and did not make such a time distinction in that rulemaking. Therefore, the agency is not adopting the two classifications of IPPUAD and intestinal distress and is defining a digestive aid drug product as "a drug product intended to relieve the symptoms of gastrointestinal distress (including fullness, pressure, bloating, and stuffed feeling (commonly referred to as gas), and minor pain and cramping) following the ingestion of food."

The agency does not believe it is appropriate to expand the scope of this rulemaking to include gastrointestinal distress other than that related to food. As discussed in the preamble above, there is significant overlap with respect to ingredients and claims within the digestive aid rulemaking and other OTC drug rulemakings, i.e., antacid, antiflatulent, exocrine pancreatic insufficiency, overindulgence in food and drink, and stomach acidifier. For example, the final monograph for OTC antacid drug products includes the indication for the relief of heartburn, sour stomach, acid indigestion, and upset stomach associated with these symptoms. The labeling does not specify the etiology of the symptoms and, therefore, would not preclude the use of antacids for relieving upset stomach associated with heartburn, sour stomach, or acid indigestion that may occur following the ingestion of food or from other causes, e.g., stress, etc. Further, the term "acid indigestion" suggests a food-related cause.

In order to avoid duplication, the agency is limiting the digestive aid rulemaking to include only those ingredients that have not been adequately covered by other OTC drug rulemakings that address similar claims related to relief of symptoms of gastrointestinal distress. As discussed above, antacid ingredients and simethicone have been adequately considered for gastrointestinal distress claims in the rulemakings for OTC antacid drug products and OTC antiflatulent drug products, respectively. In addition, as discussed in comments 8

and 10 below, pancreatic enzyme ingredients and stomach acidifier ingredients have been reviewed for use in aiding digestion in the rulemakings for OTC exocrine pancreatic insufficiency drug products and OTC stomach acidifier drug products, respectively. After reviewing the ingredients evaluated by the Panel, the agency has determined that the following ingredients are appropriate for consideration in the digestive aid rulemaking: Bismuth sodium tartrate, cellulase, charcoal, dehydrocholic acid, duodenal substance, garlic, hemicellulase, homatropine methylbromide, ox bile extract, papain, peppermint oil, pepsin, and sorbitol. Because no new data for any of these ingredients were submitted following publication of the Panel's recommendations, the agency is concurring with the Panel's categorization of these ingredients as follows:

Ingredient	Categorization
Bismuth sodium tartrate	II
Cellulase	III
Charcoal, activated and Charcoal, wood	III
Dehydrocholic acid	III
Duodenal substance	III
Garlic, dehydrated	III
Hemicellulase	III
Homatropine methylbromide	III
Ox bile extract	III
Papain	II
Peppermint oil	III
Pepsin	III
Sorbitol	II

In addition, the agency is aware of another enzyme (lactase) that 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. Lactase deficiency is extremely prevalent, estimated to occur in about 75 percent of adults (Ref. 1). Although the condition can be controlled by ingesting a lactose-free diet, the agency believes that lactase enzyme products could be potentially useful for those persons who do not wish to avoid lactose in their diets. However, no submissions were made to the agency regarding these products, nor is the agency aware of any specific data that would establish general recognition of safety and effectiveness. Therefore, the agency invites specific data and information regarding the use of lactase enzyme products. After review and evaluation of the data submitted, the agency will consider lactase for inclusion in the final monograph for OTC digestive aid drug products.

Based on the above discussion, the agency is proposing the following indication for OTC digestive aid drug products: "For relief of symptoms of gastrointestinal distress such as" (select one or more of the following: "fullness," "pressure," "bloating," or "stuffed feeling") (optional: "(commonly referred to as gas),") (optional: "pain," and/or "cramping") "which occur(s) after eating." Although the Panel included the word "distention" in its indication statements for IPPUAD and intestinal distress drug products, the agency is not proposing this word in the indication statement in this tentative final monograph. Based on the discussion in comment 7 below, the agency has determined that "distention" is not a word that is used by consumers in describing symptoms of gastrointestinal distress.

References

(1) "The Merck Manual of Diagnosis and Therapy," 14th Edition, edited by R. Berkow; Merck and Co., Inc., Rahway, NJ, p. 779, 1982.

5. Several comments objected to the Panel's review of simethicone as a digestive aid ingredient and requested that the final monograph for OTC antiflatulent drug products be neither revoked nor modified based on the Panel's conclusions that there is no conclusive evidence that excess gas is the causative agent in producing undesirable gastrointestinal symptoms such as bloating, pressure, or fullness. The comments added that there is no new and significant data that question the safety or effectiveness of simethicone, which was included in the final monograph for OTC antiflatulent drug products (21 CFR Part 332). Several comments stated that the Panel misinterpreted its charge from the agency which was to review the safety and effectiveness data submitted on antiflatulent ingredients other than simethicone in order to determine whether such ingredients should be added to the antiflatulent monograph. Referring to the call-for-data notice published in the Federal Register of August 27, 1975 (40 FR 38183), the comments stated that a re-review of simethicone for use in relieving the symptoms of gas is contrary to established OTC drug review procedures and to the specific charge to the Panel that it should not review ingredients for conditions that had been previously reviewed by other panels. The comments argued that there is no legal basis to restrict labeling to claims or situations where definitive proof of causation has been established and that OTC drug products are used to provide relief of the symptoms, not the cause. The comments stated that it is irrelevant whether excess gas actually causes the symptoms described by consumers as "gas," provided an ingredient can be shown to be safe and effective in relieving those symptoms.

The agency agrees with the comments that the final monograph for OTC antiflatulent drug products should not be revoked or modified based on the Panel's recommendations. Although the agency agrees with the Panel that data are insufficient to demonstrate that excess gas actually causes the symptoms of bloating, pressure, and fullness, data are available to demonstrate that "gas" is a word used by consumers to describe these symptoms. In developing the antiflatulent final monograph, the agency relied on the results of two double-blind studies (Refs. 1 and 2) which demonstrated the effectiveness of simethicone in relieving symptoms of upper gastrointestinal distress. (See 38 FR 31266.) In both studies, the symptoms described as bloating, fullness, pressure, and stuffed feeling were among those evaluated. Although the studies did not demonstrate that the symptoms were actually caused by excess gas, simethicone was demonstrated to be effective in relieving the symptoms. In addition, the results of a consumer survey indicate that the terms "bloating," "pressure," "stuffed feeling," and "fullness" are very meaningful to and used by consumers in describing what is commonly, if not accurately, referred to as "gas." (See comment 7 below.) Therefore, the agency agrees with the comments that evidence need not be available demonstrating the cause of a symptom as long as there is sufficient evidence to show that an ingredient provides relief from the symptom.

However, as discussed in the preamble above, the agency is limiting the digestive aid rulemaking to those ingredients and labeling claims which have not been adequately covered by other rulemakings on OTC drug products. Therefore, simethicone is no longer being considered in this digestive aid rulemaking. (See also comment 7 below.)

References

(1) Kasick, A., "A Summary of a Double-Blind Study Comparing the Effectiveness of Simethicone and Placebo in the Relief of Symptoms of Functional Disease of the Upper Gastrointestinal Tract," copy of unpublished study included in OTC Volume 17GTFM.

(2) "A Summary of the Double-Blind Study of the Effectiveness of Simethicone in Relieving the Symptoms of Acute Upper Gastrointestinal Distress," copy of unpublished study included in OTC Volume 17GTFM.

6. Referring to the Panel's recommended indication in § 357.350(b)(1) which states, " 'For relief of upper abdominal' (one or more of the following symptoms: 'distress,' 'bloating,' 'distention,' 'fullness,' and 'pressure') 'which occurs soon after eating,' (optional, 'and which may be described as 'gas.')", one comment suggested that the words "and which may be described as" be deleted as unnecessary and that the word "gas" be placed among the other allowable words such as "bloating, distress, distention, fullness, and pressure."

The agency agrees with the Panel that data are insufficient to demonstrate that excess gas actually causes the symptoms of gastrointestinal distress that may occur after eating. However, data are available demonstrating that "gas" is a word that is commonly, although not accurately, used by consumers to describe those symptoms. (See comment 7 below.) Because the word "gas" is used by consumers to describe those symptoms, the agency has no objection to its use in the labeling of OTC digestive aid drug products provided there is 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. Likewise, there should be no implication that "gas" is a symptom distinct or different from the terms used by consumers to describe the symptoms of what they perceive as "gas," i.e., "bloating," "pressure," "fullness," "stuffed feeling." Therefore, the agency does not agree that "gas" should be placed among the other allowable words because it would imply a symptom different from the others when, in fact, it is a term used to collectively describe those symptoms.

As discussed in comment 4 above, the agency is proposing the following indication for OTC digestive aid drug products: "For relief of symptoms of gastrointestinal distress such as" (select one or more of the following: "fullness," "pressure," "bloating," or "stuffed feeling") (optional: "(commonly referred to as gas),") (optional: "pain," and/or "cramping") "which occur(s) after eating."

7. Referring to a previously submitted petition (Ref. 1), one comment requested the agency to expand the labeling indications of antiflatulent drug products to include the terms "bloating," "gas pressure," "stuffed feeling," and "fullness," as descriptive words for the symptoms of gas. Noting the results of a consumer survey (Ref. 1), the comment contended that these terms are used by consumers to describe the symptoms of gas and there is no basis to preclude the use of these terms in the labeling of OTC antiflatulent drug products. The comment also requested that the term "antigas" be included in the monograph because it is more meaningful to consumers than the term "antiflatulent."

The agency has reviewed and evaluated the available data and determined that the terms requested by the comment are appropriate for inclusion in the monograph for OTC antiflatulent drug products. In developing the antiflatulent monograph, the agency relied on the results of two double-blind studies (Refs. 2 and 3) which demonstrated the effectiveness of simethicone in relieving symptoms of upper gastrointestinal distress. (See 38 FR 31266.) In both studies the symptoms described as "bloating," "fullness," "pressure," and "stuffed feeling" were among those evaluated. In both studies, simethicone was demonstrated to be effective for relieving these symptoms.

In addition, the results of the consumer survey (Ref. 1) indicate that the terms "bloating," "pressure," "stuffed feeling," and "fullness," are very meaningful to and used by consumers in describing what is commonly, if not accurately, referred to as "gas." Based on these data, the agency is proposing elsewhere in this issue of the Federal Register to amend the antiflatulent monograph to include the following indication: (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." The agency is also proposing to amend that monograph to include a "statement of identity" section to conform with the format of other final OTC drug monographs. The agency agrees that the term "antigas" is an appropriate statement of identity as an alternative or in addition to the term "antiflatulent" provided there are not statements elsewhere in the labeling implying that the symptoms are caused by the presence of excess gas. For example, phrases such as "antigas formulation relieves gas trapped in the intestine" or "for gas pain" would be considered inappropriate.

Reference

(1) Petition from Plough, Inc., dated May 18, 1976, on file under Docket No. 76P-0218, Dockets Management Branch.

(2) Kasich, A., "A Summary of a Double-Blind Study Comparing the Effectiveness of Simethicone and Placebo in the Relief of Symptoms of Functional Disease of Upper Gastrointestinal Tract," copy of unpublished study included in OTC Volume 17GTFM.

(3) "A Summary of the Double-Blind Study of the Effectiveness of Simethicone in Relieving the Symptoms of Acute Upper Gastrointestinal Distress," copy of unpublished study included in OTC Volume 17GTFM.

8. One comment believed that there were inconsistencies in the Panel's conclusions regarding the classification of pancreatin and pancrelipase and their components. The comment questioned why pancreatin and pancrelipase were classified by the Panel as Category III for the symptoms of intestinal distress when their major constituents, amylase, lipase, and protease, were classifed as single ingredients in Category II. Furthermore, the comment contended that the Panel's Category III classification for the combination of lipase, amylase, protease, and hemicellulase contradicts its own statement (47 FR 462) that any combination of ingredients containing one or more Category II ingredients is Category II.

The agency acknowledges that it seems the Panel was inconsistent with its own combination policy in classifying pancreatin and pancrelipase as Category III when the major components of these substances, as single ingredients, are classified Category II. However, pancreatin and pancrelipase are extracts of natural origin that contain amylase, lipase, and protease, and, as such, are considered by "The United States Pharmacopeia/ The National Formulary" as single substances when these components are combined as specified in the compendia (Ref. 1). Therefore, the Panel considered pancreatin and pancrelipase as single ingredients.

The agency concurs with the Panel's conclusion that there are no data to support the use of amylase, lipase, or protease other than as the combination of the three principal components. Therefore, amylase, lipase, and protease as single ingredients are Category II. The ingredients pancreatin and pancrelipase were considered by the agency in the tentative final monograph for OTC exocrine pancreatic insufficiency drug products, published in the Federal Register of November 8, 1985 (50 FR 46594). In that document, the agency concurred with the Panel's recommendation that pancreatin and pancrelipase are beneficial only in cases of pancreatic enzyme insufficiency. The agency is not aware of any well-controlled studies demonstrating the effectiveness of these ingredients in aiding or facilitating the digestive process, except in cases of diagnosed pancreatic enzyme insufficiency.

Therefore, those ingredients are not being reconsidered in this rulemaking.

Hemicellulase will remain in Category III as a digestive aid single ingredient.

Reference

(1) "The United States Pharmacopeia XXI-National Formulary XVI," United States Pharmacopeial Convention, Inc., Rockville, MD, pp 777 and 779, 1985.

9. Several comments opposed the testing guidelines recommended by the Panel for Category III OTC digestive aid drug products. Three comments objected to the Panel's recommendation that the test population consist only of individuals who have consulted a gastroenterologist for treatment of their symptoms because these individuals are not representative of the general population who experience the symptoms of IPPUAD or intestinal distress. One comment suggested that a more representative test population would be composed of individuals who, following food consumption, successfully self-medicate with OTC drug products to relieve the occasional symptoms of gas, fullness, bloating, distention, and/or pressure. Two comments emphasized that the Panel's requirement that complete relief be demonstrated within 30 minutes of administration of medication is overburdensome with regard to establishing efficacy. The comment stressed that significant relief of symptoms within an appropriate amount of time, even if relief is only partial, is an important criterion. Two comments criticized the Panel's criteria for admission into the study. These comments contended that the requirements for comprehensive medical histories with expensive diagnostic testing are unrealistic and unnecessary.

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 procedures 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.*)

10. One comment noted that although the Panel's report on OTC digestive aids does not deal directly with its product (which is labeled for use as a stomach acidifier), the report does review the active ingredient (glutamic acid hydrochloride) contained in its product for general use in the treatment of IPPUAD and intestinal distress. The comment requested that submissions made to the rulemaking for OTC stomach acidifier drug products (Refs. 1, 2, and 3) be incorporated by reference in this rulemaking because the symptoms that characterize IPPUAD and intestinal distress are among the recognized symptoms of gastric acid deficiency. The comment contended that when the symptoms of IPPUAD and intestinal distress are due to deficiencies of hydrochloric acid its product has been shown to provide effective therapy. The comment recommends that the agency classify glutamic acid hydrochloride as a Category I digestive aid. Furthermore, the comment contended that this product is exempt from review under the "grandfather" provisions of the 1938 act and the 1962 amendments to the act.

As discussed in comment 4 above, the agency is limiting the digestive aid rulemaking to include only those ingredients that have not been adequately covered by other OTC drug rulemakings for similar claims. Glutamic acid hydrochloride was reviewed in the rulemaking for OTC stomach acidifier drug products (Docket No. 79N-0176). The use evaluated was as an aid to digestion by increasing the amount of hydrochloric acid in the stomach in cases of achlorhydria or hypochlorhydria. In the tentative final monograph for OTC stomach acidifier drug products, published in the Federal Register of January 15, 1985 (50 FR 2184), the agency classified stomach acidifier active ingredients, including glutamic acid hydrochloride, in Category II because the conditions of hypochlorhydria and achlorhydria are not established medical conditions causing any specific symptoms that require treatment. Further, the Panel stated that it knows of no proven relationship between hypoacidity or anacidity of the stomach and the symptoms of IPPUAD (47 FR 465) and the symptoms of intestinal distress (47 FR 497). The Panel also stated that it was not aware of any adequate and well-controlled clinical studies demonstrating the effectiveness of glutamic acid hydrochloride in treating the symptoms of IPPUAD (47 FR 465) or intestinal distress (47 FR 479). The Panel concluded that glutamic acid hydrochloride is not generally recognized as an effective treatment for these conditions. Based on the Panel's findings and the conclusions presented in the tentative final monograph for OTC stomach acidifier drug products, the agency does not believe it would be appropriate to further consider glutamic acid hydrochloride in this digestive aid rulemaking.

The agency also addressed the "grandfather" status of the glutamic acid hydrochloride product in the tentative final monograph for OTC stomach acidifier drug products (50 FR 2186). Based on that discussion, the agency reaffirms that the glutamic acid hydrochloride product is subject to the OTC drug review.

The discussion in this tentative final monograph is the agency's final consideration of glutamic acid hydrochloride in the rulemaking for OTC digestive aid drug products. The agency's final conclusions with respect to the indications for glutamic acid hydrochloride referred to in the comment will appear in the final rule for OTC stomach acidifier drug products. The final regulations for OTC stomach acidifier drug products, not the final regulations for OTC digestive aid drug products, will be those applicable to this glutamic acid hydrochloride product.

References

(1) OTC Volume 170103.
(2) OTC Volume 170184.
(3) OTC Volume 170124.

11. One comment recommended that the agency not adopt the Panel's recommended warning for aluminum-containing antacid products, which reads, "If you have kidney disease, do not take this product except under the supervision of a physician." (See 47 FR 466.) The comment argued that a fair balance of the literature indicates that the association of ingested aluminum-containing drug products in patients with impaired kidney function and encephalopathy has not been demonstrated; therefore, the recommended warning should not be adopted.

The agency reviewed all available data concerning aluminum toxicity and published its conclusions on these data in the notice of proposed rulemaking for OTC hypophosphatemia and hyperphosphatemia drug products in the Federal Register of January 15, 1985 (50 FR 2160). The agency concluded that the largest body of evidence of toxicity associated with aluminum is strongest for encephalopathy that occurs in renal failure patients undergoing dialysis. (See 50 FR 2162.) Although aluminum has not been proven to be a causative factor, there is considerable indirect evidence that it has a role in development of this syndrome. Because of this potential role, the agency believes it is appropriate to

provide warning labeling to this effect. However, the agency believes that the persons at highest risk to aluminum toxicity are those with severe renal failure who are generally under the care of a physician. The agency thus concluded that it would be more prudent to inform health professionals of the potential risks involved rather than to require the kidney-disease warning recommended by the Panel. The agency reaffirms its previous conclusion (50 FR 2162) that additional information be provided in the professional labeling section of the antacid monograph (21 CFR 331.31) for aluminum-containing antacids.

II. The Agency's Tentative Conclusions on 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 made some changes in the categorization of digestive aid active ingredients recommended by the Panel. In addition, as discussed in the comments above, the agency is limiting the digestive aid rulemaking to include only those ingredients that have not been adequately covered by other OTC drug rulemakings for similar claims related to relief of symptoms of gastrointestinal distress. As a convenience to the reader, the following list is included as a summary of the categorization of digestive aid active ingredients recommended by the Panel and the proposed categorization by the agency. Where the ingredient has been classified in another rulemaking, that rulemaking and the classification therein is stated.

CATEGORIZATION OF INGREDIENTS

Degestive aid active ingredients	Panel		Agency
	(IP-PUAD [1])	(ID [2])	
Almadrate sulfate.	III		Antacid (I)
Aluminum hydroxide.	III		Antacid (I)
Bismuth sodium tartrate.		II	II
Calcium carbonate.	III		Antacid (I)
Cellulase	II	III	III
Charcoal, activated and Charcoal, wood.		III	III
Dehydrocholic acid.	II	II	II
Dihydroxyaluminum sodium carbonate.	III		Antacid (I)
Duodenal substance.		II	II
Garlic, dehydrated.	II	II	II
Glutamic acid hydrochloride.	II	II	Stomach Acidifier (II)
Hemicellulase.		III	III
Homatropine methylbromide.	II	III	III
Lactase			([3])
Magnesium hydroxide.	III	III	Antacid (I)
Magnesium trisilicate.	III		Antacid (I)
Ox bile extract.	II	II	II
Pancreatin and pancrelipase.	II	III	Exocrine Pancreatic Insufficiency (I)
Papain		II	II
Peppermint oil.	III		III
Pepsin	II	II	II
Simethicone.	III	III	Antiflatulent (I)
Sodium bicarbonate.	III	III	Antacid (I)
Sodium citrate.	III	III	Antacid (I)
Sorbitol	II	II	II

[1] Immediate postprandial upper abdominal distress.
[2] Intestinal distress.
[3] Not categorized at this time. See discussion in comment 4 above.

2. *Testing of Category II and Category III conditions.* Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any digestive aid ingredient or condition included in this rulemaking 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. The agency is not adopting the two classifications (IPPUAD and intestinal distress) for digestive aid drug products recommended by the Panel and is proposing a new definition for OTC digestive aid drug products. (See comment 4 above.) Based on this change, the definitions section of the tentative final monograph has been modified accordingly.

2. The agency is limiting the digestive aid rulemaking to include only those ingredients that have not been adequately covered by other OTC drug rulemakings that address similar claims related to relief of symptoms of gastrointestinal distress. (See comment 4 above and Part II. paragraph A.I. above—Summary of ingredient categories.)

3. The agency is proposing a new indication statement for OTC digestive aid drug products. (See comments 4 and 6 above.)

4. 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 basic 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.

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 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 proposed 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 a 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. 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 invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on OTC digestive aid drug products. No comments on economic impacts were received. Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by May 31, 1988. 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) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Interested persons may, on or before March 29, 1988, 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 on the proposed regulation. 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 May 31, 1988. 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 January 30, 1989, 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 March 29, 1989. These dates are consistent with the time 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 March 29, 1989. 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 in 21 CFR Part 357

Labeling, Over-the-counter drugs, Digestive aid drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 357 by adding new Subpart D, consisting of §§ 357.301–357.350, to read as follows:

PART 357—MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart D—Digestive Aid Drug Products

Sec.
357.301 Scope.
357.303 Definition.
357.310 Digestive aid active ingredients. [Reserved]
357.350 Labeling of digestive aid drug products.

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 5.10 and 5.11.

Subpart D—Digestive Aid Drug Products

§ 357.301 Scope.

(a) An over-the-counter digestive aid drug product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this subpart and each of the general conditions established in § 330.1

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 357.303 Definition.

As used in this subpart:

Digestive aid drug product. A drug product intended to relieve the symptoms of gastrointestinal distress (including fullness, pressure, bloating, and stuffed feeling (commonly referred to as gas), and minor pain and cramping) following the ingestion of food.

§ 357.310 Digestive aid active ingredients. [Reserved]

§ 357.350 Labeling of digestive aid 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 a "digestive aid."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: "For relief of symptoms of gastrointestinal distress such as" (select one or more of the following: "fullness," "pressure," "bloating," or "stuffed feeling") (optional: "(commonly referred to as gas),") (optional: "pain," and/or "cramping") "which occur(s) after eating." 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), 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.

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

(1) "If symptoms of distress persist, stop this medication and consult your doctor."

(2) "Do not use this product in children under 12 years of age except under the supervision of a doctor."

(d) *Directions.* [Reserved]

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

Dated: October 30, 1987.

Frank E. Young,

Commissioner of Food and Drugs.

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