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Part VIII

Department of Health and Human Services

Food and Drug Administration

Digestive Aid Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 357

[Docket No. 81N-0106]

Digestive Aid Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of proposed rulemaking that would establish conditions under which over-the-counter (OTC) digestive aid drug products (drugs for the treatment of the symptoms of immediate postprandial upper abdominal distress (IPPUAD), or drugs for the treatment of the symptoms of intestinal distress) are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by April 5, 1982, and reply comments by May 5, 1982.

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's Office) (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on January 19, 1979 a report on OTC digestive aid drug products from the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the Federal Register a proposed order containing: (1) The monograph recommended by the Panel, which established conditions under which OTC digestive aid drug products are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it.

After reviewing all comments submitted in response to this document, FDA will issue in the Federal Register a tentative final monograph for OTC digestive aid drug products as a notice of proposed rulemaking. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final monograph, which has the status of a final rule.

The agency's position on OTC digestive aid drug products will be stated initially when the tentative final monograph is published in the Federal Register as a notice of proposed rulemaking. In that notice of proposed rulemaking, the agency also will announce its initial determination whether the proposed rule is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the notice of proposed rulemaking is published. At that time FDA also will consider whether the proposed rule has a significant impact on the human environment under 21 CFR Part 25 (proposed in the Federal Register of December 11, 1979, 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC digestive aid drug products. Types of impact may include, but are not limited to, the following: increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing, if any. Comments regarding the impact of this rulemaking on OTC digestive aid drug products should be accompanied by appropriate documentation.

A monograph for OTC antiflatulent drug products (21 CFR Part 332) was established in response to data and information submitted with regard to the report of the Advisory Review Panel on OTC Antacid Drug Products. (See 38 FR 31266.) Because the agency recognized that information concerning other antiflatulent ingredients may have been available, but not submitted to the Antacid Panel, the agency advised interested persons to submit such information to the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. (See 38 FR 31266 and 39 FR 19871). The Federal Register notices published on November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179) requested data and information on various miscellaneous internal drug ingredients, including "antiflatulents." These antiflatulent ingredients are used in drug products with such labeling indications as flatulence, gas, bloating, fullness, and symptoms of food indiscretions.

After reviewing the data on antiflatulent ingredients submitted to it, the Miscellaneous Internal Panel recommended in this document that antiflatulent ingredients and claims be classified in Category III, requiring further testing before inclusion in a final monograph on digestive aid drug products. The Panel also classified simethicone, the only ingredient currently included in the antiflatulent monograph (21 CFR Part 332), in Category III as a digestive aid for treating the symptoms of immediate postprandial upper abdominal distress (IPPUAD) and intestinal distress. The agency at this time requests comments on the appropriate classification of antiflatulent ingredients and claims. FDA will publish its tentative conclusions concerning antiflatulents in the tentative final monograph (notice of proposed rulemaking) on digestive aid drug products. In that publication, the agency will also address the question of whether to revoke or modify the current antiflatulent monograph (21 CFR Part 332).

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC digestive aid drug products submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug

Administration, after February 4, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD–510) (address above).

FDA published in the Federal Register of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations 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.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of 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 because that was the framework in which the Panel conducted its evaluation of the data.

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 6 months after the date of publication of the final monograph in the Federal Register. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions which would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered or introduction into interstate commerce. Further, any OTC drug products subject to this monograph which are 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 voluntarily comply with the monograph at the earliest possible date.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the Federal Register of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the Federal Register of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC miscellaneous internal drug products was issued in the Federal Register of November 16, 1973 (38 FR 31696). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.' " In the Federal Register of August 27, 1975 (40 FR 38179), a notice supplemented the initial notice with a detailed, but not necessarily all-inclusive, list of active ingredients in miscellaneous internal drug products to be considered in the OTC drug review. The list, which included digestive aid ingredients, was provided to give guidance on the kinds of active ingredients for which data should be submitted. The notices of November 16, 1973, and August 27, 1975, informed OTC drug product manufacturers of their opportunity to submit data to the review at that time and of the applicability of the monographs from the OTC drug review to all OTC drug products.

Under § 330.10(a)(1) and (5), the Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report on the safety, effectiveness, and labeling of the active ingredients in these OTC miscellaneous internal drug products:

John W. Norcross, M.D., Chairman
Ruth Eleanor Brown, R.Ph. (resigned May 1976)
Elizabeth C. Giblin, M.N., Ed. D.
Richard D. Harshfield, M.D.
Theodore L. Hyde, M.D.
Claus A. Rohweder, D.O.
Samuel O. Thier, M.D. (resigned November 1975)
William R. Arrowsmith, M.D. (appointed March 1976)
Diana F. Rodriguez-Calvert, Pharm. D. (appointed July 1976)

Representatives of consumer and industry interests served as nonvoting members of the Panel. Eileen Hoates, nominated by the Consumer Federation of America, served as the consumer liaison until September 1975, followed by Michael Schulman, J.D. Francis J. Hailey, M.D., served as the industry liaison, and in his absence John Parker, Pharm. D., served. Dr. Hailey served until June 1975, followed by James M. Holbert, Sr., Ph. D. All industry liaison members were nominated by the Proprietary Association.

The following FDA employees assisted the Panel: Armond M. Welch, R.Ph., served as the Panel Administrator; Enrique Fefer, Ph. D., served as the Executive Secretary until July 1976, followed by George W. James, Ph. D., until October 1976, followed by Natalie Morgenstern until May 1977, followed by Arthur Auer until October 1978. Roger Gregorio served as the liaison for the Office of New Drug Evaluation beginning November 1978. Joseph Hussion, R.Ph., served as the Drug Information Analyst until July 1976, followed by Anne Eggers, R.Ph., M.S., until October 1977, followed by John R. Short, R.Ph.

To expand its scientific base, the Panel called upon the following consultants for advice in areas which required particular expertise:

Ralph B. D'Agostino, Ph. D. (statistics)
Lynn R. Brady, Ph. D. (pharmacognosy)
Arthur E. Schwarting, Ph. D. (pharmacognosy)

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products was charged with the review of many categories of drugs. Due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents its conclusions and recommendations for digestive aid drug products in this document. The review of all other categories of miscellaneous internal drug products is being

continued by the Panel, and its findings are being published periodically in the Federal Register.

Ingredients reviewed by the Panel for treatment of the symptoms of IPPUAD were referred to as "antiflatulents" in the Federal Register notices published on November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179). These ingredients are used in drug products with such labeling indications as flatulence, gas, bloating, fullness, stomachic (digestive tonic), and food indiscretions. The Panel reviewed all of thiese ingredients for treatment of symptoms of IPPUAD because the claims made for them apply to conditions occurring in the upper abdomen soon after eating (within 30 minutes). (See part III. below—Drug Products for the Treatment of the Symptoms of Immediate Postprandial Upper Abdominal Distress.)

Ingredients reviewed by the Panel for treatment of the symptoms of intestinal distress were referred to as "digestive aids" in the Federal Register notices published on November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179). Included in this review are ingredients used in drug products which claim to correct conditions of intestinal discomfort that do not involve enzyme deficiency. Those products which claim effectiveness for the treatment of exocrine pancreatic insufficiency were reviewed in a separate document entitled "Exocrine Pancreatic Insufficiency Drug Products for Over-the-Counter Human Use," published in the Federal Register of December 12, 1979 (44 FR 75666).

Conditions such as irritation and inflammation of the intestinal tract were grouped by the Panel under the heading of "intestinal distress" because these are conditions that occur in the intestines from 30 minutes to several hours following a meal. Ingredients used in drug products claiming to treat symptoms of these conditions were accordingly reviewed by the Panel for treatment of the symptoms of intestinal distress. (See part IV. below—Drug Products for the Treatment of the Symptoms of Intestinal Distress.)

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings at which digestive aid drug products were discussed were held on February 23 and 24, March 23 and 24, April 27 and 28, June 22 and 23, September 21 and 22, November 16 and 17, 1975; February 8 and 9, March 7 and 8, April 11 and 12, May 9 and 10, July 11 and 12, October 10 and 11, 1976; February 20 and 21, April 3 and 4, May 15 and 16, July 9, 10, and 11, October 15, 16, and 17, December 2, 3, and 4, 1977; January 28, 29, and 30, March 10, 11, and 12, May 5, 6, and 7, June 23, 24, and 25, August 4, 5, and 6, September 29 and 30, October 1, and November 17, 18, and 19, 1978; and January 19, 1979.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above).

The following individuals were given an opportunity to appear before the Panel to express their views on OTC digestive aid drug products either at their own or at the Panel's request:

William Bachrach, M.D.
Paul Bass, Ph. D.
Allen R. Cooke
Warren Dennis, Ph. D.
Robert G. Flynn, R.Ph., M.S.
Morton I. Grossman, Ph. D., M.D.
Frank Hurley, Ph. D.
Robert John, M.D.
John Johnson
Louis Lasagna, M.D.
M. D. Levitt, M.D.
Armand Littman, M.D., Ph. D.
Myron Lover, Ph. D.
Fred J. McIlreath, M.D.
C. Harold Mielke, Jr.
Daniel Minelli
Robert G. Pinco, Esq.
Stephen Schwartz, M.S.
E. Clinton Texter, Jr., M.D.
Julian Villarreal
Ralph O. Wallerstein
Joseph M. White, M.D.
Daniel Winship, M.D.

No person who so requested was denied an opportunity to appear before the Panel to discuss digestive aid drug products.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent information submitted through January 19, 1979 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations in § 330.10, the Panel's findings with respect to OTC digestive aid drug products are set out in three categories:

Category I. Conditions under which OTC digestive aid drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC digestive aid drug products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel reviewed 109 active ingredients for use in treating the symptoms of IPPUAD or intestinal distress. No ingredients were placed in Category I. The Panel placed 60 ingredients in Category II and 10 ingredients in Category III for the symptoms of IPPUAD and 48 ingredients in Category II and 9 ingredients in Category III for the symptoms of intestinal distress. (The number of ingredient classifications does not equal the number of ingredients reviewed because some ingredients were reviewed for more than one labeled use.)

I. Submission of Data and Information

Pursuant to the notices published in the Federal Register of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on OTC miscellaneous internal drug products, the following firms made submissions related to products used as digestive aids. The Panel defined digestive aids to encompass those ingredients used to treat the symptoms of IPPUAD and intestinal distress. (See part II. paragraph A. below—Definitions of Terms.)

A. Submission by Firms

Based on its review, the Panel classified the submission as being relevant to either IPPUAD or intestinal distress as follows:

1. *For treatment of the symptoms of IPPUAD.*

Firms and Marketed Products

Bowman Pharmaceuticals, Canton, OH 44702—Controflex Phosphorated syrup.

Carter Products, Cranbury, NJ 08512—Gastroenterase tablets.

Dorsey Laboratories, Lincoln, NB 68501—Kanulase tablets.

Father Francis' Herbs, Chicago, IL 60629M—Medicinal Herb Tea No. 3.

Lewis-Howe Co., St. Louis, MO 63102—Discarbosil tablets, Tums tablets.

Purdue Frederick Co., Norwalk, CT 06856—Probilagol liquid.

Reed and Carnrick, Kenilworth, NJ 07033—Laxsil liquid, Phasil tablets, Phazyme tablets.

Rilox Co., New Orleans, LA 70122—Brodie's Cordial liquid.

Van Patten Pharmaceutical Co., Chicago, IL 60640—Allimin tablets.

Warner-Chilcott, Morris Plains, NJ 07950—Gelusil liquid, Gelusil tablets.

Warner-Lambert Co., Morris Plains, NJ 07950—Bromo-Seltzer, Rolaids tablets, hydrate magnesium aluminate activated sulfate liquid and tablets.

2. *For treatment of the symptoms of intestinal distress.*

Firms and Marketed Products

Carter Products, Cranbury, NJ 08512—Gastroenterase tablets.

Chattanooga Medicine Co., Chattanooga, TN 37409—Cardui liquid.

Dorsey Laboratories, Lincoln, NB 68501—Kanulase tablets.

Father Francis' Herbs, Chicago, IL 60629M—Medicinal Herb Tea No. 1.
Hoechst-Roussel, Pharmaceuticals, Inc., Somerville, ND 08876—Festal tablets.
Palafox Laboratories, Inc., Anthony, TX 88021—Palagastra liquid.
Parke-Davis & Co., Detroit, MI 48232—Panteric capsules, tablets, and granules.
Purdue Frederick Co., Norwalk, CT 06856M—Probilagol liquid.
Reed and Carnrick, Kenilworth, NJ 04033—Laxsil liquid, Phasil tablets, Phazyme tablets.
Requa Mfg. Co., Inc., Bronx, NY 10470—Requa's charcoal tablets, Requa's activated charcoal tablets and capsules.
Rilox Co., New Orleans, LA 70122—Brodie's Cordial liquid.
Signet Laboratories, Inc., Burbank, CA 91502—Dihepatone tablets.
Van Patten Pharmaceuticals Co., Chicago, IL 60640—Allimin tablets.
Warner-Lambert Co., Morris Plains, NJ 07950—Bromo-Seltzer.
Winthrop Laboratories, New York, NY 10016—Stamyl tablets.

B. Ingredients Reviewed by the Panel

1. *For treatment of the symptoms of IPPUAD*—a. *Labeled ingredients contained in products submitted to the Panel.*

Acetaminophen
Aluminum hydroxide
Bean
Calcium carbonate, U.S.P.
Catechu, tincture
Cellulase
Cinnamon oil
Citric acid
Dehydrocholic acid
Dihydroxyaluminum sodium carbonate
Dog grass
Elecampane
Galega
Garlic, dehydrated
Glutamic acid hydrochloride
Homatropine methylbromide
Horsetail
Huckleberry
Hydrate magnesium aluminate activated sulfate
Johnswort
Linden
Magnesium hydroxide, N.F.
Magnesium trisilicate
Nettle
Orthophosphoric acid
Ox bile extract
Pancreatic enzyme concentrate
Pancreatin, N.F.
Peppermint oil
Peppermint spirit
Pepsin
Simethicone
Sodium bicarbonate
D-sorbitol
Strawberry
Sucrose
Tannic acid

b. *Other ingredients.* In addition to those ingredients included in the products submitted to the Panel, the following ingredients were listed in the **Federal Register** notice of August 27, 1975 (40 FR 38179).

Alcohol
Anise seed
Aromatic powder
Asafetida
Belladonna alkaloids
Belladonna leaves, powdered extract
Bismuth subcarbonate
Bismuth subgallate
Capsicum
Capsicum, fuild extract of
Carbon
Cascara sagrada extract
Catnip
Chamomile flowers
Charcoal, activated
Chloroform
Cinnamon tincture
Diastase
Ether
Ginger
Gylcine
Hydrastis fluid extract
Hydrochloric acid
Iodine
Kaolin, colloidal
Lactic acid
Lavender compound, tincture of
Mannitol
Myrrh, fluid extract of
Nux vomica extract
Pancrelipase
Pectin
Potassium bicarbonate
Potassium carbonate
Rhubarb fluid extract
Sodium salicylate
Strychnine

2. *For treatment of the symptoms of intestinal distress*—a. *Labeled ingredients contained in products submitted to the Panel.*

Acetaminophen
Amylase
Blessed thistle (*Cnicus benedictus*)
Buckthorn
Catechu, tincture
Cellulase
Charcoal, activated
Charcoal, wood
Cinnamon oil
Citric acid
Dehydrocholic acid
Duodenal substance
Garlic, dehydrated
Glutamic acid hydrochloride
Golden Seal (*Hydrastis canadensis*)
Hemicellulase
Homatropine methylbromide
Johnswort
Juniper
Knotgrass
Lipase
Magnesium hydroxide, N.F.
Ox bile extract
Pancreatic enzyme concentrate
Pancreatin, N.F.
Pancreatin (triple strength)
Papain
Peppermint
Peppermint oil
Pepsin
Protease
Senna
Simethincone
Sodium bicarbonate
Sodium bismuthyltartrate
D-sorbitol
Tannic acid
Woodrull

b. *Other ingredients.* In addition to those ingredients included in the products submitted to the Panel, the following ingredients were listed in the **Federal Register** notice of August 27, 1975 (40 FR 38179).

Aluminum hydroxide
Aspergillus oryza enzymes
Bacillus acidophilus
Betaine hydrochloride
Black radish powder
Calcium gluconate
Citrus pectin
Diastase malt
Fennel acid
Glycine
Hectorite
Iron ox bile
Lactose
Lysine hydrochloride
Mycozyme
Niacinamide
Nickel-pectin
Orthophosphoric acid
Pancrelipase
Papaya, natural
Phenacetin
Prolase
Sodium chloride
Stem bromelain
Trillium
Vitamin B–1
Vitamin B
Vitamin B–3

C. Classification of Ingredients

1. *For treatment of the symptoms of IPPUAD*—a. *Active ingredients.*

Almadrate sulfate (hydrate magnesium aluminate activated sulfate)
Aluminum hydroxide
Calcium carbonate (calcium carbonate, U.S.P.)
Cellulase
Dehydrocholic acid
Dihydroxyaluminum sodium carbonate
Garlic, dehydrated
Glutamic acid hydrochloride
Homatropine methylbromide
Magnesium hydroxide (magnesium hydroxide, N.F.)
Magnesium trisilicate
Ox bile extract
Pancreatin and pancrelipase (pancreatin, N.F.; pancreatic enzyme concentrate)
Peppermint oil
Pepsin
Simethicone
Sodium bicarbonate
Sodium citrate (citric acid)
Sorbitol (*D*-sorbitol)

b. *Inactive ingredients.*

Sucrose

c. *Other ingredients.* The Panel was neither able to locate nor it is aware of any significant body of data demonstrating the safety and

effectiveness of the following OTC ingredients in treating the symptoms of IPPUAD. The Panel, therefore, classifies these ingredients as Category II for this use, and they will not be reviewed further in this document.

Alcohol
Anise seed
Aromatic powder
Asafetida
Bean
Belladonna alkaloids
Belladonna leaves, powdered extract
Bismuth subcarbonate
Bismuth subgallate
Capsicum
Capsicum, fluid extract of
Carbon
Cascara sagrada extract
Catechu, tincture
Catnip
Chamomile flowers
Charcol, activated
Chloroform
Cinnamon oil
Cinnamon tincture
Diastase
Dog grass
Elecampane
Ether
Galega
Ginger
Glycine
Horsetail
Huckleberry
Hydrastis fluid extract
Hydrochloric acid
Iodine
Johnswort
Kaolin, colloidal
Lactic acid
Lavender compound, tincture of
Linden
Mannitol
Myrrh, fluid extract of
Nettle
Nux vomica extract
Orthophosphoric acid
Pectin
Peppermint spirit
Potassium bicarbonate
Potassium carbonate
Rhubarb fluid extract
Sodium salicylate
Strawberry
Strychnine
Tannic acid

d. *Ingredient deferred to and reviewed by the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products as published in the* **Federal Register** of July 8, 1977 (42 FR 35345).

Acetaminophen

2. *For treatment of the symptoms of intestinal distress*—a. *Active ingredients.*

Bismuth sodium tartrate (sodium bismuthyltartrate)
Blessed thistle (*Cnicus benedictus*)
Cellulase and hemicellulase
Charcoal, activated and charcoal, wood
Dehydrocholic acid
Duodenal substance
Garlic, dehydrated
Glutamic acid hydrochloride
Golden seal (*Hydrastis canadensis*)
Homatropine methylbromide
Magnesium hydroxide (magnesium hydroxide, N.F.)
Ox bile extract
Pancreatin and pancrelipase (pancreatin, N.F.; pancreation (triple strength); pancreatic enzyme concentrate)
Papain
Pepsin
Simethicone
Sodium bicarbonate
Sodium citrate (citric acid)
Sorbitol (*D*-sorbitol)

b. *Inactive ingredients.* None.

c. *Other ingredients.* The Panel was neither able to locate nor is it aware of any significant body of data demonstrating the safety and effectiveness of the following OTC ingredients in treating the symptoms of intestinal distress. The Panel, therefore, classifies these ingredients as Category II for this use, and they will not be reviewed further in this document.

Aluminum hydroxide
Amylase
Aspergillus oryza enzymes
Bacillus acidophilus
Betaine hydrochloride
Black radish powder
Buckthorn
Calcium gluconate
Catechu, tincture
Cinnamon oil
Citrus pectin
Diastase malt
Fennel acid
Glycine
Hectorite
Iron ox bile
Johnswort
Juniper
Knotgrass
Lactose
Lipase
Lysine hydrochloride
Mycozyme
Nickel-pectin
Orthophosphoric acid
Papaya, natural
Peppermint
Peppermint oil
Phenacetin
Protease
Prolase
Senna
Sodium chloride
Stem bromelains
Tannic acid
Trillium
Woodruff

d. *Ingredients deferred to and reviewed by other panels*—(1) *Ingredients deferred to and reviewed by the Advisory Review Panel on OTC Vitamin, Mineral, and Hematinic Drug Products as published in the* **Federal Register** *of March 16, 1979 (44 FR 16126)*

Niacin (niacinamide)
Thiamine (vitamin B–1)
Riboflavin (vitamin B–2)
Vitamin B–3

(2) *Ingredient deferred to and reviewed by the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products as published in the* **Federal Register** *of July 8, 1977 (42 FR 35345).*

Acetaminophen

CATEGORIZATION OF SINGLE INGREDIENTS CONSIDERED BY THE PANEL FOR SAFETY AND EFFECTIVENESS AS DIGESTIVE AIDS

Ingredients	IPPUAD [1]		ID [2]	
	Category	Basis [3]	Category	Basis
Almadrate sulfate	III	E		
Aluminum hydroxide	III	E		
Bismuth sodium tartrate			II	S, E
Calcium carbonate	III	E		
Cellulase	II	E	III	E
Charcoal, activated and Charcoal, wood			III	E
Dehydrocholic acid	II	E	II	E
Dihydroxyaluminum sodium carbonate	III	E		
Duodenal substance			II	S, E
Garlic, dehydrated	II	E	II	E
Glutamic acid hydrochloride	II	E	II	E
Hemicellulase			III	E
Homatropine methylbromide	II	E	III	E
Magnesium hydroxide	III	E	III	E
Magnesium trisilicate	III	E		
Ox bile extract	II	E	II	E
Pancreatin and pancrelipase	II	E	III	E
Papain			II	E
Peppermint oil	III	E		
Pepsin	II	E	II	E
Simethicone	III	E	III	E
Sodium bicarbonate	III	E	III	E
Sodium citrate	III	E	III	E
Sorbitol	II	E	II	E

[1] IPPUAD—Immediate postprandial upper abdominal distress.
[2] ID—Intestinal distress.
[3] Basis for Categorization: S (Safety), E (Effectiveness).

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons in response 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). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on display after February 4, 1982, in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. Definitions of Terms

For the purpose of this document, the Panel agreed on the following definitions:

1. *Aerophagia.* The swallowing of air.

2. *Antiflatulent.* An agent that relieves or prevents flatulence.

3. *Eructation.* The act of belching.

4. *Flatulence.* The presence of excessive amounts of air or other gas in the stomach and/or intestines.

5. *Flatus.* Gas passed by rectum.

6. *Immediate postprandial upper abdominal distress (IPPUAD).* A symptom complex consisting of the sensations of bloating, distention, fullness, or pressure with upper abdominal discomfort occurring immediately (within 30 minutes) after a meal, excluding symptoms of aerophagia or hyperacidity.

7. *Intestinal distress.* A syndrome consisting of abdominal discomfort occurring 30 minutes to several hours after a meal. It is self-limiting and not attributable to any known organic disease, nor accompanied by diarrhea or constipation. This syndrome is characterized by one or more of the following symptoms: Bloating, distention, fullness, pressure, pain, or cramps.

8. *Postprandial.* Occurring shortly after eating.

9. *Symptom.* Any subjective evidence of a patient's condition, as perceived by the patient.

10. *Syndrome.* A set of symptoms which occur together; a symptom complex.

B. General Discussion

The Panel reviewed drug products which were claimed to alleviate symptoms in the stomach as well as the intestines following the ingestion of food. The Panel has designated this group of drugs as digestive aids and has divided the group into two classifications: (1) Those drugs for treating the symptoms of IPPUAD—symptoms occurring within 30 minutes after ingestion of food, and (2) those drugs for treating the symptoms of intestinal distress—symptoms occurring from 30 minutes to several hours after ingestion of food.

1. *For treatment of the symptoms of IPPUAD.* A final monograph for "antiflatulent active ingredients" was published in the **Federal Register** of June 4, 1974 (39 FR 19877). The agency, in establishing this monograph, allowed the continued marketing of simethicone (maximum daily dose of 500 milligrams (mg)) as an OTC antiflatulent in combination with "* * * any generally recognized as safe and effective antacid ingredient(s) if it is indicated for use solely for the concurrent symptoms of gas associated with heartburn, sour stomach, or acid indigestion" (21 CFR 332.15). The term antiflatulent was specifically defined as a drug able "to alleviate or relieve the symptoms of gas" (21 CFR 332.30(a)). In the **Federal Register** of November 12, 1973 (38 FR 31266), the agency noted that other ingredients may also be useful as antiflatulents and requested that any available data be submitted to the OTC Miscellaneous Internal Drug Products Panel for review. The antiflatulent monograph would then be amended to include any additional safe and effective antiflatulent active ingredients.

The agency has concluded that at least one antiflatulent ingredient is effective and one would infer that the symptoms referred to in the statement, " 'to alleviate or relieve the symptoms of gas,' " are indeed caused by excess gas. The Panel has reviewed all available data and has found no conclusive evidence that excess gas is the causative agent in producing undesirable symptoms, specifically the symptoms of bloating, distention, fullness, or pressure associated with IPPUAD.

The Panel looked at "antiflatulent" drugs which were claimed to alleviate symptoms of discomfort (bloating, distention, fullness, or pressure) that occur in the abdomen in the immediate postprandial period. The term "flatulent" is commonly associated with some amount of gas, but because this Panel does not accept gas as a causative agent of distress in the upper gastrointestinal tract, the Panel considered it contradictory and inappropriate to review, as antiflatulents, those drugs which were claimed to relieve immediate postprandial symptoms. Therefore, the concept of IPPUAD was developed by the Panel in order to describe more accurately the therapeutic intent of these drug products.

The Panel acknowledges the fact that a large segment of the population occasionally has immediate postprandial upper abdominal complaints which are commonly and, in the opinion of the Panel, erroneously attributed to "excess gas." The terms "excess gas," "gaseousness," "flatulence," "bloating," "distention," and "fullness" have different meanings to different people; consequently, it is important to determine accurately the meaning of the terms as they are used to describe various consumer complaints.

One medical dictionary defines "flatulence" as "the presence of an excessive amount of gas in the stomach and intestines" (Ref. *1*). Another medical dictionary describes "flatulence" as "the presence of excessive amounts of air or gases in the stomach or intestine, leading to distention of the organs" (Ref. *2*). It is a well-known fact, however, that a certain amount of gas is constantly present in the gastrointestinal tract, and that not all people complain of flatulence.

The Random House Dictionary of English Usage defines "flatulent" as (1) "generating gas in the intestinal canal, as food," and (2) "attended with, caused by, or suffering from, such an accumulation of gas" (Ref. *3*). The first definition stems from the knowledge that certain foods (beans and onions) are prone to undergo bacterial fermentation in the large bowel, producing gases which are passed rectally without pain, as flatus. Preparations used for the relief of intestinal distress are also the subject of this document. (See part IV. below—Drug Products for the Treatment of the Symptoms of Intestinal Distress.)

The second definition above (Ref. *3*) apparently refers to accumulations of gas in the gastrointestinal tract which causes distress. This definition appears to be the one almost universally accepted by the lay public, and the Panel acknowledges that, on occasion, a large segment of the population may experience symptoms in the immediate postprandial period which it interprets as due to the presence of excessive gas. This ill-defined syndrome (upper abdominal bloating, distention, fullness, or pressure) which occurs in the immediate postprandial period is a common reason for taking "antiflatulent" drugs. The Panel, however, does not accept "excessive gas" as the causative agent, and, in fact, is not aware of any objective study which definitely establishes gas as the

causative agent for the IPPUAD symptom complex.

The Panel firmly believes that more studies are essential to definitely establish the etiology or etiologies of the IPPUAD syndrome. If such studies prove that gas is the etiologic agent, they must also show that the ingredient under evaluation relieves the symptoms, and that it decreases the amount of gas present.

The Panel acknowledges that everyone swallows some air, especially with food or liquid, and particularly if food is eaten rapidly and/or large quantities are ingested. It has been estimated that this "swallowed air" accounts for the major portion of gas in the gastrointestinal tract (Ref. *4*). Swallowed air (aerophagia) commonly results in eructation (belching). Gas that is released by belching consists entirely of swallowed air or carbon dioxide, and that which is not released by belching passes rapidly through the intestinal tract where it mixes with gas from food fermentation and is either absorbed or passed rectally as flatus. Such gas amounts to a normal physiologic mechanism and does not usually cause distress or require medication.

Another authority has stated that:

> Air in significant volumes may be admitted to the gastrointestinal tract without bothersome symptoms, other than flatulence, providing the gas-handling mechanisms are operational. Otherwise normal persons may become symptomatic when large quantities of food are ingested, possibly representing an overload phenomenon (Ref. *5*).

In reviewing the pertinent literature the Panel became aware of one study of 22 patients which found that the volume of gastrointestinal gas did not differ significantly in 12 patients with chronic complaints of excess gas compared to 10 controls who were free of abdominal complaints (Ref. *6*). When gas was infused into the intestines of the patients and the control group, more gas tended to reflux into the stomach of, and intestinal transit times were longer for, those patients who complained of abdominal pain (excess gas). This led the authors to conclude that an abnormal motility exists which results in disordered passage of gas through the bowel, with a painful response to an overall intestinal gas volume well tolerated by normal subjects.

Because the Panel believes that excessive gas is not the cause of IPPUAD, and has been unable to find any studies to support this excessive gas theory, it is the opinion of the Panel that the term "antiflatulent" or similar terms should not be used in the labeling or promotional material of drugs which claim to relieve the symptoms of IPPUAD, unless it is proven by scientific studies that excess gas is actually present and causing symptoms.

The Panel, of course, is aware that some persons complaining of the symptoms of IPPUAD have an organic basis for their complaints and may be suffering from abnormalities or disease of the gastrointestinal tract or other organ systems. Persons with persistent or chronic symptoms should have a thorough medical evaluation.

At the present time the Panel is not aware of any ingredients which have been adequately demonstrated to be effective in treating the symptoms of IPPUAD. However, the Panel has classified several ingredients as Category III in order to allow further testing and evaluation to establish effectiveness. (See part III, paragraph C. below—Category III Conditions.)

The Panel is aware of the following proposed mechanisms of action for ingredients which were claimed to relieve the symptoms of IPPUAD: (1) Reduction of the surface tension of the contents of the stomach, (2) altering stomach emptying by changing the acidity or osmolarity of the stomach, and (3) hastening stomach emptying by increasing smooth muscle contraction. However, the Panel is not convinced that any of these are the mechanism by which these IPPUAD ingredients work.

Studies attempting to demonstrate the effect of acids on gastric emptying have shown that the greater the acidity, the slower will be the emptying rate. Hunt and Knox (Ref. *7*) have shown that as the stomach became less acidic, the rate of gastric emptying was enhanced. Steinberg and Almy (Ref. *8*) suggest that alkalinization of the gastric contents is one of the mechanisms responsible for the relief of distention and pressure.

Steinberg and Almy (Ref. *8*) also proposed that distention of the stomach caused by evolution of carbon dioxide by certain medicinal agents and subsequent decrease in distention by eructation of gas could relieve the distress. Temporary distention such as that which is produced by the reaction of active ingredients with the gastric acid may hasten stomach emptying by the motor mechanism described by Weisbrodt et al. (Ref. *9*), i.e., high antral contractile activity and low duodenal contractile activity.

References

(*1*) "Stedman's Medical Dictionary," 22d Ed., Williams and Wilkins, Baltimore, 1972, s.v. "flatulence."

(*2*) "Dorland's Illustrated Medical Dictionary," 25th Ed., W. B. Saunders Co., Philadelphia, 1965, s.v. "flatulence."

(*3*) "The Random House Dictionary of the English Language, the Unabridged Edition," Random House, New York, 1966, s.v. "flatulence."

(*4*) Roth, J. A., "The Sympton Patterns of Gaseousness," *Annals of the New York Academy of Sciences*, 150:109–127, 1968.

(*5*) Danhof, T. E., "Gaseousness," *in* "Current Therapy, 1976," W. B. Saunders Co., Philadelphia, pp. 376–379, 1976.

(*6*) Lasser, R. B., J. H. Bond, and M. D. Levitt, "The Role of Intestinal Gas in Functional Abdominal Pain," *New English Journal of Medicine*, 293:524–526, 1975.

(*7*) Hunt, J. N., and M. T. Knox, "Regulation of Gastric Emptying," *in* "Handbook of Physiology," Volume IV, Section 6, American Physiology Society, Washington, pp. 1917–1935, 1968.

(*8*) Steinberg, H., and T. P. Almy, "Drugs for Gastrointestinal Disturbances," *in* "Drugs of Choice 1966–1967," edited by W. Modell, The C. V. Mosby Co., St. Louis, pp. 318–352, 1966.

(*9*) Weisbrodt, H. S., et al., "A Relation Between Gastroduodenal Muscle Contractions and Gastric Emptying," *Gut*. 10:543–548, 1969.

2. *For treatment of the symptoms of intestinal distress.* The Panel has recognized a syndrome of IPPUAD as described in the General Discussion above. In a significant segment of the population, the intestinal distress syndrome starts 30 minutes to several hours after eating. This syndrome is characterized by one or more of the following abdominal distress symptoms: Bloating, distention, fullness, pressure, excess flatus, pain, or cramps. The syndrome is self-limiting, not attributable to any known organic disease, and not accompanied by constipation or diarrhea. It should be emphasized that these symptoms may occur as the result of a multitude of disease states and if they persist, medical consultation should be obtained.

These symptoms have been attributed by the lay population to, and further popularized in advertising by some drug firms as caused, by, excess gas. It is probable that many physiologic factors are involved, which are poorly understood at the present time, such as the transit time of food materials through the small and large intestine, the nature of the food materials, the character of the bacterial population in the large intestine, etc. Gas is normally present in the small and large intestine in varying amounts. However, the Panel has been unable to find any conclusive proof that gas is a causative agent of any of the symptons of this syndrome.

C. Physiology Review

1. *For treatment of the symptoms of IPPUAD.* In order to better evaluate the mechanisms of action of the ingredients under its review, the Panel looks at the role of "gas" in the gastrointestinal tract

and its possible relationship to the symptoms of IPPUAD—unpleasant sensations perceived within the first 30 minutes following a meal and commonly described as bloating, distention, fullness, or pressure. These sensations are commonly attributed by the sufferer to "gas". However, some authors consider the cause to be gastric distention or altered physiology of gastric emptying.

The rate of gastric emptying is determined by the chemical and physical properties of the stomach contents as well as the gastric motility. Contents with a pH below 3.5 delay the emptying time, as does the presence of fats. Contents with an osmotic pressure of 200 milliosmoles are optimal for rapid emptying. The autonomic nervous system and various hormones also affect the rate of gastric emptying.

Stomach gas accumulates as a result of air swallowed during the meal, and air trapped in food and frothy saliva. Some people may swallow a half a liter (approximately one pint) or air with a meal. Air may also be swallowed between meals, as a result of gum chewing, smoking, or anxiety (Ref. *1*). Most swallowed air is belched or passed into the small intestine, where it either rapidly diffuses into the blood or passes into the colon. The stomach of an adult human normally contains about 50 milliliters (mL) of gas (Ref. *2*).

The Panel is unable to document through the scientific literature that gas resulting from swallowed air or any other gases present in the stomach are responsible for the symptom of bloating, distention, fullness, or pressure that occur in the immediate postprandial period. The scientific literature does, however, discuss the relationship between gas that is present in the lower gastrointestinal tract and the discomforts of intestinal distress. (See part IV. below—Drug Products for the Treatment of the Symptoms of Intestinal Distress.)

References

(*1*) Roth, J. A., "The Symptom Patterns of Gaseousness," *Annals of the New York Academy of Sciences*, 150:109–127, 1968.

(*2*) Davenport, H. W., "Physiology of the Digestive Tract," 3d ED., Year Book Medical Publishers, Inc., Chicago, p. 214, 1971.

2. *For treatment of the symptoms of intestinal distress.* Abdominal discomfort with sensations of bloating and fullness cannot be correlated with the volume of gas in the bowel. The discomfort is related to the rate of motility of the intestinal contents and may be due to abnormal sensitivity to distention of the bowel. Intestinal motility is regulated by intrinsic and extrinsic innervation. The motility is increased by mild distention but inhibited by marked distention or by irritation of the walls of the intestine. Emotional states may influence motility (Ref. *1*).

The normal transit time through the intestinal tract for intragastric oxygen ranges from 25 to 45 minutes. The transit time for food ranges from 15 to 36 hours, depending on the amount of bulk in the diet (Ref. *2*).

About 70 percent of intestinal gas is swallowed air. The remainder is the product of chemical reactions during digestion, diffusion exchange, and fermentation of partially digested food substances in the colon. The composition of the diet, the degree of the digestion, and the rate of food transit influence the amount and composition of the gases produced by bacterial fermentation. Hydrogen, carbon dioxide, and methane are the principal gaseous products of fermentation (Ref. *3*). The amount of flatus passed by individuals varies from 380 to 1,600 mL per day. Some hydrogen, methane, and carbon dioxide is excreted through the lungs.

Digestion of carbohydrates, proteins, and fats is dependent upon the activity of enzymes. Salivary amylase normally digests a portion of the polysaccharide intake and the remainder is digested by pancreatic amylase in the duodenum (Refs. *4*). The optimal pH for amylase activity is 6.9.

Only 10 to 15 percent of protein foods are split into amino acids by the action of pepsin in the stomach, and normal nitrogen balance can be maintained in the absence of this enzyme. Pancreatic proteolytic enzymes are responsible for the major part of protein digestion. About 10 percent of the protein remains undigested and enters the colon, where it is digested by bacteria (Refs. *4* and *5*).

Fats are hydrolysed by pancreatic and intestinal lipase. The optimal pH for lipase activity is from 6 to 8 (Ref. *5*).

Bile salts facilitate the activity of pancreatic lipase and absorption of fats. Bile salts are largely reabsorbed from the terminal ileum and then resecreted by the liver during digestion of a meal. Additional bile acids are synthesized by the liver to replace those that are not reabsorbed (Ref. *4*). The rate of synthesis is governed by the rate of reabsorption of the bile salts. High concentrations of bile acids are toxic to the epithelial cells of the intestine and, therefore, inhibit the absorption of sugars, amino acids, electrolytes, and water.

References

(*1*) Vander, A. J., J. H. Sherman, and D. S. Luciano, "Human Physiology, The Mechanisms of Body Function," McGraw-Hill, New York, pp. 378–391, 1970.

(*2*) Presentation by Ivan E. Danhof, M.D., to the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, October 16, 1977 (Attached to letter from Hoechst-Roussel Pharmaceuticals, Inc., dated November 8, 1977, in Panel Administrator's File (OTC Volume 17GPAII).

(*3*) Gall, L.S., "The Role of Intestinal Flora in Gas Formation," *Annals of the New York Academy of Sciences*, 150:27–30, 1968.

(*4*) Davenport, H. W., "Physiology of the Digestive Tract," 3d Ed., Year Book Medical Publishers, Inc., Chicago, p. 113, 1971.

(*5*) Magee, D. F., "Secretions of the Digestive Tract," *in* "Howell-Fulton Physiology and Biophysics, Vol. III: Digestion, Metabolism, Endocrine Function and Reproduction," 20th Ed., edited by C. Ruch and H. D. Patton, W. B. Saunders, Philadelphia pp. 45–54, 1973.

D. Rationale For Use

1. *For treatment of the symptoms of IPPUAD.* The Panel believes that the rationale for use of agents intended for the treatment of the symptoms of IPPUAD is to provide significant symptomatic relief, within a short period of time, from the complaints of upper abdominal bloating, distention, fullness, or pressure occurring in the immediate postprandial period (within 30 minutes following a meal). These agents are designed to be taken when symptoms occur and are expected to benefit a clinically significant number of the target population. It is to be expected that not all persons will benefit from any one agent, nor will all agents be equally effective. It is also recognized that other agents not submitted for review or known to the Panel may be effective.

The doses recommended by the Panel are generally recognized to be safe when taken as directed by the majority of adults in good general health. Persistence of symptoms may indicate organic disease that needs professional medical attention. Those who respond only to higher than recommended doses should also seek professional care.

Prophylactic use is considered by the Panel to be inappropriate because the symptoms for which these drugs are taken occur intermittently and are self-limiting. There have been no data presented to the Panel which indicate that any agent intended for the treatment of the symptoms of IPPUAD is safe and effective for prophylactic use.

2. *For treatment of the symptoms of intestinal distress.* The Panel believes that the rationale for the use of agents intended for the treatment of the symptoms of intestinal distress is to provide significant symptomatic relief, within a short period of time, of

complaints of intestinal bloating, distention, fullness, pressure, pain, cramps, or excess flatus occurring 30 minutes to several hours after eating. These agents are designed to be taken when symptoms occur and are expected to benefit a clinically significant number of the target population. It is to be expected that not all persons will benefit from any one agent, nor will all agents be equally effective. It is also recognized that other agents not submitted for review or known to the Panel may be effective.

The doses accepted by the Panel are those generally recognized to be safe when taken as directed by the majority of adults in good general health. Persistence of symptoms may indicate organic disease that needs professional medical attention. Those who respond only to higher than recommended doses should also seek professional care.

Prophylactic use is considered by the Panel to be inappropriate because the symptoms for which these drugs are taken occur intermittently and are self-limiting. There have been no data presented to the Panel which indicate that any agent intended for the treatment of the symptoms of intestinal distress is safe and effective for prophylactic use.

E. Combination Policy

The Panel has reviewed FDA's general combination policy on OTC drug products (21 CFR 330.10(a)(4)(iv)) and believes that the policy as follows is rational.

An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel believes that all combination products used as digestive aids must conform to all three requirements of this general combination policy.

The Panel also believes that if a combination of ingredients is intended to treat separate but concurrent conditions, the labeling of the combination should convey to the consumer that it is to be used only when the symptoms of both conditions are present.

A number of combination drug products submitted to the Panel were subsequently categorized by the Panel as digestive aids and further subdivided for their usefulness in treating the symptoms of IPPUAD and intestinal distress. Each combination submitted has been classified into either Category II or Category III for its respective uses as designated in the chart below, and with the exception of the combination of blessed thistle and golden seal, they will not be reviewed further in this document.

DIGESTIVE AIDS AS COMBINATION INGREDIENTS

Combinations submitted	IPPUAD [1]		ID [2]	
	Category	Basis [3]	Category	Basis
Cellulase, pancreatin, glutamic acid HCl, ox bile extract, and pepsin	II	E	II	E
Cellulase, dehydrocholic acid, pancreatic enzyme concentrate, and pepsin	II	E	II	E
Alcohol, pepermint oil, cinnamon oil, tannic acid, and tincture of catechu	II	E	II	E
Sorbitol and homatropine methylbromide	II	E	II	E
Pancreatin and simethicone	II	E	III	E
Bean, dog grass, elecampane, galega, horsetail, huckelberry, johnswort, nettle, linden, and strawberry.	II	E		
Peppermint spirit and orthophosphoric acid	III	E		
Aluminum hydroxide and magnesium trisilicate	III	E		
Magnesium hydroxide and simethicone	III	E	III	E
Blessed thistle and golden seal			II	E
Ox bile extract, papain, pepsin, pancreatin, duodenal substance, dehydrocholic acid, and charcoal (activated).			II	E
Pancreatin, hemicellulase, and ox bile extract			II	E
Senna, buckthorn, johnswort, woodruff, juniper, peppermint, and knotgrass			II	E
Lipase, amyulase, protease, and hemicelkulase			III	E
Combination of acetaminophen with a Category III digestive aid ingredient	III	E	III	E

[1] IPPUAD—Immediate postprandial upper abdominal distress.
[2] ID—Intestinal distress.
[3] Basis for Categorization: S (Safety), E (Effectiveness).

The individual ingredients in the Category II combinations for IPPUAD and intestinal distress were found to be generally recognized as safe but each combination contains at least one ingredient which was found to be ineffective for the respective indication, i.e., the symptoms of IPPUAD or intestinal distress. The Panel concludes that any combination used for the treatment of the symptoms of IPPUAD or intestinal distress and containing one or more Category II ingredients is hereby placed in Category II for the respective indication. In addition, in accordance with the adopted combination policy stated above, none of the combinations was demonstrated to be effective.

The individual ingredients in the Category III combinations for IPPUAD and intestinal distress were found to be generally recognized as safe but there are insufficient data available to demonstrate whether or not the combinations are effective in treating the symptoms of IPPUAD or intestinal distress. The Panel recommends that testing of the Category III combinations be performed according to the testing guidelines. (See part III. paragraph D.1. below—Guidelines for developing a protocol for evaluating OTC drugs for the treatment of the symptoms of IPPUAD or part IV. paragraph D. below—Guidelines for Developing Protocols for Evaluating OTC Drugs for the Treatment of the Symptoms of Intestinal Distress.) The requirements of the combination policy stated above must also be taken into consideration when devising specific studies.

One of the combination products submitted contains an internal analgesic in addition to a digestive aid ingredient. The internal analgesic ingredient is present only to relieve a concurrent condition (headache). The Panel has evaluated such a combination and considers it rational because it meets the needs of a defined target population. The Panel, therefore, recommends that acetaminophen, a safe and efffective internal analgesic ingredient (as published in the Federal Register of July 8, 1977 (42 FR 35412)), may be combined with any Category III (which may eventually become Category I) digestive aid ingredient when such a combination is used for the treatment of headache or minor aches and pains occurring concurently with the symptoms of IPPUAD or intestinal distress.

F. Labeling

The Panel has carefully reviewed the submitted labeling claims made for products promoted for the relief of the symptoms of IPPUAD and intestinal distress and has categorized them according to their acceptability into Category I, Category II, or Category III. The Panel is aware that there may be other terms that would be acceptable in expressing the same Category I indications.

In order for any labeling to be acceptable, it must include (a) the indication(s) for use, (b) pertinent warnings and contraindications, and (c)

the recommended dosage range. Only those indications and warnings listed under Category I are generally recognized to be acceptable at this time. (See part III. pargraph A.2. below—Category I labeling and part IV. paragraph A.2. below—Category I labeling.)

The Panel believes that all labeling should be clear, concise, and easily read and understood by most consumers. It has followed this concept in the development of all Category I labeling. The Panel is also concerned about the size and color of the print used in labeling of these and all drug products, and recommends that the industry make the necessary effort to design labeling which can be read easily by consumers.

One of the primary functions of this Panel is to attempt to eliminate confusing labeling claims. Much of the labeling on currently marketed digestive aid drug products tends to be overly complicated, vague, unsupported by scientific data, and in some cases false and misleading.

The indications for use should be simply and clearly stated, the directions for use should provide the user with enough information for safe and effective use of the product, and the label should include a statement that the product is intended only for the temporary relief of the symptoms of IPPUAD and/or intestinal distress.

The Panel is also concerned that if two ingredients are indistinguishable with regard to effectiveness, it is misleading to claim superiority for one of the ingredients. The Panel wishes to make it clear that its function is not to compare various ingredients to determine the OTC drug of choice, but to determine the safety and effectiveness for active OTC miscellaneous internal drug ingredients, as well as proper dosage ranges, warnings, and contraindications.

Undocumented, vague, or misleading claims such as "gasid indigestion," "biliousness," "indigestion," and colloquial or provincial expressions that do not have meaning to a majority of people must not be used. Statements which recommend prophylactic use to prevent the onset of symptoms shall not appear on the label. The Panel believes that this practice might lead to overuse of the medication. In the labeling, effectiveness shall not be related to the taste, odor, consistency, or other physical characteristics of the product except as they may affect the action of the active ingredients. Phrases such as "superior to ordinary," "specially improved or selected ingredients," "extra strength," and "contains more active ingredient per dose" may be vague and misleading and should be avoided unless supported by sound scientific data. Phrases such as "works internally" or "travels through the bloodstream" give the implication that the product has a unique physiological action which is unjustified.

The Panel has noted that the use of certain labeling claims related to the safety and/or effectiveness of products and their ingredients is not supported by sound scientific evidence. Until there is acceptable proof that "excess gas" is the causative agent of the syndrome of IPPUAD, the Panel concludes that labeling should not include any word or words directly or indirectly implying or indicating that the medication relieves symptoms due to "gas" or "excess gas." The labeling should not make any such claims until there has been a demonstration by acceptable scientific methods that increased gas volume does exist in this syndrome, that it is decreased by the drug for which "anti-gas" activity is claimed, and that symptomatic relief is associated with a decrease in the gas volume.

The Panel is aware of the prevalent perception among consumers who buy medicine for abdominal distress that their self-diagnosis of "gas" describes their condition and that the word "gas" is a descriptive term for those symptoms. Consequently, the Panel has authorized the phrase "sometimes described as gas" to be used in conjunction with Category I labeling claims. Any claims regarding a drug's specific "anti-gas" activity should not be allowed in the labeling until the drug's effectiveness for this purpose has been demonstrated according to the Category III proposed guidelines, and the final monograph has been appropriately amended.

Phrases like "relief of belching" are not considered by the Panel to be applicable to this group of drugs, because the common causative mechanism for "belching" is aerophagia. To the knowledge of the Panel, no proof exists that any one of these drugs reduces the incidence or extent of aerophagia.

This Panel concurs with the recommendations of the Advisory Review Panel on OTC Antacid Drug Products (as published in the **Federal Register** of April 5, 1973 (38 FR 8719)), and the conclusions of FDA (21 CFR 331.30(b)(4) and (5)) that warnings should be included in the labeling of drugs containing sodium and magnesium but recommends that the wording be as follows: (1) For products containing more than 5 milliequivalents (meq) of sodium in the maximum recommended daily dosage: "If you are on a sodium-restricted diet, do not take this product except under the supervision of a physician"; and (2) For products containing more than 50 meq of magnesium in the maximum recommended daily dosage: "If you have kidney disease, do not take this product except under the supervision of a physician."

The Panel is aware of the current OTC labeling regulation dealing with warning statements (21 CFR 330.1(g)). The Panel concurs with the warning, "Keep this and all drugs out of the reach of children," and believes that it should be incorporated in the labeling for digestive aid products. However, the Panel recommends that the other warning statement required by § 330.1(g) "In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately" be revised to read as follows: "In case of accidental overdose, contact a Poison Control Center, emergency medical facility, or physician immediately for advice." The Panel believes that this revision will be more informative to the consumer.

Because OTC products can be purchased by anyone, it is the view of the Panel that the public generally does not regard these products as medicines which, if used improperly, can result in injurious or potentially serious consequences. The public needs to be continually alerted to the idea that these products, like all medicine, carry some risk and should be treated with respect. The consumer should also be informed of any possible signs of known toxicity or any symptom requiring discontinuation of the use of the drug so that appropriate steps may be taken before more severe consequences become apparent.

In addition, the Panel recommends that drug product labeling contain instructions for the most effective preparation and use of the product ("shake well before using," "mix thoroughly," etc.) and that instructions for product use, which are intended to facilitate and improve the delivery and availability of the active ingredient, be prominently displayed on all package labeling.

As previously stated, the Panel believes that the labeling of combination products intended to treat separate but concurrent conditions should convey to the consumer that the product is to be used only when the concurrent symptoms, which require treatment by each type of active ingredient, are present.

The Panel believes that the label should contain a listing of all ingredients

and that it should clearly indicate which are active and which are inactive. Active ingredients should be listed by their established names, and the label should state the quantity of the active ingredients per dosage unit.

G. Dosing Considerations

Each dosage recommended in this document is within the range suggested by either the product manufacturer, official compendia, or authorities in the appropriate medical specialty. The dose ranges are usually based on average adult weight and size (70 kilograms (kg)). Some of the factors that can alter availability and the therapeutic effects for each dose are: (a) Age, (b) size (surface area), (c) body weight, (d) general physical condition, (e) allergies, (f) smoking and drinking patterns, (g) other medication taken concurrently, (h) the type of container used for measuring and administering liquid medication, and (i) when taken in relation to eating.

The Panel recognizes that many factors may alter the activity, rate of metabolism, and excretion of any drug administered. These factors are most critical in very young and elderly persons.

III. Drug Products for the Treatment of the Symptoms of Immediate Postprandial Upper Abdominal Distress

A. Category I Conditions

The following are Category I conditions under which drug products used for the treatment of the symptoms of IPPUAD are generally recognized as safe and effective and are not misbranded.

1. *Category I active ingredients.* None.

2. *Category I labeling.* Although the Panel has not classified any ingredients in Category I, it recommends the following Category I labeling for drug products used to treat the symptoms of IPPUAD as being generally recognized as safe and effective and not misbranded, as well as the specific labeling discussed in the individual ingredient statements.

a. *Indications.* The labeling of the product contains one of the following statements under the heading "Indications":

(1) "Relieves the over-full feeling in the upper abdomen which occurs soon after eating."

(2) "For relief of upper abdominal" [optional, (any or all of the following symptoms): "distress," "bloating," "distention," "fullness," and "pressure"] "which occur(s) soon after eating."

(3) "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'."]

As previously discussed, the Panel is fully aware that although "gas" has not been proven to be the cause of IPPUAD, the consumer may perceive his or her upper abdominal symptoms (distress, bloating, distention, fullness, or pressure) as being due to "gas." Therefore, the Panel, after much deliberation, concludes that claim (3) may be allowed in the labeling of these products.

The word "stomach" may be substituted for the words "upper abdomen" or "upper abdominal" in the respective claims above.

b. *Warnings.* All labeling for products used to treat the symptoms of IPPUAD should contain the following under the heading "Warnings":

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

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

B. Category II Conditions

The following are Category II conditions under which drug products used for the treatment of the symptoms of IPPUAD are not generally recognized as safe and effective or are misbranded.

1. *Category II active ingredients.*

Cellulase
Dehydrocholic acid
Garlic, dehydrated
Glutamic acid hydrochloride
Homatropine methylbromide
Ox bile extract
Pancreatin and pancrelipase
Pepsin
Sorbitol

In addition, the Panel has classified other ingredients as Category II elsewhere in this document. (See part I. paragraph C.1.c. above—Other ingredients.)

a. *Cellulase.* The Panel concludes that cellulase is safe for OTC use in the dose noted below, but is not generally recognized as effective in treating the symptoms of IPPUAD.

(1) *Safety.* Cellulase is obtained from molds such as *Aspergillus oryzae* and *Penicillium notatum* as well as from various other sources (Refs. *1* and *2*). Cellulase has been utilized as a digestive aid in doses of 9 to 50 mg three times daily (Refs. *3* and *4*). The Panel concludes that it is safe when used as a digestive aid in these doses.

(2) *Effectiveness.* Some data were submitted demonstrating cellulase digestive activity on vegetable foods (Ref. *3*) but the Panel is not aware of any adequate and well-controlled clinical studies demonstrating the effectiveness of cellulase in treating the symptoms of IPPUAD. Therefore, the Panel concludes that cellulase is not generally recognized as an effective treatment for the symptoms of IPPUAD.

(3) *Evaluation.* The Panel concludes that cellulase is generally recognized as safe for OTC use in the dose specified but its effectiveness has not been demonstrated in treating the symptoms of IPPUAD.

Cellulase has been further reviewed by this Panel for its use in treating the symptoms of intestinal distress and the conclusions are included later in this document. (See part IV. paragraph C.1.a. below—Cellulase and hemicellulase.)

References

(*1*) Pigman, W., "Enzymes Acting on Hemicelluloses, Gum and Wood," *in* "The Enzymes," Volume I, edited by J. B. Sumner and K. Myrback, Academic Press, New York, pp. 739–744, 1951.

(*2*) Courtois, J. E., "Some Biochemical Aspects of Cellulases and Hemicellulases," *Glasnik Hemijskog Drugstvaw*, 32:365–388, 1967.

(*3*) OTC Volume 170049.

(*4*) OTC Volume 170100.

b. *Dehydrocholic acid.* The Panel concludes that dehydrocholic acid is safe for OTC use in the dose noted below, but is not generally recognized as effective in treating the symptoms of IPPUAD.

(1) *Safety.* The Panel is aware of one animal study which determined the LD_{50} (median lethal dose) of dehydrocholic acid to be 14.7 grams/kilogram (g/kg) in rats. The study further reported that no hepatic damage was found to result from the chronic administration of 3 and 5 g daily to dogs for 3 to 7 months, nor from the administration of 333 milligrams/kilogram (mg/kg) daily to rats for 32 days (Ref. *1*).

The Panel concurs with the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products, in a report published in the Federal Register of March 21, 1975 (40 FR 12902), which found dehydrocholic acid to be safe in an adult dose of 750 to 900 mg per day when used as a laxative (40 FR 12910). That Panel did not approve its use in children under 12 years of age.

Based on the available data, the Panel concludes that dehydrocholic acid is safe for OTC use in the above dosage.

(2) *Effectiveness.* Dehydrocholic acid, which is a partially synthetic derivative of cholic acid, stimulates the liver to increase the volume of bile by increasing its water content without increasing other constitutents (hydrocholeretic) (Refs. *2* and *3*).

Dehydrocholic acid has been used as an OTC laxative, but the Panel is not aware of any adequate and well-controlled clinical studies demonstrating its effectiveness in treating the symptoms of IPPUAD; nor is dehydrochloic acid generally recognized as an effective treatment for the symptoms of IPPUAD. Therefore, the Panel concludes that dehydrocholic acid is not an effective treatment for the symptoms of IPPUAD.

(3) *Evaluation.* The Panel concludes that dehydrocholic acid is generally recognized as safe for OTC use in the dose specified above but its effectiveness in treating the symptoms of IPPUAD has not been demonstrated. This conclusion is in agreement with the following decision of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products (as published in the **Federal Register** of March 21, 1975 (40 FR 12910)):

> There is no evidence in support of the claim that dehydrocholic acid relieves "indigestion", "excessive belching", "after meal discomfort", or "the sensation of abdominal fullness". These claims constitute mislabeling and dehydrocholic acid is placed in Category II with respect to these claims.

Dehydrocholic acid has been further reviewed by this Panel for treating the symptoms of intestinal distress and the conclusions are included elsewhere in this document. (See part IV. paragraph B.1.c. below—Dehydrocholic acid.)

References

(*1*) Berman, A. L., E. Snapp, A. C. Ivy, and A. J. Atkinson, "The Effect of Long-Continued Ingestion of Oxidized Bile Acids on the Dog and Rat," *American Journal of Digestive Diseases,* 7:260–284, 1940.

(*2*) Harvey, S.C., "Gastric Antacids and Digestants," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, p. 973, 1975.

(*3*) DiPalma, J. R., "Drill's Pharmacology in Medicine," 4th Ed., McGraw-Hill, New York, pp. 972–973, 1971.

c. *Garlic, dehydrated.* The Panel concludes that dehydrated garlic is safe for OTC use in the dose noted below, but is not generally recognized as effective in treating the symptoms of IPPUAD.

(1) *Safety.* Garlic has been widely used as a food for many years with no known harmful effects. It is considered by the Panel to be safe in the recommended OTC dose of 0.6 gram (g) after meals (Ref. *1*).

(2) *Effectiveness.* The principal active ingredients of dehydrated garlic are allyl propyl disulfide and diallyl disulfide (Ref. *2*).

Some data were submitted regarding dehydrated garlic's effectiveness as a carminative (expelling gas from the alimentary canal), but the Panel is not aware of any adequate and well-controlled clinical studies demonstrating the effectiveness of dehydrated garlic or its principal active ingredients in treating the symptoms of IPPUAD; nor is it generally recognized as an effective treatment for the symptoms of IPPUAD.

(3) *Evaluation.* The Panel concludes that dehydrated garlic is generally recognized as safe for OTC use in the dose specified, but its effectiveness has not been demonstrated in treating the symptoms of IPPUAD.

Dehydrated garlic has been further reviewed by this Panel for treating the symptoms of intestinal distress and the conclusions are included elsewhere in this document. (See part IV. paragraph B.1.e. below—Garlic, dehydrated.)

References

(*1*) OTC Volume 170003.

(*2*) Bordia, A., H. C. Bonsal, S. K. Arora, and S. V. Singh, "Effect of the Essential Oils of Garlic and Onion on Alimentary Hyperlipemia," *Atherosclerosis,* 21:15–19, 1975.

d. *Glutamic acide hydrocholoride.* The Panel concludes that glutamic acid hydrochloride is safe for OTC use in the dose noted below, but is not generally recognized as effective in treating the symptoms of IPPUAD.

(1) *Safety.* Available clinical data and marketing experience have shwon glutamic acid hydrochloride to be safe for OTC use in the dose of 1.02 g three times daily as a stomach acidifier. (Ref. *1*).

(2) *Effectiveness.* Glutamic acid hydrochloride has been marketed as an agent intended to increase the amount of acid present in the stomach and thus favorably alter the pH of the gastric environment (Refs. *2* and *3*). However, the Panel knows of no proven relationship between hypoacidity or anacidity of the stomach and the symptoms of IPPUAD, nor is the Panel aware of any adequate and well-controlled clinical studies demonstrating the effectiveness of glutamic acid hydrochloride in treating the symptoms of IPPUAD. Furthermore, glutamic acid hydrochloride is not generally recognized as an effective treatment for this condition.

(3) *Evaluation.* The Panel concludes that glutamic acid hydrochloride is generally recognized as safe for OTC use in the dose specified, but its effectiveness has not been demonstrated in treating the symptoms of IPPUAD.

The Panel is aware that glutamic acid hydrochloride has been employed as a stomach acidifier in the treatment of achlorhydria and hypochlorhydria but does not find it has any usefulness in treating these conditions. The Panel has published a separate document on OTC stomach acidifier drug products in the **Federal Register** of October 19, 1979 (44 FR 60316).

Glutamic acid hydrochloride has been further reviewed by this Panel for treating the symptoms of intestinal distress, and the conclusions are included elsewhere in this document. (See part IV. paragraph B.1.f. below—Glutamic acid hydrochloride.)

References

(*1*) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 1082–1083, 1977.

(*2*) OTC Volume 170023.

(*3*) OTC Volume 170049.

e. *Homatropine methylbromide.* The Panel concludes that homatropine methylbromide is safe for OTC use in the dose noted below, but is not generally recognized as effective in treating the symptoms of IPPUAD.

(1) *Safety.* In a study to determine the minimal toxic dose of homatropine methylbromide, Berger and Ballinger reported toxicity in individuals ingesting doses ranging from 68 to 273 mg per day (Ref. *1*). This is far in excess of the usually recommended dosage of 2.5 to 5.0 mg four times daily (Ref. *2*). There was no evidence of toxic or cumulative effects at the smaller dosage of 1 mg three times daily before meals (Ref. *1*).

"Slight cerebral symptoms" have resulted from the use of maximum doses of 20 mg per day, but no cumulative effects have been reported (Ref. *3*). Homatropine methylbromide is about one-half as potent as atropine in its effect on the gastrointestinal tract and is claimed to be one-thirtieth as toxic on the central nervous system (Ref. *4*). Its use is generally accompanied by fewer central nervous system side effects than atropine (Ref. *4*). Therefore, the Panel concludes that homatropine methylbromide is generally recognized as safe in the above doses.

(2) *Effectiveness.* Homatropine methylbromide is a quaternary ammonium cholinergic blocking agent and is much less active than atropine on the central nervous system. Like homatropine, it is a weaker autonomic blocking agent than atropine. It is used to reduce the motility of the intestinal tract (Ref. *2*).

Although the effectiveness of atropine-like substances on the motility of the gastrointestinal tract is well recognized, the Panel is not aware of any adequate and well-controlled

clinical studies demonstrating the effectiveness of homatropine methylbromide in treating the symptoms of IPPUAD nor is it generally recognized as an effective treatment for the symptoms of IPPUAD.

(3) *Evaluation.* The Panel concludes that homatropine methylbromide is generally recognized as safe for OTC use in a maximum dose of 5 mg four times daily, but its effectiveness in treating the symptoms of IPPUAD has not been demonstrated.

Homatropine methylbromide has been further reviewed by this Panel for treating the symptoms of intestinal distress and the conclusions are included elsewhere in this document. (See part IV. paragraph C.1.c. below—Homatropine methylbromide.)

References

(*1*) Berger, A. R., and J. Ballinger, "The Relative Toxicity of Atropine and Novatrine in Man," *American Journal of Medical Sciences,* 214:156–158, 1947.

(*2*) Harvey, S. C., "Antimuscarinic Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol and J. E. Hoover, Mack Publishing Co., Easton, PA, p. 841, 1975.

(*3*) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics," 7th Ed., Lea and Febiger, Philadelphia, p. 351, 1970.

(*4*) Krantz, J. C., and C. J. Carr, "The Pharmacologic Principles of Medical Practice," 7th Ed., Williams and Wilkins, Baltimore, p. 404, 1969.

f. *Ox bile extract.* The Panel concludes that ox bile extract is safe for OTC use in the dose noted below, but is not generally recognized as effective in treating the symptoms of IPPUAD.

(1) *Safety.* The Panel believes the usual dose of 300 to 500 mg given two to three times daily after meals to be safe for healthy individuals (Ref. *1*). However, for individuals who have biliary obstruction or some other forms of liver disease, exogenous bile salts further contribute to an already undesirable increase in plasma and blood concentrations of bile salts (Ref. *2*). Commercial ox bile preparations may produce diarrhea (Ref. *3*).

(2) *Effectiveness.* Ox bile extract is a powdered or granular extract of ox bile with a characteristic odor and taste containing an amount of the sodium salts of ox bile acids equivalent to approximately 45 percent cholic acid (Ref. *1*).

Bile contains bile salts, bile pigments, lecithin, cholesterol, mucin, and other proteins, fatty acids, and inorganic salts. Of these constituents, the most important are the bile salts, which occur as sodium salts of conjugated bile acids (Ref. *1*). The bile salts constitute approximately three percent of the total bile secreted daily (Ref. *2*).

Bile acids are synthesized by the liver and secreted into the duodenum as conjugated bile salts. A high percentge of the bile salts is reabsorbed in the lower small intestine and is recirculated through the liver by way of the enterohepatic circulation.

Bile salts enhance the absorption of lipids and are necessary for the absorption of fat-soluble vitamins and cholesterol. They play an important role in maintaining the normal solubility of cholesterol in the bile (Ref. *3*). Bile salts also promote digestion of fats by stimulating pancreatic secretion and by activating pancreatic lipase (Ref. *2*).

The large volume of bile secreted into the duodenum helps to neutralize the acidic contents but is less important than pancreatic secretions in this respect (Ref. *2*).

Bile salts "* * * can be given to promote the flow of bile or to increase intrabiliary pressure; however, much expert medical opinion now holds that the administration of bile salts is often unnecessary or inappropriate and can sometimes cause undue pain or danger to the patient" (Ref. *2*). "Bile salts are no better than placebos in nonobstructive, noncholestatic biliary tract disorders or in various malfunctions of the intestine" (Ref. *2*).

Ox bile extract "* * * is promoted for the replacement therapy in patients who have an insufficient concentration of bile salts in the intestine, but it is ineffective. Use of ox bile extract is inadvisable, for it does not provide an adequate amount of bile salts" (Ref. *3*).

Ox bile extract has been used for many years in OTC products, but the Panel is not aware of any adequate and well-controlled clinical studies demonstrating its effectiveness in treating the symptoms of IPPUAD, nor is ox bile extract generally recognized as an effective treatment for the symptoms of IPPUAD.

(3) *Evaluation.* The Panel concludes that ox bile extract is generally recognized as safe for OTC use in the dose specified but its effectiveness has not been demonstrated in treating the symptoms of IPPUAD.

Ox bile extract has been further reviewed by this Panel for treating the symptoms of intestinal distress, and the conclusions are included elsewhere in this document. (See part IV. paragraph B.1.g. below—Ox bile extract.)

References

(*1*) "The United States Dispensatory," 27th Ed., edited by A. Osol and R. Pratt, J. B. Lippincott Co., Philadelphia, p. 820, 1972.

(*2*) Harvey, S. C., "Gastric Antacids and Digestants," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, pp. 971–973, 1975.

(*3*) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, p. 1084, 1977.

g. *Pancreatin and pancrelipase.* The Panel concludes that pancreatin preparations (pancreatin or pancrelipase) are safe for OTC use in the dose noted below, but are not generally recognized as effective in treating the symptoms of IPPUAD.

(1) *Safety.* The Panel has determined that pancreatin preparations (pancreatin or pancrelipase) are safe in the usual recommended daily dosage of up to 14 g of triple strength pancreatin when given in divided doses (Ref. *1*). Side effects of nausea, vomiting, and diarrhea may occur at high doses (Ref. *1*). Because pancreatin preparations are obtained mainly from hogs, they should not be used by individuals who are allergic to pork.

(2) *Effectiveness.* Pancreatin preparations (pancreatin or pancrelipase) are a combination of natural enzymes usually obtained from the pancreas of hogs. Their principal components are amylase, lipase, and protease (Refs. *1, 2,* and *3*).

Pancreatin preparations (pancreatin or pancrelipase) are effective as aids to digestion when normal exocrine pancreatic secretion is deficient and have considerable usage for treatment of this condition (Refs. *1, 2,* and *3*).

Pancreatin preparations (pancreatin or pancrelipase) are components of several combination digestive aid preparations, but the Panel is not aware of any adequate and well-controlled clinical studies demonstrating their effectiveness in treating the symptons of IPPUAD. In addition, pancreatin preparations (pancreatin or pancrelipase) are not generally recognized as providing effective treatment for the symptons of IPPUAD.

(3) *Evaluation.* The Panel concludes that pancreatin preparations (pancreatin or pancrelipase) are generally recognized as safe for OTC use in the dose specified but their effectiveness has not been demonstrated in treating the symptons of IPPUAD.

Pancreatin preparations (pancreatin or pancrelipase) have been further reviewed by this Panel for treating the symptons of intestinal distress, and the conclusions are included elsewhere in this document. (See part IV. paragraph C. 1.e. below—Pancreatin and pancrelipase).

References

(1) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 1085–1086, 1977.

(2) Harvey, S. C., "Gastric Antacids and Digestants," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, p. 971, 1975.

(3) Gibb, J. W., "Enzymes," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol and J. E. Hoover, Mack Publishing Co., Easton, PA, p. 973, 1975.

h. *Pepsin.* The Panel concludes that pepsin is safe for OTC use in the dose noted below, but is not generally recognized as effective in treating the symptons of IPPUAD.

(1) *Safety.* No safety data were submitted. However, based upon the continued marketing of pepsin over many years with no reports of adverse effects the Panel concludes that it is safe in a daily dose of up to 1,000 mg (Ref. *1*).

(2) *Effectiveness.* Pepsin is a proteolytic enzyme obtained from the glandular layer of fresh hog stomach (Ref. *2*) and is similar to human pepsin (Ref. *1*). Although its presence is not required for protein digestion, since intestinal enzymes can function without it, pepsin has been used when endogenous human pepsin is deficient or absent. The Panel is not aware of any convincing evidence that added pepsin is of therapeutic usefulness (Refs. *2, 3,* and *4*).

No data were submitted for the effectiveness of pepsin and the Panel is not aware of any adequate and well-controlled clinical studies demonstrating its effectiveness in treating the symptoms of IPPUAD nor is it generally recognized as an effective treatment for the symptons of IPPUAD.

(c) *Evaluation.* The Panel concludes that pepsin is generally recognized as safe for OTC use in the dose specified but its effectiveness has not been demonstrated in treating the symptoms of IPPUAD.

Pepsin has been further reviewed by this Panel for treating the symptoms of intestinal distress and the conclusions are included elsewhere in this document. (See part IV. paragraph B.1.i. below—Pepsin.)

References

(1) "The United States Dispensatory and Physician's Pharmacology," 26th Ed., edited by A. Osol, R. Pratt, and M. D. Altschule, J. B. Lippincott Co., Philadelphia, p. 874, 1967.

(2) Wilson, C. O., O. Grisvold, and R. F. Doerge, "Text Book of Organic Medical and Pharmacological Chemistry," 6th Ed., J. B. Lippincott Co., Philadelphia, pp. 904–905, 1971.

(3) Harvey, S. C., "Gastric Antacids and Digestants," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, p. 971, 1975.

(4) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, p. 1083, 1977.

i. *Sorbitol.* The Panel concludes that sorbitol, also known as *D*-sorbitol, is safe for OTC use in the dose noted below, but is not generally recognized as effective in treating the symptoms of IPPUAD.

(1) *Safety.* The Panel considers sorbitol safe in the suggested oral dose of 4.5 g three times daily (Ref. *1*).

Steinke et al. (Ref. *2*) reported finding no evidence of gastrointestinal side effects and no increase in insulin requirements in 143 juvenile diabetics, aged 5 to 15 years, following the administration of 41 g of sorbitol per day in 3 equal doses for periods of 8 to 48 days. In another study some patients were reported to develop borborygmus (intestinal rumblings) and hyperperistalsis or diarrhea following either large single doses of sorbitol (40 g) for gall bladder studies or the administration of 7 g before meals for up to 20 to 60 days (Ref. *3*).

(2) *Effectiveness.* Sorbitol is a six-carbon polyhydric alcohol. It is more slowly absored from the gastrointestinal tract than dextrose. Its main use is as an osmotic diuretic. Fifty percent is metabolized or converted to glycogen and stored in the liver (Ref. *4*). Oxidation to fructose occurs in both the liver and kidney (Ref. *2*).

Maximal contraction of the gall bladder has been found to occur 30 minutes after the administration of 9, 18, and 27 g of sorbitol (Ref. *5*). Eighty percent of 64 patients with hepatobiliary disorders who were treated with 7 g of sorbitol before meals for periods of from 20 to 60 days were reported to have obtained relief from dyspepsia and abdominal swelling, as well as some other symptoms (Ref. *3*).

The Panel is aware that sorbitol is used as an osmotic diuretic and more generally as a laxative, sweetener, humectant, and vehilce (70 percent weight/weight solution) (Ref. *6*); but the Panel is not aware of any adequate and well/controlled clinical studies demonstrating the effectiveness of this ingredient in treating the symptoms of IPPUAD in the absence of hepatobiliary disease. In addition, sorbitol is not generally recognized as an effective treatment for the symptoms of IPPUAD.

(3) *Evaluation.* The Panel concludes that sorbitol is generally recognized as safe for OTC use in the dose specified but its effectiveness has not been demonstrated in treating the symptoms of IPPUAD.

Sorbitol has been further reviewed by the Panel for treating the symptoms of intestinal distress, and the conclusions are included elsewhere in this document. (See part IV. paragraph B.1.j. below—Sorbitol.)

References

(1) OTC Volume 170042 (Section V.A.I.).

(2) Steinke, J., et al., "Evaluation of Sorbitol in the Diet of Diabetic Children at Camp, "*Diabetes,* 10:218–227, 1961.

(3) Piccinelli, O., and G. Timossi, "D–Glucitol in the Therapy of Hepatobiliary Diseases," *Minerva Medica,* 49:77–82, 1958.

(4) DiPalma, J. R., "Drill's Pharmacology in Medicine," 4th Ed., McGraw-Hill, New York, p. 229, 1971.

(5) OTC Volume 170042 (Section V.A.I.).

(6) Swinyard, E. A., "Pharmaceutical Necessities," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol and J. E. Hoover, Mack Publishing Co., Easton, PA, p. 1235, 1975.

2. *Category II labeling.* The Panel concludes that some labeling claims are either vague, misleading, unsupported by scientific data, unrelated to the symptoms of IPPUAD, or in some instances unsupported by sound theoretical reasoning. The claims listed below and other related terms are, therefore, classified as Category II labeling for drug products used to relieve the symptoms of IPPUAD.

a. "Stomach acid medication."
b. "Carminative."
c. "For mild stomach disturbances."
d. "Astringent."
e. "For prompt relief of nausea."
f. "Relieves belching."
g. "Stomachic."
h. "Fast," "fast acting," "long lasting," and any other claims which vaguely and nonspecifically relate to the speed of action.
i. "For the prevention of IPPUAD symptoms."
j. "For relief of gasid indigestion."
k. "For relief of biliousness."
l. "Indigestion."
m. "Superior to ordinary."
n. "Specially improved."
o. "Selected ingredients."
p. "Extra strength."
q. "Contains more active ingredients per dose."
r. "Works internally."
s. "Travels through the bloodstream."
t. "Guaranteed."

C. Category III conditions

The following are Category III conditions for which the available data are insufficient to permit final classification at this time.

1. *Category III active ingredients.* The Panel concludes that the safety of the following ingredients in the recommended doses is unquestioned, except as noted in the individual ingredient writeups:

Almadrate sulfate
Aluminum hydroxide
Calcium carbonate
Dihydroxyaluminum sodium carbonate
Magnesium hydroxide
Magnesium trisilicate
Peppermint oil
Simethicone
Sodium bicarbonate
Sodium citrate

a. *Almadrate sulfate.* The Panel concludes that almadrate sulfate is safe for OTC use in the dose noted below, but data are insufficient to demonstrate its effectiveness in treating the symptoms of IPPUAD.

Almadrate sulfate is also known as aluminum magnesium hydroxide oxide sulfate and hydrate magnesium aluminate activated sulfate.

(1) *Safety.* The Panel believes that almadrate sulfate is safe at the dose stated below.

Since the publication of the final monograph for OTC antacid drug products on June 4, 1974 (39 FR 19862), information has been reported strongly suggesting that ingested aluminum is absorbed, resulting in increased blood and brain levels of aluminum (Ref. *1*). Experimental evidence suggests that hyperparathyroidism, such as found in patients with severe kidney disease, may further increase the ability of the body to absorb aluminum and cause increased deposition in the brain which may lead to encephalopathy. An appropriate warning is included under the heading "Labeling" section below.

(2) *Effectiveness.* Almadrate sulfate is a chemical combination of aluminum hydroxide and magnesium sulfate which, in the presence of gastric hydrochloric acid, forms aluminum hydroxide (the principal active antacid) and magnesium chloride (Ref. *2*). The Panel could find no reports in the medical or pharmaceutical literature regarding the use of this ingredient for treatment of the symptoms of IPPUAD. Almadrate sulfate has been evaluated by the Advisory Review Panel on OTC Antacid Drug Products, in a report published in the **Federal Register** of April 5, 1973 (38 FR 8714). The agency concurred with the evaluation of that Panel and placed almadrate sulfate in Category I as an antacid (21 CFR 331). One series of studies submitted to this Panel failed to distinguish between the accepted antacid activity of almadrate sulfate and its effectiveness in relieving the symptoms of IPPUAD (Ref. *2*). The Panel therefore recommends that almadrate sulfate be tested according to the proposed testing guidelines to determine whether or not it is effective for the treatment of the symptoms of IPPUAD.

(3) *Proposed dosage.* The Panel believes that it is not possible to impose strict dosage limitations at this time, because there are so little data upon which to base a recommended effective dose. However, the Panel believes that the usually administered dosage of up to 1.7 g four times daily is safe for OTC use but should not be taken for longer than 2 weeks except upon the advice of a physician.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used for the treatment of symptoms of IPPUAD. (See part III. paragraph A.2. above—Category I labeling.) In addition, the Panel recommends that the following warnings statements be required to appear in the labeling of drug products containing almadrate sulfate:

(i) "If you have kidney disease, do not use this product except under the supervision of a physician."

(ii) "If you are taking other drugs, consult your physician as this drug may interfere with their effectiveness."

(iii) "Do not take for longer than 2 weeks or in greater than recommended amounts, except upon the advice of a physician."

(5) *Evaluation.* The Panel recommends that adequate testing of almadrate sulfate be performed according to the proposed testing guidelines to determine whether or not it is effective for treatment of the symptoms of IPPUAD. (See part III. paragraph D.1. below—Guidelines for developing a protocol for evaluating OTC drugs used for the treatment of the symptoms of IPPUAD.)

References

(*1*) Mayor, G. H., J. A. Keiser, D. Makdani, and P. K. Ku, "Aluminum Absorption and Distribution: Effect of Parathyroid Hormone," *Science,* 197:1187–1189, 1977.

(*2*) OTC Volume 170128.

b. *Aluminum hydroxide.* The Panel concludes that aluminum hydroxide is safe for OTC use in the dose noted below, except for individuals with severe kidney diseases, but data are insufficient to demonstrate its effectiveness in treating the symptoms of IPPUAD.

(1) *Safety.* Aluminum hydroxide has been widely used as an antacid and has been evaluated as safe for this use by the Advisory Review Panel on OTC Antacid Products, in a report published in the **Federal Register** of April 5, 1973 (38 FR 8714). FDA concurred with the evaluation of that Panel regarding the safety of aluminum hydroxide (21 CFR 331).

Since the publication of the final monograph for OTC antacid drug products on June 4, 1974 (39 FR 19862), information has been reported that strongly suggests that ingested aluminum is absorbed, resulting in increased blood and brain levels of aluminum (Ref. *1*). Experimental evidence suggests that hyperparathyroidism, such as found in patients with severe kidney disease, may further increase the ability of the body to absorb aluminum and cause increased deposition in the brain which may lead to encephalopathy. An appropriate warning is included below under the heading "Labeling."

Aluminum hydroxide has the potential for affecting the actions of various drugs, including tetracyclines, phenothiazines, isoniazid, oral anticoagulants, anticholinergics, barbiturates, quinine, quinidine, and digoxin (Refs. *2* and *3*). The Panel believes that the lableing of antacids containing aluminum should alert the consumer to potential drug interactions as specified below under the heading "Labeling."

(2) *Effectiveness.* Aluminum hydroxide reacts with hydrocholoric acid in the stomach to form aluminum chloride. However, preparations of aluminum hydroxide vary widely in their capacity to neutralize acid. On the average, each ml of aluminum hydroxide gel neutralizes 1.2 to 2.5 meq of acid, and 1 g of the dried compound neutralizes 25 meq of acid (Ref. *4*).

Aluminum hydroxide is considered to be a potentially useful drug for the treatment of the symptoms of IPPUAD. Further testing according to the proposed testing guidelines should be conducted to determine whether or not it is effective.

(3) *Proposed dosage.* The Panel concludes that aluminum hydroxide is safe in the usually recommended doses up to 500 mg taken between meals and at bedtime with a maximum daily dose of 2 g, but should not be taken for longer than 2 weeks except upon the advice of a physician.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used in the treatment of the symptoms of IPPUAD. (See part III. paragraph A.2. above—Category I labeling.) In addition, the Panel recommends that the following warning statements be required to appear in the labeling of drug products containing aluminum hydroxide.

(i) "If you are taking other drugs, consult your physician as this drug may interfere with their effectiveness."

(ii) "If you have kidney disease, do not take this product except under the supervision of a physician."

(iii) "Do not take for longer than 2 weeks or in greater than recommended amounts, except upon the advice of a physician."

(5) *Evaluation.* The Panel recommends that adequate testing of aluminum hydroxide (specifying the degree of reactivity) be performed according to the proposed testing guidelines to determine whether or not it is effective for treatment of the symptoms of IPPUAD. (See part III. paragraph D.1. below—Guidelines for developing a protocol for evaluating OTC drugs for the treatment of the symptoms of IPPUAD.)

References

(*1*) Mayor, G. H., J. A. Keiser, D. Makdani, and P. K. Ku, "Aluminum Absorption and Distribution: Effect of Parathyroid Hormone," *Science,* 197:1187–1189, 1977.

(*2*) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, p. 1036, 1977.

(*3*) "Evaluations of Drug Interactions," American Pharmaceutical Association, 2d Ed., Washington, pp. 25 and 227, 1976.

(*4*) Harvey, S. C., "Gastric Antacids and Digestants," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, pp. 961–962, 1975.

c. *Calcium carbonate.* The Panel concludes that calcium carbonate is safe for OTC use in the dose noted below, but data are insufficient to demonstrate its effectiveness in treating the symptoms of IPPUAD.

(1) *Safety.* Calcium carbonate was reviewed by the Advisory Review Panel on OTC Antacid Products, in a report published in the **Federal Register** of April 5, 1973 (38 FR 8714). FDA concurred with the evaluation of that Panel regarding the safety of the drug (21 CFR 331) when taken in a dosage of not more than 8 g per day. The Panel concurs that such a dosage is safe when used for relief of symptoms of IPPUAD.

Some antacids are known to decrease the effectiveness of many drugs and an appropriate warning must be included on the label. In addition, the Panel is concerned with other potentially unsafe characteristics of excessive amounts of calcium carbonate. Documented adverse reactions which are well known include alkalosis, hypercalcemia, acid rebound, milk-alkali syndrome, and constipation. These reactions usually occur with igestion of larger than recommended doses and/or with chronic engestion (Ref. *1*). Appropriate warnings are included below under the heading "Labeling."

(2) *Effectiveness.* Calcium carbonate acts to neutralize acid in the stomach, releasing carbon dioxide in the process. It has been suggested that increasing the pH of the stomach contents results in more rapid emptying and that rapid emptying relieves the symptoms of IPPUAD (Ref. *2*). It has also been suggested that carbon dioxide released by calcium carbonate in the stomach increases gastric distention which is also conducive to more rapid gastric emptying. To the Knowledge of the Panel no one has conclusively established a correlation between gastric emptying time and symptoms of IPPUAD, and the actual pathogenesis of this syndrome remains in doubt.

Although studies were presented comparing calcium carbonate to placebo (Refs. *3* and *4*) and to simethicone (Ref. *2*) in an attempt to demonstrate relief of the symptoms of IPPUAD, the Panel considered these studies to be unsatisfactory with respect to test design, setting, and method of sample population selection. The Panel therefore recommends that calcium carbonate be tested according to the proposed testing guidelines to determine whether or not it is effective in relieving the symptoms of IPPUAD.

(3) *Proposed dosage.* The Panel concurs with § 331 (21 CFR 331) that calcium carbonate is safe in a dose of not more than 8 g/day taken in four divided doses, but should not be taken for longer than 2 weeks except upon the advice of a physician.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used in the treatment of the symptoms of IPPUAD. (See part III. paragraph A.2. above—Category I labeling.) In addition, the Panel recommends that the following warning statements be required to appear in the labeling of drug products containing calcium carbonate:

(i) "If you are taking other drugs, consult your physician as this drug may interfere with their effectiveness."

(ii) "Do not take for longer than 2 weeks or in greater than recommended amounts, except on the advice of a physician."

(5) *Evaluation.* The Panel recommends that adequate testing of calcium carbonate be performed according to the proposed testing guidelines to determine whether or not it is effective for treatment of the symptoms of IPPUAD. (See part III. paragraph D.1. below—Guidelines for developing a protocol for evaluating OTC drugs for the treatment of the symptoms of IPPUAD.)

References

(*1*) Levant, J. A., J. H. Walsh, and J. I. Isenberg, "Stimulation of Gastric Secretion and Gastrin Release by Single Oral Doses of Calcium Carbonate in Man," *New England Journal of Medicine,* 289:555–558, 1973.

(*2*) OTC Volume 170053.

(*3*) OTC Volume 170098.

(*4*) OTC Volume 170058.

d. *Dihydroxyaluminum sodium carbonate.* The Panel concludes that dihydroxyaluminum sodium carbonate (DASC) is safe for OTC use in the dose noted below, except for individuals with severe kidney diseases, but data are insufficient to demonstrate its effectiveness in treating the symptoms of IPPUAD.

(1) *Safety.* DASC was reviewed by the Advisory Review Panel on OTC Antacid Products, in a report published in the **Federal Register** of April 5, 1973 (38 FR 8714), and found "* * * safe in amounts usually taken orally in antacid products * * *" (38 FR 8717). That Panel established that the maximum safe daily dosage of antacids containing sodium is 200 meq of sodium for persons under 60 years of age and 100 meq for persons aged 60 or older (38 FR 8719). This Panel agrees with this dosage restriction and the warning statement for those persons who are on a sodium-restricted diet (38 FR 8719). FDA also concurs with these recommendations (21 CFR Part 331).

Since the publication of the final monograph for OTC antacid drug products on June 4, 1974 (39 FR 19862), information has been reported strongly suggesting that ingested aluminum is absorbed, resulting in increased blood and brain levels of aluminum (Ref. *1*). Experimental evidence suggests that hyperparathyroidism, such as found in patients with severe kidney disease, may further increase the ability of the body to absorb aluminum and cause increased deposition in the brain which may lead to encephalopathy. An appropriate warning is included below under the heading "Labeling."

The Panel agrees that DASC is safe for individuals who are not on a sodium-restricted diet when taken for symptomatic treatment of IPPUAD in a dosage of up to 8 g in a 24-hour period by those persons not on a sodium-restricted diet (Ref. *2*).

Some antacids are known to interact adversely with such drugs as digoxin, isoniazid, sodium polystyrene sulfonate, and oral tetracyclines (Ref. *3*). A warning concerning the possibility of interactions with other drugs must be included on the label.

(2) *Effectiveness.* DASC acts as a buffering antacid in the stomach. Reaction products are sodium ion, carbon dioxide, and aluminum chloride (Ref. *2*). Such reactions would be expected to shorten the emptying time of the stomach and alter mechanical pressures as well as having a neutralizing effect on gastric contents.

Submissions received by the Panel included four research reports for evaluating the effectiveness of DASC in relieving the symptoms of IPPUAD. Of these, one study used either one or two tablets each of two presumably active

preparations which were taken before, during, or after meals (Ref. *4*). The medications were undisguised; the study was not placebo controlled and was based on a diary method of reporting symptoms, some of which were clearly in the spectrum of hyperacidity. The Panel considered the data unreliable due to defects in the protocol.

Another study was well designed and supervised and demonstrated effectiveness only at a p value of 0.083 (Ref. *5*). A third study evaluated results in 99 subjects using the diary method (Ref. *6*). The subjects took the tablets before, during, or after meals, and the study showed no statistical difference between the active substances and placebo in providing relief from the symptoms of IPPUAD. This evaluation postulated that menthol, used as a flavoring agent, might actually be an active ingredient. The same question was raised in a fourth study which also revealed no statistical difference between DASC and placebo in relief of IPPUAD symptoms (Ref. *7*). In view of these inconclusive results the Panel recommends that further testing be performed according to the proposed testing guidelines to determine whether or not DASC is effective for relief of the symptoms of IPPUAD.

(3) *Proposed dosage.* Dihydroxylauminum sodium carbonate is safe when taken in doses not to exceed a total of 8 g (55 meq of sodium) in a 24 hour period, but should not be taken for longer than 2 weeks except under the advice of a physician (Ref. *2*).

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used in the treatment of the symptoms of IPPUAD. (See part III. paragraph A.2. above—Category I labeling.) In addition, the Panel recommends that the following warning statements be required to appear in the labeling of drug products containing DASC:

(i) "If you are taking other drugs, consult your physician as this drug may interfere with their effectiveness."

(ii) "If you have kidney disease, do not take this product except under the supervision of a physician."

(iii) "Do not take for longer than 2 weeks or in greater than recommended amounts, except on the advice of a physician."

(iv) *For products containing more than 5 meq of sodium in the maximum recommended daily dose.* "If you are on a sodium-restricted diet, do not use this product except under the supervision of a physician."

(5) *Evaluation.* The Panel recommends that adequate testing of dihydroxyaluminum sodium carbonate (DASC) be performed according to the proposed testing guidelines to determine whether or not it is effective for treatment of the symptoms of IPPUAD. (See part III. paragraph D.1. below—Guidelines for developing a protocol for evaluating OTC drugs for the treatment of the symptoms of IPPUAD.)

References

(*1*) Mayor, G. H., J. A. Keiser, D. Makdani, and P. K. Ku, "Aluminum Absorption and Distribution: Effect of Parathyroid Hormones," *Science*, 197:1187–1189, 1977.

(*2*) OTC Volume 170061.

(*3*) "Adverse Interactions of Drugs," *The Medical Letter on Drugs and Therapeutics*, The Medical Letter, Inc., New Rochelle, NY, 19:8–9, 1977.

(*4*) OTC Volume 170061 (Research report 966–0004—Section V.C.1.c.).

(*5*) OTC Volume 170061 (Research report 955–0787—Section V.C.1.d.).

(*6*) OTC Volume 170137 (Research report 955–0880).

(*7*) OTC Volume 170137 (Research report 955–0892).

e. *Magnesium hydroxide.* The Panel concludes that magnesium hydroxide is safe for OTC use in the dose noted below, but data are insufficient to demonstrate its effectiveness in treating the symptoms of IPPUAD.

(1) *Safety.* If kidney function is normal, magnesium hydroxide is considered safe for use when taken in the dosage noted below.

Magnesium hydroxide is generally considered to be a poorly absorbed antacid. However, absorption of as little as 5 to 10 percent (Ref. *1*) to as much as 15 to 30 percent (Ref. *2*) has been reported. It is well known that excessive magnesium blood levels may result from ingestion of magnesium by persons with kidney damage, and, therefore, a warning label should be present on any magnesium hydroxide preparation in which the maximal daily dose exceeds 50 meq of magnesium.

Magnesium hydroxide has the potential for drug interactions with bishydroxycoumarin and related anticoagulants (Ref. *3*), and tetracycline antibiotics (Ref. *4*). The Panel believes that the consumer should be alerted to the potential for drug interactions and recommends that a warning appear on the label.

(2) *Effectiveness.* Convincing data supporting the effectiveness of magnesium hydroxide in the treatment of the symptoms of IPPUAD have not been presented. The Panel considers magnesium hydroxide to be a potentially useful drug for the treatment of the symptoms of IPPUAD and recommends that it be tested according to the proposed testing guidelines to determine whether or not it is effective.

(3) *Proposed dosage.* The Panel concludes that the OTC use of magnesium hydroxide is safe in the usual recommended dose of up to 15 mL of a suspension of up to 8.5 percent magnesium hydroxide taken three to four times daily (Ref. *1*). This is equivalent to a total daily dose of up to 5.1 g of magnesium hydroxide, but should not be taken for more than 2 weeks except upon the advice of a physician.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used in the treatment of IPPUAD. (See part III. paragraph A.2. above—Category I labeling.) In addition, the Panel recommends that the following warning statements be required to appear in the labeling of drug products containing magnesium hydroxide:

(i) "If you are taking other drugs, consult your physician as this drug may interfere with their effectiveness."

(ii) "Do not take for longer than 2 weeks or in greater than recommended amounts, except upon the advice of a physician."

(iii) *For products containing more than 50 meq of magnesium in the recommended daily dosage.* "If you have kidney disease, do not use this product except under the supervision of a physician."

(5) *Evaluation.* The Panel recommends that adequate testing of magnesium hydroxide be performed according to the proposed testing guidelines to determine whether or not it is effective for treatment of the symptoms of IPPUAD. (See part III. paragraph D.1. below—Guidelines for developing a protocol for evaluating OTC drugs for the treatment of the symptoms of IPPUAD.)

Magnesium hydroxide has also been reviewed by this Panel for treatment of the symptoms of intestinal distress and the conclusions are included elsewhere in this document. (See part IV. paragraph C.1.d. below—Magnesium hydroxide.)

References

(*1*) Harvey, S. C., "Gastric Antacids and Digestants," *In* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, pp. 964–965, 1975.

(*2*) Dretchen, K., D. Hollander, and J. B. Kirsner, "Roundup on Antacids and Anticholinergics, *"Patient Care*, 9:94–114, 1975.

(*3*) Ambre, J. J., and L. J. Fischer, "Effect of Co-Administration of Aluminum and Magnesium Hydroxides on Absorption of Anticoagulants in Man," *Clinical Pharmacology and Therapeutics*, 14:231–237, 1973.

(*4*) Hussar, D. A., "Drug Interactions," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol and J. E. Hoover, Mack Publishing Co., Easton, PA, p. 1741, 1975.

f. *Magnesium trisilicate.* The Panel concludes that magnesium trisilicate is safe for OTC use in the dose noted below, but data are insufficient to demonstrate its effectiveness in treating the symptoms of IPPUAD.

(1) *Safety.* If kidney function is normal, magnesium trisilicate is generally considered safe for use when taken in the dosage cited below.

One study reviewed by the Panel showed that significant elevation of serum magnesium resulted from the oral ingestion of magnesium trisilicate in some subjects (Ref. *1*). The dosage used in this study was in excess of that being recommended by the Panel.

It is well known that excessive magnesium levels may result from magnesium ingestion by persons with kidney damage. The Panel concurs with the Advisory Review Panel on OTC Antacid Drug Products (38 FR 8714) and with FDA (21 CFR Part 331) that a warning label should be present on any magnesium trisilicate preparation for which the maximal daily dose exceeds 50 meq of magnesium (38 FR 8719).

There is also an increase in silica absorption from ingestion of magnesium trisilicate, but formation of silica renal calculi has rarely been associated with magnesium trisilicate ingestion (Ref. *2*).

Mangesium trisilicate has been found to absorb various alkaloids and antibiotics in vitro under certain conditions (Refs. *3* and *4*). The possibility of drug interactions involving magnesium trisilicate should be more adequate explored.

(2) *Effectiveness.* Magnesium trisilicate reacts with gastric acid to form hydrated silica gel and magnesium ion for acid neutralization. Hydrated silica gel is known to have absorptive and antifoam properties in addition to antacid properties (Ref. *5*). There is partial gastrointestinal absorption of magnesium ion and silicate with subsequent excretion via the kidney in the normal person.

Magnesium trisilicate has been demonstrated to have antifoam action in vitro (Ref. *5*) but data are insufficient to demonstrate its effectiveness in treating the symptoms of IPPUAD.

The Panel reviewed two submitted studies that suggest the effectiveness of magnesium trisilicate in treating the symptoms of IPPUAD (Ref. *6*). However, the Panel was concerned with some of the details of the studies, particularly the selection of the subjects. Other studies discussed the effect of magnesium trisilicate on gas (Ref. *7*); the Panel, however, does not accept gas as the cause of the IPPUAD symptoms. The Panel recommends further testing according to the proposed protocol to determine whether or not magnesium trisilicate is effective in treating the symptoms of IPPUAD.

(3) *Proposed dosage.* The Panel concludes that magnesium trisilicate is safe at a maximum dose of 1 g three times daily, but should not be taken for longer than 2 weeks except upon the advice of a physician.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used in the treatment of the symptoms of IPPUAD. (See part III. paragraph A.2. above—Category I labeling.) In addition, the Panel recommends that the following warning statements be required to appear on the labeling of drug products containing magnesium trisilicate:

(i) "If you are taking other drugs, consult your physician as this drug may interfere with their effectiveness."

(ii) "Do not take for longer than 2 weeks or in greater than recommended amounts, except on the advice of a physician."

(iii) *For products containing more than 50 meq of magnesium in the recommended daily dosage.* "If you have kidney disease, do not use this product except under the supervision of a physician."

(5) *Evaluation.* The Panel recommends that adequate testing of magnesium trisilicate be performed according to the proposed testing guidelines to determine whether or not it is effective for treatment of the symptoms of IPPUAD. (See part III. paragrapn D.1. below—Guidelines for developing a protocol for evaluating OTC drugs for the treatment of the symptoms of IPPUAD.)

References

(*1*) West, E. S., and C. Pennoyer, "Some Effects of Magnesium Trisilicate Ingestion Upon Blood, Urine, and Feces of Human Subjects," *American Journal of Digestive Diseases,* 12:199–202, 1945.

(*2*) Joekes, A. M., G. A. Rose, and J. Sutor, "Multiple Renal Silica Calculi," *British Medical Journal,* 1:146–147, 1973.

(*3*) El-Nakeeb, M. A., and R. T. Yousef, "Influence of Various Materials on Antibiotics in Liquid Pharmaceutical Preparations," *Acta Pharmaceutica Suecica,* 5:1–8, 1968.

(*4*) Khalil, S. A., and M. A. Moustafa, "The In-Vitro-Adsorption of Some drugs on Antacids," *Pharmazie,* 28:116–118, 1973.

(*5*) OTC Volume 170054.

(*6*) OTC Volume 170054 (Studies I and II).

(*7*) OTC Volume 170054 (Research Reports 932–0332 and 950–0001).

g. *Peppermint oil.* The Panel concludes that peppermint oil is safe for OTC use in the dose noted below, but data are insufficient to demonstrate its effectiveness in treating the symptoms of IPPUAD.

Oil of peppermint is the rectified volatile oil obtained by distillation from the fresh leaves and stems of *Mentha piperita.* It contains not less than 50 percent menthol both as the alcohol and as the menthyl acetate ester (Ref. *1*). The other constituents are a complex of numerous terpenes and aliphatic alcohols, aldehydes, and acids.

(1) *Safety.* Peppermint oil has been in substantial use for many years with no reports of clinical toxicity, although volatile oils as a group are generally regarded as potent substances. It is important to distinguish between oil of peppermint and "spirit" of peppermint since the potency of the oil is ten times as potent as the spirit. Oil of peppermint has been used extensively in pharmaceutical preparations with no known adverse effects, and the Panel concludes that it is safe in a maximum dose of 0.3 mL daily.

About 70 percent of the annual domestic production of peppermint oil, representing millions of pounds, is used in confections and foods.

(2) *Effectiveness.* Clinical and pharmacological studies have described the action of oil of peppermint (Refs. *1* through *11*). The physiologic action of the oil is to decrease gastric emptying time, relax the lower esophageal sphincter, increase gastric secretion and stomach motility, and either stimulate or inhibit muscular activity of isolated intestinal tissue, depending on the concentration.

The Panel knows of no study which demonstrates that oil of peppermint is effective in relieving the symptoms of IPPUAD. However, due to its known physiologic effects on the stomach, the Panel recommends that it be tested in order to determine whether or not it is effective for this indication.

The Panel recognizes that oil of peppermint is used as a flavoring agent in many pharmaceutical formulations, but in the quantities used it would have no benefit in relieving the symptoms of IPPUAD.

(3) *Proposed dosage.* The dosage of oil of peppermint considered to be safe is no more than 0.1 mL (approximately 1 drop) per dose three times a day, a total daily maximum of 0.3 mL. This dosage is based on the dose of peppermint spirit, as an official preparation in National Forumlary XIV, of 1 mL three times daily. Peppermint oil is the primary constituent of the spirit in a concentration of 10 percent.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used in the treatment of the symptoms of IPPUAD. (See part III: paragraph A.2. above—Category I labeling.)

(5) *Evaluation.* The Panel recommends that data be required to determine whether or not peppermint oil is effective in relieving the symptoms of

IPPUAD; however, the proposed testing guidelines may not be appropriate since double-blind studies are probably precluded for this ingredient. (See part III. paragraph D.1. below—Guidelines for developing a protocol for evaluating OTC drugs for the treatment of the symptoms of IPPUAD.)

References

(1) Swinyard, E. A., and W. Lowenthal, "Pharmaceutical Necessities," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol and J. E. Hoover, Mack Publishing Co., Easton, PA, p. 1233, 1975.

(2) Sapoznik, H. I., R. A. Arens, J. Meyer, and H. Necheles, "The Effect of Oil of Peppermint on the Emptying Time of the Stomach," *Journal of the American Medical Association*, 104:1792–1794, 1935.

(3) Sigmund, C. J., and E. F. McNally, "The Action of a Carminative on the Lower Esophageal Sphincter," *Gastroenterology*, 56:13–18, 1969.

(4) Meyer, J., L. Scheman, and H. Necheles, "Action of Oil of Peppermint on the Secretion and Motility of the Stomach in Man," *Archives of Internal Medicine*, 56:88–97, 1935.

(5) van Liere, E. J., and D. W. Northrup, "The Effect of Carminatives on the Emptying Time of the Normal Human Stomach," *Journal of Pharmacology and Experimental Therapeutics*, 76:39–43, 1942.

(6) Necheles, H., and J. Meyer, "On the Inhibition of Gastric Secretion by Oil of Peppermint," *American Journal of Physiology*, 110:686–691, 1935.

(7) Plant, O. H., "The Effect of Carminative Volatile Oils on the Muscular Movements of the Intestine," *Journal of Pharmacology and Experimental Therapeutics*, 16:311–325, 1921.

(8) Plant, O. H., and G. H. Miller, "Effects of Carminative Volatile Oils on the Muscular Activity of the Stomach and Colon," *Jounal of Pharmacology and Experimental Therapeutics*, 26:149–164, 1926.

(9) Muirhead, A. L., and H. F. Gerald, "The Action of Certain Volatile Oils on Isolated Intestinal Segments," *The Journal of Pharmacology and Experimental Therapeutics*, 8:253–260, 1916.

(10) Berk, J. E., "Gastrointestinal Gas," *Annals of the New York Academy of Sciences*, 150:178–190, 1968.

(11) Thompson, W. G., "Burbulence (Indigestion Due to Gas)," *Canadian Medical Association Journal*, 106:1220, 1972.

h. *Simethicone.* The Panel concludes that simethicone is safe for OTC use in the dose noted below, but available evidence is insufficient to demonstrate its effectiveness in treating the symptoms of IPPUAD.

(1) *Safety.* The Panel concurs with the determination of FDA, as stated in the antiflatulent final monograph (21 CFR 332.10), that simethicone is safe in a maximum daily dosage of 500 mg as an OTC product.

Simethicone is a mixture of dimethylpolysiloxane and approximately 5 percent silica gel. Toxicological studies and the wide use of dimethylpolysiloxane in chemical combination with silica gel for many years without evidence of adverse effects have established its safety for human use (Ref. *1*). This Panel has determined that silica gel is nontoxic in normally ingested amounts (Ref. *2*).

(2) *Effectiveness.* The Panel, in reviewing all submissions of data and information on drug products containing simethicone that claim to receive the symptoms of IPPUAD, and in reviewing the current literature, concludes that there are insufficient data demonstrating that simethicone is effective in the OTC treatment of the symptoms of IPPUAD.

Dimethylpolysiloxane has been used in many food preparations as an antifoam agent since 1947. Silica gel is added as a dispersing agent and adsorbs the dimethylpolysiloxane, probably by hydrogen bonding. In a study by Birtley et al. (Ref. *3*), this combination was found to be more effective than either agent alone in reducing foam produced in rat stomachs.

The antifoaming properties of simethicone have been established in vitro (Ref. *4*), and simethicone has been demonstrated to decrease the presence of foam or bubbles found occasionally in the human stomach during gastroscopy. Its use as an antifoaming agent has been recommended as a treatment for bloating in ruminants, in which its use would permit "* * * gases to pass freely through the food mass" (Ref. *5*). Other researchers have been disappointed in the results of using silicones to prevent foaming of ingested material in ruminants (Ref. *6*).

One research group has proposed several hypotheses for small gas bubbles causing gastrointestinal symptoms in humans: the small bubbles may be tenacious and resist movement, the specific gravity of multiple small bubbles having a mucus covering is greater than that of the same gas in the free form, and there is resistance to deformation of a bubble wall due to the effects of surface tension (Ref. *7*). The group further postulated that surface tension is not a factor when air is not entrapped in bubbles, resistance of the mucus-entrapped gas may result in decreased movement through narrowed portions of the gut, the resistance is not as great for free gas, and the total liquid volume (liquid and entrapped gas) of the gastrointestinal tract will be decreased by the elimination of the gas trapped in the mucus.

Although the above hypotheses may be valid, the Panel is not aware of any evidence which actually establishes that small bubbles entrapped in mucus are the cause of the symptoms of IPPUAD. The Panel, therefore, concludes that data are insufficient to demonstrate that simethicone is effective in treating the symptoms of IPPUAD, notwithstanding its action on gas bubbles in the stomach. Further testing according to the proposed testing guidelines should be performed to determine whether or not simethicone is effective in relieving the symptoms of IPPUAD.

(3) *Proposed dosage.* The Panel concludes that a maximum recommended daily dosage of 500 mg of simethicone is safe (21 CFR 332.10) for treatment of IPPUAD.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used in the treatment of the symptoms of IPPUAD. (See part III. paragraph A.2. above—Category I labeling.)

(5) *Evaluation.* The Panel has extensively reviewed the pertinent literature and listened to medical gastrointestinal experts, and to the best of the Panel's knowledge, no data have been presented which demonstrate to the satisfaction of the Panel that gas is the etiologic agent of IPPUAD. Therefore, the Panel concludes that data are insufficient to demonstrate the effectiveness of simethicone for OTC use in relieving the specific symptoms of IPPUAD: Bloating, distention, fullness, and pressure.

In arriving at its decision, the Panel is aware of FDA's conclusion regarding antiflatulent products (21 CFR Part 332). The agency concluded that simethicone is an effective antiflatulent drug. This Panel emphasizes that no convincing evidence was submitted that demonstrates that "gas" is the cause of IPPUAD. The Panel recommends that adequate testing be performed according to the proposed testing guidelines to determine whether or not simethicone is effective for treatment of the symptoms of IPPUAD. (See part III. paragraph D.1. below—Guidelines for developing a protocol for evaluating OTC drugs for the treatment of the symptoms of IPPUAD.) Special attention must be paid to the addendum to the proposed protocol for products wishing to claim "anti-gas" activity.

Simethicone has been further reviewed by this Panel for treating the symptoms of intestinal distress and the conclusions are included elsewhere in this document. (See part IV. paragraph C.1.f below—Simethicone.)

References

(1) Rowe, V. K., H. C. Spencer, and S. L. Bass, "Toxicological Studies on Certain Commercial Silicones: II. Two Year Dietary Feeding of DC 'Antifoam A' to Rats," *Archives of Industrial Hygiene and Occupational Medicine*, 1:539–544, 1950.

(2) OTC Volume 170054.

(3) Birtley, R. D. N., et al., "The Effect of Free Silica on the Mucosal Protective and Antiflatulent Properties of Polydimethylsiloxane," *Journal of Pharmacy and Pharmacology*, 25:859–863, 1973.

(4) Rider, J. A., "Experience with the Use of a Defoaming Agent in the Treatment of Gastrointestinal Gas," *Annals of the New York Academy of Sciences*, 150:170–178, 1968.

(5) Barondes, R. de R., W. D. Judge, C. G. Towne, and M. L. Baxter, "The Silicones of Medicine," *The Military Surgeon*, 106:379–387, 1950.

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(7) Comments to Antacid Proposed Monograph, Docket No. 75N–0357, C00010, Volume II, Exhibit C, Plough, Inc. (6/1/73), pp. 67–80, in Panel Administrator's File (OTC Volume 17GPAII).

i. *Sodium bicarbonate.* The Panel concludes that sodium bicarbonate is safe for OTC use in the doses noted below, but data are insufficient to demonstrate its effectiveness in treating the symptoms of IPPUAD.

(1) *Safety.* Sodium bicaronate (baking soda) is an alkalinizing agent which releases carbon dioxide when neutralized by acid. Sodium bicarbonate has a long history of use as an antacid and for the symptomatic relief of upper addominal distress. It may be used as an ingredient in effervescent preparations in which the alkali is buffered or partially neutralized by an acidic compound. The Panel considers sodium bicarbonate to be safe when used as specified in the dosage section below, and under the labeling restrictions noted.

(2) *Effectiveness.* The Panel is not aware of any scientific evidence which establishes the effectiveness of sodium bicarbonate as a treatment for the symptoms of IPPUAD.

One gram of sodium bicarbonate will neutralize approximately 115 mL of O.1 N hydrochloric acid, releasing carbon dioxide (Ref.*1*). Reduction of gastric acidity, decreasing gastric emptying time, and the belching of carbon dioxide alter intragastric pressures. The Panel considers sodium bicarbonate to be a potentially useful drug for the treatment of the IPPUAD syndrome, and recommends further testing according to the proposed testing guidelines to determine whether or not it is effective.

(3) *Proposed dosage.* This Panel concurs with the recommendation of the Advisory Review Panel on OTC Antacid Drug Products published in the **Federal Register** of April 5, 1973 (38 FR 8714), that a maximum safe daily dosage of preparations containing sodium is 200 meq of sodium for persons under 60 years of age and 100 meq for persons aged 60 years or older (38 FR 8719). Because of the sodium content the dose of sodium bicarbonate should not exceed 16.8 g (200 meq of sodium) per day.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used in the treatment of the symptoms of IPPUAD. (See part III. paragraph A.2. above—Category I labeling.)

The Panel concurs with the recommendation of the Advisory Review Panel on OTC Antacid Drug Products, published in the **Federal Register** of April 5, 1973 (38 FR 8714), that a warning statement should be required on preparations containing sodium (38 FR 8719). This Panel recommends that the following warning statements be required in the labeling of preparations containing sodium:

(i) "If you are 60 years of age or older, the maximum *daily* dose should not exceed 8.4 g 1 heaping teaspoon) of this drug."

(ii) "Do not take for longer than 2 weeks or in greater than recommended amounts, except upon the advice of a physician."

(iii) *For products containing more than 5 meq of sodium in the recommended daily dose.* "If you are on a sodium-restricted diet, do not use this product except under the supervision of a physician."

(5) *Evaluation.* The Panel recommends that adequate testing of sodium bicarbonate be performed according to the proposed testing guidelines to determine whether or not it is effective for treatment of the symptoms of IPPUAD. (See part III. paragraph D.l. below—Guidelines for developing a protocol for evaluating OTC drugs for the treatment of the symptoms of IPPUAD.)

Sodium bicarbonate has been further reviewed by this Panel for treatment of the symptoms of intestinal distress and the conclusions are included elsewhere in this document. (See part IV. paragraph C.l.g. below—Sodium bicarbonate.)

Refference

(*l*) *Swinyard, E. A., "Gastrointestinal Drugs," in* "Remington's Pharmaceutical Sciences." 15th ED., edited by A. Osol and J. E. Hoover, Mack Publishing Co., Easton, PA, pp. 736–737, 1975.

j. *Sodium citrate.* The Panel concludes that sodium citrate (sodium salt of citric acid) is safe for OTC use in the dose noted below, but data are insufficient to demonstrate its effectiveness in treating the symptoms of IPPUAD.

(1) *Safety.* Sodium citrate was reviewed by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products, in a report published in the **Federal Register** of September 9, 1976 (41 FR 38367), and found to be safe when used within the dosage limitation of 24 g daily. This Panel concurs with the antacid monograph (21 CFR 331) which limits the daily sodium intake to 200 meq for persons under 60 years of age and 100 meq for persons 60 years or older.

(2) *Effectiveness.* Commonly, citric acid is formulated in combination with sodium bicarbonate in a solid dosage form. When this combination is dissolved in water, effervescence occurs (carbon dioxide evolves) and the active antacid ingredient, buffered sodium citrate, is produced. The Panel is aware of the antacid property of sodium citrate but data are insufficient to demonstrate its effectiveness in relieving the symptoms of IPPUAD. The Panel recommends that sodium citrate be tested according to the proposed testing guidelines in order to determine whether or not it is effective for this indication.

(3) *Proposed dosage.* The Panel concludes that a maximum safe daily dose of preparations containing sodium is 200 meq of sodium for persons under 60 years of age and 100 meq for persons aged 60 years or older; therefore, the oral dose of sodium citrate should not exceed 17.2 g daily (200 meq of sodium).

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used in the treatment of the symptoms of IPPUAD. (See part III. paragraph A.2. above—Category I labeling.)

The Panel concurs with the recommendation of the Advisory Review Panel on OTC Antacid Drug Products, published in the **Federal Register** of April 5, 1973 (38 FR 8714), that a warning statement should be required on preparations containing sodium (38 FR 8719). This Panel recommends that the following warning statements be required in the labeling of preparations containing sodium:

(i) "If you are 60 years of age or older, the maximum *daily* dose should not exceed 8.6 g (1 heaping teaspoon) of this drug."

(ii) "Do not take for longer than 2 weeks or in greater than recommended amounts, except upon the advice of a physician."

(iii) *For products containing more than 5 meq of sodium in the recommended daily dose.* "If you are on a sodium-resticted diet, do not use this product except under the supervision of a physician."

(5) *Evaluation.* The Panel recommends that the adequate testing of sodium citrate be performed according to the proposed testing guidelines to determine whether or not it is effective for treatment of the symptoms of IPPUAD. (See part III. paragraph D.1 below—Guidelines for developing a protocol for evaluating OTC drugs for the treatment of the symptoms of IPPUAD.)

Sodium citrate has been further reviewed by this Panel for treatment of the symptoms of intestinal distress and the conclusions are included elsewhere in this document. (See part IV. paragraph C.1.h below—Sodium citrate.)

2. *Category III labeling.* The Panel has repeatedly stated that, at present, it does not accept "gas" or "excess gas" as the cause of IPPUAD. The Panel recommends that firms not use the following "anti-gas" claims for these products while they are attempting to demonstrate by objective measures that increased gas is a cause of IPPUAD symptoms and that the reduction of the volume of gas by their product is associated with a decrease in the symptoms of IPPUAD:

a. "Anti-gas."
b. "For relief of distress and/or discomfort due to gas."
c. "Reduces distress and/or discomfort caused by excess gas in the stomach."
d. "For expelling gas from the stomach."
e. "For flatulence (or gas)."
f. "Antiflatulent."
g. "Releases entrapped gas."
h. "Relieves discomfort and pain of entrapped gas."
i. "Reduces gaseousness."

The Panel requires data to substantiate any claim which reflects the specific time range of action of these drugs, and therefore places the following claim in Category III:

j. "Effective within—minutes." (anytime within 30 minutes).

This claim is compatible with the time range allowed by the Panel's proposed testing guidelines. (See part III paragraph D.1 below—Guidelines for developing a protocol for evaluating OTC drugs for the treatment of the symptoms of IPPUAD.)

Any nonspecific claim for speed of action ("Fast-acting") has been previously categorized and will not be allowed in the labeling. (See part III. paragraph B.2. above—Category II labeling.)

D. Data Required for Evaluation

Guidelines for developing a protocol for evaluating OTC drugs for the treatment of the symptoms of IPPUAD.

The Panel recognizes that currently there is a lack of guidelines for testing products used for the treatment of the symptoms of IPPUAD. It has developed a proposed protocol to aid investigators in designing tests of effectiveness for these drugs. This Panel does not imply that the protocol presented below is the only means by which these ingredients may be evaluated. However, it suggests that if an investigator's protocol deviates from this protocol, it should be discussed with appropriate FDA personnel prior to initiation of testing.

a. *Objective of the study.* The objective is to determine whether the substance under study provides significantly better relief of the symptoms of IPPUAD than placebo. This will be accomplished by use of a randomized, placebo-controlled, double-blind, crossover study design which uses a test meal to produce symptoms.

b. *Test population.* The sample population for the study will be subjects who have presented themselves to physicians complaining of symptoms occurring with some regularity and with varying frequency in the absence of organic gastrointestinal disease. The results from the study of this sample population will be assumed to be applicable to the target population, which includes those with only occasional symptoms.

c. *Test setting.* The test should be conducted by qualified gastroenterologists in a large clinic or academic setting where there may be a greater probability of obtaining the proper sample population in sufficient numbers. The extensive screening required prior to entrance into the study would probably restrict the study to subjects who have already required the services of a specialist located in a clinic or academic setting because of the persistence and frequency of their symptoms.

d. *Criteria for admisssibility into sample.* In order to exclude all but the functional gastrointestinal problems which give rise to the symptoms being evaluated, patients will have been screened to exclude significant organic disease, with special reference to gastrointestinal disorders, to the satisfaction of the gastroenterologist conducting the study.

Within 6 months preceding entrance into the study, appropriate data will have been generated on the subjects, including at least: History and physical exam, complete blood count, blood chemistries (SMA-12 or equivalent), urinalysis, gall bladder X-ray, chest X-ray, upper GI X-ray, and a guaiac test for fecal occult blood.

e. *Symtoms.* Acceptable symptoms of IPPAUD are those which occur during the test meal or within 15 minutes after the test meal and which the patient may attribute to "gas" and describe as bloating, distention, fullness, or pressure. The investigator should be certain that the meaning of the symptom(s) as described by the patient are understood.

f. *Test meal.* The symptom-producing meal must be tested by being consumed on two occasions prior to the test and the patient must repond consistently. The meal must be (1) standardized as to composition and, individually, as to amount, (2) capable of consistently producing symptoms which last more than 30 minutes in the susceptible individual (the total timed duration of the provoked symptoms should be noted), and (3) completely consumed within a standardized time period. The enviornment should be held constant during the test. The subjects should be adequately separated to prevent communication betaween them during the test meal and for a period immediately after eating. The test meals should be separated by at least 4-day intervals.

g. *Concomitant medication.* Concomitant medication, including vitamins and aspirin, is not allowed for 24 hours prior to and during the testing period. Alcohol must be avoided the day of the test meal.

h. *Test design.* The test design shall be randomized, placebo-controlled, double-blind, and crossover in which approximately half the subjects receive the placebo before the drug and approximately half receive the drug before the placebo. The drug or placebo will be taken at the time the first symptom appears, the time required to obtain clear and complete relief of symptoms will be determined, and the test will end 30 minutes after the onset of symptoms. If complete relief is not obtained, this treatment will be recorded as a failure.

If a positive control is used in addition to a placebo, a Latin square design is recommended.

If more than one person is to be tested on any day, then some of the subjects on that day should receive the placebo and the others the drug product.

i. *Analysis of data.* The statistical analysis should include at least the correlated proportions test.

j. *Number of patients.* The assumption is made that 30 percent of patients would respond to placebo. If 60 pe.cent respond beneficially to treatment, the results would be clinically significant. On this basis, at least 33 who complete the study would be sufficient to detect differences between drug and placebo that are clinically and statistically significant. (Type I error=0.05, type II error=0.20).

k. *Number of studies.* Two separate studies, each consisting of at least 33 patients who complete the study, will be required. Each study must be conducted at a different geographical site and performed by different investigators. The sample population from each site should be representative, with respect to

age and sex, of the patients at that clinic who meet the test population criteria explained above.

1. *Addendum.* For those manufacturers wishing to claim "anti-gas" on their label they must first demonstrate by acceptable objective methods that increased gas volume actually does exist in patients with immediate postprandial distress symptoms, that this gas is decreased by the drug for which they claim anti-gas activity, and that symptomatic relief is associated with this decrease.

2. *Background on the guidelines for developing a protocol for evaluating OTC drugs for the treatment of the symptoms of IPPUAD*—a. *Objective of the study.* The stated objective of the proposed protocol is "to determine whether the substance under study provides significantly better relief of symptoms of IPPUAD than placebo." Originally, the protocol was to be written to supply a proper procedure for evaluating "antiflatulent" drugs (drugs having an "anti-gas" effect) or those drugs which are claimed to relieve symptoms attributable to "gas." After extensive discussions by the Panel, in which the input of a number of experts was considered in addition to the Panel's extensive reviews of the submissions made by pharmaceutical firms for "antiflatulent" drugs, the Panel reached two important conclusions:

(1) The relationship of the presence of gas in the upper gastrointestinal tract to the symptoms of IPPUAD has not been established, and it has not been established that the removal of gas is correlated with the relief of the symptoms of IPPUAD.

(2) While the studies submitted by drug firms and reviewed by the Panel discussed "excess gas," "gaseousness," "flatulence," etc., the real concern of these studies was to establish that the drugs were effective in the relief of IPPUAD. In some cases, drugs which actually cause gas to elaborate (calcium carbonate) have been evaluated as "antiflatulent" drugs.

After reaching these conclusions, the Panel deleted the term "antiflatulent" from the proposed protocol and replaced it with "treatment of the symptoms of IPPUAD." To be judged effective by this protocol a drug does not have to demonstrate an "anti-gas" effect. However, for those desiring to make an "anti-gas" claim, an addendum to the protocol requires that they "demonstrate by acceptable objective methods that increased gas actually does exist in patients with IPPUAD symptoms, that this gas is decreased by using the drug for which they claim "anti-gas" activity, and that symptomatic relief is associated with this decrease."

b. *Test population.* The target population includes individuals who have recurrent symptoms with varying frequency but who do not have organic disease causing the symptoms. At first glance it might be thought that the ideal procedure to follow would be to obtain a random sample of this target population and use it in the study; however, from a statistical point of view this is not optimal. In order to judge the effectiveness of the drug, the individuals in the study must have the symptoms during the study so that the drug can be given to them. They must be bothered by IPPUAD to such a degree and frequency that it is possible to evoke the symptoms consistently and specifically for the study. Persons who only occasionally have the symptoms, therefore, would not be good subjects for the study. In light of this, the Panel decided that an appropriate test or sample population would be subjects "who have presented themselves to physicians complaining of symptoms occurring with some regularity and with varying frequency in the absence of organic gastrointestinal disease." The Panel believes the results of the study done on these subjects will be applicable to the target population.

c. *Test setting and criteria for admissibility into sample.* The protocol states that the study "should be conducted by qualified gastroenterologists in a large clinic or academic setting." In this way, the study would usually be restricted to subjects who have required the services of a medical specialist because of the regularity and frequency of their symptoms.

Many "antiflatulent" studies submitted to the Panel were not carried out in a clinical or academic setting and none involved the stringent admissibility criteria demanded by this protocol. After the Panel's discussion and consultation with outside experts, the protocol's settings were deemed appropriate. There exist many such settings where a large pool of admissible subjects would be available. Furthermore, while the clinical screening studies involved in the admissibility criteria are extensive, it is realistic to require them. First, the study should not include those persons with organic diseases. Second, it is assumed that the patients under consideration probably will have required the services of a specialist and already would have had many of the required studies.

The Panel recognizes that there may be other appropriate test populations, test settings, and admissibility criteria. A good valid study does not necessarily have to be restricted to those who have required the services of a medical specialist nor does it necessarily need all the extensive testing of the proposed protocol. In particular, the Panel realizes that an experienced investigator is the key element in such a study and deviations from the proposed protocol could be made and still perform a good study. The Panel suggests that if an investigator desires to perform a study whose protocol deviates from the proposed protocol on these or other matters, then these deviations should be discussed with appropriate FDA personnel prior to initiation of the study.

d. *Symptoms.* The symptoms of IPPUAD, which the patient may attribute to "gas" and describe as bloating, distention, fullness, or pressure, are all subjective. After extensive investigation, the Panel determined that a satisfactory objective measure related to IPPUAD and its relief has not yet been found.

For the protocol the term "immediate" is defined as occurring during the test meal or within 15 minutes after completion of the test meal. While the definition of IPPUAD does include symptoms occurring up to 30 minutes after the meal, the Panel decided to use 15 minutes in the protocol in order to ensure that the subjects in the study are experiencing IPPUAD and not some other condition such as intestinal distress which also may occur after a meal. Symptoms of intestinal distress have been defined as those beginning 30 minutes or later after a meal. However, in particular subjects, they may begin earlier. The Panel wanted to exclude such subjects from the study.

In the studies submitted to the Panel at least eight symptoms were investigated (bloating, distention, fullness, and pressure, plus heartburn, acid eructation, belching, and indigestion). After a review of these studies, it was determined that, except for the first four symptoms, the others might indicate conditions other than those with which the Panel is concerned. For example, heartburn and acid eructation are generally due to hyperacidity, and belching is most commonly caused by swallowed air.

It is understood that there is no agreement among individual patients with regard to the exact meaning of the four symptoms (bloating, distention, fullness, and pressure) and that it is possible that two people with exactly the same IPPUAD symptoms will use different terms to describe the condition (one person may say "distention" and others may describe the symptom as "fullness" or "bloating" or "pressure").

In order to have a meaningful statistical analysis, there must be agreement between the subjects and the investigator. To ensure this, the protocol states that "the investigator should be certain that the meaning of the symptom(s) as described by the patient is understood." The discussion between the patient and the investigator will make it clear to the investigator whether the patient is suffering from symptoms germane to this study.

e. *Test meal.* In order to test the drug under investigation, the symptoms must be produced during the study. This is the function of the test meal. It is not necessary to state explicitly in the protocol the content and amount of this meal. This will be the responsibility of the investigator. Different studies do not need to use the same test meal. The important requirements are that this symptom-producing meal must be taken twice prior to the test; and the patient must respond consistently both times. To guarantee standardization the protocol requires that:

(1) The meal must be "standardized as to composition and individually as to amount." Each patient in a study should eat the same test meal throughout the study and all patients will qualitatively receive the same meal.

(2) The meal must be "capable of consistently producing symptoms which last more than 30 minutes in the susceptible individual (the total timed duration of the provoked symptoms should be noted)." The symptoms under investigation are often of short duration. If, during the placebo and drug-administering stage of the study, complete relief is attained within 30 minutes after onset of the first symptom, this will be judged to be the result of a drug or a placebo effect. It is essential that this relief not be the natural consequence of a short duration distress.

(3) The meal should be "completely consumed within a standardized time period." The protocol does not impose the actual fixed time period in which the meal should be consumed. It is, however, essential that each study should have such a time period.

(4) Each patient will eat four meals during the complete run of the study (twice prior to the test, i.e., the placebo and drug-administering stage of the study, once before receiving the placebo and once before receiving the drug). To remove any carryover effect, both psychological and physiological, the "meals should be separated by at least 4-day intervals."

As stated in the Panel's proposed protocol, the test meal must be taken twice prior to the test and the patient must have the symptoms on both of these occasions. It was pointed out to the Panel that the inclusion of this screening process, as part of the study, might be responsible for a large dropout rate. The Panel was well aware of this and realized that a valid study might be possible without including these two screening meals. A study could consist of only two test meals: One given before the drug and one given before the placebo. A subject then would be considered included in the study only if the symptoms occurred on both occasions. This latter study has some major problems and the Panel does not recommend it. First, without the screening meals it would be uncertain if the symptoms would last 30 minutes. Second, in such a test there could possibly be a substantial number of individuals who would have symptoms on only one occasion. The temptation would then be present to attempt to include the data on these cases in the analysis. The interpretation of such an analysis is extremely difficult.

The environment should be held constant during the test and the subjects should be adequately separated to prevent communication between them. The Panel was concerned about the validity of the study's results if subjects were allowed to eat together and witness each others' distress. While there are statistical procedures which can be used with varying degrees of success to make adjustments for the possible confounding effects of environmental influence, it is best not to allow these effects to enter into the study.

Some information not mentioned in the protocol may prove useful and may be collected during and after the test meal. First, the length of time the subject takes to finish the test meal could be noted. Distress and the intensity of distress may be related to speed of eating. Second, some subjects may not consume all their meal before the onset of the symptoms. A record of the amount of food consumed up to this point might be useful if the amount of food in the stomach at the time of occurrence of symptoms is related to time of relief. Similarly, the length of time from completion of the meal to onset of distress may also produce useful information.

Although the protocol does not concern itself with relief of symptoms other than the four described above (bloating, distention, fullness, and pressure), the subjects may experience other forms of distress. A stratification or statistical control by these other symptoms may be useful in the statistical analysis but is not of prime interest to the Panel. Adjustments would be made then for possible nonhomogeneous subjects with predisposing factors to differential treatment response. Further, it might be the case that the subjects experience distress in varying degrees of intensity. A stratification or control according to this or a rating scale to quantify the intensity of distress may also be useful. If desired, a stratification or control by both "non-gas" symptoms and intensity of the protocol's symptoms may also produce useful information. A greater number of patients would be required for these additional studies.

f. *Concomitant medication.* In order not to confound, interfere with, or cloud the drug's effect, the protocol states that "concomitant medication, including vitamins and aspirin, is not allowed for 24 hours prior to and during the test period. Alcohol must be avoided during the day of the test meal."

g. *Test design.* In a study of the type of drugs under consideration, it is possible for subjects to act as their own control (receive both the drug and placebo, each at different times). Thus, a crossover is possible and most desirable. Further, to guard against any unsuspecting biases the drug should be administered in a random fashion "in which approximately half the subjects receive the placebo before the drug and approximately half receive the drug before the placebo." The double-blind feature will control biases favoring the drug coming from either subjects or the investigator.

. The subject must respond to the test meal twice as a prerequisite to entering the study and must not obtain complete relief without medication within 30 minutes. Then, if complete relief is attained after the test meal and within 30 minutes of the appearance of the first symptom and taking the medication, it is appropriate to view this as a success (drug or placebo success). The time of complete relief should be recorded. Further, rather than waiting indefinitely for complete relief, the Panel decided that if distress from any symptom continued beyond 30 minutes, then the complete relief is said not to be attained and this result should be considered a failure. The analysis of the data should involve both the time to complete relief (from appearance of first symptom to total relief) and the dichotomous variable "complete relief or incomplete relief."

In order to control for the variation related to the test meal being prepared on different days, the protocol stipulates that "if more than one person is to be tested on any day, then some of the

subjects on that day should receive the placebo and the others the drug products."

The Panel also considered the possibility that, in addition to a placebo, the study might also consist of a direct evaluation of the drug and a positive control. In such a case a Latin-square is recommended.

h. *Analysis of data.* The statistical analysis should include at least the correlated proportions test where the dependent variable is the dichotomous variable, "complete relief or incomplete relief" within 30 minutes of the onset of the first symptom. Relief that is "clear and complete relief of all symptoms" is considered to be of prime concern. In addition to this, the correlated "test" appears to be appropriate. This is especially true if relief is obtained by most subjects regardless of receiving the placebo or the drug. Analyses can also be done on the ordering effect (drug then placebo as compared to placebo then drug).

In addition to the above, analyses which take into account the stratification or knowledge of intensity of the protocol's symptoms and/or other "nongas" symptoms might be appropriate. Age and sex could also be considered here. Multiple logistic or multiple regression analyses could be employed.

Further, a comparison of the results obtained from the two different testing sites would be essential. Differences in these results should be explained.

i. *Number of patients.* At least 33 patients are required at each of at least two test sites. The quantity 33 arises from assuming that a random sample of subjects is possible and that all subjects are homogeneous in all important respects. A random sample is impossible and there are a number of factors (some stated above) on which the available subjects may be nonhomogeneous. The investigators should view the 33 patients as the minimum sample size required and be prepared to include more subjects in their studies.

j. *Number of studies.* While the test setting and admissibility criteria are considered to be appropriate and realistic, they do not guarantee that the resulting sample will be a random sample or a representative sample of the sample population. Even under the most favorable conditions it is possible that the subjects finally selected for the study will not be representative of the patients of the setting from which the subjects are being selected. In order to ensure that generally applicable results are obtained, two separate studies are required. These are to be performed by different investigators at different geographical sites. Further, the sample for each study should be representative, with respect to age and sex, of patients at that site.

The Panel has determined that researchers conducting the study should take care not to use sites with peculiar patient populations (e.g., all males over 65 years of age). It is expected that the two selected sites will offer a patient profile similar to what is believed to be the profile of the sample population. Further, researchers are expected to perform statistical analyses comparing the two sites with respect to the patients' response(s) to the drug.

IV. Drug Products for the Treatment of the Symptoms of Intestinal Distress

A. Category I Conditions

The following are Category I conditions under which drug products used for the treatment of the symptoms of intestinal distress are generally recognized as safe and effective and are not misbranded.

1. *Category I active ingredients.* None.

2. *Category I labeling.* The Panel recommends the following Category I labeling for drug products used to relieve the symptoms of intestinal distress as being generally recognized as safe and effective and not misbranded. Any specific labeling discussed in the individual ingredient statements should also be considered.

Indications. The product labeling should contain one of the following statements:

a. "For relief of intestinal distress occurring 30 minutes to several hours after eating and often accompanied by complaints of bloating, distention, fullness, pressure, pain, or cramps."

b. "For relief of" (one or more of the following symptoms: "Bloating," "distention," "fullness," "pressure," "pain," or "cramps,") "sometimes described as 'gas', which occurs 30 minutes to several hours after eating."

The Panel is fully aware that although "gas" has not been proven to be the cause of intestinal distress, the consumer may perceive his or her symptoms as being due to "gas." Therefore, the Panel, after much deliberation, concludes that indication b. above may be allowed on these products.

B. Category II Conditions

The following are Category II conditions under which drug products used for the treatment of the symptoms of intestinal distress are not generally recognized as safe and effective or are misbranded.

1. *Category II active ingredients.*

Bismuth sodium tartrate
Blessed thistle and golden seal
Dehydrocholic acid
Duodenal substance
Garlic, dehydrated
Glutamic acid hydrochloride
Ox bile extract
Papain
Pepsin
Sorbitol

In addition, the Panel has classified other ingredients as Category II elsewhere in this document. (See part I. paragraph C.2.c. above—Other ingredients.)

a. *Bismuth sodium tartrate.* The Panel concludes that bismuth sodium tartrate, also referred to as sodium bismuthyltartrate, is not generally recognized as safe or effective for OTC use in treating the symptoms of intestinal distress.

(1) *Safety.* The Panel has not been presented with evidence demonstrating the oral safety of this compound nor is it aware of any such evidence.

This Panel is aware that the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products, in a report published in the **Federal Register** of March 21, 1975 (40 FR 12930), found bismuth subsalicylate to be safe orally in doses of 0.6 to 2 g taken three to four times daily but the safety of bismuth subnitrate in maximum doses of 5.6 g for adults and 0.475 g for children ages 3 to 6 in 4 hours is in question.

However, since publication of the Panel's report, bismuth encephalopathy has been reported from the oral use of 5 to 20 g daily (for several months to several years) of bismuth salts in Australia and France (Refs. 1 through 5) and from topical use of bismuth skin creams in England (Ref. 6). The bismuth salts causing this syndrome include the subgallate, subnitrate, silicate, aluminate, carbonate, subcarbonate, phosphate, oxyquinolate, pectate, and citrate. The implication is that the bismuth portion of the compound is toxic to the nervous system in these cases, although the mechanism involved is not clear.

The Panel concludes that evidence is not available to establish the safety of bismuth sodium tartrate for OTC use in treating the symptoms of intestinal distress.

(2) *Effectiveness.* Although some studies have suggested that bismuth preparations may be helpful in healing peptic ulcerations (Ref. 7), no studies have been presented nor is the Panel aware of any studies that demonstrate bismuth sodium tartrate to be effective in treating the symptoms of intestinal distress. In the absence of such data the Panel concludes that bismuth sodium

tartrate is not generally recognized as effective in treating this condition.

(3) *Evaluation.* The Panel concludes that bismuth sodium tartrate is not generally recognized as safe and effective for OTC use in treating the symptoms of intestinal distress. The safety of bismuth salts in oral preparations is seriously questioned by the recent demonstration that they may cause encephalopathy, and there is no information available to the Panel demonstrating the effectiveness of bismuth sodium tartrate in the treatment of the symptoms of intestinal distress.

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(*5*) Martin-Bouyer, G., "Intoxications par les sels de bismuth administres par voie orale. Enquete epidemiologique," *Therapie,* 31:683–702, 1976.

(*6*) Kruger, G., et al., "Disturbed Oxidative Metabolism in Organic Brain Syndrome Caused by Bismuth in Skin Creams," *The Lancet,* 2:485–487, 1976.

(*7*) OTC Volume 170135.

b. *Blessed thistle and golden seal.* The Panel reviewed one preparation containing the extract of the whole plant blessed thistle (*Cnicus benedictus*), and the roots and rhizomes of golden seal *(Hydrastis canadensis)* and concludes that the preparation is safe for OTC use in the dose recommended by the manufacturer, but is not generally recognized as effective in treating the symptoms of intestinal distress. The effectiveness data submitted do not convince the Panel that it is effective for this indication and the Panel, therefore, places it in Category II. Both ingredients have a history of use in folk medicine as a bitter tonic.

c. *Dehydrocholic acid.* The Panel concludes that dehydrocholic acid is safe for OTC use in the dose noted below, but is not generally recognized as effective in treating the symptoms of intestinal distress.

(1) *Safety.* The Panel is aware of one animal study which determined the LD^{50} of dehydrocholic acid to be 14.7 g/kg in rats (Ref. *1*). The study further reported that no hepatic damage was found to result from the chronic administration of 3 and 5 g daily to dogs for 3 to 7 months, nor from the administration of 333 mg/kg daily to rats for 32 days (Ref. *1*).

The Panel concurs with the recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products, published in the **Federal Register** of March 21, 1975 (40 FR 12902), that dehydrocholic acid is safe in an adult dose of 750 to 900 mg per day when used as a laxative (40 FR 12910). That Panel did not approve its use in children under 12 years of age.

Based on the available data, the Panel concludes that dehydrocholic acid is safe for OTC use in the above dosage.

(2) *Effectiveness.* Dehydrocholic acid, which is a partially synthetic derivative of cholic acid, stimulates the liver to increase the volume of bile by increasing its water content without increasing its constituents (hydrocholeretic) (Ref. *2* and *3*).

Dehydrocholic acid has been used as an OTC laxative, but the Panel is not aware of any adequate and well-controlled clinical studies demonstrating its effectiveness in treating the symptons of intestinal distress nor is dehydrocholic acid generally recognized as an effective treatment for the symptoms of intestinal distress.

(3) *Evaluation.* Although dehydrocholic acid is considered to be generally recognized as safe for OTC use in the dose specified above, the Panel concludes that it has not been demonstrated to be effective for relief of the symptoms of intestinal distress. This conclusion is in agreement with the following decision of the Advisory Review Panel on OTC Laxative Antidiarrheal, Emetic, and Antiemetic Drug Products (published in the **Federal Register** of March 21, 1975 (40 FR 12910):

> There is no evidence in support of the claim that dehydrocholic acid relieves "indigestion", "excessive belching", "after meal discomfort", or "the sensation of abdominal fullness." These claims constitute mislabeling and dehydrocholic acid is placed in Category II with respect to these claims.

References

(*1*) Berman, A. L., E. Snapp, A. C. Ivy, and A. J. Atkinson, "The Effect of Long-Continued Ingestion of Oxidized Bile Acids on the Dog and Rat," *American Journal of Digestive Diseases,* 7:280–284, 1940.

(*2*) Harvey, S.C., "Gastric Antacids and Digestants," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, p. 973, 1975.

(*3*) DiPalma, J. R., "Drill's Pharmacology in Medicine," 4th Ed., McGraw-Hill, New York, pp. 972–973, 1971.

d. *Duodenal substance.* The term duodenal substance appears to lack a precise meaning in the current medical literature. Presumably the term refers to one or more mixtures of peptide substances such as cholecystokinin, gastrin, pancreozymin, and secretin which are secreted by the intestinal mucosa. The latter peptide substances act physiologically to facilitate digestion by stimulating the release by the gastrointestinal tract or the pancreas of various enzymes and other exocrine substances. The Panel is unware of any accepted therapeutic indication for these peptides.

In the absence of such data, the Panel concludes that duodenal substance is not generally recognized as safe and effective in treating the symptoms of intestinal distress.

e. *Garlic, dehydrated.* The Panel concludes that dehydrated garlic is safe for OTC use at the dose noted below, but is not generally recognized as effective in treating the symptoms of intestinal distress.

(1) *Safety.* Garlic has been widely used as a food for many years with no known harmful effects. It is considered by the Panel to be safe as a carminative (expelling gas from the alimentary canal) in the recommended OTC dose of 0.6 g after meals (Ref. *1*).

(2) *Effectiveness.* The principal active ingredients of dehydrated garlic are allyl propyl disulfide and diallyl disulfide (Ref. *2*).

Some data were submitted regarding dehydrated garlic's effectiveness as a carminative, but the Panel is not aware of any adequate and well-controlled clinical studies demonstrating the effectiveness of dehydrated garlic or its principal active ingredients in treating the symptoms of intestinal distress; nor is it generally recognized as an effective treatment for the symptoms of intestinal distress.

(3) *Evaluation.* The Panel concludes that dehydrated garlic is generally recognized as safe for OTC use in the dose specified but its effectiveness has not been demonstrated in treating the symptoms of intestinal distress.

References

(*1*) OTC Volume 170003.

(*2*) Bordia, A., H. C. Bonsal, S. K. Arora, and S. V. Singh, "Effect of the Essential Oils of Garlic and Onion on Alimentary Hyperlipemia," *Atherosclerosis,* 21:15–20, 1975.

f. *Glutamic acid hydrochloride.* The Panel concludes that glutamic acid hydrochloride is safe for OTC use in the dose noted below, but is not generally recognized as effective in testing the symptoms of intestinal distress.

(1) *Safety.* Available clinical data and marketing experience have shown

glutamic acid hydrochloride to be safe for OTC use in the dose of 1.02 g three times daily as a stomach acidifier (Ref. *1*).

(2) *Effectiveness.* Glutamic acid hydrochloride has been marketed as an agent intended to increase the amount of acid present in the stomach, and thus favorably altering the pH of the gastric environment (Ref s. *2* and *3*). However, the Panel knows of no proven relationship between hypoacidity or anacidity of the stomach and the symptoms of intestinal distress, nor is the Panal aware of any adequate and well-controlled clinical studies demonstrating the effectiveness of glutamic acid hydrochloride in treating the symptoms of intestinal distress. Furthermore, glutamic acid hydrochloride is not generally recognized as an effective treatment of this condition.

(3) *Evaluation.* The Panel concludes that glutamic acid hydrochloride is generally recognized as safe for OTC use in the dose specified but its effectiveness has not been demonstrated in treating the symptoms of intestinal distress.

The Panel is aware that glutamic acid hydrochloride has been employed as a stomach acidifier in the treatment of achlorhydria and hypochlorhydria but does not find it has any usefulness in treating these conditions. The Panel has prepared a separate document on OTC stomach acidifier drug products discussing the merits of stomach acidifiers published in the **Federal Register** of October 19, 1979 (44 FR 60316).

References

(*1*) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 1082–1083, 1977.

(*2*) OTC Volume 170023.

(*3*) OTC Volume 170049.

g. *Ox bile extract.* The Panel concludes that ox bile extract is safe for OTC use in the dose noted below, but is not generally recognized as effective in treating the symptoms of intestinal distress.

(1) *Safety.* The Panel believes the usual dose of 300 to 500 mg given two to three times daily after meals to be safe for healthy individuals (Ref. *1*). However, for individuals who have biliary obstruction or some other forms of liver disease, exogenous bile salts further contribute to an already undesirable increase in plasma and blood concentrations of bile salts (Ref. *2*). Commercial ox bile preparations may produce diarrhea (Ref. *3*).

(2) *Effectiveness.* Ox bile extract is a powdered or granular extract of ox bile with a characteristic odor and taste containing an amount of sodium salts of ox bile acids equivalent to approximately 45 percent cholic acid (Ref. *1*).

Bile contains bile salts, bile pigments, lecithin, cholesterol, mucin, and other proteins, fatty acids, and inorganic salts. Of these constituents, the most important are the bile salts, which occur as sodium salts of conjugated bile acids (Ref. *1*). The bile salts constitute approximately 3 percent of the total bile secreted daily (Ref. *2*).

Bile acids are synthesized by the liver and secreted into the duodenum as conjugated bile salts. A high percentage of the bile salts is reabsorbed in the lower small intestine and recirculated through the liver by way of the enterohepatic circulation.

Bile salts enhance the absorption of lipids and are necessary for the absorption of fat-soluble vitamins and cholesterol. They play an important role in maintaining the normal solubility of cholesterol in the bile (Ref. *3*). Bile salts also promote digestion of fats by stimulating pancreatic secretion and by activating pancreatic lipase (Ref. *2*).

The large volume of bile secreted into the duodenum helps to neutralize the acidic contents but is less important than pancreatic secretions in this respect (Ref. *2*).

Bile salts "* * * can be given to promote the flow of bile or to increase intrabiliary pressure; however, much expert medical opinion now holds that the administration of bile salts is often unnecessary or inappropriate and can sometimes cause undue pain or danger to the patient" (Ref. *2*). "Bile salts are no better than placebos in nonobstructive, noncholestatic biliary tract disorders or in various malfunctions of the intestine" (Ref. *2*).

Ox bile extract "* * * is promoted for the replacement therapy in patients who have an insufficient concentration of bile salts in the intestine, but it is ineffective. Use of ox bile extract is inadvisable, for it does not provide an adequate amount of bile salts" (Ref. *3*).

Even though ox bile extract has been used for many years in OTC products, the Panel is not aware of any adequate and well-controlled clinical studies demonstrating its effectiveness in treating the symptoms of intestinal distress, nor is ox bile extract generally recognized as an effective treatment for the symptoms of intestinal distress.

(3) *Evaluation.* The Panel concludes that ox bile extract is generally recognized as safe for OTC use in the dose specified but its effectiveness has not been demonstrated in treating the symptoms of intestinal distress.

References

(*1*) "The United States Dispensatory," 27th Ed., edited by A. Osol and R. Pratt, J. B. Lippincott Co., Philadelphia, p. 820, 1973.

(*2*) Harvey, S. C., "Gastric Antacids and Digestants," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, pp. 971–973, 1975.

(*3*) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, p. 1084, 1977.

h. *Papain.* The Panel concludes that papain is safe for OTC use at the dose noted below, but is not generally recognized as effective in the treatment of the symptoms of intestinal distress.

(1) *Safety.* Papain is used as a meat tenderizer and about one-half million pounds are imported annually for this purpose (Ref. *1*). The Panel is unaware of any toxic or adverse symptoms that have arisen from its use, except the occasional allergic reaction in patients sensitive to papain. The Panel concludes that it is otherwise safe in the recommended daily dose of 100 to 600 mg (Ref. *2*). However, papain is contraindicated in patients taking anticoagulant medication (Ref. *2*).

(2) *Effectiveness.* Papain is a proteolytic enzyme from the fruit of the tropical melon tree (*Carica papaya*) (Ref. *3*). Over the years it has been used in products intended to prevent or treat a variety of inflammatory states (Ref. *3* and *4*). No data were submitted, nor is the Panel aware of data demonstrating the effectiveness of papain in treating the symptoms of intestinal distress.

(3) *Evaluation.* The Panel concludes that papain is generally recognized as safe for OTC use in the dose specified but its effectiveness has not been demonstrated in treating the symptoms of intestinal distress.

References

(*1*) Breeling, L., "The Nature and Nutritive Value of Papaya Juice," *Journal of the American Medical Association,* 210:2100, 1969.

(*2*) "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 829–830, 1973.

(*3*) Gibb, J. W., "Enzymes," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol and J. E. Hoover, Mack Publishing Co., Easton, PA, p. 975, 1975.

(*4*) Swinyard, E. A., "Locally Acting Drugs," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., Inc., New York, pp. 958–959, 1975.

i. *Pepsin.* The Panel concludes that pepsin is safe for OTC use at the dose noted below, but is not generally recognized as effective in treating the symptoms of intestinal distress.

(1) *Safety.* No safety data were submitted, However, based upon the continued marketing of pepsin over many years with no reports of adverse effects the Panel concludes that it is safe in a daily dose of up to 1,000 mg (Ref. *1*).

(2) *Effectiveness.* Pepsin, a proteolytic enzyme obtained from the glandular layer of fresh hog stomach, (Ref. *2*) is similar to human pepsin. Although its presence is not required for protein digestion, because intestinal enzymes can function without it, pepsin has been used when endogenous human pepsin is deficient or absent. The Panel is not aware of any convincing evidence that added pepsin is of therapeutic usefulness (Ref. *2, 3,* and *4*). It also is eventually inactivated by the higher pH of the intestines (Ref. *5*).

No data were submitted to demonstrate the effectiveness of pepsin and the Panel is not aware of any adequate and well-controlled clinical studies demonstrating its effectiveness in treating the symptoms of intestinal distress, nor is pepsin generally recognized as an effective treatment for the symptoms of intestinal distress.

(3) *Evaluation.* The Panel concludes that pepsin is generally recognized as safe for OTC use in the dose specified but its effectiveness has not been demonstrated in treating the symptoms of intestinal distress.

References

(*1*) "The United States Dispensatory and Physician's Pharmacology," 26th Ed., edited by A. Osol, R. Pratt, and M. D. Altschule, J. B. Lippincott Co., Philadelphia, p. 874, 1967.

(*2*) Wilson, C. O., O. Grisvold, and R. F. Doerge, "Text Book of Organic Medical and Pharmacological Chemistry," 6th Ed., J. B. Lippincott Co., Philadelphia, pp. 904–905, 1971.

(*3*) Harvey, S. C., "Gastric Antacids and Digestants," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, p. 971, 1975.

(*4*) "AMA Drug Evaluations," 2d Ed., Publishing Sciences Group, Inc., Acton, MA, p. 812, 1973.

(*5*) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, p. 1083, 1977.

j. *Sorbitol.* The Panel concludes that sorbitol, also known as *D*-sorbitol, is safe for OTC use in the dose noted below, but is not generally recognized as effective in treating the symptoms of intestinal distress.

(1) *Safety.* The Panel considers sorbitol safe for use in the suggested oral dose of 4.5 g three times daily (Ref. *1*).

Steinke reported finding no evidence of gastrointestinal side effects and no increase in insulin requirements in 143 juvenile diabetics, aged 5 to 13 years, following the administration of 41 g of sorbotol per day in 3 equal doses, for periods of 8 to 48 days (Ref. *2*). In another study some patients were reported to develop borborygmus and hyperperistalsis or diarrhea following either single large doses of sorbitol (40 g) for gall bladder studies or the chronic administration of 7 g before meals for 20 to 60 days (Ref. *3*).

(2) *Effectiveness.* Sorbitol is a six-carbon polyhydric alcohol. It is more slowly absorbed from the gastrointestinal tract than dextrose. Its main use is as an osmotic diuretic. Fifty percent is metabolized or converted to glycogen and stored in the liver (Ref. *4*). Oxidation to fructose occurs in both the liver and kidney (Ref. *2*).

Maximal contraction of the gall bladder has been found to occur 30 minutes after the administration of 9, 18, and 27 g of sorbitol (Ref. *5*). Eighty percent of 64 patients with hepatobiliary disorders who were treated with 7 g of sorbitol before meals for periods of from 20 to 60 days were reported to have obtained relief from dyspepsia and abdominal swelling, as well as some other symptoms (Ref. *3*).

The Panel is aware of the use of sorbitol as an osmotic diuretic and its more general usage as a laxative, sweetener, humectant, and as a vehicle (70 percent weight/weight solution) (Ref. *6*), but the Panel is not aware of any adequate and well-controlled clinical studies demonstrating the effectiveness of sorbitol in treating the symptoms of intestinal distress in the absence of hepatobiliary disease. In addition, sorbitol is not generally recognized as an effective treatment for the symptoms of intestinal distress.

(3) *Evaluation.* The Panel concludes that sorbitol is generally recognized as safe for OTC use in the dose specified but its effectiveness has not been demonstrated in treating the symptoms of intestinal distress.

References

(*1*) OTC VoLume 170042 (Section V.A.I.).

(*2*) Steinke, J., et al., "Evaluation of Sorbitol in the Diet of Diabetic Children at Camp," *Diabetes,* 10:218–227, 1961.

(*3*) Piccinelli, O., and G. Timossi, "D-Glucitol in the Therapy of Hepatobiliary Diseases," *Minerva Medica,* 49:77–82, 1958.

(*4*) DiPalma, J. R., "Drill's Pharmacology in Medicine," 4th Ed., McGraw-Hill, New York, p. 299, 1971.

(*5*) OTC Volume 170042 (Section V.A.I.).

(*6*) Swinyard, E. A., "Pharmaceutical Necessities," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol and J. E. Hoover, Mack Publishing Co., Easton, PA, p. 1235, 1975.

2. *Category II labeling.* The Panel concludes that some portions of the following labeling claims are either unsupported by scientific date, vague, misleading, unrelated to the symptoms of intestinal distress, or in some instances unsupported by sound reasoning. The claims listed below and other related terms are, therefore, classified as Category II labeling for drug products used to treat the symptoms of intestinal distress.

a. "Stimulates the cells of the stomach to help increase the amount of gastric juice and thus improve digestion and nutrition."

b. "Helps create a healthy intestinal environment for more normal digestion."

c. "Stomachic."

d. "For relief of biliary indigestion."

e. "Choleretic."

f. "Digestive."

g. "Carminative."

h. "Helps to improve poor appetite."

i. "Gastrointestinal distress due to irritation and inflammation of the intestinal tract."

j. "Helps prevent loose bowels due to excess fat content."

k. "For enteritis."

l. "Digestive supplement."

m. "Aids digestion of hard to digest foods."

n. "Digestant." (Except as noted under Category III Labeling.)

o. "For relief of gastrointestinal digestive disturbances."

p. "Permits a regular, comfortable digestion of foods previously not tolerated."

q. "For temporary relief of indigestion due to overeating."

r. "For expelling gas from the stomach and intestine."

s. "Helps to relieve heartburn due to indigestion."

t. "Relieves discomfort and pain of entrapped gas caused by air swallowing and overindulgence in food."

u. "Relieves belching, bloating, and flatulence."

v. "Helps reduce discomfort due to gas in the stomach and intestines."

w. "An anti-gas digestive aid to help relieve belching, bloating, or an over-full feeling."

x. "For relief of constipation and headache, heartburn and gas that may be caused by constipation."

y. "For relief of constipation, especially when accompanied by flatulence or gas distress."

z. "For relief of constipation."

aa. Phrases such as "long-lasting" which vaguely and nonspecifically relate to the speed of action.

bb. "For the prevention of intestinal distress."

cc. "Superior to ordinary."

dd. "Specially improved."

ee. "Selected ingredients."

ff. "Extra strength."

gg. "Contains more active ingredients per dose."

hh. "Works internally."

ii. "Travels through the bloodstream."

jj. "Can be used to improve digestion of geriatric patients."

kk. "To alleviate simple postprandial discomfort (bloating, belching, flatulence, and a sense of fullness) due to over eating or insufficient mastication of food."
ll. "Postgastrectomy syndrome."
mm. "Chronic pancreatitis."
nn. "Pancreatic necrosis."
oo. "Chronic hepatitis."
pp. "Gallbladder disease."
qq. "Surgical patients following cholecystectomy, subtotal pancreatectomy, and other surgery of the upper gastrointestinal tract."
rr. "Overindulgence in excessively fatty meals."
ss. "Abdominal rumblings."

C. Category III conditions

The following are Category III conditions for which the available data are insufficient to permit final classification at this time.

1. *Category III active ingredients.* The Panel concludes that the safety of the following ingredients in the recommended doses is unquestioned, except as noted in the individual ingredient writeups:

Cellulase and hemicellulose
Charcoal, activated and charcoal, wood
Homatropine methylbromide
Magnesium hydroxide
Pancreatin and pancrelipase
Simethicone
Sodium bicarbonate
Sodium citrate

a. *Cellulase and hemicellulase.* The concludes panel that cellulase and hemicellulase are safe for OTC use in the dose noted below, but data are insufficient to demonstrate their effectiveness in treating symptoms of intestinal distress.

(1) *Safety.* Cellulase and hemicellulase are obtained from molds such as *Aspergillus oryzae* and *Penicillium notatum* as well as from various other sources (Refs. *1* and *2*). Those derived for medicinal use are normally obtained from *Aspergillus oryzae.* Cellulases have been utilized as digestive aids for many years. Based on the available data, the Panel Concludes that they are safe when used as OTC digestive aids and in the doses recommended below.

(2) *Effectiveness.* Cellulase and hemicellulase are not normal constituents of the human bowel. These enzymes are capable of hydrolyzing cellulose and hemicellulose contained in ingested plant foods. They have been reported to be effective in dissolving bezoars and phytobezoars (Ref. *3*) and in reducing the amount of roughage in the stool (Refs. *4* and *5*).

The Panel is not aware of any adequate and well-controlled clinical studies demonstrating the effectiveness of cellulase or hemicellulase in treating the symptoms of intestinal distress. Based upon the pharmacological action, the Panel concludes that cellulase and hemicellulase have the potential for this OTC use and therefore, recommends that they be further tested according to the testing guidelines to determine whether or not they are effective.

(3) *Proposed dosage.* The Panel concludes that cellulase and hemicellulase are safe as single ingredient products in the usual and recommended daily doses of 9 to 50 mg for cellulase (Refs. *6* and *5*) and 50 to 100 mg for hemicellulase (Refs. *6* and *7*) taken three times daily.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used in the treatment of the symptoms of intestinal distress (See part IV. paragraph A.2. above—Category I labeling.)

(5) *Evaluation.* The Panel recommends that adequate testing of cellulase and hemicellulase be performed according to the testing guidelines to determine whether or not they are effective for treatment of the symptoms of intestinal distress. (See part IV. paragraph D. below—Data Required for Evaluation: Guidelines for Developing Protocols for Evaluating OTC Drugs for the Treatment of the Symptoms of Intestinal Distress.)

References

(*1*) Pigman, W., "Enzymes Acting on Hemicelluloses, Gums, and Wood," *in* "The Enzymes," Volume I, edited by J. B. Sumner and K. Myrback, Academic Press, Inc., New York, pp. 739–744, 1951.

(*2*) Courtois, J. E., "Some Biochemical Aspects of Cellulases and Hemicellulases," *Glasnik Hemijskog Drustvaw,* 32:365–388, 1967.

(*3*) OTC Volume 170100.

(*4*) Friend, D. G., "Effect of Oral Enzyme Therapy on Roughage Content of Stools," *The Journal of New Drugs,* 5:236–239, 1965.

(*5*) OTC Volume 170049.

(*6*) OTC Volume 170034.

(*7*) OTC Volume 170144.

b. *Charcoal, activated and charcoal, wood.* The Panel concludes that activated charcoal and wood charcoal are safe for OTC use in the dose noted below, but data are insufficient to demonstrate their effectiveness in treating the symptoms of intestinal distress.

(1) *Safety.* Activated charcoal is ingested in usual doses of 30 g or more as an adjunct in the treatment of acute toxic ingestion. Yatzidis has given up to 50 g of activated charcoal daily to uremic patients for up to 20 months with no apparent ill effects (Ref. *1*); however, the Panel is concerned that because activated charcoal is a nonspecific adsorbent, chronic usage might cause depletion of certain essential nutrients. The Panel is aware of no studies which conclusively establish the safety of the chronic ingestion of activated charcoal in humans and at the present time the Panel recommends that the dosage be restricted to no more than 10 g daily in divided doses for a period of no more than 7 days for the treatment of symptoms of intestinal distress. In addition, activated charcoal will adsorb many other drugs which a person might be taking concurrently, and a suitable warning is included below under the heading "Labeling."

Based on the available data, the Panel concludes that activated charcoal is safe when used as a digestive aid and in accordance with the restrictions noted below.

(2) *Effectiveness.* Activated charcoal is known to adsorb many gases, organic and inorganic compounds, toxins, etc. The causes of intestinal distress have not been conclusively established and the effectiveness of activated charcoal in relieving these symptoms has not been demonstrated at the present time.

Nonactivated charcoal has one-third or less the adsorbent capacity of activated charcoal and because of this lack of uniform activity, its use for this condition is not recommended.

Activated charcoal has been used for many years in the management of ostomy patients by some physicians to reduce odor and gas (Ref. *2*). It has also been recommended in the past for treatment of dysentery. The Panel is not aware of any adequate and well-controlled clinical studies demonstrating the effectiveness of activated charcoal for its use in treating the symptoms of intestinal distress. Based on the pharmacological action, the Panel concludes that activated charcoal has the potential for this OTC use and, therefore, recommends that further testing be done according to the testing guidelines to determine whether or not it is effective for treatment of the symptoms of intestinal distress.

(3) *Proposed dosage.* The Panel concludes that activated charcoal is safe for OTC use when its ingestion is limited to 10 g daily in divided doses for a period of no more than 7 days for treating the symptoms of intestinal distress.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used in the treatment of the symptoms of intestinal distress. (See part IV. paragraph A.2. above—Category I labeling.) In addition, the Panel recommends that the following warning statements be required to appear in the labeling of drug products containing activated charcoal:

(i) "If you are taking other drugs, consult your physician as this drug may interfere with their effectiveness."

(ii) "Do not take for longer than 1 week or in greater than recommended amounts, except upon the advice of a physician."

(5) *Evaluation.* The Panel recommends that adequate testing of activated charcoal be performed according to the testing guidelines to determine whether or not it is effective for treatment of the symptoms of intestinal distress. (See part IV, paragraph D. below—Data Required for Evaluation: Guidelines for Developing Protocols for Evaluating OTC Drugs for the Treatment of the Symptoms of Intestinal Distress.)

References

(*1*) Yatzidis, H., "Activated Charcoal Rediscovered," *British Medical Journal,* 4:51, 1972.

(*2*) Marino, A. W. M. Jr., H. W. N. Mancini, and A. W. M. Marino Sr., "Colostomy Simplified", *Modern Treatment,* 8:892–908, 1971.

c. *Homatropine methylbromide.* The Panel concludes that homatropine methylbromide is safe for OTC use in the dose noted below, but data are insufficient to demonstrate effectiveness in treating the symptoms of intestinal distress.

(1) *Safety.* In a study to determine the minimal toxic dose of homatropine methylbromide, Berger and Ballinger reported toxicity in individuals ingesting doses ranging from 68 to 273 mg per day (Ref. *1*). This is far in excess of the usually recommended prescribed dosage of 2.5 to 5.0 mg four times daily (Ref. *2*). There was no evidence of toxic or cumulative effects at the smaller dosage of 1 mg three times daily before meals (Ref. *1*).

"Slight cerebral symptoms" have resulted from the use of maximum doses of 20 mg per day, but no cumulative effects have been reported (Ref. *3*). Homatropine methylbromide is about one-half as potent as atropine in its effect on the gastrointestinal tract, and it is claimed to be only one-thirtieth as toxic on the central nervous system (Ref. *4*). Its use is generally accompanied by fewer central nervous system side effects than atropine (Ref. *4*).

The Panel concludes that homatropine methylbromide is safe for OTC use in treating the symptoms of intestinal distress at a maximum dose of 5 mg four times daily.

(2) *Effectiveness.* Homatropine methylbromide is a quaternary ammonium cholinergic blocking agent and is much less active than atropine on the central nervous system. Like homatropine, it is a weaker autonomic blocking agent than atropine. It is used to reduce the motility of the intestinal tract (Ref. *2*).

The Panel is not aware of any adequate and well-controlled clinical studies demonstrating the effectiveness of homatropine methylbromide in treating the symptoms of intestinal distress. The effectiveness of atropine-like substances on the motility of the intestinal tract is well recognized and based on this pharmacological action, the Panel concludes that homatropine methylbromide has the potential for this OTC use and, therefore, recommends that it be further tested according to the testing guidelines to determine whether or not it is effective.

(3) *Proposed dosage.* The Panel concludes that homatropine methylbromide is safe for OTC use at a maximum dose of 5 mg four times daily.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used in the treatment of the symptoms of intestinal distress (See part IV. paragraph A.2. above—Category I labeling.)

(5) *Evaluation.* The Panel recommends that adequate testing of homatropine methylbromide be performed according to the testing guidelines to determine whether or not it is effective for treatment of the symptoms of intestinal distress. (See part IV. paragraph D. below—Data Required for Evaluation: Guidelines for Developing Protocols for Evaluating OTC Drugs for the Treatment of the Symptoms of Intestinal Distress.)

References

(*1*) Berger, A. R., and J. Ballinger, "The Relative Toxicity of Atropine and Novatrine in Man," *American Journal of Medical Sciences,* 214:156–158, 1947.

(*2*) Harvey, S. C., "Antimuscarinic Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol and J. E. Hoover, Mack Publishing Co., Easton, PA, p. 841, 1975.

(*3*) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics," 7th Ed., Lea and Febiger, Philadelphia, p. 351, 1970.

(*4*) Krantz, J. C., and C. J. Carr, "The Pharmacologic Principles of Medical Practice," 7th Ed., Williams and Wilkins, Baltimore, p. 404, 1969.

d. *Magnesium hydroxide.* The Panel concludes that magnesium hydroxide is safe for OTC use in the dose noted below, but data are insufficient to demontrate its effectiveness in treating the symptoms of intestinal distress.

(1) *Safety.* If kidney function is normal, magnesium hydroxide is considered safe for use when taken in the dosage noted below.

Magnesium hydroxide is generally considered to be a poorly absorbed antacid. However, absorption of as little at 5 to 10 percent (Ref. *1*) to as much as 15 to 30 percent has been reported (Ref. *2*). It is well known that excessive magnesium blood levels may result from ingestion of magnesium by persons with kidney damage, and, therefore, a warning label should be present on any magnesium hydroxide preparation in which the maximal daily dose exceeds 50 meq of magnesium.

Magnesium hydroxide has the potential for drug interactions with bishydroxycoumarin and related anticoagulants (Ref. *3*) and with tetracycline antibiotics (Ref. *4*). The Panel believes that the consumer should be alerted to the potential for drug interactions and recommends that a warning appear on the label.

(2) *Effectiveness.* The Panel is aware of the antacid and laxative properties of magnesium hydroxide but other action in the intestines is not well established. The Panel recommends further testing according to the testing guidelines to determine whether or not magnesium hydroxide is effective in treating the symptoms of intestinal distress.

(3) *Proposed dosage.* The Panel concludes that the OTC use of magnesium hydroxide is safe in the usual recommended dose of up to 15 mL of a suspension of up to 8.5 percent magnesium hydroxide taken three to four times daily (Ref. *1*). This is equivalent to a total daily dose of up to 5.1 g of magnesium hydroxide, but should not be taken for more than 2 weeks except upon the advice of a physician.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used in the treatment of the symptoms of intestinal distress. (See part IV. paragraph A.2. above—Category I labeling.) In addition, the Panel recommends that the following warning statements be required to appear in the labeling of drug products containing magnesium hydroxide:

(i) "If you are taking other drugs, consult your physician as this drug may interfere with their effectiveness."

(ii) "Do not take for longer than 2 weeks or in greater than recommended amounts, except on the advice of a physician."

(iii) *For products containing more than 50 meq of magnesium in the recommended daily dosage.* "If you have kidney disease, do not use this product except under the supervision of a physician."

(5) *Evaluation.* The Panel recommends that adequate testing of magnesium hydroxide be performed according to the testing guidelines to determine whether or not it is effective for treatment of the symptoms of intestinal distress. (See part IV. paragraph D. below—Data Required for Evaluation: Guidelines for Developing Protocols for Evaluating

OTC Drugs for the Treatment of the Symptoms of Intestinal Distress.)

References

(1) Harvey, S. C., "Gastric Antacids and Digestants," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, pp. 964–965, 1975.

(2) Dretchen, K., D. Hollander, and J. B. Kirsner, "Roundup on Antacids and Anticholinergics," *Patient Care*, 9:94–114, 1975.

(3) Ambre, J. J., and L. J. Fischer, "Effect of Co-Administration of Aluminum and Magnesium Hydroxides on Absorption of Anticoagulants in Man," *Clinical Pharmacology and Therapeutics*, 14:231–237, 1973.

(4) Hussar, D. A., "Drug Interactions," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol and J. E. Hoover, Mack Publishing Co., Easton, PA, p. 1741, 1975.

e. *Pancreatin and pancrelipase.* The Panel concludes that pancreatin preparations (pancreatin or pancrelipase) are safe for OTC use in the dose noted below, but data are insufficient to demonstrate their effectiveness in treating the symptoms of intestinal distress in the absence of a deficiency of pancreatic enzymes.

(1) *Safety.* The Panel has determined that pancreatic preparations (pancreatin or pancrelipase) are safe in the usual daily dosage of up to 14 g of triple strength pancreatin when given in divided doses (Ref. *1*). Side effects of nausea, vomiting, and diarrhea may occur at high doses (Ref. *1*). Because pancreatin preparations (pancreatin or pancrelipase) are obtained mainly from hogs, they should not be used by individuals who are allergic to pork.

(2) *Effectiveness.* The enzymes of the pancreas are obtainable as a preparation known as pancreatin. Pancreatin is an amorphous substance obtained from fresh hog pancreas. It contains principally amylase, protease, and lipase (Ref. *1*). Pancreatin is principally employed in the treatment of conditions in which the secretion of pancreatic juice is deficient. The evidence for effectiveness of pancreatic enzymes as an aid to digestion in the absence of decreased secretion of pancreatic juice is less impressive than when compared with a pancreatic deficiency. Pancreatin was shown to be ineffective in steatorrhea in patients when the condition was due to disease of the small bowel or other conditions in which pancreatic secretion was normal (Ref. *2*). There are numerous reports of improvement in symptoms of intestinal distress following administration of pancreatic preparations (Ref. *3*), but in general these are uncontrolled or poorly controlled studies. Preliminary reports of controlled studies suggest that there may be some benefit, but the evidence is inconclusive (Ref. *3*).

The Panel recommends that pancreatic preparations (pancreatin or pancrelipase) be tested according to the testing guidelines to determine whether or not they are effective in treating the symptoms of intestinal distress, in the absence of a deficiency of pancreatic enzymes.

(3) *Proposed dosage.* The Panel concludes that pancreatic preparations (pancreatin or pancrelipase) for OTC use are safe in the usual and recommended daily dose of up to 14 g of triple strength pancreatin (or its equivalent) when given in divided doses with meals. These preparations may contain variations of the standard pancreatin proportions of amylase, lipase, and protease as defined in the National Formulary.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used to treat the symptoms of intestinal distress where no pancreatic deficiency exists: (See part IV. paragraph A.2. above—Category I labeling.) In addition, the Panel recommends that the following warning statement be required on pancreatin preparations (pancreatin or pancrelipase):

"If you are allergic to pork products, do not take this product."

(5) *Evaluation.* The Panel recommends that adequate testing of pancreatin preparations (pancreatin or pancrelipase) be performed according to the testing guidelines to determine whether or not they are effective for treatment of the symptoms of intestinal distress. (See part IV. paragraph D. below—Data Required for Evaluation: Guidelines for Developing Protocols for Evaluating OTC Drugs for the Treatment of the Symptoms of Intestinal Distress.) The Panel considers that individuals with any exocrine pancreatic insufficiency (as shown by usual laboratory tests) should be excluded from intestinal distress testing.

The Panel is aware that pancreatin preparations (pancreatin or pancrelipase) are used extensively in treating patients with a prediagnosed exocrine pancreatic insuffiency. The Panel has prepared a separate document on OTC Exocrine Pancreatic Insufficiency Drug Products published in the Federal Register of December 21, 1979 (44 FR 75666).

References

(1) "AMA Drug Evaluations," 3d Edition, Publishing Sciences Group, Inc., Littleton, MA, pp. 1085–1086, 1977.

(2) Marks, I. N., S. Bank, and E. M. Airth, "Pancreatic Replacement Therapy in the Treatment of Pancreatic Steatorrhoea" *Gut*, 4:217–222, 1963.

(3) OTC Volumes 170144, 170145, and 170146.

f. *Simethicone.* The Panel concludes that simethicone is safe for OTC use in the dose noted below, but data are insufficient to demonstrate its effectiveness in treating the symptoms of intestinal distress.

(1) *Safety.* The Panel concurs with the determination of FDA, as stated in the antiflatulent final monograph (21 CFR 332.10), that simethicone is safe in a maximum daily dosage of 500 mg as an OTC product.

Simethicone is a mixture of dimethylpolysiloxane and approximately 5 percent silica gel. Toxicological studies and the wide use of dimethylpolysiloxane in chemical combination with silica gel for many years without evidence of adverse effects have established its safety for human use (Ref. *1*). This Panel has determined that silica gel is nontoxic in usually ingested amounts (Ref. *2*).

(2) *Effectiveness.* The antifoaming properties of simethicone have been established in vitro (Ref. *3*), and simethicone has been shown to decrease the presence or foam or bubbles found occasionally in the human stomach during gastroscopy (Ref. *4*).

Simethicone has been found to accelerate the transit time of various gases through the intestine but it did not decrease the amount of gas or frequency of passage of gas (Ref. *5*).

Although many papers have been published with the conclusions that simethicone is effective in reducing symptoms attributed to gas in the small and large intestine, of those reviewed only one study was conducted in a well-controlled double-blind manner (Ref. *6*). This double-blind study found simethicone to produce a statistically significant reduction of the symptoms of intestinal bloating, distention, fullness, and pressure.

There is some suggestion that simethicone is effective in relieving the symptoms of post-operative intestinal distress (Ref. *5*). However, since the Panel believes that additional studies are needed to determine the effectiveness of simethicone in treating the symptoms of intestinal distress occurring 30 minutes to several hours after eating, the Panel recommends further testing according to the testing guidelines to determine whether or not simethicone is effective in treating the symptoms of intestinal distress.

(3) *Proposed dosage.* The Panel concludes that a maximum recommended daily dosage of 500 mg is

safe (21 CFR 332.10). The administration of doses should be at appropriate intervals.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used in the treatment of the symptoms of intestinal distress. (See part IV. paragraph A.2. above—Category I labeling.)

(5) *Evaluation.* The Panel recommends that adequate testing of simethicone be performed according to the testing guidelines to determine whether or not it is effective for treatment of the symptoms of intestinal distress. (See part IV. paragraph D. below—Data Required for Evaluation: Guidelines for Developing Protocols for Evaluating OTC Drugs for the Treatment of the Symptoms of Intestinal distress.)

References

(1) Rowe, V. K., H. C. Spencer, and S. L. Bass, "Toxicologic Studies on Certain Commercial Silicones: II. Two Year Dietary Feeding of 'DC Antifoam A' to Rats." *Archives of Industrial Hygiene and Occupational Medicine,* 1:539–544, 1950.

(2) OTC Volume 170054.

(3) Rider, J. A., "Experience with the Use of a Defoaming Agent in the Treatment of Gastrointestinal Gas" *Annals of the New York Academy of Science,* 150:170–178, 1968.

(4) Gasster, M., J. O. Westwater, and W. E. Molle, "Use of Defoaming Agent in Gastroscopy," *Gastroenterology,* 27:652–655, 1954.

(5) Danhof, I. E., and J. J. Stavola, "Accelerated Transit of Intestinal Gas with Simethicone," *Obstetrics and Gynecology,* 44:148–154, 1974.

(6) Bernstein, J. E., and A. M. Kasich, "A Double-Blind Trial of Simethicone in Functional Disease of the Upper Gastrointestinal Tract," *The Journal of Clinical Pharmacology,* 14:617–623, 1974.

g. *Sodium bicarbonate.* The Panel concludes that sodium bicarbonate is safe for OTC use in the doses noted below, but data are insufficient to demonstrate its effectiveness in treating the symtoms of intestinal distress.

(1). *Safety.* Sodium bicarbonate (baking soda) is an alkalinizing agent which releases carbon dioxide when neutralized by acid. Sodium bicarbonate has a long history of use as an antacid and for the symptomatic relief of upper abdominal distress. It may be used as an ingredient in effervescent preparations in which the alkali is buffered or partially neutralized by an acidic compound. The Panel considers sodium bicarbonate to be safe when used as specified in the dosage section below, and under the labeling restrictions noted.

(2). *Effectiveness.* The Panel is aware of the antacid properties of sodium bicarbonate but its action in the intestines is not well established. The Panel recommends further testing according to the testing guidelines to determine whether or not sodium bicarbonate is effective in treating the symptoms of intestinal distress.

(3). *Proposed dosage.* This Panel concurs with the recommendations of the Advisory Review Panel on OTC Antacid Products, published in the **Federal Register** of April 5, 1973 (38 FR 8714), that a maximum safe daily dosage of preparations containing sodium is 200 meq of sodium for persons under 60 years of age and 100 meq for persons aged 60 years or older (38 FR 8719). Because of the sodium content the dose of sodium bicarbonate should not exceed 16.8 g (200 meq of sodium) per day.

(4). *Labeling.* The Panel recommends Category I labeling for ingredients used in the treatment of the symptoms of intestinal distress. (See part IV. paragraph A.2. above—Category I labeling.)

The Panel concurs with the recommendation of the Advisory Review Panel on OTC Antacid Products, published in the **Federal Register** of April 5, 1973 (38 FR 8714), that warning statements should be required in the labeling of preparations containing sodium. This Panel recommends that the following warning statements be required in the labeling of products containing sodium:

(i) "If you are 60 years of age or older, the maximum *daily* dose should not exceed 8.4 g (1 heaping teaspoon) of this drug."

(ii) "Do not take for longer than 2 weeks or in greater than recommended amounts, except upon the advice of a physician."

(iii). *For products containing more than 5 meq of sodium in the recommended daily dose.* "If you are on a sodium-restricted diet, do not use this product except under the supervision of a physician."

(5). *Evaluation.* The Panel recomends that the adequate testing of sodium bicarbonate be performed according to the testing guidelines to determine whether or not it is effective for treatment of the symptoms of intestinal distress. (See part IV. paragraph D. below—Data Required for Evaluation: Guidelines for Developing Protocols for Evaluating OTC Drugs for the Treatment of the Symptoms of Intestinal Distress.)

h. *Sodium citrate.* The Panel concludes that sodium citrate (sodium salt of citric acid) is safe for OTC use in the doses noted below, but data are insufficient to demonstrate its effectiveness in relieving the symptoms of intestinal distress.

(1) *Safety.* Sodium citrate was reviewed by the Advisory Review Panel on OTC Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products, in a report published in the **Federal Register** of September 9, 1976 (41 FR 38367), and found to be safe when used within the dosage limitation of 24 g daily. This Panel concurs with the antacid monograph (21 CFR Part 331), which limits the daily sodium intake to 200 meq for persons under 60 years of age and 100 meq for persons 60 years or older.

(2) *Effectiveness.* Commonly, citric acid is formulated in combination with sodium bicarbonate in a solid dosage form. When this combination is dissolved in water, effervescence occurs (carbon dioxide evolves) and the active ingredient, buffered sodium citrate, is produced.

The Panel recommends that sodium citrate be tested according to the testing guidelines in order to determine whether or not it is effective in the treatment of the symptoms of intestinal distress.

(3) *Proposed dosage.* The Panel concludes that a maximum safe daily dose of preparations containing sodium is 200 meq of sodium for persons under 60 years of age and 100 meq for persons aged 60 years and older; therefore, the oral dose of sodium citrate should not exceed 17.2 g daily (200 meq of sodium).

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used in the treatment of the symptoms of intestinal distress. (See part IV. paragraph A.2. above—Category I labeling.)

The Panel concurs with the recommendation of the Advisory Review Panel on OTC Antacid Products published in the **Federal Register** of April 5, 1973 (38 FR 8714), that a warning statement should be required on preparations containing sodium. This Panel recommends that the following warning statements be required in the labeling of preparations containing sodium:

(i) "If you are 60 years of age or older, the maximum *daily* dose should not exceed 8.6 g (1 heaping teaspoon) of this drug."

(ii) "Do not take for longer than 2 weeks or in greater than recommended amounts, except upon the advice of a physician."

(iii) *For products containing more than 5 meq of sodium in the recommended daily dose.* "If you are on a sodium-restricted diet, do not use this product except under the supervision of a physician."

(5) *Evaluation.* The Panel recommends that adequate testing of sodium citrate be performed according to the testing guidelines to determine whether or not it is effective for treatment of the symptoms of intestinal distress. (See

part IV. paragraph D. below—Data Required for Evaluation: Guidelines for Developing Protocols for Evaluating OTC Drugs for the Treatment of the Symptoms of Intestinal Distress.)

2. *Category III labeling.* The Panel concludes that available data are insufficient to permit final classification of the following claims:

a. "For intestinal gas."
b. "For the distress of intestinal gas."
c. "Digestive aid." (When used as a claimed indication.)
d. "As an aid to digestion."
e. "Assists digestion."
f. "Digestant." (Enzyme-containing products only.)
g. "For relief of indigestion arising 30 minutes to several hours following a meal."
h. "Supplementation of natural digestive enzymes." (Enzyme-containing products only.)
i. "Improved digestion and relief of the discomfort due to excess intestinal gas (including rectal gas)."
j. "A temporary aid in the adsorption of intestinal gas causing flatulence."
k. "To relieve the discomforts of intestinal gas."
l. "As a digestive aid for the temporary relief of the symptoms of gastrointestinal gas (including rectal gas)."
m. "An adsorbent to arrest toxins and/or gas in the intestine which may cause discomfort, cramping, and flatulence."

D. Data Required for Evaluation: Guidelines for Developing Protocols for Evaluating OTC Drugs for the Treatment of the Symptoms of Intestinal Distress

The Panel recognizes that currently there is not available a generally accepted protocol for the testing of drug products used for the treatment of the symptoms of intestinal distress. Further, because of the several categories of drugs marketed for the relief of these symptoms and the different mechanisms of these drugs, the Panel realizes that it is unlikely that a single protocol, that would be appropriate for all of these drugs, can be developed and it did not attempt to produce one. However, the Panel does believe that there are important issues that must be considered to ensure proper evaluation of these drugs and has developed the following guidelines to aid investigators in designing tests of effectiveness. The Panel suggests that deviations from these guidelines be discussed with the appropriate FDA personnel prior to initiation of a study.

1. *Objective(s) of the study.* The primary objective is to determine whether the drug under investigation provides significantly better relief of the symptoms of intestinal distress than a placebo indistinguishable from the drug. If the drug is believed to have a specific mechanism (relief of gas) for which the drug company desires to make a label claim, then the study objectives should include specific reference to that claim. The objectives should be stated in a complete and unambiguous manner.

2. *Study population.* The preferred sample population for the study is one of outpatient subjects who have presented themselves to physicians complaining of symptoms occurring with some regularity and with varying frequency (at least twice weekly) in the absence of organic gastrointestinal disease. The selected sample population should be fully specified and pertinent characteristics should be thoroughly described.

3. *Study setting and investigator.* The Panel prefers the study to be conducted by qualified gastroenterologists in large clinics or academic settings. Other investigators and settings may be acceptable to FDA. The drug company should be prepared to justify deviations from the Panel's suggestion.

4. *Admissibility and exclusion criteria.* In order to exclude all but the functional gastrointestinal problems which give rise to the symptoms being evaluated and also to exclude other potential sources of bias and confounding, subjects should be screened to determine their suitability. A reasonable set of exclusion criteria are:

a. Organic gastrointestinal tract disease or anatomic abnormality.
b. Enzyme deficiency (lactase or pancreatic).
c. Recent intestinal surgery.
d. Sensitivity to the test drug(s).
e. Patients requiring other drug therapy which might confuse the interpretation of the results.
f. Significant recent involuntary weight loss.

If the drug under investigation is believed to have a specific mechanism for which the drug company desires to make a label claim, subjects admitted into the study must be shown to have the appropriate condition. For example, for drugs claiming to relieve gas, it must be shown by appropriate techniques that the subjects in the study have "excess gas" and that this is related to their distress. Later, in order to establish the efficacy claim, it must be shown that the amount of gas is reduced and that relief of the symptoms is related to the reduction.

5. *Study designs.* The study must be a randomized, double-blinded, placebo controlled, crossover design. The Panel also prefers that the study involve a test meal. (See part III. paragraph D.1. above—Guidelines for developing a protocol for evaluating OTC drugs for the treatment of the symptoms of IPPUAD.) The test meal should be given twice as screening meals before the medication stage (drug or placebo) in order to establish that the symptoms can be consistently produced in the study setting and that they last for sufficient time (starting 30 minutes or more after eating and lasting for several hours). The test meal should be given once before the placebo administration and once before the drug administration in order to produce the symptoms for relief by the medication. The test meals should be separated by an adequate number of days to eliminate any carry over effects. Similarly in the crossover, there should be a sufficient "wash-out period" between the placebo and drug administrations.

The Panel realizes that there may be some drugs for which a study involving a test meal may not be appropriate and where a diary study design may be needed. The Panel feels that diary studies contain many problematic elements (patient recall, appropriate length of study, and patient adherence to protocol) and does not recommend them. An investigator who feels that a diary study is needed should be prepared to justify why a study with a test meal would be impossible or inappropriate.

6. *Study variables of effectiveness.* The primary effectiveness variable should be relief of symptoms of intestinal distress. The Panel feels that for test meal studies the most appropriate version of this variable is the dichotomous variable: complete relief of all symptoms within a fixed time period (4 hours after the meal) versus incomplete or no relief within that time period. The Panel, however, also recognizes the validity of degrees of relief (none, some, complete) and the use of composite scores in which each symptom group is rated separately and the ratings are then combined. For these composite scores the Panel recognizes three symptom groups (Group 1—bloating, distention, fullness, pressure; Group 2—excess flatus; Group 3—pain or cramps). For diary studies the composite score adjusted for the pretreatment score is appropriate. Also of use, but on a secondary level, are variables such as investigators' and/or patients' overall evaluations (evaluations made at the end of a study in which the investigator and/or patient is asked to say which medication was more effective).

Wherever possible, objective measurements should be made in preference to subjective judgments. However, such measurements should be

relevant to the symptoms of intestinal distress. Also, as stated previously, in those studies involving drugs for which a label claim concerning a specific mechanism of action is desired, appropriate objective techniques must be used to show that the action does take place and relief of the symptoms is related to it.

7. *Statistical tests and sample size.* Appropriate statistical tests should be used to establish efficacy. Sample sizes should be determined to give a P value of .05 for testing equality in effectiveness of the drug and the placebo, and a sufficiently small probability of error of not detecting a significant clinical superiority of the drug over the placebo. The drug company should be prepared to discuss what it means by a significant clinical superiority.

8. *Number of clinical trials.* Two separate trials, at different geographical sites and performed by different investigators, should be conducted.

The drug company should select study sites which have a patient profile similar to what is believed to be the profile of the sample population. Further, the sample from each site should be representative of the site with respect to important variables (age and sex).

Therefore, under the Federal Food, Drug, and Cosmetic Act (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)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 (see 46 FR 26052; May 11, 1981), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended by adding in Part 357, a new Subpart D, to read as follows:

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

Subpart D—Digestive Aid Drug Products

Sec.

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); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

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 condition in this subpart and each general condition established in § 330.1 of this chapter.

(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 Definitions.

As used in this subpart:

(a) *Aerophagia.* The swallowing of air.

(b) *Immediate postprandial upper abdominal distress.* A symptom complex consisting of the sensations of bloating, distention, fullness, or pressure with upper abdominal discomfort occurring immediately (within 30 minutes) after a meal, excluding symptoms of aerophagia or hyperacidity.

(c) *Intestinal distress.* A syndrome consisting of abdominal discomfort occurring 30 minutes to several hours after a meal. It is self-limiting and not attributable to any known organic disease, nor accompanied by diarrhea or constipation. This syndrome is characterized by one or more of the following symptoms: bloating, distention, fullness, pressure, pain, or cramps.

(d) *Symptom.* Any subjective evidence of a patient's condition, as perceived by the patient.

(e) *Syndrome.* A set of symptoms which occur together; a symptom complex.

§ 357.310 Digestive aid active ingredients for the treatment of immediate posprandial upper abdominal distress. [Reserved]

§ 357.312 Digestive aid active ingredients for the treatment of intestinal distress. [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 contains a statement of the indications under the heading "Indications" that is limited to the following phrases:

(1) *For products containing any ingredient identified in § 357.310 for the treatment of immediate postprandial upper abdo. inal distress.* (i) "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'.").

(ii) "Relieves the over-full feeling in the upper abdomen which occurs soon after eating."

(iii) *Other allowable statement.* The word "stomach" may be substituted for the words "upper abdomen" or "upper abdominal" in the indications in paragraphs (a)(1) (i) and (ii) of this section.

(2) *For products containing any ingredient identified in § 357.312 for the treatment of intestinal distress.* (i) "For relief of intestinal distress occurring 30 minutes to several hours after eating and often accompanied by complaints of bloating, distention, fullness, pressure, pain, or cramps."

(ii) "For relief of" (one or more of the following symptoms: "Bloating," "distention," "fullness," "pressure," "pain," or "cramps") "sometimes described as 'gas', which occurs 30 minutes to several hours after eating."

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

(1) *For products containing any ingredient identified in § 357.310 for the treatment of immediate postprandial upper abdominal distress.* (i) "If symptoms of upper abdominal distress persist, stop this medication and consult your physician."

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

(2) *For products containing any ingredient identified in § 357.312 for the treatment of intestinal distress.* [Reserved]

(d) *Direction.* [Reserved]

Interested persons may, on or before April 5, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may

submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before May 5, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 23, 1981.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: December 17, 1981.

Richard S. Schweiker,

Secretary of Health and Human Services.

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