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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

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OVER-THE-COUNTER DRUGS

Proposed Establishment of Monographs for OTC Laxative, Antidiarrheal, Emetic and Antiemetic Products

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 334, 335, 336, 337]

OVER-THE-COUNTER DRUGS

Proposal To Establish Monographs for OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Products

Pursuant to Part 330 (21 CFR Part 330), the Commissioner of Food and Drugs received on February 10, 1975, the report of the Advisory Review Panel on over-the-counter (OTC) laxative, antidiarrheal, emetic and antiemetic drug products. In accordance with § 330.10 (a)(6), the Commissioner is issuing (1) a proposed regulation containing the monographs recommended by the Panel establishing conditions under which OTC laxative, antidiarrheal, emetic and antiemetic drugs are generally recognized as safe and effective and not misbranded, (2) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel 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 on the basis of a determination by the Panel that the available data are insufficient to classify such conditions under either (1) or (2) above, and (4) the conclusions and recommendations of the Panel to the Commissioner. The summary minutes of the Panel meetings are on public display in the Office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852.

The purpose of issuing the unaltered conclusions and recommendations of the Panel is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The Commissioner has not yet evaluated the report, but has concluded that it should first be issued as a formal proposal in order to obtain full public comment before any decision is made on the recommendations of the Panel. The report of this Panel represents their best scientific judgment. It has been prepared independently of the Food and Drug Administration and does not necessarily reflect the Agency's position on any particular matter contained therein. After a careful review of this document and all comments submitted in response to it, the Commissioner will prepare a tentative final regulation to establish monographs for OTC laxative, antidiarrheal, emetic and antiemetic products.

In accordance with § 330.10(a)(2), all data and information concerning OTC laxative, antidiarrheal, emetic, and antiemetic drug products submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and the Food and Drug Administration. All such data and information shall be put on public display at the office of the Hearing Clerk, Food and Drug Administration, on or before April 21, 1975, except to the extent that the person submitting it demonstrates that it still 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 shall be submitted to the Food and Drug Administration, Bureau of Drugs, Division of OTC Drug Products Evaluation (HFD–109), 5600 Fishers Lane, Rockville, MD 20852.

Based upon the conclusions and recommendations of the Panel, the Commissioner proposes, upon publication of the final regulation:

1. That the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient to classify such conditions either as generally recognized as safe and effective and not misbranded or as not being generally recognized as safe and effective or would result in misbranding (Category III) be permitted to remain in use for 2 years after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel.

The conclusions and recommendations contained in the report of the Advisory Review Panel on OTC laxative, antidiarrheal, emetic and antiemetic drug products to the Commissioner are as follows:

In the FEDERAL REGISTER of January 5, 1972 (37 FR 85), the Commissioner of Food and Drugs announced a proposed review of the safety, effectiveness and labeling of all OTC drugs by independent advisory review panels. On May 8, 1972, the Commissioner signed the final regulations providing for the OTC drug review under § 330.10 (formerly § 130.301) published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), which were made effective immediately. Pursuant to these regulations the Commissioner issued a request for data and information on all laxative, antidiarrheal, emetic, and antiemetic active ingredients in drug products, in the FEDERAL REGISTER of February 8, 1973 (38 FR 3614).

The Commissioner appointed the following panel to review the data and information submitted, and to prepare a report on the safety, effectiveness, and labeling of OTC laxative, antidiarrheal, emetic, and antiemetic drug products pursuant to § 330.10(a)(1):

Nicholas C. Hightower, Jr., M.D., Ph. D., Chairman
Carol R. Angle, M.D.
James C. Cain, M.D.
Ivan E. Danhof, M.D., Ph. D.
James W. Freston, M.D., Ph. D.
Albert L. Picchioni, Ph. D.
Sheila West, Pharm. D.

The Panel was first convened on April 30, 1973, in an organizational meeting. Working meetings were held on June 15–16, August 3–4, September 21–22, November 16–17, 1973; January 25–26, April 5–6, May 31–June 1, July 19–20, September 26–28, October 11, and November 11, 1974, and January 24–25, 1975. All Panel members attended all meetings.

Four non-voting liaison representatives served on the Panel. Mrs. Dennis Hanson, nominated by an ad hoc group of consumer organizations, served until she resigned from the Panel in September 1973, and was replaced by Mr. Kevin V. Brennan, also nominated by the consumer organizations. William E. O'Malley, M.D., Ph. D., nominated by the Proprietary Association, served until he resigned from the Panel in April 1974 and was replaced by Hugh Miller, M.D., also nominated by the Proprietary Association.

Pierre J. Deslauriers, an employee of the Food and Drug Administration, served as Executive Secretary to the Panel. John T. McElroy, J.D., an employee of the Food and Drug Administration, served as Panel Administrator. Lee Quon, R. Ph., served as Drug Information Analyst until August 1973, followed by Thomas H. Gingrich, R. Ph.

In addition to the Panel members and liaison representatives, the Panel utilized the advice of the following consultants:

K. Ashgar, Ph. D.
William Bachrach, Ph. D., M.D.
James Christensen, M.D.
C. A. Dujovne, M.D.
Asher Graybiel, M.D.
Walter Hansen
A. F. Hofmann, M.D.
C. T. G. King, Ph. D.
J. Lamar, Ph. D.
Henry Laurens, M.D.
Albert I. Mendeloff, M.D.
L. F. Schoenfield, Ph. D., M.D.
Samuel Shapiro, M.D.
J. L. Thistle, M.D.
Richard L. Wikoff, Ph. D.
James G. Wilson, Ph. D.

The following individuals were given an opportunity to appear before the Panel to express their views either at their own or the Panel's request:

Clealand Baker
Paul Bass, Ph. D.
Ivan T. Beck, M.D.
E. W. Cantrell, Ph. D.
Charles S. David, M.D.
Bruce Doerr, D.V.M.
Herbert L. Dupont, M.D.
Michael Hospador, Ph. D.
C. H. Kratochvil, M.D., Ph. D.
Ben Marr Lanman, M.D.
Harry Leyland, Ph. D.
Stanley Lorber, M.D.
H. J. Lutz
Robert M. Rees, M.D.
David Schlichting, Ph. D.
C. Boyd Shaffer, Ph. D.

No person who so requested was denied an opportunity to appear before the Panel.

Because the charge to the Panel required the review of four classes of OTC drugs (i.e. laxative, antidiarrheal, emetic and antiemetic drugs), the Panel has prepared its conclusions and recommendations in four separate sections. Each section covers the submission of data and information, a listing of claimed active ingredients, and the classification of the ingredients by the Panel for each class of OTC drugs.

The Panel has thoroughly reviewed the literature, and the various data submissions, has listened to additional testimony from interested parties and has considered all pertinent data and information submitted through September 28, 1974, in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to these classes of drugs are set out in three categories:

I. Conditions under which laxative products are generally recognized as safe and effective and are not misbranded.

II. Conditions under which laxative products are not generally recognized as safe and effective or are misbranded.

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

The Panel recommends the following for each category of drugs:

1. That the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient to classify such conditions either as generally recognized as safe and effective and not misbranded or as not being generally recognized as safe and effective or would result in misbranding (Category III) be permitted to remain in use for 2 years after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel.

I. LAXATIVES

Pursuant to the notice published in the FEDERAL REGISTER of February 8, 1973 (38 FR 3614) requesting the submission of data and information of OTC laxative drugs, the following firms made submissions relating to marketed products:

A. DATA AND INFORMATION SUBMISSIONS

Firm	Marketed Products
Abbott Laboratories, North Chicago, Ill. 60064	Maltsupex, Maltsupex Filmtab.
Beecham, Inc. Clifton, N.J. 07012	Syllamalt Effervescent, Syllamalt Powder, Eno.
Boehringer Ingelheim Ltd., Elmsford, N.Y. 10523.	Dulcoax Suppositories, Dulcolax Tablets.
Briston-Myers Co., New York, N.Y. 10022	Bran Tablets, Sal Hepatica.
Burton, Parson & Co., Inc., Washington, D.C. 20027.	Konsyl, L. A. Formula, Psyllium Hydrophilic Mucilloid with Dextrose.
Carter Wallace, Inc., Cranbury, N.J. 08512	Carter's Little Pills.
Chattem Drug & Chemical Co., Chattanooga, Tenn. 37409.	Black-Draught Granulated, Black-Draught Powder, Black-Draught Senna-Lax Tablet, Syrup of Black-Draught.
Combe Inc., White Plains, N.Y. 10604	Espotabs.
Cooper Laboratories, Inc., Cedar Knoll, N.J. 07927.	Kondremul Plain, Kondremul with Cascara, Kondremul with Phenophthalein, Neo-Kondremul.
Denver Chemical Manufacturing Co., Stamford, Conn. 06904.	Rectalad Enema.
Dorsey Laboratories, Lincoln, Nebr. 68501	Vacuetts Suppositories.
Ex-Lax, Inc., Brooklyn, N.Y. 11217	Ex-Lax Chocolated, Ex-Lax Instant Mix, Ex-Lax Unflavored.
C. B. Fleet Co., Inc., Lynchburg, Va. 24505	Fleet Phospho-Soda, Fleet Phospho-Soda Flavored, Fleet Enema, Fleet Enema Pediatric.
Forest Laboratories, Inc., New York, N.Y. 10022.	Mel-o-Lax.
Gray Pharmaceutical Co., Norwalk, Conn. 06586.	X-Prep Liquid, X-Prep Powder.
Hoechst Roussel Pharmaceuticals, Inc., Somerville, N.J. 08876.	Doxan, Doxidan, Doxinate, Doxinate Solution, Surfak.
ICI, United States, Inc., Wilmington, Del. 19899.	Dialose, Dialose Plus, Effersyllium Instant Mix.
Lewis Howe Co., Saint Louis, Mo. 63102	Milk of Magnesia (concentrated), Nature's Remedy Juniors, Nature's Remedy Regular.
Marcen Laboratories, Inc., New Rochelle, N.Y. 10801.	Acelax.
Merit Remedy Co., Dayton, Ohio 45405	Gall-Solve, Merit Cathartics.
Miles Laboratories, Inc., Elkhart, Ind. 46514	Decholin.
National Magnesia Co., Inc., Brooklyn, N.Y. 11227.	Citrate of Magnesia.
Parke, Davis and Co., Detroit, Mich. 48232	Alophen Pills, Cascara Sagrada Aromatic, Cascara Sagrada Fluid-extract Aromatic, Cascara Sagrada Extract Filmseal, Cas-Evac, Desicol, DeS–S, D–S–S Plus, Geriplex, FS, Geriplex FS, Geriplex FS Liquid, Glycerin Suppositories, Milk of Magnesia, USP, Sibiln, Sibiln Tablets, Tabron.
Pharmaseal Laboratories, Inc., Irwindale, Calif. 91706.	Oil Retention Enema, Sigmol Enema.
Plough, Inc., Memphis, Tenn. 38101	Correctol, Fenn-A-Mint, Feen-A-Mint Chewing Gum, Saraka.
The Purdue Frederick Co., Norwalk, Conn. 06856.	Gentlax Granules, Gentlax-S, Gentlax Tablet, Senokap DSS Capsules, Senokot, Senokot Granules, Senokot Suppositories, Senokot Syrup, Senokot with Psyllium.
Riker Laboratories, Inc., Northridge, Calif. 91234.	Dorbane, Dorbanthyl, Dorbantyl Forte.
Sandoz Pharmaceuticals, East Hanover, N.J. 07936.	Glysennid.
Scott Laboratories, Inc., Corpus Christi, Tex. 78408.	Castor Oil, Citrate of Magnesia, Glycerine.
Searle Laboratories, Chicago, Ill. 60680	Metamucil Instant Mix, Metamucil Powder.
E. R. Squibb & Sons, Inc., New Brunswick, N.J. 08903.	Castor Oil, Glycerine Suppositories, Milk of Magnesia, Milk of Magnesia Tablets, Mineral Oil, Mint-O-Mag.
Sterling Drug Inc., New York, N.Y. 10016	Andrews Salts, Caroid and Bile Salts, Dr. Caldwell Senna Laxative, Fletcher's Castoria, Haley's M-O, Mil Par, Mucilose Flakes, Mucilose Granules, Mucilose Powder, Phillips' Milk of Magnesia, Phillips' Milk of Magnesia Tablets, Sal Andrews.
Stuart Pharmaceuticals (See ICI United States, Inc.).	
The Upjohn Co., Kalamazoo, Mich. 49001	Bile Salts-Phenophthalein Compound, Casakol Capsules, Casyllium, Hydrolose Syrup, Imbicoll with Vitamin B1, Imbicoll with Cascara, Phenolax, Polykol.
USV Pharmaceutical Corp., Tuckahoe, N.Y. 10707.	Neo-Cultol.
Warner Lambert Co., Morris Plains, N.J. 07950.	Cellothyl, Veracolate.
Warren Teed Pharmaceutical, Inc., Columbus, Ohio 43215.	Modane, Modane Mild.

Whitehall Laboratories, Inc., New York, N.Y. 10017.	Petro Syllium No. 1 Plain, Petro Syllium No. 2 with Phenolphthalein, Preparation H Regulator.
J. B. Williams Co., Inc., Cranford, N.J. 07016__	Serutan Concentrated Powder, Serutan Concentrated Powder, Fruit Flavored, Serutan Toasted Granules.
Wyeth Laboratories, Inc., Philadelphia, Pa. 19101	Cascara Petrogalar, Glycerin Suppositories, Adult, Glycerin Suppositories for Infants and Young Children, Petrogalar, Phenolphthalein Petrogalar.

In addition, the following firms made related submissions:

Firm	Submissions
American Cyanamid Co, Pearl River, N.Y. 10965.	Dioctyl Sodium Sulfosuccinate.
Merrick Medicine Co., Waco, Tex. 76703_____	Rhubarb Fluidextract.

B. LABELED INGREDIENTS CONTAINED IN SUBMITTED PRODUCTS

Agar
Aloe
Aloin
Belladonna extract
Bile, desiccated whole
Bile salts
Bisacodyl
Bismuth subnitrate
Bran tablets
Calcium hydroxide
d-Calcium pantothenate
Capsicum
Caroid (digestive enzyme from *Carica papaya*)
Carrageenan (*Chondrus crispus*)
Cascara sagrada
Cascara sagrada bark
Cascara sagrada extract
Cascara sagrada fluid extract
Casanthranol
Castor oil
Citric acid, anhydrous
Danthron
Dehydrocholic acid
Dioctyl calcium sulfosuccinate
Dioctyl potassium sulfosuccinate
Dioctyl sodium sulfosuccinate
Disodium phosphate
Frangula
Ginger
Glycerin
Guar gum
Ipecac powder
Karaya (sterculia)
Magnesium citrate, anhydrous tribasic
Magnesium hydroxide
Magnesium sulfate dihydrate
Malt soup extract
Methylcellulose
Mineral oil
Monosodium phosphate
Oxgall
Papain
Phenolphthalein
Phenolphthalein, yellow
Plantago ovata husk
Plantago seed
Podophyllum resin (podophyllin)
Poloxalkol (polykol, polymers of ethylene and propylene oxide)
Potassium carbonate
Prune concentrate dehydrate
Prune powder
Psyllium, hemicellulose of
Psyllium hydrophilic mucilloid (psyllium hydrocolloid)
Psyllium seed husks, blond
Psyllium seed husks
Psyllium seed
Rhubarb fluidextract
Senna
Senna concentrate
Senna fruit extract
Sennosides A and B
Sodium acid pyrophosphate
Sodium biphosphate
Sodium carbonate
Sodium carboxymethylcellulose
Sodium citrate, anhydrous tribasic
Sodium oleate
Sodium phosphate
Sorbitol
Tartaric acid
Thiamin
Vitamins (multivitamins) and minerals

The Panel also undertook a review of the following:

Bran, dietary
Calomel
Laxative resins (colocynth, elaterin, gamboge, ipomea and jalap)
Polycarbophil

C. CONSTIPATION AND THE USE OF OTC LAXATIVES

In Dorland's Medical Dictionary "constipation" is defined simply as "infrequent, or difficult evacuation of the feces" (Ref. 1). The Panel is unable to improve upon this simple definition.

In the United States, preoccupation with the bowel seems to be the concern of a significant proportion of our population judging from the inordinately large number of laxative agents available and by the significant expenditure for OTC laxatives (Refs. 2 and 3). The Panel is of the opinion that a large segment of the population is not only "bowel-conscious" but also has many misconceptions of normal bowel function. The laity is under the impression that serious and health endangering consequences will occur if the bowel is not evacuated daily.

The Panel is of the opinion that there is widespread overuse of self-prescribed laxatives. Extensive advertising by the pharmaceutical industry has contributed to this problem. The Panel is aware that the FDA is limited in its jurisdiction to package labeling and not to advertising. However, the Panel is concerned that control of package labeling alone may be insufficient in assuring proper use of laxative agents. The Panel is hopeful that as a result of this review that all forms of advertising will be monitored by those having the appropriate jurisdiction, to insure that adequate warning and cautionary statements as found in product labeling will be carried over and incorporated in all advertising and promotional activities for these products.

Only recently have quantitative data become available to better define the normal bowel habits in man. In one study of 115 healthy adult men, stool weight, consistency, and time of evacuation were recorded on 8,267 stools. The ages of the subjects ranged from 20 to 57 years. The average stool weight was 123.6 grams; average interval between stools was 27.6 hours, with a range of 9 to 57 hours. Subjective estimates of consistency showed that 46 percent of the stools were firm; 36 percent semiformed, 15 percent soft or mushy, and 3 percent loose, watery or diarrhetic (Ref. 4). From a social and psychological viewpoint, the subjects in this study cannot be considered representative of the normal population because they were prisoners in a minimal custody Federal Correction Institution. However, the Panel considers the data of value in defining bowel habits under controlled conditions.

In another study, 1,055 industrial workers in the greater London area were interviewed regarding bowel habits. This group was composed of 655 women and 400 men. Also included in this study, were 400 patients of a family practitioner in Northwest London, including 134 males and 266 females who had no known diseases of the gastrointestinal tract. The ages of the patients ranged from 1 year to over 70. It was found that 99.3 percent of the industrial workers and 98.25 percent of the patients were within the frequency limits of 3 bowel movements per week to 3 bowel movements per day (Ref. 5). From these results, it is suggested that fewer than 3 bowel movements per week or more than 3 bowel movements per day are unusual. No simple correlation was observed between bowel habits and age.

There was a positive correlation between increasing bowel frequency and the subject's opinion of the stool being "loose." The proportion of subjects who took laxatives increased with age in both groups studied (Ref. 5). The frequency limits suggested by this study are potentially biased, as 20 percent of all subjects interviewed took a laxative more than once a week. However, the Panel considers the data a contribution in the study of bowel habits in the population.

The terms "laxative", "cathartic", and "purgative" are frequently confused. All three terms denote agents that act to promote evacuation of the bowel; the difference between the terms is largely one of degree. The terms "cathartic" and "purgative" are interchangeable and are best defined as agents which quickly produce bowel evacuation and obvious alteration of stool consistency (Ref. 6). These actions in a laxative agent are less pronounced. Large doses of a laxative may produce a cathartic effect. For purposes of simplicity and consistency only the term "laxative" will be used in this report.

Prolonged laxative use can seriously impair normal bowel function. Use of laxatives for acute abdominal pain, vomiting, and other digestive symptoms can lead to serious complications. The Panel is of the opinion that simple constipation most often results from improper diet, inadequate fluid intake, possibly in-

sufficient exercise and/or from a change of habits due to travel. There are few valid indications for the use of laxatives. Relief for simple constipation often may be achieved by proper diet, including foods with adequate fiber content, adequate fluid intake, and the prompt response to the urge to evacuate the bowels. The Panel is concerned because many people are using laxatives that don't need them (Refs. 4 and 5).

REFERENCES

(1) Dorland's Illustrated Medical Dictionary, 24th Ed., W. B. Saunders Company, Philadelphia, p. 338, 1965.

(2) Danhof, Ivan E., "Methods of Clinical Evaluation of Laxative Agents," Proceedings of a Conference sponsored by the Scientific Development Committee of the Proprietary Association, Washington, DC, 1972.

(3) Sehnert, K. W., "Review of Pharmacology of Bowel Evacuants and Laxatives," Nebraska State Medical Journal, 50:54–58, 1965.

(4) Rendtorf, R. C. and M. Kashgarian, "Stool Patterns of Healthy Adult Males," Diseases of the Colon and Rectum, 10:222–228, 1967.

(5) Connell, A. M., C. Hilton, G. Irvine, J. E. Lennard-Jones and J. J. Misiewicz, "Variation of Bowel Habit in Two Population Samples," British Medical Journal, 2:1095–1099, 1965.

(6) Webster's New Collegiate Dictionary, G & C Merriam Company, Springfield, MA 1973.

D. LABELING OF LAXATIVES

The Panel reviewed the general and specific labeling requirements previously adopted by the Food and Drug Administration for OTC laxative preparations. These requirements provide for labeling information concerning the identity of ingredients, directions for use, and general and specific warnings. The Panel concurs that these requirements are appropriate for OTC laxative preparations and the labeling will be discussed elsewhere in this document.

After review of all labels of OTC laxative preparations submitted, the Panel recommends the following additional requirements:

1. *Indications.* The indications for use of a laxative should be simple and clearly stated. If the product is taken for specific indications such as to increase the frequency of bowel movements, to soften the stool, or to increase the bulk of the stool, the label should so state. The directions for use should be clear and provide the user a reasonable expectation of the results anticipated from use of the product. Statements of indications for use should be specific and confined to the conditions the product is recommended for such as infrequent, difficult, or painful passage of stools. No reference should be made, or implied, regarding the alleviation or relief of symptoms unrelated to the condition that is an indication for use of the product.

2. *Ingredients.* Laxative products should contain only active ingredient(s) plus such inactive ingredients as may be necessary for formulation. The label should state in metric units the quantity of each active ingredient contained in the recommended dose, e.g., teaspoonful, tablet, etc.

A product containing more than 1.0 mEq (23 mg) sodium per maximum daily dose should be labeled as to the sodium content per dosage unit. Furthermore, if the product contains more than 15 mEq (345 mg) sodium in the maximum recommended daily dose, the label should state: "Do not use this product except under the advice and supervision of a physician if you are on a low salt diet." And in addition, "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

If the product contains more than 25 mEq (975 mg) potassium in the maximum recommended daily dose, labeling should state: "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

If the product contains more than 50 mEq (600 mg) magnesium in the maximum recommended daily dose, the labeling should state:

Do not use this product except under the advice and supervision of a physician if you have kidney disease.

The Panel strongly recommends that all inactive ingredients be listed with or without a statement of their quantity, since the consumer may need to know for a variety of reasons, the ingredient in a product. However, the product cannot be promoted on the basis of its inactive ingredients, nor can the label emphasize the inclusion of the inactive ingredients.

3. *Mode of action.* The Panel reviewed and concurred with the regulation (21 CFR 1.102a) for over-the-counter drug and device identity labeling in package form which states:

a. "The principal display panel of an over-the-counter drug or device in package form shall bear as one of its principal features a statement of the identity of the commodity.

b. "Such statement of identity shall be in terms of the established name of the drug, if any there be, followed by an accurate statement of the general pharmacological category (categories) of the drug or the principal intended action(s) of the drug. In the case of an over-the-counter drug that is a mixture and that has no established name, this requirement shall be deemed to be satisfied by a prominent and conspicuous statement of the general pharmacological action(s) of the mixture or of its principal intended action(s) in terms that are meaningful to the layman. Such statements shall be placed in direct conjunction with the most prominent display of the proprietary name or designation and shall employ terms descriptive of general pharmacological category (categories) or principal intended action(s); for example, 'laxative', 'antidiarrheal', 'emetic', 'antiemetic', etc. The indications for use shall be included in the directions for use of the drug, as required by section 502(f)(1) of the act and by the regulations in this part.

c. "The statement of identity shall be presented in bold face type on the principal display panel, shall be in a size reasonably related to the most prominent printed matter on such panel, and shall be in lines generally parallel to the base on which the package rests as it is designed to be displayed."

Thus a prominent and conspicuous statement must be made of general pharmacologic action. In addition, the Panel recommends that the label contain a clear indication of the category of laxative as described below in paragraph E with the specific modes of action when known so that the consumer's expectation is correct; for example, a bulk forming laxative promotes the evacuation of the bowel by increasing bulk volume and water content of the stools.

4. *Effectiveness and claimed advantages.* Effectiveness must be defined without vague or unsupported claims. Phrasing that promises general benefits in good health or well being or warns against the hazards of constipation is unproven and thus unacceptable. Undocumented claims that laxatives relieve "indigestion," "excessive belching," "after-meal discomfort," "headaches," or "biliousness" foster the notion among the laity that such symptoms are caused by constipation. Such claims are not supported by scientific evidence and thus are not acceptable. The Panel has no objection to statements regarding the source of the laxative ingredient. However, the suggestion that a laxative is somehow "natural" because of its source is misleading, because it implies that the product or ingredient is a "natural way" to induce laxation. It is not considered "natural" to take any laxative.

The Panel found no evidence for claims that any laxative has a particular advantage for individuals simply on the basis of sex, age, or other demographic characteristics. However, bulk-forming laxatives may be justified in individuals who consume a diet low in fiber content.

Reference to palatability should not be used to support claims of effectiveness or to promote frequent and continued use, nor should it dominate the label.

5. *Directions for use.* The label should include a clear statement of the usually effective, minimum and maximum dose per time interval, broken down by age groups, and if appropriate, may be followed by "except under the advice and supervision of a physician." It is axiomatic and should be emphasized that the smallest dose of a laxative that is effective is the optimal dose to use.

6. *Warnings.* The Panel has reviewed the current regulation (21 CFR 369.20) regarding labeling of laxatives which states:

WARNING.—Do not use when abdominal pain, nausea, or vomiting are present. Frequent or prolonged use of this preparation may result in dependence on laxatives.

Mercury preparations should have added to the 'frequent use' statement, the words 'and serious mercury poisoning.'

Phenolphthalein preparations should bear, in addition to the general warning, the following statement:

CAUTION.—If skin rash appears, do not use this or any other preparation containing phenolphthalein.

The Panel found it difficult to clearly define the word "dependence" as it appears in the regulation, and recommends deletion of the following warning on all laxative labels: "Frequent or prolonged use of this preparation may result in dependence on laxatives." Specific warnings concerning laxative dependency is listed with the Panel's recommendations for each class of laxative ingredient.

The Panel concluded that the warning regarding mercury is now inappropriate since the Panel has recommended removal of such preparations from OTC status. (See discussion for Calomel below in the Category II laxative active ingredient statement.) Warnings for reactions considered by the Panel to be of sufficient frequency or severity will be listed with the Panel's recommendation regarding each class of active ingredients. The warning should be accompanied by specific instructions for avoiding specific side effects (e.g., labels of bulk-forming laxatives should state "drink a full glass of liquid with each dose," and directions should a side effect occur (e.g., "stop medication at once and consult a physician").

The label must also contain a warning as follows:

If you have noticed a sudden change in bowel habits that persists over a period of 2 weeks, consult a physician before using a laxative. If the recommended use of this product for 1 week has had no effect, discontinue use and consult a physician.

The reason for this recommendation is that a sudden change in bowel habits may be due to serious disease (e.g., cancer, stricture), and the continued use of a laxative may delay diagnosis of such conditions. The Panel is of the opinion that the available scientific evidence shows that very few indications warrant the use of any laxative beyond 1 week, except under the advice of a physician.

E. Definitions and Classification of Active Ingredients

The Panel adopted the definitions identified below and elected to classify the active ingredients of laxative products on the basis of the usually accepted pharmacological classes as follows:

1. *Adequate liquid intake.* The ingestion of a full glass (8 oz.) of liquid with each dose.

2. *Age (dosage) range.* Infant (not more than 2 years), child (2 years and over but not more than 12 years), and adult (12 years and over).

3. *Bulk forming laxative.* An agent that promotes the evacuation of the bowel by increasing bulk volume and water content of the stools.

4. *Constipation.* Infrequent, or difficult bowel movement.

5. *Hyperosmotic laxative.* An agent that attracts water into the stool.

6. *Laxative.* Any agent used for the relief of constipation.

7. *Lubricant laxative.* An agent that lubricates the contents of the intestinal tract, thus promoting easier bowel movements.

8. *Oral Dosage.* The dosage range (minimum and maximum amounts) that is generally recognized as safe and effective by mouth.

9. *Rectal dosage.* The dosage range (minimum and maximum) that is generally recognized as safe and effective by rectum.

10. *Saline laxative.* An agent that increases water in the intestine thereby promoting bowel movement.

11. *Short-term use.* Use of a laxative for no longer that a 1 week period.

12. *Stimulant laxative.* An agent that promotes bowel movement by one or more direct actions on the intestine.

13. *Stool softner laxative.* An agent that penetrates and softens the stool.

It is recognized that the mode of action of some ingredients is unknown or different from that described in some textbooks and older literature. For example, it is now known that at least some "stimulant" laxatives promote laxation by means other than "stimulating" peristalsis. Nevertheless, the traditional classification is used for simplicity, and the mode of action, when known, is described for each ingredient.

The Panel found that many laxative products contained more than one active ingredient. In some of these products, the amount of one or more of the active ingredients is considered irrational in that the amount of the ingredient is as little as one-tenth of the recommended effective dose. The Panel concluded that any ingredient causing laxation at an appropriate dosage is considered to be an active agent.

F. Review of Active Ingredients

The Panel reviewed all claimed active ingredients which were the subject of submissions made to and accepted by the Panel. In addition, the Panel reviewed bran (dietary), calomel, laxative resins (colocynth, elaterin, gamboge, ipomea and jalap) and polycarbophil. The Panel considered all pertinent data and information in arriving at its conclusions and recommendations.

1. *Conditions under which laxative products are generally recognized as safe and effective and are not misbranded.* After carefully reviewing all data available to the Panel the following laxative ingredients identified below were classified as safe and effective and not misbranded:

Bulk Forming Laxatives

- Bran, Dietary
- Cellulose derivatives, semi-synthetic (methylcellulose, sodium carboxymethylcellulose)
- Karaya (Sterculia Gum)
- Malt Soup Extract
- Polycarbophil
- Psyllium Preparations
  - Plantago seeds
  - Plantago ovata husks
  - Psyllium, hemicellulose of
  - Psyllium, hydrophilic mucilloid (psyllium hydrocolloid)
  - Psyllium seed
  - Psyllium seed, blond
  - Psyllium seed husks

Stimulant Laxatives

- Anthraquinones
  - Aloe
  - Cascara sagrada preparations
    - Aromatic cascara fluidextract
    - Casanthranol
    - Cascara sagrada bark
    - Cascara sagrada fluidextract
    - Cascara sagrada extract
  - Danthron
  - Senna preparations
    - Senna leaf powder
    - Senna fluidextract
    - Senna fruit extract
    - Senna syrups
    - Sennosides A and B, crystalline
    - Senna pod concentrate
- Bisacodyl
- Castor oil
- Dehydrocholic acid
- Phenolphthalein (white or yellow)

Saline Laxatives

- Magnesium salts
  - Magnesium citrate
  - Magnesium hydroxide
  - Magnesium sulfate
- Phosphate preparations (combined)
  - Disodium Phosphate
  - Monosodium Phosphate
  - Sodium Biphosphate
  - Sodium Phosphate

Hyperosmotic Laxatives

- Glycerin
- Sorbitol

Lubricant Laxatives

- Mineral oil, emulsified
- Mineral oil, plain

Stool Softener Laxatives

- Sulfosuccinate preparations
  - Dioctyl Calcium Sulfosuccinate
  - Dioctyl Potassium Sulfosuccinate
  - Dioctyl Sodium Sulfosuccinate

Miscellaneous Laxative

- Released Carbon Dioxide

(a) *Active ingredients classified as bulk-forming laxatives.* The Panel is of the opinion that bulk-forming laxatives are among the safest of laxatives. These agents are generally not absorbed from the digestive tract. They increase the frequency of bowel movements and soften stools by holding water in the stool. Most bulk-forming laxatives require the ingestion of a glassful of liquid with each dose to minimize the risk of obstruction of the digestive tract which has rarely been caused by these agents. Examples of useful labeling information describing the mode of action for purposes of labeling include "Promotes evacuation of the bowels by increasing bulk volume and water content of stools" and "Increases the frequency of bowel movements and softens stools by holding water in the stool."

(1) *Bran, dietary.* The Panel concludes that bran is safe and effective in the amounts (approximately 6 to 14 grams per day) usually taken in the diet when accompanied with adequate fluid intake and believes it unnecessary to impose a specific dosage limitation at this time.

Bran can be obtained from a number of sources but usually is derived from the milling of wheat. Wheat bran consists largely of hemicellulose, cellulose and

"crude fiber" of uncertain chemical composition. When fed to animals and man as bran, these components escape digestion and result in decreased intestinal transit time and increased stool bulk, weight and water content.

Bran's laxative action seems related to its hydrophilic properties and to the direct action on the colon of undefined substances produced by the bacterial action on the bran.

Dietary fiber seems to play the major role in the action of bran. The role of fiber in the gut is not precisely understood because of the incomplete knowledge of its composition and the inadequate techniques for measuring each component.

Bran-rich breakfast cereals and wholewheat bread are convenient sources of crude fiber: 100 grams of bran flakes (various brands) contain between 2.7 to 6.5 grams of crude fiber and one slice of wholewheat bread contains 1–2 grams. As with other bulk laxatives, intestinal obstruction may occur if bran is given for constipation in patients with partial obstruction of the digestive tract.

Bran tablets, as opposed to dietary bran, are classified in Category III. (See discussion of Bran Tablets below).

REFERENCES

(1) Payler, D. K., "Food Fibre and Bowel Behavior," Lancet, 1:1394, 1973.

(2) Cummings, J. H., "Progress Report: Dietary fibre," Gut, 14:69–81, 1973.

(3) The Medical Letter, "Laxatives and Dietary Fiber," 15:98–100, 1973.

COMMENTS REGARDING DIETARY FIBER

Recent epidemiological studies indicate that the low fiber content in the refined foods of technologically advanced countries may contribute to the high prevalence of diverticular disease of the colon, the irritable bowel syndrome, appendicitis and colonic cancer in these countries. There are references to the usefulness of bulk laxatives in the treatment of diverticulosis and irritable bowel syndrome. The rationale for the use of bulk-forming agents in these conditions is purported to be related to increased intraluminal pressures which occur in the large bowel in patients with diverticulosis and irritable bowel syndrome. The pressure within the bowel (lumen) is related to the tension of the muscles in the wall of the bowel as well as the diameter of the lumen of the bowel cavity. The pressure within the bowel lumen increases as the tension of the muscles of the bowel wall increases but decreases as the radius (one-half the diameter) of the lumen increases. These relationships are known as the Law of LaPlace and are expressed in the following formula:

$$P=t/r$$

where P is intraluminal pressure, t is tension of the bowel wall, and r is the radius of the bowel lumen. Thus, intraluminal pressure elevations could theoretically be lowered by increasing the radius of the lumen by bulk producing agents. Conclusive studies testing this hypothesis have not yet appeared.

REFERENCES

(1) Irving, D. and B. S. Draser, "Fibre and Cancer of the Colon," British Journal of Cancer, 28:462–463, 1973.

(2) Burkitt, D. P., "The Aetiology of Appendicitis," British Journal of Surgery, 58:695–699, 1971.

(3) Painter, N. S. and D. P. Burkitt, "Diverticular Disease of the Colon: A Deficiency Disease of Western Civilization," British Medical Journal, 2:450–454, 1971.

(4) The Medical Letter, "Laxatives and Dietary Fiber," 15:98–100, 1973.

(5) Eastwood, M. A., N. Fisher, C. T. Greenwood and J. B. Hutchinson, "Perspectives on the Bran Hypothesis," Lancet, 1:1029–1033, 1974.

(6) Burkitt, D. P., A. R. P. Walker, and N. S. Painter, "Dietary Fiber and Disease," Journal of the American Medical Association, 229:1068–1073, 1974.

(7) Painter, N. S., "Below the Belt," Lancet, 2:381–382, 1971.

(2) *Cellulose derivatives, semi-synthetic.* The Panel concludes methylcellulose and sodium carboxymethylcellulose to be safe and effective in amounts usually taken orally: 4 to 6 grams per day when accompanied with adequate fluid intake. The dosage for children over 6 years is 1 gm to 1.5 gm per day when accompanied by adequate fluid intake.

The hydrophilic cellulose derivatives, methylcellulose and sodium carboxymethylcellulose, when mixed with water produce a clear to opalescent viscous colloidal suspension with a pH of approximately 7.0. In the colon, the solution loses water to form a gel which increases the bulk of stool. Cellulose has been shown to bind digitalis, nitrofurantoin and salicylate although the clinical significance of this is not yet defined. As with other bulk-forming laxatives, esophageal and large bowel obstructions and fecal impactions have been described in man following the ingestion of methylcellulose with insufficient quantities of liquid. No data are available on the absorption of the 6.5–9.5 percent sodium of sodium carboxymethylcellulose, although edema has been reported in the unsuccessful attempted treatment of obesity with 90 grams of sodium methoxycellulose (255–375 mEq Na) per day.

LABELING

Bulk-forming laxatives should be clearly labeled stressing the importance of adequate fluid intake (drinking a full glass (8 oz.) of liquid) with each dose. The label should also carry a warning against use of the product if the user is taking a drug containing salicylates or a prescription drug containing digitalis or nitrofurantoin. The labeling should state: "This product may combine with certain other drugs. Do not take this product if you are presently taking salicylates or a prescription drug."

REFERENCES

(1) AMA Drug Evaluations, 2nd Edition, American Medical Association, Chicago, p. 800, 1973.

(2) Crane, M. G., J. J. Harris, R. Herber, S. Shankel and N. Specht, "Excessive Fluid Retention Related to Cellulose Ingestion: Studies on Two Patients," Metabolism, 18:945–960, 1969.

(3) Gray, H. and M. L. Tainter, "Colloid Laxatives Available for Clinical Use," Journal of Digestive Disease, 8:130–139, 1941.

(4) Littman, A., "Nutritional and Gastrointestinal Effects of Poorly Absorbed Carbohydrates in Man," Draft of unpublished paper included in OTC Volume 090134.[1]

(5) GRAS (Generally Recognized as Safe) Food Ingredients-Cellulose and Derivatives, Informatics, Inc., Rockville, Md., FDA 72-104, Dec. 15, 1972.

(6) The Pharmacopeia of the United States of America, 18th Revision, The United States Pharmacopeial Convention, Inc., Bethesda, Md., p. 613, 1970.

(3) *Karaya (sterculia gum).* The Panel concludes karaya to be safe and effective in amounts usually taken orally: 5 to 10 grams per day when accompanied with adequate fluid intake.

Karaya is a hydrophilic vegetable gum obtained from the barks of various species of sterculia and cochlospermum. These substances are indigestible polysaccharides which act by absorbing water and increasing the bulk of the stool. These vegetable gums exert little systemic effect. For example, up to 3 grams per kilogram of karaya has been fed to rats (which is the highest dose that could be physically administered to rats) without systemic effect. However, rare cases of allergic reactions and urticaria in man caused by karaya have been reported.

LABELING

The label should stress the importance of drinking a full glass of liquid immediately with each dose. The labeling should state: "Drink a full glass (8 oz.) of liquid immediately with each dose."

PROFESSIONAL LABELING

Professional labeling should contain a warning that rare cases of allergic reactions and urticaria caused by karaya have been reported. Also, inadequate fluid intake may cause large bowel obstructions.

REFERENCES

(1) Ivy, A. C. and B. L. Isaacs, "Karaya Gum as a Mechanical Laxative," American Journal of Digestive Diseases and Nutrition, 5:315–321, 1938.

(2) The Merck Index, 8th Ed., Merck and Company, Inc., Rahway, New Jersey, p. 598, 1968.

(3) Darlington, R. C., "Laxatives," Handbook of Non-prescription Drugs, American Pharmaceutical Association, Washington, D.C., pp. 62–76, 1973.

(4) Ireson, J. D. and G. B. Leslie, "An In Vitro Investigation of Colloidal Bulk-forming Laxatives," The Pharmaceutical Journal, 205: 540, 1970.

(4) *Malt soup extract.* The Panel concludes malt soup extract to be safe and effective in amounts usually taken orally: infants (not more than 2 years), 6 to 32 grams, and adults, 12 to 64 grams, when accompanied with adequate fluid intake (full glass (8 oz.) of liquid).

[1] Cited OTC Volumes refer to the submissions made by interested persons pursuant to the call for data notice published in the FEDERAL REGISTER of February 8, 1973 (38 FR 3614). The volumes are on file in the office of the Hearing Clerk, Food and Drug Administration, Room 465, 5600 Fishers Lane, Rockville, MD 20852.

Malt soup extract is obtained from partially germinated grain of one or more varieties of barley containing amylolytic enzymes. The evaporated aqueous extract constitutes malt extract. The powdered malt soup extract contains 73 percent maltose, 7 percent protein, and 1.5 percent potassium. In addition, there are small quantities of calcium, phosphorus, magnesium and vitamins of the B Group and C. Although the Panel considered malt soup extract with the bulk-forming laxatives, the Panel is aware that increase in fecal volume probably is not the sole mechanism of action. Precisely how malt soup extract produces increased softness of the stool is not clearly understood. It has been well documented that malt soup extract will lower fecal pH, and it is purported to exert its beneficial effect as a result of the altered pH. It seems likely that the reduced fecal pH occurs as a result of bacterial conversion of maltose into lactic acid, pyruvic acid, and carbon dioxide.

LABELING

Although reduction in stool pH has also been cited as the reason for the claimed effectiveness of malt soup extract in reducing the symptoms of pruritis ani, the Panel concludes that there is insufficient evidence to support the claim that malt soup extract is effective when used alone in the treatment of pruritis ani. (See discussion of malt soup extract below in Category III statement.)

REFERENCES

(1) Calloway, N. O., "Clinical Investigation of Fecal pH in Geriatric Constipation: Corrective Therapy," Journal of the American Geriatric Society, 12:368–372, 1964.

(2) Crawford, O. W. and N. O. Calloway, "Clinical Study of Fecal pH in Pediatric Constipation," Illinois Medical Journal, 128:320–322, 1965.

(3) Brooks, L. H. "Further Studies of the Management of Pruritus Ani," Diseases of the Colon and Rectum. 12:193–195, 1969.

(4) OTC Volume 090018.[1]

(5) *Polycarbophil.* The Panel concludes that polycarbophil is safe and effective in amounts usually taken orally: infants (not more than 2 years) 0.5 to 1.0 gram, children (2 to 5 years) 1.0 to 1.5 grams, children (6 to 12 years) 1.5 to 3.0 grams and adults 4 to 6 grams per day as a laxative (or when used as an antidiarrheal preparation).

Polycarbophil, a hydrophilic polyacrylic resin (polyacrylic acid crosslinked with divinyl glycol) has a marked capacity for binding water and absorbs about 60 times its original weight. This property is the basis for its use as an intestinal hydrosorptive agent.

The seemingly paradoxical utilization of this hydrosorptive agent in the treatment of both diarrhea and constipation is based on its modifying effect on abnormal fecal consistency. In diarrheal states, it is presumed the hydrophilic agent absorbs free fecal water forming a gel in the lumen of the intestine. In constipation, the agent retains water intraluminally and opposes dehydrating forces in the bowel. The water-retaining capacity of polycarbophil is considerably greater than that of methylcellulose or psyllium mucilloid. The degree of hydrophilia (cubic centimeters/gram) of polycarbophil in synthetic intestinal juice is about 120, while for psyllium, methylcellulose and agar-agar the values are 30, 36, and 14, respectively.

In animal studies the ingestion of polycarbophil has been shown to be free of toxicity, to be nonabsorbable, to have no effect on digestive enzymes, to have no influence on nutritional status, and to be metabolically inactive.

LABELING

"Drink a full glass (8 oz.) of liquid with each dose."

REFERENCES

(1) Grossman, A. J., R. C. Batterman and P. Leifer, "Polyacrylic Resin: Effective Hydrophilic Colloid for the Treatment of Constipation," Journal of the American Geriatric Society, 5:187–192, 1957.

(2) Roth, J. L. A., "Effect of Polycarbophil as Enteral Hydrosorbent in Diarrhea," *American Journal of Digestive Diseases,* 5:965–971, 1960.

(3) Pimparker, B. D., F. F. Paustian, J. L. A. Roth and H. L. Bockus, "Effect of Polycarbophil on Diarrhea and Constipation," Gastroenterology, 40:397–404, 1961.

(4) Rutledge, M. L., M. M. Willner and J. T. King, "Calcium Polycarbophil in Acute Childhood Diarrhea," Clinical Pediatrics, 2:61–63, 1963.

(5) Winkelstein, A., "Effect of Calcium Polycarbophil (CARBOFIL[2]) Suspension on Gastrointestinal Transit Time," Current Therapeutic Research, 6:572–583, 1964.

(6) *Psyllium preparations [plantago seed, plantago ovata husks, psyllium (hemicellulose), psyllium hydrophilic mucilloid (psyllium hydrocolloid), psyllium seed, psyllium seed (blond)], psyllium seed husks.* The Panel concludes psyllium preparations to be safe and effective in amounts usually taken orally (2.5 to 30.0 grams per day) provided the unit dose is taken with a full glass (8 oz.) of liquid and believes it is unnecessary to impose a specific daily dosage limitation at this time. The dosage for children over 6 years is 1.25 to 15.0 grams per day with the same fluid intake requirement.

Psyllium preparations are obtained from the seeds of various species of *Plantago,* i.e., *P. psyllium, P. ovata,* and *P. indica.* The dried ripe seeds have a high content of mucilage which acts by imbibing water and increasing the bulk of the feces. The hydrophilic mucilloid of psyllium preparations is a hemicellulose that is indigestible, nonabsorbable and presumably nonallergenic.

Experimentally, it has been demonstrated that renal tubular pigmentation, the nature of which has not been identified, occurs in animals fed large quantities of the whole ground psyllium seed (*P. psyllium* and *P. indica*). Blond psyllium seed (*P. ovata*) and the purified hydrophilic mucilloid do not cause renal pigmentation. Despite the presence of the renal tubular pigment, urea clearance in treated rats was not different from that found in untreated control rats. In man, phenolsulfonphthalein excretion and urinalysis were normal in 9 human subjects who ingested 7 to 14 grams of psyllium agar flakes daily for 2 to 7 years. It is the opinion of the Panel that the renal pigmentation is probably harmless. Chronic ingestion of psyllium products will cause an increase in bile salt excretion in the feces in the rat and man. In addition, a slight reduction in serum cholesterol has been observed in man. The theoretical complication of increased gallstone formation due to a reduced bile salt pool has not been described.

Esophageal, gastric, small intestinal and rectal obstruction due to accumulation of mucilaginous derivatives of psyllium preparations have been described on several occasions. The common denominator in most cases has been insufficient water intake or underlying organic disease which resulted in compromise of the intestinal lumen. Considering the widespread use of psyllium products, the incidence of esophageal and intestinal obstruction is extremely rare.

LABELING

The label must state "Drink a full glass (8 oz.) of liquid with each dose."

REFERENCES

(1) Souter, W. A., "Bolus Obstruction of Gut After Use of Hydrophilic Colloid Laxatives," British Medical Journal, 1:166–168, 1965.

(2) Tirsch, H. S. and S. Rosenfeld, "Correction of Constipation in Severely Incapacitated Invalids and in Patients with Neurologic Disease," American Journal of Gastroenterology, 31:702–705, 1959.

(3) Stanley, M., D. Paul, D. Gacke and J. Murphy, "Comparative Effects of Cholestyramine, Metamucil and Cellulose on Bile Salt Excretion in Man," Gastroenterology, 62:816, 1972.

(4) Fingl, E., "Cathartics and Laxatives," Pharmacological Basis of Therapeutics, 4th Ed., Edited by Goodman, L. S. and A. Gilman, MacMillan, New York, p. 1026, 1970.

(b) *Active ingredients classified as stimulant laxatives.* The Panel is of the opinion that the so called "stimulant" group of laxative preparations should be used only occasionally, and not more than daily for a week, for the relief of simple constipation.

LABELING

In addition to specific labeling requirements for the individual ingredients listed below, it must be stated on the label of this group of laxatives that

Prolonged or continued use of this product can lead to laxative dependency and loss of normal bowel function. Serious side effects from prolonged use or overdose may occur;

and

This product should be used only occasionally, but, in any event, no longer than daily for 1 week, except on the advice of a physician.

(1) *Anthraquinones.* The Panel concludes the following anthraquinone to be safe and effective in the following amounts usually taken orally in laxative products for occasional use only:

Anthraquinone	*Usual Dose*
Aloe	120 to 250 mg daily for adults; 40 to 80 mg daily for children 6 to 8 years, and 80 to 120 mg daily for 8 to 15 years. (Not recommended for children under 6 years).
Cascara Sagrada Preparations:	
Aromatic Cascara Fluidextract	2 to 6 ml daily (infants not more than 2 years: 1–2 ml/dose).
Casanthranol	30 to 90 mg daily.
Cascara Sagrada Bark	300 mg to 1 gm daily.
Cascara Sagrada Extract	200 to 400 mg daily.
Cascara Sagrada Fluidextract	0.5 to 1.5 ml daily.
The usual dose for infants under 2 years is ¼ the adult dose and for children (2 to 12 years) ½ the adult dose of cascara preparations.	
Danthron	75 to 150 mg daily (No pediatric dose recommended for children under 12 years).
Senna Preparations (single dose):	
Senna Fluidextract	2 ml.
Senna Leaf Powder	0.5 to 2 gm.
Senna Pod Concentrate	0.6 to 1 gm (1–4 times daily).
Senna Fruit Extract	3.4 to 4 gm.
Senna Syrup	8 ml.
Sennosides A & B, Crystalline	12 to 36 mg.

The usual childhood dose of the senna preparations is ⅛ of the adult dose for infants under 2 years, ¼ of the adult dose for children 1 to 5 years, and ½ of the adult dose for children 6 to 12 years of age.

The laxative action of aloe, cascara sagrada, and senna is attributed to hydroxyanthraquinone derivatives that exist in the plants as glycosides and, in the case of the synthetic compound danthron, as the free anthraquinone. The laxative action of the anthraquinones is limited mainly to the large intestine where the glycosides in the plant derivatives arrive intact and are subsequently hydrolyzed by colonic microflora to free anthraquinone. The precise mechanism by which these compounds promote bowel movement is not known. Proposals that suggest the active constituents act by a direct irritant effec on the mucosa or that they stimulate intramural nerve plexi lack experimental confirmation.

Danthron is partially absorbed from the upper gastrointestinal tract and a large part of the drug is metabolized by the liver. The metabolic products are excreted by the kidneys, sometimes causing a harmless discoloration of the urine as occurs with all anthraquinones. Anthraquinone also is excreted in the milk of nursing mothers but in insufficient amounts to cause laxation in the nursing infant. Melanotic pigmentation of the mucous membrane of the colon has been observed in persons who have taken anthraquinone drugs for years. This pigmentation is thought to be benign and is reversible after the medication is discontinued.

LABELING

Labeling should include statements identified above for stimulant laxatives. Professional labeling for senna preparations may also include "for the preparation of the colon for X-ray and endoscopic examination."

REFERENCES

(1) AMA Drug Evaluations, 2nd Ed., Publishing Sciences Group, Acton, Mass. p. 801, 1973.

(2) Greenhalf, J. O. and H. S. D. Leonard, "Laxatives in the Treatment of Constipation in Pregnant and Breast-feeding Mothers," Practitioner, 210:259–263, 1973.

(3) Jones, F. A. and E. W. Godding, "Management of Constipation," Blackwell Scientific Publications, London, p. 62–64, 1972.

(4) Travell, J., "Pharmacology of Stimulant Laxatives," Annals of the New York Academy of Sciences, 58:416–425, 1954.

(2) *Bisacodyl.* The Panel concludes that bisacodyl is safe and effective in the amounts usually taken orally (5–15 milligrams daily at bedtime) and rectally (10 milligrams suppository) for occasional use. The usual oral dose is 0.3 mg/Kg/day or 5 mg for children over 3 years of age. The rectal dose is 5 mg for children under 2 years.

Bisacodyl, (4,4′-(2-pyridylmethylene) diphenol diacetate), when in contact with the colonic mucosa, after either oral or rectal administration, promotes evacuation by inducing mass movements in the colon. The agent is considered a "contact" laxative owing to the fact that its action may be blocked by mucosally applied local anesthetics. After rectal administration, it is usually effective within 15 minutes to 1 hour. Bisacodyl is very poorly absorbed, if at all.

The action of bisacodyl is said to be limited to the colon by acting on the mucosa or the submucosal plexi of the large bowel. However, studies in animals indicate bisacodyl may inhibit sodium and potassium adenosine triphosphatase thereby limiting sodium and water reabsorption in the small intestine. It may also inhibit tyrosine and glucose absorption resulting in intraluminal retention of osmotically attracted water in the small bowel as well as inducing active secretory processes in the colon. With excessive use, or accidental overdose, severe side effects have been reported including diarrhea with metabolic acidosis, muscular weakness due to hypokalemia, and metabolic alkalosis leading to tetany in the presence of persistent hypokalemia.

LABELING

The label of the enteric coated tablets of bisacodyl must state: (1) "Do not chew." (2) "Do not give to children under 3 years of age or to persons who cannot swallow without chewing." (3) "Do not take this product within 1 hour after taking an antacid and/or milk." (4) "This product may cause abdominal discomfort, faintness, rectal burning and mild cramps." Labeling for both tablets and suppositories should state: "Store in a cool place at temperature not above 86° F (30° C)."

PROFESSIONAL LABELING

The Panel concludes that additional indications for professional labeling may include for use in preparation of the patient for surgery or for preparation of the colon for x-ray and endoscopic examination.

REFERENCES

(1) Anon: "Purgatives," British Medical Journal, 4:543–544, 1969.

(2) Cooke, W. T., "Laxatives and Purgatives," Practitioner, 206:77–80, 1971.

(3) Ewe, K., "Effect of Laxatives on Intestinal Water and Electrolyte Transport," European Journal of Clinical Investigation, 2:283, 1972.

(4) Rider, J. A., "Treatment of Acute and Chronic Constipation with Bisoxatin Acetate and Bisacodyl: Double-blind Crossover Study." Current Therapeutic Research, 13:386–392, 1971.

(5) Goldfinger, P., "Hypokalemia, Metabolic Acidosis, and Hypocalcemic Tetany in a Patient Taking Laxatives. A Case Report." Journal of Mount Sinai Hospital, 36:113–116, 1969.

(3) *Castor oil.* The Panel concludes castor oil to be safe and effective in amounts (15 to 60 milliliters) taken orally as a single dose. The usual dose for infants (not more than 2 years) is 1 to 5 ml and for children (2 to 12 years) 5–15 ml.

The laxative action of castor oil is due to ricinoleic acid which is produced when castor oil is hydrolyzed to the fatty acid in the small intestine by pancreatic lipase. The precise mode by which ricinoleic acid promotes bowel movement is not known, although recent experimental evidence indicates that it causes the colon to secrete water and electrolytes. There is no experimental evidence to support the assumption that the laxative acts to increase peristalsis through a direct irritant effect on the intestinal mucosa.

Some castor oil may be absorbed from the gastrointestinal tract; its systemic effect and metabolic fate are unknown. Ricinoleic acid is also absorbed and it is metabolized in a manner similar to other fatty acids. Its single action usually results in a complete clearance of the lower bowel which makes it useful to prepare the patient for proctoscopy or for x-ray studies of the gastrointestinal tract.

Castor oil affects the small intestine and regular use may cause excessive loss of water, electrolyte and unabsorbed nutrients. These potential side effects preclude its repeated administration as a therapeutic agent in the management of constipation.

LABELING

The label of castor oil containers must state: (1) "For the treatment of isolated bouts of constipation." (2) "Not to be used on a daily basis except under the direction of a physician." (3) "Castor oil affects the small intestine and regular use may cause excessive loss of water, and body salts, which can have debilitating effects." Professional labeling may also include "for the preparation of the colon for x-ray and endoscopic examination."

REFERENCES

(1) AMA Drug Evaluations, 2nd Ed., American Medical Association, Chicago, p. 801, 1973.

(2) Jones, F. A. and E. W. Godding, "Management of Constipation," Blackwell Scientific Publications, London, p. 57, 1972.

(3) "Report of NAS–NRC Drug Efficacy Study Group," Published in the Federal Register of May 24, 1972 (37 FR 10521).

(4) Watson, W. C., R. S. Gordon, Jr., A. Karmen and A. Jover, "Absorption and Excretion of Castor Oil in Man," Journal of Pharmacy and Pharmacology, 15:183–188, 1963.

(5) Phillips, S. F., "Diarrhea: A Current View of the Pathophysiology," Gastroenterology, 63:495–518, 1972.

(6) Christensen, J. and B. W. Freeman, "Circular Electromyogram in the Cat Colon: Local Effect of Sodium Ricinoleate," Gastroenterology, 63:1011–1015, 1972.

(4) *Dehydrocholic acid.* The Panel concludes that dehydrocholic acid is safe and effective as a laxative when given in recommended doses of 750 to 900 milligrams per day. The Panel has no data to support a recommended pediatric dose and accordingly should not be used in any child under 12 years of age.

Dehydrocholic acid is the oxidation product of cholic acid, a natural bile acid. It differs from the natural bile acids and their conjugates in at least two respects: (a) it does not readily form micelles (small aggregates of bile acids, fats, and phospholipids necessary for normal fat absorption) and (b) it is a potent hydrocholeretic (increases the volume and water content of bile). Animal toxicity studies have disclosed a remarkably high LD_{50} (14.7 gm/kg in rats). Chronic administration of doses as high as 5 gm/kg/day in dogs failed to produce hepatoxicity and no hepatic damage was found in rats fed 333 mg/kg daily for 32 days. In man, reports of the oral and intravenous administration of dehydrocholic acid for a variety of conditions have failed to disclose consistent or serious toxicity (with the exception of rare anaphylactic reactions following the intravenous administration of this substance for the measurement of circulation times).

The mechanism by which dehydrocholic increases the frequency of bowel movements is unkown. There is no experimental basis for the early literature references to "biliary constipation" or the relief of constipation due simply to the hydrocholeretic action of dehydrocholic acid. It is possible that this bile acid has a direct effect on the colonic mucosa to inhibit the absorption of sodium and water and stimulate the secretion of sodium bicarbonate and water as has been demonstrated with naturally occurring bile acids.

LABELING

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) King, J. C., "Practical Ambulatory Therapy of Functional Constipation," American Journal of Digestive Diseases, 22:102–108, 1955.

(5) *Phenolphthalein (white or yellow).* The Panel concludes phenolphthalein to be safe and effective in the amounts 30 to 270 milligrams daily for adults, 15 to 20 milligrams per day for children (2 to 5 years), and 30 to 60 milligrams for children 6 years and older usually taken orally in laxative products for occasional use only. The drug is not recommended for use in children less than 2 years of age unless under the advice and supervision of a physician.

Phenolphthalein exerts its primary laxative action on the colon, but may also increase the activity of the small intestine. The main mode of action appears to be as a noncompetitive inhibitor of the enzymes, sodium and potassium adenosine triphosphatase, resulting in failure of salt and water absorption. The glucuronide and disulfide derivatives of phenolphthalein have no effect on enzymatic activity. Yellow phenolphthalein is said to be about three times as potent as white phenolphthalein, but this is not adequately supported by clinical studies. Up to 15 percent of a therapeutic dose may be absorbed and excreted by the kidney, giving a pink color to alkaline urine. The major side effects of phenolphthalein, which occur infrequently, are excessive laxation or electrolyte depletion in chronic use and various skin reactions including nonspecific rashes and pigmentation.

LABELING

In addition to the general requirements for labeling as a laxative, the following specific caution must appear: "If a skin rash appears, do not use this or any other preparation containing phenolphthalein."

REFERENCES

(1) Phillips, R. A., A. H. G. Love, T. G. Mitchell and E. M. Neptune, Jr., "Cathartics and the Sodium Pump," Nature, 206:1367–1368, 1965.

(2) Chigneil, C., "The Effect of Phenolphthalein and Other Purgative Drugs on Rat Intestinal ($Na^+ + K^+$) Adenosine Triphosphatase," Biochemical Pharmacology, 17:1207–1212, 1968.

(3) Ditkowsky, S., and F. Steigmann, "Phenolphthalein in Childhood: Dosage and Efficacy," Journal of Pediatrics, 45:169–178, 1954.

(4) Savin, J. A., "Current Causes of Fixed Drug Eruptions," British Journal of Dermatology, 82:546–549, 1970.

(c) *Active ingredients classified as saline and hyperosmotic laxatives*—(1) *Saline laxatives.* Although the saline laxatives (magnesium and phosphate ions) have long been assumed to act by the hyperosmotic effect of poorly absorbed ions within the small bowel, recent evidence suggests that saline laxatives exert a complex series of actions on the gastrointestinal tract. The Panel recognizes that the following commentary may undergo significant revision on the basis of current and future research into the mechanisms of action of the saline laxatives. Further, the Panel concludes that the saline laxatives should be restricted to occasional use only, as serious electrolyte disturbances have been reported with their long-term or daily use.

LABELING

The label should contain a warning concerning prolonged usage such as, "For occasional use only. Do not take longer than 1 week. Serious side effects from prolonged use or overdosage may occur."

(i) *Magnesium salts.* The Panel concludes that the following magnesium salts are safe and effective in the amounts taken orally in laxative products for occasional use:

Magnesium Salt—Usual daily dose (taken in divided doses).

Magnesium Citrate—11–18 gm (77–141 mEq Mg^{++}) or for children 2 to 5 years 2.5 to 5 gm, 6 years and older 5 to 10 gm.

Magnesium Hydroxide—2.4–4.8 gm (82–164 mEq Mg^{++}) or for children 2 to 5 years 0.4 to 1.2 gm, for children 6 years and older 1.2 to 2.4 gm.

Magnesium Sulfate—10–30 gm (81–243 mEq Mg^{++}) or for children 2 to 5 years 2.5 to 5 gm, 6 years and older 5 to 10 gm.

Magnesium salts are one of a group of the saline laxatives classically thought to exert a laxative effect by osmotically attracting water into the intestinal lumen. Current work suggests that the mechanism of action may be due in large part to the release of the gastrointestinal hormone cholecystokinin-pancreozymin (CCK–PZ) and its subsequent stimulation of the motor and secretory activity in the gastroentestinal tract. Most studies suggest a minimally effective dose of magnesium is approximately 80 mEq, although lower doses may, in the future, be shown to be effective for activity unrelated to any osmotic action.

Absorption of administered magnesium is approximately 15 to 30 percent, which may cause systemic toxicity in the presence of renal insufficiency.

Anhydrous Magnesium Citrate is usually formulated in combinations of citric acid and anhydrous sodium citrate; these latter two substances are considered sequestering agents that allow magnesium to be held in solution as a soluble complex ion. Citric acid and anhydrous sodium citrate are not considered laxative agents in themselves and should not be claimed as active ingredients.

Magnesium hydroxide is occasionally promoted as both an antacid and a laxative. This dual claim is permissible owing to the activity of this compound, but the public should be aware that when used regularly as an antacid, magnesium hydroxide causes significant laxation. Claims of superior laxation on the basis of the antacid properties are not allowed because the Panel is not aware of any scientific data that establishes a relationship between acid secretion and constipation.

LABELING

For those products in which the maximal daily dose exceeds 50 milliequivalents of magnesium, the label should contain a statement such as, "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

Labeling of the magnesium citrate solution should indicate the need for storage in a cold place (refrigerator temperature) to retard decomposition.

SODIUM WARNING LABEL

See laxative labeling statement (paragraph D) above for sodium warning.

REFERENCES

(1) Welt, L. G. and W. B. Blythe, "Cations: Calcium, Magnesium, Barium, Lithium and Ammonium," "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman MacMillan, New York, pp. 811–813, 1970.

(2) Seed, J. C. and R. Harris, "Some Factors in the Design of Aperient Studies," Annals of the New York Academy of Science, 58:426–437, 1954.

(3) Harvey, R. F. and A. E. Read, "Saline Purgatives Act by Releasing Cholecystokinin," Lancet, 2:185–187, 1973.

(4) Montilla, E., "Treatment of Chronic Constipation With An Emulsion of Milk of Magnesia and Mineral Oil." Clinical Medicine, 73:75–77, 1966.

(ii) *Phosphate Salts.* The Panel concludes that each of these phosphate salts is safe and effective in amounts taken orally or rectally in a single dose of the following ingredients:

Phosphate Salt	Usual daily dose of all ingredients combined (gm)	
	Oral	Rectal
Disodium Phosphate	1.9–3.8	3.8
Monosodium Phosphate	8.3–16.6	16.6
Sodium Biphosphate	9.6–19.2	19.2
Sodium Phosphate	3.6–7.2	7.2

The usual oral dosage for children 5 to 10 years of age: ¼ of the adult dose, children 10 years and older: ½ the adult dose of phosphate salts. The usual rectal dosage for children over 2 years of age is ½ of the adult dosage of phosphate salts.

The oral phosphate salts are considered to be rapidly acting laxatives whose mechanism of action may involve more complex activity in the gastrointestinal tract than that of a hyperosmotic agent. When given as an enema rectally, four ounces of the hypertonic solution containing approximately 26 grams of phosphate salt is also considered effective although the extent to which effectiveness reflects the volume of liquid introduced rectally is unknown. The amount of total sodium contained in the effective and safe range is 88 to 176 milliequivalents. The amount of sodium absorption from the enema varies from 1.6 to 31 milliequivalents of sodium; the extent of sodium absorption from the oral preparations is unknown. By either route, there is risk of acute elevation of sodium concentration in the serum and dehydration, particularly in children with megacolon. Elevated levels of serum phosphates and decreased levels of serum calcium have been reported with prolonged use or in patients with renal disease.

LABELING

The labeling for saline laxatives discussed above should be included. The label should also contain a warning against use in the presence of kidney disease. The label should also contain a warning against use by children under the age of 6 for oral preparations and by children under the age of 2 years for rectal preparations, except under the advice of a physician.

SODIUM WARNING LABEL

See laxative labeling statement (paragraph D) above for sodium warning.

PROFESSIONAL LABELING

The labeling provided to health professionals (but not to the general public) for all phosphate laxatives should provide the total dose of sodium in mEq (mg) per standard dose. The label should carry the following warnings: "Do not use in patients with megacolon, as hypernatremic dehydration may occur. Use with caution in patients with impaired renal function as hyperphosphatemia and hypocalcemia may occur."

REFERENCES

(1) Fonkalsrud, E. and J. Keen, "Hypernatremic Dehydration from Hypertonic Enemas in Congenital Megacolon," Journal of the American Medical Association, 199:584–586, 1967.

(2) The National Formulary, 12th Ed., The American Pharmaceutical Association, Washington, D.C. p. 372, 1965.

(3) Page, S. G., C. R. Riley and H. B. Haag, "A Comparative Clinical Study of Several Enemas," Journal of the American Medical Association, 157:1208–1210, 1955.

(4) Rosenfield, H. H., L. Burke and H. Rubin, "Disposable Enema Unit in Obstetrics," Obstetrics and Gynecology, 222–225, 1958.

(5) Zumoff, B. and L. Hellman, "Rectal Absorption of Sodium from Hypertonic Sodium Phosphate Solutions," Sloan Kettering Institute for Cancer Research, New York, N.Y., Draft of unpublished paper included in OTC Volume 0900—.

(6) McConnell, T. H., "Fatal Hypocalcemia from Phosphate Absorption from Laxative Preparation," Journal of the American Medical Association, 216:147–148, 1971.

(2) *Hyperosmotic Laxatives*—(i) *Glycerin.* The Panel concludes that glycerin is safe and effective in the amounts usually used rectally as an aid in evacuation of the bowel: 3 grams as a suppository; 5 to 15 milliliters as an enema. Children under 6 years 1 to 1.5 gm as a suppository or 2 to 5 ml as an enema.

Glycerin is a clear, colorless trihydroxy alcohol which is miscible with water and alcohol. Three possible modes of action of glycerin on the rectal mucosa have been proposed: (1) Being hypertonic, it causes mild dehydration of the tissues resulting in reflex defecation; (2) it is locally irritating and produces reflex defecation; (3) possessing hygroscopic properties, it softens fecal material and hydrates hardened dry feces.

Moderate doses orally or parenterally (in proper dilution) are safe and cutaneous application in copious amounts does not produce systemic effects. Owing to its sweet taste, it has been used as a sweetening agent. When taken orally, it is rapidly absorbed and metabolized providing calories. Large doses orally can exert toxic effects and may lead to symptoms including restlessness, vomiting, loose stools, fever, convulsive seizures, hemoglobinuria, progressive narcosis, and circulatory failure. The Panel, therefore, concludes that glycerin is unsafe at the effective dose level as an oral laxative.

Compounds related to glycerin, with the exception of propylene glycol, are much more toxic than the parent compound and may cause nephro- and hepatotoxicity.

The use of glycerin as rectal suppositories in adults and children is effective in producing a bowel movement, usually within 30 minutes, in the majority of children and adults with only minimal incidence of side effects including rectal discomfort, rectal burning or griping, and cramping pain. Glycerin administered rectally is considered to be safe but may produce in some individuals rectal mucosal hyperemia, minimal hemorrhage, and mucorrhea.

LABELING

The labeling should state: (1) "For rectal use only and not for oral use. Large doses of glycerin if taken orally can lead to serious toxic effects." (2) "Glycerin administered rectally may produce in some individuals rectal discomfort or a burning sensation."

REFERENCES

(1) Staples, R., A. Misher and J. Wardell, Jr., "Gastrointestinal Irritant Effect of Glycerin as Compared with Sorbitol and Propylene Glycol in Rats and Dogs," Journal of Pharmaceutical Sciences, 56:398–400, 1967.

(2) Sloviter, H. A. and R. M. Tietze, "Effects of the Intravenous Administration of Glycerol Solutions to Animals and Man," Journal of Clinical Investigation, 37:619–626, 1958.

(3) Pinter, G. G. and D. B. Zilversmit, "Mechanism of Hemolysis After Intravenous Glycerol Administration," American Journal of Physiology, 198:895–898, 1960.

(4) Barowsky, H., "A Rectal Suppository for Inducing Lower Bowel Evacuation. Its Comparative Effectiveness to the Glycerin Variety," American Journal of Gastroenterology, 39:183–186, 1963.

(5) Brocklehurst, J. C., "Treatment of Constipation and Fecal Incontinence in Old People," Practitioner, 193:779–782, 1964.

(ii) *Sorbitol.* The Panel concludes that sorbitol is safe and effective in amounts usually administered rectally (120 milli-

liters as a 25 to 30 percent solution) in laxative products for occasional use (Children 2 years and older 30 to 60 ml in same concentration, administered rectally).

Sorbitol is a poorly absorbed polyalcohol of the hexose sugar, sorbose. Because of its limited absorption from the gastrointestinal tract, if given orally in sufficient quantities, it promotes an osmotic diarrhea. The oral laxative minimum effective dose in man appears to be about 50 grams. This dose is used occasionally to produce laxation in patients with some complicated disease, but is not approved for use as an oral laxative in OTC products. When administered rectally as a hypertonic solution, it promotes defecation.

Sorbitol given orally has been shown in animals to be less irritating to the intestinal mucosa than glycerin, but the observed changes are qualitatively similar and dose and concentration dependent.

LABELING

"For rectal use only."

REFERENCES

(1) Adcock, L. H. and C. H. Gray, "The Metabolism of Sorbitol in the Human Subject," Biochemical Journal, 65:554–560, 1957.

(2) Staples, R., A. Misher and J. Wardell, Jr., "Gastrointestinal Irritant Effect of Glycerin as Compared with Sorbitol and Propylene Glycol in Rats and Dogs," Journal of Pharmaceutical Sciences, 56:398–400, 1967.

(3) Prescott, L. G., "Pharmacokinetic Drug Interaction," Lancet, 2:1239–1243, 1969.

(4) Stempien, S. J., "Double-Blind Evaluation of Sorbitol, Phosphate, and Dextrose Enemas at Sigmoidoscopy," Gastroenterology, 36:830–831, 1959.

(5) Agostini, L., P. F. Down, J. Murison and O. M. Wrong, "Faecal Ammonia and pH During Lactulose Administration In Man: Comparison With Other Cathartics," Gut, 13:859–866, 1972.

(d) *Active ingredients classified as stool softener and lubricant laxatives.* The active ingredients as stool softener laxatives and lubricant laxatives are particularly useful when the stools are hard and dry or when disease of the anus and rectum exist that make the passage of a firm stool painful. These products should be used only occasionally or no longer than a week when taken daily as they may interfere with the absorption of a number of nutrients including some vitamins. If relief of the condition for which the product is taken is not obtained in a week, the user should consult a physician. The following ingredients are considered, by the Panel, to be safe and effective when taken as directed.

(1) *Stool softener laxatives*—(i) *Dioctyl sulfosuccinate preparations.* The Panel concludes that the following dioctyl sulfosuccinate preparations are safe and effective in amounts usually taken orally or rectally in laxative products.

Sulfosuccinate	*Usual daily dose*
Dioctyl calcium sulfosuccinate (oral)	50–360 mg/day (25 mg for infants under 2 years, 50–150 mg/day for children).
Dioctyl potassium sulfosuccinate (rectal)	50–250 mg/day (100 mg/day for children).
Dioctyl Sodium sulfosuccinate (oral)	50–360 mg/day (20–50 mg for infants under 2 years, 50–150 mg/day for children).

The mechanism of action of dioctyl sodium sulfosuccinate (DSS) salts is not completely understood. Published literature based on in vitro studies suggests that they act by a detergent action which lowers surface tension at the oil-water interface permitting water and lipid to penetrate the fecal mass and soften the stool. Absorption of DSS does occur in the duodenum and jejunum. The clinical significance of intestinal absorption of DSS has not been determined.

Recent evidence suggests that the laxative properties of DSS may be explained by its ability to stimulate secretion of electrolytes and water in the colon. The effect is associated with an increased concentration of cyclic adenosine monophosphate in the colonic mucosal cells exposed to DSS.

Significant toxicity in the human has not been attributed to DSS when used alone as a laxative. Hepatic toxicity has occurred when DSS was used in combination with oxyphenisatin, but this drug combination is no longer being marketed.

Published reports available to the Panel concerning studies made in many types of constipated patients show DSS to be effective in softening the stool. Only minimal and insignificant side effects have been attributed to its use.

In spite of the reported record of safety, DSS possesses potent detergent properties and the Panel recognizes that it might facilitate gastrointestinal or hepatic cell uptake of other drugs, thereby, potentiating their activity. The absorption of mineral oil (a lubricant laxative described elsewhere in this document) may be enhanced by DSS, and therefore, these agents should not be taken concurrently. The doses of DSS and dioctyl calcium sulfosuccinate (DCS) should be as small as possible to give the desired result.

Current information does not warrant a need to restrict the use of DSS, DCS, or dioctyl potassium sulfosuccinate (DPS), but reevaluation may be needed as additional data become available.

LABELING

Because of possible drug interaction, the label should contain a statement such as:

WARNING.—Do not take this product if you are presently taking a prescription drug or mineral oil.

The label should also contain a statement such as:

CAUTION.—This product should be used only occasionally, but in any event no longer than daily for 1 week.

REFERENCES

(1) Dujovne, C. A., and D. W. Shoeman, "Toxicity of a Hepatotoxic Laxative Preparation in Tissue Culture and Excretion in Bile in Man," Clinical Pharmacology and Therapeutics, 13:602–608, 1972.

(2) Hyland, C. M. and J. D. Foran, "Dioctyl Sodium Sulphosuccinate as a Laxative in the Elderly," Practitioner, 200:698–699, 1968.

(3) Donowitz, M. and H. J. Binder, "Dioctyl Sodium Sulfosuccinate (DSS) Stimulates Large Intestinal Water and Electrolyte Secretions: Mechanism of Laxative Action?," Gastroenterology, 66:A184/838, 1974.

(4) Phelps, D. K. "Effect of Dioctyl Sodium Sulfosuccinate on Bowel Function in Mental Patients," Journal of the Indiana State Medical Association, 51:646–648, 1958.

(5) Sanders R. C. and P. W. Wright, "Colonic Preparation: A Controlled Trial of Dulcodos, Dulcolax and Senokot DX," British Journal of Radiology, 43:245–247, 1970.

(2) *Lubricant laxatives*—(i) *Mineral oil, plain.* The Panel concludes mineral oil preparations to be safe and effective in the amounts usually administered orally only at bedtime (adults, 15 to 45 milliliters, and children over 6 years 10 to 15 milliliters) and rectally (adults, 120 milliliters, and children 6 years of age and older—60 milliliters) provided the specific directions and limitations are carefully followed.

Mineral oil, a mixture of colorless, tasteless, liquid aliphatic hydrocarbons obtained from petroleum, is a laxative agent that acts by a lubricating effect on the intestinal mucosa and a lubricating or softening action on fecal material. It is non-irritating, not digested by endogenous gastrointestinal enzymes, and minimally absorbed.

Side effects with the proper use of mineral oil are few. Absorption of a number of dietary nutrients including fat soluble vitamins may be impaired by concurrent ingestion of mineral oil. Thus, mineral oil should be taken orally at bedtime, when the stomach is empty. Administration of mineral oil may lower prothrombin levels probably secondary to impaired vitamin K absorption and regular use in pregnancy may predispose to hemorrhagic disease of the newborn. As the absorption of mineral oil may be enhanced by dioctyl sodium sulfosuccinate (a stool softener described elsewhere in this document), these agents should not be taken concurrently. With chronic use and particularly with excess dosage, anal leakage, and dermatologic reactions may ocur.

On very infrequent occasions, mineral oil may be aspirated and cause lipid pneumonitis particularly in young children and debilitated elderly persons. Deposition of mineral oil in various tissues may simulate neoplasms. Mineral oil should not be given to patients with esophageal or gastric retention.

LABELING FOR ORAL PREPARATIONS

The label must state: "Caution: To be taken only at bedtime. Do not take for more than 1 week. Do not administer orally to infants or children under 6 years of age, to pregnant women, to bedridden or aged patients, to persons with difficulty in swallowing, recent vomiting or regurgitation, or abdominal pain ex-

cept on the advice and supervision of a physician.

Because of possible drug interaction, the label should contain a statement such as: "Do not use this product if you are currently taking a stool softener laxative." (See dioctyl sodium sulfosuccinate section of this document for explanation).

(ii) *Mineral oil emulsion.* The Panel concludes certain mineral oil emulsions are safe and effective in amounts usually administered orally twice a day with the first dose taken on arising and the second dose taken at bedtime and neither dose at mealtimes (adults 15 to 45 ml of mineral oil component of emulsion, children over 6 years of age 0.25 to 5 ml of mineral oil component of emulsion). Emulsification of mineral oil by magnesium hydroxide or other agents reduces the size of oil droplets, and there is evidence that this properly results in enhanced penetration of mineral oil into the fecal mass. Emulsification would theoretically enhance intestinal absorption but the Panel is unaware of evidence that this occurs.

LABELING FOR ORAL PREPARATIONS

The Panel concludes that the labeling which applies to plain mineral oil, should also apply to mineral oil emulsion with the exception of the bedtime ingestion limitation for plain mineral oil. That limitation should be modified to permit a twice daily dosage regimen for mineral oil emulsion with the first dose taken on arising and the second dose taken at bedtime and neither dose at mealtime.

LABELING FOR RECTAL PREPARATIONS

The precautions listed above for oral administration do not apply to rectal administration of mineral oil.

LABELING FOR HEALTH PROFESSIONALS

Professional labeling may contain as additional indications: "For the preparation of the colon for x-ray and endoscopic examination."

Labeling shall contain the following: "Side effects with the proper use of mineral oil are few. However, with chronic use and particularly with excess dosage, excessive laxation, anal leakage and dermatologic reactions may occur. Owing to its property as a lipid solvent, liquid paraffin (mineral oil) may interfere with the absorption of pro-vitamin A, vitamin A, and vitamin D leading to impairment of calcium and phosphorus metabolism. This occurs only under conditions of chronic usage. Administration of mineral oil may lower prothrombin levels, probably secondary to impaired vitamin K absorption, and regular use in pregnancy may predispose to hemorrhagic disease of the newborn. Because of possible interference with nutrition, mineral oil should not be ingested in close proximity to meals. These side effects occur very rarely and then only with chronic and abusive use."

REFERENCES

(1) AMA Drug Evaluations, 1st Ed., AMA Council on Drugs, American Medical Association, Chicago, pp. 598–601, 1971.

(2) Martin, E. W., Hazards of Medication, J. B. Lippincott Co., Philadelphia, pp. 577 and 686, 1971.

(3) Anderson, N. P., "Contact Dermatitis; Its Relation to Petroleum Products," Industrial Medicine and Surgery, 22:270–273, 1953.

(4) Steigmann, F., H. Popper, H. Dyniewica and I. Maxwell, "Critical Levels of Mineral Oil Affecting the Absorption of Vitamin A," Gastroenterology, 20:587–594, 1952.

(5) Javert, C. T. and C. Macri, "Prothrombin Concentration and Mineral Oil," American Journal of Obsterics and Gynecology, 42:409–414, 1941.

(6) Poppel, M. H. and C. K. Bangappa," "The Induction of a Disordered Motor Function Pattern in the Small Bowel by the Administration of Mineral Oil," American Journal of Roentgenology, 83:926–927, 1960.

(7) Salm, R. and E. W. Hughes, "A Case of Chronic Paraffin Pneumonitis," Thorax, 25: 762–768, 1970.

(8) Nairn, R. C. and M. F. A. Woodruff, "'Paraffinoma' of the Rectum," Annals of Surgery, 141:536–540, 1955.

(e) *Active ingredient classified as a miscellaneous laxative—(i) Released carbon dioxide from combined sodium biphosphate anhydrous, sodium acid pyrophosphate and sodium bicarbonate.* The Panel concludes that rectal suppositories which release carbon dioxide are safe and effective in the amounts usually used rectally once a day as an aid in evacuation of the bowel (no pediatric dosage for children under 12 years).

The suppository dosage form contains 1.2 gm to 1.5 gm sodium biphosphate anhydrous, 0.04 gm to 0.05 gm sodium acid pyrophosphate and 1.0 gm to 1.5 gm sodium bicarbonate, and works through the production of carbon dioxide (approximately 230 ml) in the rectum. The active ingredient, carbon dioxide, is produced by the action of water on these ingredients. The expanding gas induces a gentle pressure in the rectum thereby promoting bowel movement. The suppository should be placed under a water tap for about 30 seconds or immersed in a cup of water for at least 10 seconds prior to rectal insertion.

LABELING

The product should be labeled for rectal use only. To facilitate the release of carbon dioxide, the labeling should state: "Do not lubricate with mineral oil or petrolatum jelly, prior to rectal insertion." In addition, the following warning should be included:

WARNING.—Rectal bleeding, or failure to evacuate may indicate a serious condition and a physician should be consulted.

REFERENCES

(1) Hamilton, W., and W. Walker, "Carbon Dioxide Suppositories as Preparation for Sigmoidoscopy," Journal of the National Medical Association, 57(6):496–7, 1965.

(2) Slotkin, R., "A Study of the Vacuett Suppository in the Pediatric Patient," Journal Pediatrics, 66(5): 954–6, 1965.

(3) Welsh, J., "Preparation of Outpatients for Proctoscopic Examination," The Journal of the Oklahoma State Medical Association, 6:467–9, 1968.

(4) Barowsky, H., "A Rectal Suppository for Inducing Lower Bowel Evacuation," American Journal Gastroenterology, 39(2): 183–6, 1963.

(5) Blumberg, N., "A New Suppository for Functional Constipation," Medical Times, 91(1):45–7, 1963.

(6) Culp, C., "Bowel Preparation for Proctosigmoidoscopy," Nebraska State Medical Journal, 50(2):79–82, 1965.

2. *Conditions under which laxative products are not generally recognized as safe and effective or are misbranded.* After carefully reviewing all data submitted, as well as additional evidence provided by the Food and Drug Administration and consultants to the Panel and the results of an extensive literature search, the Panel concluded that some OTC laxative ingredients should be removed from the market because of the lack of data supporting their safety. The Panel found no scientific basis or even sound theoretical reasons for claimed effectiveness of a number of ingredients used in OTC laxatives. In addition, certain labeling claims were considered misbranding. Statements and suggestions that laxatives "improve well being" or "promote good health" are unproven and unacceptable. "Irregularity" as an indication for use is misleading because "regularity" of bowel movement is not essential to health or well being. Laxative products are not appropriate for use solely on the basis of a lack of "regularity," because variability of frequency of bowel movements is normal within the limits referred to elsewhere in this document. All undocumented claims such as "stimulates colonic peristalsis," "acts naturally," and "promotes gentle movements" are unacceptable.

The Panel concludes that the following ingredients, labeling, and combination drugs involved should be removed from the market unless and until further scientific testing supports their use:

ACTIVE INGREDIENTS

Calomel
Carrageenan, degraded
Podophylum resin (podophyllin)
Other laxative resins
- Colocynth
- Elaterin
- Gamboge
- Ipomea
- Jalap

COMBINATIONS WITH NONLAXATIVE ACTIVE INGREDIENTS

Belladonna extract (belladonna alkaloids)
Bismuth subnitrate
Capsicum
Caroid papain
Ginger
Ipecac powder
Thiamin, multivitamin preparations, and minerals

LABELING CLAIMS FOR SPECIFIC INGREDIENTS

Bile acids and ox bile
Dehydrocholic acid
Magnesium compounds

a. *Active ingredients*—(1) *Calomel (mercurous chloride).* The Panel concludes that calomel is unsafe and unreliable as a laxative.

No data on calomel were submitted to the Panel for review. However, a review of the presently available literature by the Panel requires classification of this compound in Category II and merits special comment, especially with regard

to the conclusion that it is unsafe to use as a laxative (Ref. 1).

Calomel is relatively insoluble; however, in the presence of alkali and bile in the intestine, it is oxidized to some extent to mercuric ion, which is responsible for the toxicity of the drug (Refs. 2 and 3). In the event that calomel fails to produce prompt laxation, appreciable amounts of mercury may be absorbed and cause systemic mercury poisoning (Refs. 2, 3, and 4). Autopsies of two women who had been chronic users of calomel-containing laxatives revealed renal tubular and cerebellar damage and chronic colitis. In addition to having kidney failure and necrosis of the colon, the two patients before death had central nervous system manifestations such as personality change and failure of cognition, and at autopsy elevated mercury levels in the kidneys, brain, and colon (Refs. 5 and 6). In infants, administration of calomel has caused a severe febrile, (erythematous disease known as acrodynia (pink disease) (Refs. 3, 4, and 7).

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(2) *Carrageenan, degraded (Chondrus crispus, Irish moss).* The Panel concludes that, owing to potential hazards associated with absorbed degraded carrageenan, this material cannot be considered safe on the basis of current evidence.

Native carrageenans which are used in foods possess molecular weights within the range of 100,000 to 800,000. If the cross-linkages of the polymer are broken, degraded carrageenans with molecular weights less than 30,000, are formed. In most animal species tested, native carrageenans (See Category III discussion below) are poorly absorbed, but degraded carrageenans are much more amenable to absorption, especially in herbivorous animals. When added to the drinking water of guinea pigs and rabbits, degraded carrageenans caused diarrhea, severe colonic ulceration, hyperplasia of the intestinal mucosa, and weight loss (Refs. 1 through 6). Degraded carrageenan in the drinking water ingested by Rhesus monkeys was extensively deposited in the reticuloendothelial cells and was still present in Kupffer cells 6 months after cessation of carrageenan administration (Ref. 7).

Owing to the observation that degraded carrageenan may inhibit the proteolytic activity of gastric enzymes, the material has been used in man in the treatment of peptic ulcer (Refs. 5 and 9). Because many of these studies were poorly controlled, the significance of these observations is open to question.

The parenteral administrations of carrageenan produces a wide variety of effects. These include, among others, the following: induction of irritation, inflammation, and edema; granuloma formation; release of kinins, probably by activation of the plasmin system; hypotension; anticoagulation; inhibition of complement fixation; and inhibition of immediate and delayed hypersensitivity reactions (Ref. 5).

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(9) Evans, P. R. C., S. Nowell, and I. A. P. Thomas, "Blind Trial of a Degraded Carrageenin and Aluminum Hydroxide Gel in the Treatment of Peptic Ulceration," Postgraduate Medical Journal, 4: 48–52, 1965.

(3) *Podophyllum resin* (podophyllin). The Panel concludes that podophyllin is unsafe for use as a laxative because of its potential embryotoxicity and systemic toxicity.

Although podophyllum resin (podophyllin) is official in the U.S. Pharmacopeia (Ref. 1), the ingredient is described only as a cytotoxic agent in the topical treatment of condylomata acuminata (Ref. 11).

Podophyllin and its chief constituent, podophyllotoxin, interfere with normal cell division in animals (Refs. 2 through 4). Because of its inhibitory effect on dividing cells, there is concern that podophyllin may produce an adverse effect on the human embryo and/or fetus. A number of investigators have tested podophyllin or podophyllotoxin in pregnant mice and rats (Refs. 4 through 8) and have demonstrated that these drugs cause a significant incidence of fetal resorption (mortality) and/or fetal growth retardation and that podophyllotoxin interrupts pregnancy in rabbits (Ref. 5). Thus, podophyllin is considered to be a strong embryocidal and fetal growth retarding agent in animals (Ref. 7).

However, the drug has not been shown to produce a significant incidence of gross morphologic (teratogenic) defects in animal fetuses (Refs. 4 through 8). Similarly, the clinical evidence that podophyllin has teratogenic properties in man is equivocal. According to one clinical report (Ref. 9), a patient ingested herbal "slimming" tablets during the first trimester of pregnancy and eventually delivered a baby having multiple deformities involving the thumb, radius, and ear. The "slimming" tablet contained in addition to podophyllin (30 mg), three other plant extractives whose teratogenic potential is unknown. In another case (Ref. 10), severe peripheral neuropathy and intrauterine death occurred in a young woman in the 32d week of pregnancy following the application of podophyllin (1.8 gm) to the vulva for the treatment of warts.

Podophyllin is reported to possess a high systemic toxicity (Ref. 11). For example, in one study, the oral LD_{50} of podophyllin in mice was found to be 68 mg/kg, and the subcutaneous LD_{50} of podophyllin in rats was determined to be 24 mg/kg (Ref. 12). Symptoms of podophyllin-induced toxicity in animals include diarrhea, acute enteritis, rapid and labored breathing, hindlimb paralysis, and convulsions (Ref. 12). Because of the well documented toxic effects of podophyllin in animals and because podophyllin has the potential to cause significant embryotoxicity and systemic toxicity in man, the Panel concludes that this drug is unsafe for use as a laxative.

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Mouse Fetuses," Toxicology and Applied Pharmacology, 27:408–414, 1974.

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(4) *Other laxative resins (colocynth, elaterin, gamboge, ipomea, jalap)*. The Panel concludes that these plant products are unsafe for use as laxatives because of their potential toxicity.

These plant resins contain active ingredients (usually glycosides) which are released in the intestines. These plant principles are profoundly irritant to the intestines and produce profuse watery stools, which may be blood-tinged, and cause considerable colic (Refs. 1 through 3). Overdose may lead to severe prostration (Ref. 1). Because of the strong action of these irritant principles on the small intestine, their injudicious and long-continued use may lead to nutritional deficiencies, potassium depletion and dehydration (Refs. 1 through 3).

Although these resinous laxatives are not widely used today, the Panel is aware that some OTC laxative mixtures contain these products (Ref. 4). There are no adequate clinical studies to demonstrate that there are safe and effective laxative doses of these irritant resins.

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(2) Bonnycastle, D. D., "Cathartics and Laxatives," Drill's Pharmacology in Medicine, Edited by J. R. Dipalma, 4th Ed., McGraw-Hill, NY, p. 981, 1971.

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b. *Combinations with nonlaxative active ingredients.* Some OTC laxative products contain nonlaxative ingredients which do not contribute to laxation and in some instances, greatly increase risk of side effects. Other products contain nonlaxative active ingredients for which the Panel can find no scientific or medical rationale. The Panel concludes that the following nonlaxative active ingredients in combination with laxatives are irrational combinations and are not appropriate therapy for a significant portion of the population.

(1) *Combinations containing nonlaxative active ingredients that increase the likelihood of side effects and/or reduce the safety of the product.—Belladonna extract (belladonna alkaloids).* The Panel concludes that the use of belladonna extract or other anticholinergic agents in combination with oral laxatives constitutes irrational and unsafe therapy.

Belladonna extract, which is extracted from the leaves of *Atropa belladonna*, contains atropine and other anticholinergic alkaloids (Ref. 1). The usual quantity of belladonna extract contained in a unit dose of a product is 8 milligrams (equivalent to 0.1 milligram belladonna alkaloids). Belladonna extract is sometimes combined with laxative mixtures containing anthraquinone compounds, presumably to counteract potential griping action of these laxatives (Ref. 2). However, due to short duration of action (2 to 3 hours) of belladonna extract, the use of this anticholinergic plant drug for this purpose is irrational because its antispasmodic action on the intestine will have subsided before the laxative action (18 to 24 hours) of the anthraquinone is manifest (Refs. 2 and 3).

The addition of belladonna extract to laxative products increases the risk of toxic side effects. The Panel is aware of serious poisoning in children who accidentally ingested laxatives that contain belladonna alkaloids (Ref. 4).

REFERENCES

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(2) *Combinations of laxative and nonlaxative ingredients for which there is no medical or scientific rationale.*

(i) *Bismuth Subnitrate.* The Panel concludes that the use of bismuth subnitrate or other bismuth salts in combination with laxatives constitutes irrational therapy.

There is no scientific evidence to indicate that bismuth salts contribute to the efficacy or safety of laxative preparations. Bismuth is considered in some textbooks as an astringent and adsorbent, and is discussed by the Panel under antidiarrheals.

REFERENCES

(1) Swinyard, E. A., "Demulcents, Emollients, Protectives and Adsorbents, Antiperspirants and Deodorants, Adsorbable Hemostatics, Astringents, Irritants, Sclerosing Agents, Caustics, Keratolytics, Antiseborrheics, Melanizing and Demelanizing Agents, Mucolytics, and Certain Enzymes," The Pharmacological Basis of Therapeutics, 4th Ed., Edited by Goodman, L. S. and A. Gilman, MacMillan, New York, p. 990, 1970.

(ii) *Capsicum.* The Panel concludes that the addition of capsicum to laxative products is irrational therapy.

Capsicum is said to be a colonic irritant that produces a sensation of heat (Ref. 1); the agent does not produce cutaneous hyperemia. The use of capsicum as a carminative is based entirely on subjective evidence. The Panel is unaware of any scientific data or even sound theoretical reasoning to indicate that capsicum should be considered an active laxative agent.

REFERENCES

(1) The United States Dispensatory and Physicians' Pharmacology, 26th Ed., Edited by Osol, A., R. Pratt and M. D. Altschule, J. B. Lippincott Co., Philadelphia, p. 237, 1967.

(iii) *Caroid-papain.* The Panel concludes that the addition of caroid-papain or other proteolytic enzymes to laxative agents is irrational therapy.

Caroid-papain, derived from *Carica papaya*, is a mixture of proteolytic enzymes containing papain, bromelin, and ficin, which possess the property of digesting collagen (Refs. 1 and 2). These agents are thought to be innocuous to viable tissues and hence may be considered safe. The Panel is unaware of any scientific data or even sound theoretical reasoning to indicate that caroid-papain should be considered an active laxative agent.

REFERENCES

(1) Miller, J. M. and B. Goldman, "Preliminary and Short Report: The Digestion of Collagen," Journal of Investigative Dermatology, 30:217–219, 1958.

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(iv) *Ginger.* The Panel concludes that, though this material has found wide use and ready acceptance as an aromatic carminative and flavoring agent, no studies have indicated its effect as a laxative agent.

Ginger, the dried rhizone of *Zingiber officinale*, contains a volatile oil, a nonvolatile mixture of substances possessing pungent principles collectively termed gingerol, and an acrid resin (Refs. 1 and 2). It has been advocated for use in man as a carminative for flatulence (Refs. 2 and 3). In addition, it has been used in veterinary medicine as a carminative for atonic indigestion as well as spasmodic colic, and has been added to veterinary purgatives to prevent griping (Ref. 1). There is no evidence of which the Panel has been made aware that ginger possesses laxative properties or is active in man.

REFERENCES

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(2) Grieve, M., "A Modern Herbal," Hafner Press, Vol. 1, pp. 353–354, 1959.

(3) Glatzel, H., "Treatment of Dyspeptic Disorders with Spice Extracts," Hippokrates, 40:916, 1959 (Ger.).

(v) *Ipecac powder.* The Panel concludes that the use of ipecac in any amounts in combination with laxatives constitutes irrational therapy.

Powdered ipecac, which is obtained from the plant *Cephaelis ipecacuanha* contains a number of emetic alkaloids, including emetine and cephaeline (Ref. 1). Powdered ipecac is now added to some laxative mixtures that contain belladonna extract, on the assumption that the emetic will induce vomiting in the event of an overdose of the laxative mixture. The Panel concludes this is irrational therapy. Furthermore, the quantity of powdered ipecac used in OTC laxative products would not provide an emetic dose, even if 100 dosage units of the laxative product were ingested (Ref. 1).

REFERENCES

(1) The Pharmacopeia of the United States of America, 18th Rev., The United States Pharmacopeial Convention, Inc., Mack Printing Co., Easton, PA, p. 345, 1970.

(vi) *Thiamin, multivitamin preparations, and minerals.* The Panel concludes that the addition of various vitamins and minerals, including trace elements, to laxative products is irrational concurrent therapy and places such combinations in Category II.

An extensive review of the available literature failed to reveal any evidence that the addition of various vitamins, minerals, and trace elements to laxative preparations contribute to a laxative effect. The Panel does not recognize any significant target population that requires laxatives and vitamins concurrently. The Panel does not recognize the use of vitamins for purposes of laxation or the inclusion of vitamins in laxative products as adjunctives to the laxative action of the product. The Panel further concurs that constipation and vitamin needs ordinarily bear no relationship to each other. The rationale of addition of vitamins and minerals intended as nutritional supplements becomes questionable due to the laxative action abrogating the bioavailability of the supplement.

Data in one study in which a combination laxative product containing thiamin was compared with control (no laxatives) are unconvincing in terms of supporting the effectiveness of the combination product, and no evaluation of thiamin alone was undertaken (Ref. 1).

The Panel concludes that the concurrent use of vitamins in OTC laxative products is irrational therapy.

REFERENCES

(1) Long, A. E., "Postpartum Bowel Function," Obstetrics-Gynecology, 11:415–420, 1958.

c. *Labeling claims for specific ingredients.* The Panel concludes the following labeling claims are untrue and represent misbranding.

(1) *Dehydrocholic acid.* There is no evidence in support of the claim that dehydrocholic acid relieve's 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. (See discussion of dehydrocholic acid which appears above in stimulant laxative statements.)

(2) *Bile salts (acids and ox bile).* Claims that these agents will "relieve headaches and biliousness" due to constipation are misleading and undocumented. Bile acids and ox bile are placed in Category II for these claims. (See discussion of bile salts (acid) and ox bile which appears below in claimed laxative active ingredients in Category III.)

(3) *Magnesium hydroxide.* Magnesium hydroxide is occasionally promoted as both an antacid and a laxative. This dual claim is permissible owing to the activity of this compound, but the public should be aware that when used regularly as an antacid, magnesium hydroxide causes significant laxation. However, the Panel is not aware of any scientific data that establishes a relationship between acid secretion and constipation. Therefore, claims of superior laxation on the basis of the antacid properties are not acceptable. (See discussion of Magnesium Compounds which appears above in saline laxative statement.)

3. *Conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available to permit final classification of the claimed active ingredients and labeling listed below:

BULK FORMING LAXATIVES

Agar
Bran tablets
Carrageenan, native (Chondrus crispus)
Guar gum

STIMULANT LAXATIVES

Aloin
Bile salts (acid) and ox bile
d-Calcium pantothenate
Frangula
Prune concentrate dehydrate and prune powder
Rhubarb, Chinese
Sodium oleate

SALINE AND HYPEROSMOTIC LAXATIVES

Tartaric acid and tartrate preparations

STOOL SOFTENERS

Poloxalkal (polykol)

LABELING CLAIM FOR SPECIFIC INGREDIENT

Malt soup extract

The Panel believes it reasonable to allow 2 years for the development and review of evidence to permit final classification of these ingredients and the claims made for them. Marketing need not cease during this time if adequate testing is undertaken. If data regarding adequate effectiveness and safety are not obtained within 2 years, however, the ingredients listed in this category should no longer be marketed as active ingredients in over-the-counter products but may be permitted as inactive ingredients if the amount employed is necessary for the pharmaceutical formulation of the product. Some ingredients may be present in products in quantities which are pharmacologically inactive by virtue of being subclinical doses. In these cases the ingredients may be included for pharmaceutical necessity such as improving the stability or palatability of the product. However, it is the opinion of the Panel that if an ingredient was originally claimed by the sponsor to be active, it cannot then also be claimed inactive and included for formulation purposes unless the following are documented: the absolute necessity for inclusion in the pharmaceutical formulation, the safety of the quantity in the finished product, and the inactivity of the quantity in the finished product.

The Panel has given careful consideration to the types of studies and types of data to be required for removing a claimed active laxative ingredient from Category III and placing it in Category I. See data required below for laxative ingredient evaluation. In general, to demonstrate effectiveness, the design of the study should have a sound scientific basis (e.g., a randomized, double-blind, cross-over study comparing claimed active ingredients to placebo), the clinical trial should be carefully controlled (e.g., consideration given to selection of subjects representative of general population as well as diet, activity, travel, etc, of subjects being studied), and quantitative measurement of various parameters appropriate for the claimed effects of the ingredient (e.g., stool frequency, stool weight, stool water content, stool consistency, etc.). To demonstrate safety, appropriate toxicological studies in experimental animals (preferably primate) and man are required as outlined elsewhere.

a. *Claimed active ingredients classified as bulk-forming laxatives*—(1) *Agar.* The Panel concludes agar is safe in amounts usually taken orally in laxative products but is unable to document effectiveness when used alone in any dose.

Agar is the dried, hydrophilic, colloidal substance extracted from *Gelidium cartilagineum* and related red algae (Refs. 1 through 3 and 5). It is rich in indigestible hemicellulose, is nonabsorbable, and apparently does not cause irritation to the gastrointestinal mucosa. Agar will absorb at least five times its weight of water at 25° C. On absorbing water, it forms a gel and theoretically increases the bulk of the stool. The claimed mechanism of laxative action is considered to be the mechanical stimulus of distention (Ref. 4). It is a common ingredient in a variety of proprietary laxatives and is probably used as an emulsifying and stabilizing agent. When used in these preparations, the amount of agar is too small to contribute to the laxative effect of the preparation.

DATA PERTINENT FOR SAFETY AND EFFECTIVENESS

Well-designed and carefully controlled clinical trials are needed to demonstrate that agar is a safe and effective bulk-forming laxative. It would be helpful to compare agar to a known effective bulk former and determine the oral dose required to produce significant changes in stool weight, volume, consistency, and water content. Regarding safety, fluid intake required to prevent obstruction of or impaction in the digestive tract should

be determined. (See paragraph I below for data pertinent for laxative ingredient evaluation.)

REFERENCES

(1) Fingl, E., "Cathartics and Laxatives," The Pharmacological Basis of Therapeutics, 4th Ed., Edited by Goodman, L. S. and A. Gilman, MacMillan, New York, p. 1026, 1970.

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(3) Swinyard, E. A. and S. C. Harvey, "Pharmaceutical Necessities," Remington's Pharmaceutical Sciences, 14th Ed., Mack Publishing Co., Easton, Pa., p. 1344, 1970.

(4) AMA Drug Evaluations, 2d Ed., American Medical Association, Chicago, p. 800, 1973.

(5) The Pharmacopeia of the United States of America, 17th Rev., The United States Pharmacopeial Convention, Washington, D.C., pp. 17–18, 1965.

(2) *Bran tablets.* The Panel concludes that there is insufficient evidence that bran in the form of tablets is an effective laxative.

The Panel has concluded that dietary bran is safe and effective as a laxative when taken in sufficient quantities (approximately 6 to 14 grams per day). Bran tablets weighing 1 gram contain 0.5 gram of granulated bran. There is insufficient evidence that compressed tablets containing processed bran produce the same laxative effect as dietary bran contained in cereals and whole wheat bread. (See discussion above for bran (dietary) in laxative active ingredients in Category I.)

DATA PERTINENT FOR EFFECTIVENESS

Uncontrolled studies of the effectiveness and safety of bran tablets have been reviewed (Ref. 1). While they demonstrate safety, the Panel concludes that evidence of effectiveness remains equivocal. A carefully controlled, double-blind clinical trial is needed to determine if bran tablets are more effective than placebo in increasing the frequency of bowel movement and/or softening their consistency. Objective methods for quantitating frequency and consistency should be employed in such a study. (See paragraph I below for data pertinent for laxative ingredient evaluation.)

REFERENCE

(1) OTC Volumes 090100 through 090103.[1]

(3) *Carrageenan, native (Chondrus crispus, Irish moss).* The Panel concludes that although native carrageenan is safe in amounts not exceeding 3.5 grams per day, definitive evidence is lacking with respect to laxative action in man.

Carrageenan is a macromolecular hydrocolloid obtained from red algae, generally from *Chondrus crispus*. Material with similar composition and physical properties has been isolated from other genera of red seaweed such as *Eucheuma* and *Gigartina*. The carrageenan from each source differs slightly as to its property. These properties are related to the amount of the two major components (designated kappa and lambda), that are separable on the basis of selective solubility in potassium chloride solutions and proportions of galactose, anhydrogalactose and sulphated galactose units.

Native carrageenan is widely used in the food industry because of its ability to combine with protein and is used as a stabilizer and as a demulcent and for its gelling properties. Food and Agriculture Organization/World Health Organization recommendations allow up to 50 mg/kg as the acceptable daily intake (ADI) in man (Ref. 1).

DATA PERTINENT FOR SAFETY AND EFFECTIVENESS

Well designed and carefully controlled clinical trials are needed to demonstrate that carrageenan is a safe and effective bulk forming laxative. It would be helpful to compare carrageenan to a known effective bulk former and determine the oral dose required to produce significant changes in stool weight, volume, consistency, and water content. Regarding safety, fluid intake required to prevent obstruction of or impaction in the digestive tract should be determined. (See paragraph I below for data pertinent for laxative ingredient evaluation.)

REFERENCES

(1) Anon: "Articles of general interest: Carrageenan," Food and Cosmetic Toxicology, 9:561–580, 1971.

(2) Abraham, R., L. Golberg, and F. Coulston, "Uptake and Storage of Degraded Carrageenan in Lysosomes of Reticuloendothelial Cells in the Rhesus Monkey, Macaca mulatta," Experimental and Molecular Pathology, 17:77–93, 1972.

(4) *Guar gum.* The Panel concludes that guar gum is safe in amounts usually taken orally but is unable to document effectiveness of this agent when used alone at any dose.

Guar gum, a polysaccharide containing polymers of d-galactose and d-mannose (i.e., a galactomannan) is derived from the endosperm seed layer of the guar plant. Galactomannans have a high affinity for water. They presumably swell when hydrated in vivo as they clearly do in vitro (Ref. 1). The hydrophilic capacity is related to the particle size in which the plant seeds are ground and to the pH of the medium to which it is exposed. Optimum hydration occurs in solutions with a pH range of 7.5 to 9.0. According to information submitted by companies which market the preparations, the laxative formulations contain particles of a size designed for minimum hydration duration the first few hours after ingestion during which time the material moves through the esophagus, stomach and upper small bowel. It is also claimed that more rapid dispersal and maximal bulk effect occurs after the agent has reached the lower intestinal tract (Ref. 2). This property would theoretically reduce the hazard of obstruction in the esophagus, stomach, and upper intestine that has rarely been associated with other bulk laxatives. There is no documentation that this is of more than theoretical advantage.

The conclusion that guar gum is safe is based largely on its widespread use in food products such as cheese, salad dressings, ice cream, sherbets, and frozen desserts and its recognition as safe as a food ingredient (Ref. 3). Partially controlled studies in which guar gum was given in combination with senna concentrate failed to demonstrate side effects that could not be attributable to the senna (Ref. 4).

The hydrophilic properties of guar gum would support the belief that it should act as other bulk forming laxatives if given in sufficient doses. The marketed preparations contain 1 gram of guar gum and there is no proof that such a quantity alters stool character or frequency in man or animals.

DATA PERTINENT FOR SAFETY AND EFFECTIVENESS

Well-designed and carefully controlled clinical trials are needed to demonstrate that Guar Gum is a safe and effective bulk-forming laxative. It would be helpful to compare Guar Gum to a known effective bulk former and determine the oral dose required to produce significant changes in stool weight, volume, consistency, and water content. Regarding safety, fluid intake required to prevent obstruction or impaction in the digestive tract should be determined. (See paragraph I below for data pertinent for laxative ingredient evaluation.)

REFERENCES

(1) Chudzikowski, R. J., "Guar Gum and its Applications," Journal of the Society of Cosmetic Chemists, 22: 43–60, 1971.

(2) OTC Volume 090084.[1]

(3) Krantz, J. C.: "Testimony Presented at the Hearings Before the Administrator, Federal Security Agency, in the matter of the standards of identity for cheese, 1947."

(4) Barcomb, A. E., "Management of Functional Constipation," Western Medicine, 7: 323–325, 1966.

b. *Claimed active ingredients classified as stimulant laxatives.*—(1) *Aloin.* The Panel concludes that there are insufficient clinical data to establish an effective and safe laxative dose for aloin.

Aloin is a microcrystalline powder consisting of a mixture of active principles, chiefly barbaloin and isobarbaloin, obtained from aloe. The drug may vary in chemical composition according to the variety of aloe from which it is obtained (Ref. 1). Although a method for the bioassay of aloin in rats has been reported (Ref. 2), there is no published information on methods presently used by manufacturers to standardize aloin for laxative action.

Aloin is usually used in combination with other laxative ingredients such as phenolphthalein or cascara sagrada (Ref. 3), and thus, there is a paucity of clinical data concerning its effectiveness as a laxative when used alone.

DATA PERTINENT FOR SAFETY AND EFFECTIVENESS

In addition to the general requirements outlined elsewhere, appropriate dose-response studies in man are needed that will clearly establish an effective and safe laxative dose for this plant extract. It would be helpful to compare aloin with another known effective stimulant laxa-

tive to determine if the incidence and severity of undesirable side effects such as cramping and griping is greater with aloin. (See paragraph I below for data pertinent for laxative ingredient evaluation.)

REFERENCES

(1) The National Formulary, 11th Ed., Mack Printing Co., Easton, Pa., p. 17, 1960.

(2) Lister, R. E. and R. R. A. Pride, "The Characterisation of Crystalline and Amorphous Aloin," Journal of Pharmacy and Pharmacology, 11:278T–282T, 1959.

(3) Darlington, R. C., "Laxatives," Handbook of Non-Prescription Drugs, Edited by G. B. Griffenhagen and L. L. Hawkins, American Pharmaceutical Association, Washington, D.C., p. 54, 1971.

(4) Fingi, E., "Cathartics and Laxatives." The Pharmacological Basis of Therapeutics, 4th Ed., Edited by Goodman, L. S. and A. Gilman, MacMillan, N.Y., p. 1028, 1970.

(2) *Bile salts (acids) and ox bile.* The Panel concludes that there is insufficient evidence that natural bile acids taken orally as a laxative are effective and safe.

Bile acids induce diarrhea if they escape reabsorption at the terminal ileum and reach the colon in sufficient concentrations. Deoxycholic acid inhibits the absorption of water and sodium by the colon of the rat, and colonic perfusion with the dihydroxy bile acids, deoxycholic and chenodeoxycholic acid in man induces secretion of sodium and water (Ref. 1). Recent studies with the feeding of cholic acid and chenodeoxycholic acid in attempts to dissolve cholesterol gallstones in man disclosed that diarrhea was common when either agent was ingested in amounts exceeding 1.5 grams daily but did not occur at doses below 0.5 gram (Refs. 2 through 4). These studies indicate that bile acids in sufficient quantities can cause diarrhea, which is not necessarily equivalent to the conclusion that smaller or equal doses are effective in relieving constipation.

One limited controlled study demonstrated that cholic acid, 0.25 gram three times daily, but not placebo or bisacodyl, significantly increased fecal frequency in five subjects with chronic constipation (Ref. 5).

The composition of ox bile resembles that of human bile. The only preparation submitted for review contains only 51 milligrams of ox bile per dose. This quantity of ox bile is far below the quantity of bile acids known to produce diarrhea following the ingestion of cholic acid or chenodeoxycholic acid (more than 0.5 gram daily).

It is anticipated that the question of safety of chronic administration of chenodeoxycholic acid at two dose levels will be settled by the National Cooperative Gallstone Study. This study, supported by the National Institutes of Health, will provide data, collected over a 3-year period from 900 patients in 10 Medical Centers, to determine the safety and effectiveness of chenodeoxycholic acid in dissolving gallstones in man. Additional studies are needed to document effectiveness of bile acids in constipated subjects.

DATA PERTINENT FOR SAFETY AND EFFECTIVENESS

In the case of bile acids, carefully controlled, double-blind studies are especially needed to show that bile acid administration significantly increases the frequency of bowel movements and stool water content. Since ox bile contains significant quantities of lithocholic acid, doses which might be shown to be effective must also be shown to be safe. (See data pertinent below for laxative ingredient evaluation.)

LABELING

Claims that these agents will relieve headaches and "biliousness" due to constipation are misleading and undocumented. Bile acids and ox bile are placed in Category II for these claims.

REFERENCES

(1) Mekhjian, H. S., S. F. Phillips and A. F. Hofmann, Colonic Secretion of Water and Electrolytes Induced by Bile Acids: Perfusion Studies in Man," Journal of Clinical Investigation, 50:1569–1577, 1971.

(2) Danzinger, R. G., A. F. Hofmann, L. J. Schoenfield and J. L. Thistle, "Dissolution of Cholesterol Gallstones by Chenodeoxycholic Acid," New England Journal of Medicine, 286:1–8, 1972.

(3) Thistle, J. L., Personal Communication, 1974, included in OTC Volume 090134.[1]

(4) Schoenfield, L. J., Personal Communication, 1974, included in OTC Volume 090134.[1]

(5) Hepner, G. W. and A. F. Hofmann, "Cholic Acid Therapy for Constipation. A controlled Study," Mayo Clinic Proceedings, 48:356–358, 1973.

(6) Seed, J. C. and R. Harris, "Some Factors in the Design of Aperient Studies." Annals of the New York Academy of Sciences, 58:426–434, 1954.

(7) Shaftel, H. E. "Modulated Laxative Action for the Geriatric Patient," Journal of the American Geriatric Society, 1:549–556, 1953.

(8) Hofmann, A. F.; Personal Communication, 1974.

(9) Palmer, R. H., "Bile Acids, Liver Injury, and Liver Disease," Archives of Internal Medicine 130:606–617, 1972.

(10) Heywood, R., et al., "Pathological Changes in Fetal Rhesus Monkey Induced by Oral Chenodeoxycholic Acid," Lancet, 2:1021, 1973.

(11) "Six Month Oral Toxicity Study in Rhesus Monkeys with Chenodeoxycholic Acid." Performed at Huntington Research Center for Weddel Pharmaceuticals Limited, England, FDA Files.

(12) "Acute and Subacute Oral Toxicity Studies in Animals with Chenodeoxycholic Acid." Conducted at International Research and Development Corp. for the National Cooperative Gallstone Study. FDA Files.

(3) *d-Calcium pantothenate.* The Panel concludes that d-calcium pantothenate is safe in amounts usually taken orally, but the evidence currently available with respect to laxative action is contradictory and additional studies are necessary to evaluate its laxative potential.

While d-calcium pantothenate serves a number of important metabolic functions, the full import of this substance on functions of the gastrointestinal tract has not been fully elucidated. The addition of pantothenic acid to diets fed to pantothenic acid deficient dogs corrected the 50 percent decrease observed in gastro-intestinal motility and the 40 to 60 percent decreases demonstrated in carbohydrate and protein digestion and absorption (Ref. 1). There is no evidence currently available supporting the concept that these functions would be enhanced in subjects with normal pantothenic acid levels. The therapeutic use of pantothenic acid has been reported as being of no value while others observed that 50 milligrams of pantothenate i.m. 1 to 3 times daily improved post-operative ileus (Ref. 2). There are no carefully controlled clinical trials that demonstrate the effectiveness of d-calcium pantothenate as a laxative (Refs. 3 through 5).

DATA PERTINENT FOR SAFETY AND EFFECTIVENESS

Data are needed first, to demonstrate that d-calcium pantothenate does indeed produce laxation as determined by quantitative measurements outlined elsewhere in this notice. If evidence of laxation is demonstrated, data are needed to determine a dose-response relationship. Additionally, the effectiveness of d-calcium pantothenate should be compared to a known effective stimulant laxative or stool softener. Data regarding safety are needed as outlined elsewhere in this document. (See paragraph I below for data pertinent for laxative ingredient evaluation.)

REFERENCES

(1) Bly, C. G., F. W. Heggeness and E. S. Nasset, "The Effects of Pantothenic Acid and Inositol Added to Whole Wheat Bread on Evaluation Time, Digestion and Absorption in the Upper Gastrointestinal Tract of Dogs," Journal of Nutrition, 26: 161–173, 1943.

(2) Haycock, C. E., W. A. Davis and T. V. Morton, Jr., "The Effect of d-Pantothenyl Alcohol upon Postoperative Discomfort," American Journal of Surgery, 97: 75–78, 1959.

(3) Paljakka, H., "The Effect of Oral Panthothenic Acid on Intestinal Function of Aged Persons," Duodecim, 76:209–213, 1960.

(4) Casassa, P. M., "Pantothenol in the Therapy of Chronic Constipation in the Aged." Acta Gerontology, 3:15–22, 1953.

(5) Aubin, C., "Study and Dissociation of the Laxative Effect of the Combination of Calcium Pantothenate-Danthron." Doctoral Thesis, College of Medicine of Paris, Paris, France, 1970, included in OTC Volume 090134.[1]

(4) *Frangula.* The Panel concludes that there are insufficient clinical data to establish an effective and safe laxative dose for frangula.

Frangula is the dried bark of *Rhamnus frangula* and contains hydroxymethylanthraquinone derivative which resemble the anthraquinones found in aloe, cascara sagrada, and senna. The chief constituent in frangula is the glycoside frangulin which consists of an anthraquinone (emodin) in combination with a sugar (rhamnose) (Refs. 1 and 2). There is no published information on how frangula bark preparations are standardized for laxative action.

Frangula bark is used in OTC laxative products in combination with other

laxative ingredients, usually a bulk forming agent such as sterculia gum or psyllium (Ref. 3).

DATA PERTINENT FOR SAFETY AND EFFECTIVENESS

There are no clinical studies with frangula bark that provide sufficient evidence to establish an effective and safe laxative dose for this plant product. Appropriate dose-response studies in man are needed to determine a dosage range of frangula bark that produces effective laxation with minimal side effects.

In addition, evidence should be provided that the laxative potency of frangula bark can be standardized so that a reproducible degree of laxation will be produced by different batches of frangula bark.

Data regarding safety are needed as outlined elsewhere in this report. (See paragraph I below for data pertinent for laxative ingredient evaluation).

REFERENCES

(1) Gunton, J. A. and G. D. Beal, "A Reinvestigation of the Proximate Composition of *Rhamnus frangula*," Journal of the American Pharmaceutical Association, 11:669–682, 1922.

(2) Longo, R., "Separation and Determination of the Hydroxyanthraquinones of Frangula," Bollettino Chimico Farmaceutica, 104:369–372, 1965.

(3) Darlington, R. C., "Laxatives," Handbook of Non-Prescription Drugs, Edited by Griffenhagen, G. B., and L. L. Hawkins, American Pharmaceutical Association, Washington, DC, p. 54, 1971.

(5) *Prune concentrate dehydrate and prune powder.* The Panel does not challenge the general belief that prunes exert a laxative effect but concludes there is insufficient evidence to document effectiveness of prune concentrate and prune powder when used alone at any dose.

The chemical nature and mechanism of action of laxative ingredients in prunes, including prune concentrate dehydrate and prune powder, are unknown. An initial claim that prune juice contains diphenylisatin (Ref. 1), which is chemically related to oxyphenisatin, has not been confirmed by other investigations (Ref. 2).

DATA PERTINENT FOR SAFETY AND EFFECTIVENESS

There are no clinical studies with prune concentrate dehydrate and prune powder that provide sufficient evidence to establish an effective laxative dose for this plant product. Appropriate dose-response studies in man are needed to determine a dosage range of prune concentrate dehydrate and prune powder that produces effective laxation.

In addition, evidence should be provided that the laxative potency of prune concentrate dehydrate and prune powder can be standardized so that a reproducible degree of laxation will be achieved by differing batches of prune concentrate dehydrate and prune powder. (See paragraph I below for data pertinent for laxative ingredient evaluation.)

REFERENCES

(1) Baum, H. M., R. G. Sanders and G. J. Straub, "The Occurrence of Diphenylisatin in California Prunes," Journal of American Pharmaceutical Association (Scientific Edition), 40:348–349, 1951.

(2) Hubacher, M. H. and S. Doernberg, "Laxatives II. Relationship Between Structure and Potency," Journal of Pharmaceutical Sciences, 53:1067–1072, 1964.

(3) Stern, F. H., "Constipation-An Omnipresent Symptom: Effect of A Preparation Containing Prune Concentrate and Cascarin," Journal of the American Geriatric Society, 14:1153–1155, 1966.

(6) *Rhubarb, Chinese.* The Panel recognizes that Chinese rhubarb (*Rheum officinale*) contains derivatives which are related to active laxative agents but concludes that there is insufficient reliable scientific evidence to permit final classification of this plant product.

Chinese Rhubarb contains several hydroxymethylanthraquinones derivatives which are chemically similar to those found in aloe, cascara sagrada, and senna. In contrast to these anthraquinone type laxatives, however, rhubarb also contains astringent ingredients such as rheotannic acid and gallic acid. The Panel found no reliable scientific data that evaluated the influence of these astringents on the anthraquinone ingredients (Refs. 1 and 2). Moreover, there are no dose response studies in man that establish an effective and safe dose for Chinese Rhubarb. In the case of Chinese Rhubarb, the Panel's concern with safety relates only to the known side effects common with all anthraquinones; American Rhubarb, which is used extensively in foods, is devoid of anthraquinone derivatives. (Ref. 1).

DATA PERTINENT FOR SAFETY AND EFFECTIVENESS

There are no clinical studies with Chinese Rhubarb that provide sufficient evidence to establish an effective and safe laxative dose for this plant product. Appropriate dose-response studies in man are needed to determine a dosage range of Chinese rhubarb that produces effective laxation with minimal side effects.

In addition, evidence should be provided that the laxative potency of Chinese Rhubarb can be standardized so that a reproducible degree of laxation will be achieved by differing batches.

Data regarding safety are needed as outlined elsewhere in this report. (See paragraph I below for data pertinent for laxative ingredient evaluation.)

REFERENCES

(1) AMA Drug Evaluations, 1st Ed. American Medical Association, Chicago, Illinois, p. 597, 1971.

(2) Sollman, T., A Manual of Pharmacology, 8th Ed., W. B. Saunders, Philadelphia, p. 211, 1957.

(7) *Sodium oleate.* The Panel concludes that sodium oleate is safe in the amounts usually taken orally in laxative preparations. However, the Panel was unable to find any evidence supporting the claim that sodium oleate produces laxation. Sodium oleate, a fatty acid salt, has been shown to influence the gastrointestinal tract of animals. (Refs. 1 through 3).

In one experimental study using an in vitro preparation of adult feline colon and electromyographic techniques, sodium oleate and sodium ricinoleate were compared. It was found that sodium ricinoleate produced electromyographic changes similar to those observed in spontaneous and castor oil-induced diarrhea in cats. Sodium oleate had no such effect (Ref. 3).

DATA PERTINENT FOR EFFECTIVENESS

Data are needed first, to demonstrate that sodium oleate produces laxation as determined by quantitative measurements outlined elsewhere in this report. If evidence of laxation is demonstrated, data are needed to determine a dose-response relationship. Additionally, sodium oleate should be compared with a stimulant laxative of known effectiveness. (See paragraph I below for data pertinent for laxative ingredient evaluation.)

REFERENCES

(1) Rochman, N. D., P. E. Lear, L. Picker, C. Mandell, "Inhibition of Gastric Secretion in the Rat with Sodium Oleate," Journal of Surgical Research, 9:213–215, 1969.

(2) Kowalski, K., "Effect of Prolonged Intravenous Infusion of Oleate Sodium on Spontaneous and Histamine Stimulated Gastric Secretion in Rats," Archives Internationales de Physiologie et de Biochimie, 78: 971–977, 1970.

(3) Christensen, J. and B. W. Freeman, "Circular Muscle Electromyogram in the Cat Colon: Local Effect of Sodium Ricinoleate," Gastroenterology, 63:1011–1015, 1972.

(c) *Claimed active ingredients classified as saline and hyperosmotic laxatives*—(1) *Tartaric acid and tartrate preparations.* The Panel concludes that there are insufficient data to establish a safe and effective dose for the tartrates.

The laxative action of the tartrates is purportedly due to the slow absorption of sodium tartrate and resulting osmotic retention of water in the intestine, but recent experiments with the saline laxatives would indicate potentially more complex mechanisms of action. The Panel was concerned that information on the metabolic fate of tartrates, as well as data on the mechanism of action, is lacking. Although 20 percent of an oral dose may appear in urine, the remaining 80 percent has not been demonstrated in the feces, and no definitive work on the fate of tartrate in the body has been done (Refs. 1, 4, and 5). Evidence exists concerning a dose-response relationship of tartrates of nephrotoxicity. Up to 1.2 percent of tartrate in the diet of rats for 2 years apparently was not harmful, but 1.5 percent was toxic. Toxicity in rabbits occurred at 250 mg/kg, and in dogs ingesting 0.99 gm/kg per day (Refs. 1 and 2). Tartrates are ubiquitous in the human diet which would suggest safety. However, a death has been reported following the oral ingestion of 30 grams of tartaric acid (Ref. 6). The Food and Agriculture Organi-

zation/World Health Organization Expert Committee on Food Additives in its eighth report recommended a conditional limit of 6–20 mg/kg/day of tartaric acid (Ref. 3).

DATA PERTINENT FOR SAFETY AND EFFECTIVENESS

The Panel knows of no studies that use modern tracer methods to determine the absorption, metabolism, and excretion of these compounds, or any quantitative description of their systemic effects and implications for renal functions. Such data are required to determine the safety of tartrates. The Panel concludes that the usual daily dose of tartrates (e.g., 5–10 grams) in laxative preparations is probably safe, but in order to justify an additional exposure for the public to tartrates in the form of a laxative, definitive, well designed studies of effectiveness and establishment of safety are necessary. (See paragraph I below for data pertinent for laxative ingredient evaluation).

REFERENCES

(1) Underhill, F. P., C. S. Leonard, E. G. Gross and T. C. Jaleski, "Studies on the Metabolism of Tartrates: II. The Behavior of Tartrate in the Organism of the Rabbit, Dog, Rat and Guinea Pig," Journal of Pharmacology and Experimental Therapeutics, 43:359–380, 1931.

(2) Krop, S. and H. Gold, "On the Toxicity of Hydroxyacetic Acid After Prolonged Administration: Comparison With its Sodium Salt and Citric and Tartaric Acids," Journal of the American Pharmaceutical Association (Scientific Edition), 34:86–89, 1945.

(3) Food and Agriculture Organization/World Health Organization Expert Committee of Food Additives, Eighth Report, Specifications for the Identity and Purity of Food Additives and their Toxicological Evaluation: Food Colours and Some Antimicrobials and Antioxidants, World Health Organization Technical Report Series, Number 309, 1965.

(4) Bauer, C. W. and R. W. Pearson, "A Comparative Study of the Metabolism in the Human Body of Some Isomers of Tartaric Acid," Journal of the American Pharmaceutical Association (Scientific Edition), 46: 575–576, 1957.

(5) Finkle, P., "The Fate of Tartaric Acid in the Human Body," Journal of Biological Chemistry, 100:349–355, 1933.

(6) Robertson, B. and L. Lonnel, "Human Tartrate Nephropathy: Report of a Fatal Case," Acta Pathologica et Microbiologica Scandinavica, 74:305–310, 1968.

d. *Claimed active ingredients classified as stool softeners or lubricants*—(1) *Poloxalkol (Polykol)*. The Panel concludes that while evidence is available suggesting that poloxalkol is safe, the evidence attesting to laxative action in man is sparse and equivocal.

Poloxalkol, an oxyalkene polymer, is a relatively tasteless nonionic surface active agent. The chemical is said to produce effects similar to dioctyl sodium sulfosuccinate, but the two drugs have not been subjected to a careful clinical comparison. Animal studies suggest that poloxalkol possesses low toxicity (Ref. 1); however, it may increase the absorption of mineral oil and the possibility of untoward effects. While the wetting properties of poloxalkol make it potentially useful as a stool softener (Ref. 2), the action is usually slow and may require several days before an effect becomes apparent.

The drug has been clinically evaluated in children (Refs. 3 and 4), young adults with serious neurologic disorders enforcing nonambulation (Ref. 5), and elderly subjects complaining of constipation. The administration of the medication showed a 3-to-5 day latency and apparent effect, and was well tolerated with few side effects (Ref. 5 and 7). Several clinical evaluations in children and older patients failed to include the use of placebos, were poorly controlled, relied almost exclusively on subjective appraisal, or involved the testing of combination products (Refs. 1 and 5 through 7).

DATA PERTINENT FOR EFFECTIVENESS

While the product appears to be safe based on animal studies and limited clinical evaluations, well-controlled, double-blind studies utilizing objective measurements in addition to subjective appraisals are necessary to establish unequivocally that this agent is a stool softener in man. Owing to the low toxicity and potential usefulness of this medication in man, the Panel urges that such definitive studies be undertaken. (See paragraph I below for data pertinent for laxative ingredient evaluation.)

REFERENCES

(1) Hardouin, J. P., and J. Aubrion, "Experimental and Clinical Study of a New Therapeutic Agent for Constipation: A Polyoxyethylene and Polyoxypropylene Polymer," La Presse Medicale, 67:1548–1550, 1959 (French).

(2) Cooke, W. T., "Laxatives and Purgatives," Practitioner, 206:77–80, 1971.

(3) Salvador-Diaz, O., "A Humectant Agent for Constipation in Children," La Semana Medica, 142:439–441, 1973 (Spanish).

(4) Rodriquez-Farina, R. N., "Poloxalcol. Humectant Agent in the Treatment of Constipation in Children," La Semana Medica, 143:788–790, 1973 (Spanish).

(5) Vincent (no initial), Girous (no initial), The Treatment of Chronic Constipation of Immobilization by a Polymer of Poly-Oxyethylene and Poly-Oxy-Propanediol 1–2, Lyon Med., 202:1079, 1959.

(6) Dugger, J. A., "Poloxalkol in the Treatment of Constipation in Children," Journal of the Michigan State Medical Society, 59: 1211, 1960.

(7) Christopher, L. J., "A Controlled Trial of Laxatives in Geriatric Patients," Practitioner, 202:821, 1969.

e. *Labeling claims for specific ingredient—Malt soup extract.* Although reduction in stool pH has also been cited as the reason for the clinical effectiveness of malt soup extract in reducing the symptoms of pruritus ani, the Panel concludes that there is insufficient evidence to support the claim that malt soup extract is effective when used alone in the treatment of pruritus ani.

G. PRODUCTS COMBINING MULTIPLE LAXATIVE INGREDIENTS

1. *General statements.* a. The Panel has followed the regulation (21 CFR 330.10(a)(4)(iv)) which states:

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 direction for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

b. The Panel concludes that, in general, the fewer the ingredients, the safer and more rational the therapy. The Panel believes that the interests of the consumer are best served by exposing the user of OTC drugs to the fewest ingredients possible at the lowest possible dosage regimen consistent with a satisfactory level of effectiveness.

c. The Panel concludes that OTC drugs should contain only such inactive ingredients as are necessary for pharmaceutical formulation.

2. *Requirement of significant contribution.* The Panel has determined that each claimed active ingredient in the combination must make a significant contribution to the claimed effect. In the absence of data showing the minimum dose necessary to achieve the intended laxative effect, the amount of ingredient present in laxative products must be at least equal to the currently accepted minimum dose level for such active ingredients as set forth elsewhere in this document.

The Panel found it impossible to develop a formula for establishing a level, below the minimum effective dose level for an ingredient as a single entity, at which it could reliably be stated that each laxative ingredient would make a contribution to a combination drug product. This may be possible with other agents such as antacid combination products where the contribution of each antacid can be determined by chemical titration. Laxatives are believed to have a minimum effective dose below which there are few measurable responses. The Panel recognizes that it is possible that some ingredients may be proved to contribute to the effectiveness of a combination product in amounts below the generally recognized minimum effective daily dose. However, because of the numerous variables involved (e.g., different laxative categories, differing modes of action, etc.), the Panel could not select one lower level of an active ingredient which may be assumed to be effective in a combination product.

Moreover, the Panel could not establish the percent of contribution that an active ingredient must make to the effectiveness of the product in order for that contribution to be considered "significant." The Panel concluded that where a combination product is permitted, as discussed below, it is sufficient to demonstrate in well-controlled clinical trials (Section I below—Data Required for Laxative Ingredient Evaluation) that each of the ingredients makes a statistically significant contribution to the claimed effect. As long as "statistical significance" is shown, the Panel concludes that the contribution toward laxa-

tion will also have been shown to be clinically "significant."

3. *Safety.* In its consideration of active ingredients, the Panel reviewed the safety and effectiveness of all the combinations submitted. All combinations that meet the criteria for Category I as set forth below, are considered safe.

The combination of dioctyl sodium sulfosuccinate and mineral oil is considered unsafe and is assigned to Category II because absorption of mineral oil may be enhanced by dioctyl sodium sulfosuccinate (Ref. 1).

4. *Effectiveness.* Combination products are regarded as effective if each active ingredient is present in the product within the dosage range set by the Panel for each Category I active laxative ingredient, as set forth elsewhere in this document. If the quantity of active ingredient is below the recognized effective dose range, the product containing the ingredient(s) is placed in Category III and testing is required for effectiveness.

The Panel considers it important that the minimum effective dose be established for each ingredient in a combination product. Data should be developed by appropriate well-controlled clinical studies to demonstrate the effectiveness as a laxative of a dosage level for any ingredient that is below the minimum set by the Panel for that ingredient when used alone.

Where the ingredients and the dosages are the same as those of the combination products this Panel has classified in Category I, further testing will not be required. Where the ingredients are different from those that have already been found safe, such testing will be required.

5. *Single active ingredients.* OTC drugs containing safe and effective single ingredients are preferred to those having multiple active ingredients because of the reduced risks of toxic effects, synergistic effects, allergic and/or idosyncratic reactions, and possible unrecognized and undesirable drug interaction(s).

It is an established medical principle to give only those medications, preferably as single entities, necessary for the safe and effective treatment of the patient. This principle applies equally to self-medication. To add needlessly to the patient's medication increases the risk of adverse reactions.

6. *Limitation of ingredients in combination products.* The Panel recognizes that combining 2 active ingredients may in some circumstances be desirable. For example, in an individual whose bowel movements are both painful and infrequent a product combining a stimulant laxative with a stool softener may be rational.

On the basis of the ingredients reviewed, the Panel could find no medical justification for combining 3 or more active laxative ingredients in a single product.

The Panel states its concern that even if situations are identified that suggest use of more than 2 active laxative ingredients, the benefit-to-risk ratio might be narrowed, and this is not in the best interest of the consumer of OTC laxatives. Therefore, products containing more than 2 active laxative ingredients are classified as Category II products and would require evaluation through the new drug procedures.

7. *Active ingredients not reviewed by the Panel.* Each claimed active ingredient must be an ingredient that has been reviewed by the Panel. If a product contains an active ingredient that has not been reviewed by the Panel and consequently not found in this document, such ingredient is automatically classified as a Category II ingredient, i.e., it is not generally recognized as safe and/or effective. Appropriate animal and human testing and prior approval by the Food and Drug Administration is required before a product containing such an ingredient may be marketed.

8. *Review of submitted combination products.* The Panel considered only those combination products submitted pursuant to the notice published in the FEDERAL REGISTER of February 8, 1973 (38 FR 3614) and included above in paragraph A. The Panel recognizes that other combination products may be in the market place but it has either no knowledge of such products, or insufficient data with respect to such products to make a reasonable judgment of safety and/or effectiveness.

Accordingly, the Panel recommends that any new combination, or any presently marketed combination not submitted to this Panel, which is not within the combinations recognized by the Panel as safe as set forth below, be evaluated through the new drug procedures, or be the subject of an appropriate petition to the Commissioner to review or amend the OTC laxative monograph.

9. *Combinations containing nonlaxative ingredients.* Products combining laxative ingredient(s) with other ingredients having nonlaxative pharmacologic effects are considered irrational, unless it can be shown that there is a significant target population requiring concurrent treatment of symptoms that require laxative(s) and nonlaxative(s) in combination. Among such combinations reviewed, the Panel could find neither a rational basis nor a significant target population that would warrant such concurrent therapy.

Nonlaxative ingredient(s) may be present as inactive ingredients in a laxative product as an aid to formulation or to palatability. However, the presence of such ingredient(s) must not be emphasized or identified as active ingredients in the labeling or in the advertisement of such product(s).

10. *Combinations allowable as Category I.* The Panel recognizes the particular combinations set forth below as safe and effective combinations and bases its opinion on the submitted material, and the Panel's expertise. Based on the combinations submitted and within the categories defined by the Panel the following are allowed, pursuant to the criteria developed by the Panel for determining Category I combinations, which combinations are set forth below:

ORAL DOSAGE FORMS

a. Dioctyl calcium sulfosuccinate and danthron.
b. Dioctyl sodium sulfosuccinate and casanthranol.
c. Dioctyl sodium sulfosuccinate and danthron.
d. Dioctyl sodium sulfosuccinate and phenolphthalein.
e. Cascara sagrada and aloe.
f. Cascara sagrada and magnesium hydroxide.
g. Cascara sagrada and phenolphthalein.
h. Malt soup extract and blond psyllium seed.
i. Malt soup extract and blond psyllium seed husks.
j. Mineral oil and casanthranol.
k. Mineral oil and cascara sagrada.
l. Mineral oil and cascara sagrada fluid extract.
m. Mineral oil, emulsified and magnesium hydroxide.
n. Mineral oil and phenolphthalein.
o. Mineral oil and psyllium seed.
p. Plantago ovata husk and methyl cellulose.
q. Phyllium and senna concentrate.
r. Senna concentrate and dioctyl sodium sulfosuccinate.
s. Sodium carboxymethylcellulose and dioctyl sodium sulfosuccinate.

RECTAL DOSAGE FORMS

a. Glycerin and dioctyl potassium sulfosuccinate.
b. Sorbitol and dioctyl potassium sulfosuccinate.

11. *Criteria for determining Category I combinations.* To qualify as a Category I combination, i.e., one that is generally recognized as safe and effective, each of the following conditions must be met:

a. The combination is limited to two Category I active laxative ingredients.

b. The specific combination of active laxative ingredients is found on the list set forth above for allowable combinations.

c. Each ingredient in the subject combination must be present within the dosage range for a Category I active laxative ingredient, as set forth elsewhere in this document.

d. The Panel developed the following concept as a reasonable means of expressing the sum of the percentage amounts of the effective dosage range (EDR) of each active ingredient which must not exceed 100, as calculated by the following formula:

$$\frac{L \text{ max } d - EDR \text{ (min)}}{EDR \text{ (max)} - EDR \text{ (min)}} \times 100 = \% \text{ EDR of each ingredient}$$

where: *L* max *d* is the labeled maximum daily dosage obtained from the labeling information for the product, *EDR* (min) is the minimum effective dosage range set by the Panel and *EDR* (max) is the maximum effective dosage range set by the Panel.

The purpose of the above formula is two-fold:

(1) to assist the manufacturer in determining which combination products require reformulation and/or testing;

(2) to encourage the use of ingredients in amounts at the minimum end of the dosage range rather than at the maximum effective range dosage.

Example: A liquid oral dosage form, laxative combination containing a stimulant laxative (326 mg. senna concentrate per teaspoonful), and a bulk former (1.0 grams psyllium per teaspoonful), having a label dosage of 1 or 2 teaspoonfuls 2 times a day.

I. Maximum daily dosage obtained from labeling for:

(1) senna concentrate—(326 mg x 2) x 2=1304 mg or 1.3 gm

(2) psyllium—(1.0 gm x 2) x 2=4.0 gm

II. Daily dose range for each Category I ingredient set by panel:

senna concentrate—1 to 4 gm daily

psyllium—2.5 to 30 gm daily

III. Calculation of percentage amount of:

senna concentrate

$$\frac{1.3-1.0}{4-1}=\frac{0.3}{3}\times 100=10\%$$

psyllium

$$\frac{4-2.5}{30-2.5}=\frac{1.5}{27.5}\times 100=5.45\%$$

Conclusion: The sum of the EDR percentages does not exceed 100 percent and therefore the combination is in Category I.

12. *Criteria for Category II combination products.* A combination is classified by the Panel as a Category II product, i.e., one that is not generally recognized as safe and or not generally recognized as effective, if any of the following apply:

a. The combination contains 3 or more active laxative ingredients, e.g., mineral oil, phenolphthalein, plantago seed; sodium carboxymethylcellulose, dioctyl sodium sulfosuccinate, casanthranol.

b. The combination contains 2 active laxative ingredients each of which is safe and effective when used alone, but in combination is found to be not safe e.g., mineral oil and dioctyl sodium sulfosuccinate.

c. The combination contains any ingredient that is listed elsewhere in this document as a Category II ingredient.

d. The combination contains any ingredient in an amount equal to the maximum dosage set by the Panel for such ingredient and contains another ingredient in an amount above the minimum dosage set by the Panel for such other ingredient.

e. The combination is such that the sum of the percentage amounts of each ingredient exceeds 100 percent. (See "Criteria for determining Category I combinations" above, for an explanation of the method for calculating the percentage amount of each ingredient).

f. The combination contains any active laxative ingredient that has not been reviewed by the Panel and accordingly not listed in this document.

13. *Criteria for Category III combination products.* A combination is classified as a category III combination if any of the following apply:

a. If one or both Category I ingredient(s) fall below the minimum dosage set for each respective ingredient.

b. If one or both ingredients are Category III ingredients, as set forth elsewhere in this document for single active laxative ingredients.

14. *Criteria for reclassification of Category III combinations to Category I combinations.* a. For any combination found in paragraph 10, ". . . combinations allowable as Category I . . .," where one or both ingredients fall below the minimum effective level as set forth elsewhere in this document for such respective ingredient(s), tests must be performed to substantiate the effectiveness of any such ingredient alone and in the respective combination.

The Panel recommends that such testing be performed and evaluated through the new drug procedures or suitable petition to the Commissioner for appropriate modification of the monograph to permit such lower dosage level(s) of ingredient(s) present in an allowable combination.

b. (1) Any combination that contains one or both ingredients in Category III, as set forth elsewhere in this document, must be tested to satisfy Category I requirements for each such ingredient.

(2) Two Category I ingredients in a combination not found in paragraph 10, ". . . combinations allowable as Category I . . .," must petition the Commissioner for an appropriate amendment to the monograph or proceed through the NDA procedures.

REFERENCES

(1) Martin, E. W., Hazards of Medication, J. B. Lippincott Co., Philadelphia, pp. 577 and 686, 1971.

H. Inactive Ingredient in Laxatives

Laxative products frequently contain a number of inactive laxative ingredients, some of which are used in the formulation of the preparation. The Panel recommends that inactive ingredients be listed on the label with or without the amounts contained in a recommended dose. The availability of sodium, potassium, and magnesium in the maximum recommended daily dose should be stated on the label. (See labeling discussion above for laxative products.) Special warnings on the label should be provided for patients with heart disease and renal disease.

The inactive ingredients identified below are added to laxative preparations to enhance their formulation or to contribute to the effervescent qualities of some preparations and should not be listed as an active laxative ingredient.

CALCIUM, POTASSIUM, AND SODIUM SALTS

Calcium hydroxide
Potassium carbonate
Sodium acid pyrophosphate
Sodium bicarbonate
Sodium biphosphate, anhydrous
Sodium carbonate
Sodium citrate

I. Data Pertinent for Laxative Ingredient Evaluation

The Panel has given considerable thought to the problem of demonstrating that a laxative is safe and effective. When a drug is available for widespread use, as in OTC products, its safety and effectiveness must be well documented by toxicological data, data on the absorption, distribution, fate and excretion of the drug, the pharmacological effects of the drug, and the mechanism of action. The drug must also meet certain effectiveness standards.

The Panel recommends that information such as the following be obtained when relevant and pertinent to the drug under study: standardization of plant derivative, toxicologic data, absorption, distribution, fate, and excretion (ADFE) data, mechanism of action, and effectiveness standards.

1. *Standardization of plant derivative laxatives.* The Panel reviewed several ingredients which are plant derivatives of varying degrees of refinement. In some cases, the crude product was a known, accepted laxative agent, but the degree to which any extracted derivatives were active was unknown (e.g., prune powder and prune concentrate). In other cases, the Panel could assume some measure of activity for the refined extract, but data were unavailable to establish effectiveness and safety.

The Panel adopts the position that an extract or derivative of a well-established crude laxative product is not efficacious or safe ipso facto. The Panel requires evidence of effectiveness and safety for the crude as well as the refined product, and data sufficient to establish dosing parameters.

The Panel recommends that the following additional information be submitted to ensure standardization of plant derivative ingredients:

a. A description of the source of material used for extraction and any refining process that it may have undergone.

b. An outline of the extraction procedure and the analyses used to establish the identity of the products.

c. Controlled clinical trials establishing effectiveness and safety and appropriate dosing regimens of the crude as well as the extracted ingredient alone.

2. *Toxicological data.* A variety of toxicological data can be obtained to demonstrate that a laxative is safe. Manufacturers are not expected to obtain all of the following data, but are expected to obtain those data relevant to the unanswered questions regarding the safety of their products. The Panel recommends that data such as the following be obtained in animal studies and in clinical studies in man. Certain data on human subjects, such as lethal doses and chronic toxicity, will only be available from poison control centers, hospitals, or medical centers, or medical examiners. However, the Panel considers such data important and attempts should be made to obtain them.

a. *Preclinical Animal Studies.* (1) The oral LD_{50} established in no less than two animal species.

(2) Determinations of histologic and biochemical alterations in animals given lethal doses acutely or low doses chronically.

(3) Studies of effects on fertility, teratogenicity and embryolethality, delivery, and nursing offspring may also be indicated.

b. *Clinical studies in man.* (1) Biochemical tests of liver and renal func-

tion and measurement of serum electrolytes after a therapeutic dose.

(2) Chronic toxicity studies in man, especially in relation to altered function and cytological changes of the mucose of the intestinal tract of man.

(3) Adverse drug reactions should be well documented. Substantial effort should be made to have physicians document side effects, especially those of a serious nature as allergic reactions, intestinal obstruction or impaction, syncope, etc.

(4) Minimal lethal dose by single oral ingestion or in divided doses when such data are available from accidental or deliberate overdosing.

(5) Maximal tolerated dose from single oral ingestion, or divided multiple oral ingestions, when such data are available from accidental or deliberate overdosing.

3. *Absorption, distribution, fate and excretion (ADFE) as determined by currently accepted methods.* Many laxatives claimed to escape intestinal absorption have been found subsequently to be absorbed and excreted in substantial quantities. Since ADFE bears directly on the safety of drugs and occasionally on the mechanism of action of laxatives, appropriate data should be provided for all active ingredients and their active metabolic products. The methods for obtaining these data are established and are not different from those used in the study of ADFE of other drugs. Data such as the following would provide sufficient information regarding ADFE. Manufacturers are not expected to obtain all of the following data, but are expected to obtain those data relevant to the unanswered questions regarding ADFE of the products:

a. The percentages of various oral doses of the drug which are absorbed in man.

b. The percentages of various oral doses which are excreted in the urine in man.

c. The percentages of various oral doses of the drug which are excreted in breast milk.

d. The metagolic fate in man of absorbed but unexcreted drug.

e. The fate of unabsorbed drug in man.

f. The net bioavailability of the drug in man.

g. The ingredients and metabolic products associated with fecally excreted drug and/or its unabsorbed intraluminal biotransformation products.

h. The ingredients and metabolic products associated with renally excreted drug and/or its renally excreted biotransformation product.

4. *Effects.* Effectiveness requires that the desired pharmacologic effect of the drug under study be laxation. The Panel recognizes that the mechanism of action of many safe and effective drugs is unknown. Nevertheless, for laxatives, a number of excellent models exist that can be used in such studies. For example, in vitro studies of water incorporated into colloid laxatives demonstrates the hydrophilic properties of such laxatives—a property easily confirmed in man by demonstrating that stools contain the colloid and an increased percentage of water. The perfused animal intestine and everted intestinal loop preparations can be employed to demonstrate alterations in intestinal absorption and secretion. Methods are available for measuring alterations of sodium and potassium adenosine triphosphatase activity in animal intestinal preparations. Similarly, preparations are available for assessing the effects of laxatives on smooth muscle contractility. In man it is also feasible to measure alterations in intestinal absorption and secretion associated with laxative use and to detect changes in intraluminal pressures. These are only a few of the methods that can be employed to clarify the mechanism of action of laxatives. It is recommended that data such as the following be obtained. Manufacturers are not expected to obtain all of the following data, but are expected to obtain those data relevant to the unanswered questions regarding the mode of action of their products:

a. Effects of oral drug on jejunal secretion and the flux of ions and water at the levels of the jejunum, ileum, proximal and distal colon.

b. Effects of the oral drug on the absorption of actively transported ions, sugars, and amino acids.

c. Effects of the oral drug on the absorption of carbohydrate, protein, lipids and fat-soluble vitamins.

d. Effects of the oral drug on the absorption of other drugs.

e. Effects of the oral drug on secretion of gastrointestinal enzymes, gastrointestinal hormones, gastrointestinal mucus, and the biliary secretion of bile, bile acids, and cholesterol.

f. Effects on intestinal smooth muscle such as contractility and electromyographic changes.

5. *Effectiveness standards.* Clinical studies in humans should usually be done in both normal and constipated persons with additional studies as indicated for specific target populations such as bedfast persons, postpartum and postoperative subjects, etc. Acceptable clinical criteria of effectiveness would be well-controlled clinical trials using randomized subjects in a double-blind, cross-over technique. "Before treatment" data should be obtained for each subject, besides basic demographic characteristics. These should include information on: (a) Diet, (b) Other medications, (c) Any other preexisting conditions which would bias analyses and (d) Pretreatment stool frequency, weight, volume, water content, transit time, etc.

One treatment group should receive a placebo for comparison purpose. If the identity of the drug cannot be masked or a suitable placebo cannot be devised, control and treatment periods should be of sufficient duration to allow the subject or patient to serve as his/her own control. Ingredients should be tested alone and in appropriate combinations. Appropriate statistical evaluations of observed effects are necessary. In addition to frequency and consistency, there are many other appropriate parameters that can be measured quantitatively to assess laxative effectiveness. Some of these parameters are more appropriate for one type of laxative than another. Thus, for a bulk-forming laxative, the following parameters would be appropriate: Volume, weight, percent water content, consistency, fecal solids, and bulk density. For stimulant laxatives, it would be more appropriate to quantitate transit time, frequency, electrolytes, and bile salt content, fecal excretion rate and stool water.

The Panel concurs that the following parameters of laxation, determined quantitatively, are appropriate for evaluating the effectiveness of drugs to produce laxation. Manufacturers are not expected to obtain all of the following data, but are expected to obtain those data relevant to the unanswered questions regarding the effectiveness of their products:

a. *Frequency.* The Panel recognizes that frequency of stool evacuation is quite variable among normal, healthy individuals and may range from three bowel movements per day to three per week. Frequency should be expressed in number of evacuations per unit time such as 24 hours or per week, etc.

b. *Consistency.* Consistency should be evaluated in some objective manner in addition to the subject's sensation of ease of passage or the observer's description of the stool as liquid, soft, hard, etc. Since major changes in the consistency of stool (and other materials) may occur with little change in either percent water or total stool weight, the Panel recommends a quantitative determination of consistency. There are few rheologic studies of colonic content (Ref. 1), but instrumentation used to quantitate the consistency of compounds, such as bread doughs, various pastes, and soils might be appropriate. If a tube viscometer is used, consistency is expressed in terms of shear rate and if a penetrometer is used, consistency is expressed in terms of kilograms per square centimeter.

c. *Volume.* The volume of stool evacuated during a unit time period is easy to determine and is usually expressed in milliliters or cubic centimeters per 24 hours or other time period. Average normal is 150 ml/24 hours.

d. *Weight.* Weight is expressed in grams per 24 hours or other unit time period. Weight is independent of consistency and important in determining the effectiveness of bulk-forming laxatives. Average normal is 110 to 130 grams per 24 hours.

e. *Water content.* Water content of the feces is usually expressed as percent water. This parameter is important in determining the effectiveness of stimulant and osmotic saline laxatives. Average normal is 60 to 85 percent.

f. *Fecal solids.* Fecal solids are usually expressed in grams per 24 hours. Average normal is 25 grams/24 hours.

g. *Bulk density.* Bulk density is expressed as unit weight per unit volume,

usually grams per cubic centimeter, and is determined by drying a known volume to constant weight at 105° C. Bulk density is an important parameter in determining the effectiveness of bulk-forming laxatives. Average normal is 0.15 to 0.18 gm/cc.

h. *Transit time.* Transit time may be expressed by either the "time method" or the "distant method" by use of nonabsorbable markers as polyethylene glycol, nonabsorbable color dyes as carmine, and nonabsorbable radioactive materials as chromium. In addition, inert colored plastic beads have been used as a marker to determine transit time. The use of some markers, such as carmine dye, is associated with considerable "streaming" and should be taken into account when markers are used to separate treatment periods. Average normal is 40 to 60 hours for complete transit of the digestive tract.

i. *Fecal excretion rate.* Fecal excretion rate is expressed in weight per unit time, usually grams per hour. Average normal fecal excretion rate is 6 grams per hour.

j. *Stool electrolytes, bile acids (salts), etc.* Feces contain a number of substances that might be appropriate to measure in evaluating laxative agents. Stool electrolytes, particularly sodium, potassium, and chloride, may be markedly altered by laxative agents. Fecal bile salts may be an appropriate parameter to measure with certain laxative agents.

REFERENCES

(1) Picologlou, B. F., P. D. Patel, and P. S. Lykoudis, "Biorheological Aspects of Colonic Activity: Part I. Theoretical Considerations," Biorheology, 10:431–440, 1973.

(2) Picologlou, B. F., P. D. Patel, and P. S. Lykoudis, "Biorheological Aspects of Colonic Activity: Part II. Experimental Investigation of Rheologic Behavior of Human Feces," Biorheology, 10:441–446, 1973.

II. ANTIDIARRHEALS

Pursuant to the notice published in the FEDERAL REGISTER of February 8, 1973 (38 FR 3614) requesting the submission of data and information on OTC antidiarrheal drugs, the following firms made submissions relating to the indicated products:

A. DATA AND INFORMATION OF SUBMISSIONS

Firm	Marketed products
Eneglotaria Medicine Co., Inc., of Puerto Rico, Santurce, PR 00907.	Kao-Gest.
Hynson, Westcott and Dunning, Inc., Baltimore, MD 21201.	Lactinex Tablets.
International Pharmaceutical Corp., Warrington, PA 18976.	Dia-Quel.
Lacto Products Co., Milwaukee, WI 53218.	Acidophilus Concentrate.
Merrick Medicine Co., Waco, TX 76703.	Percy Medicine.
Norwich Pharmacal Co., Norwich, NY 13815.	Pepto - Bismol, Pepto - Bismol Chewable Tablets.
Parke, Davis and Co., Detroit, MI 48232.	Pargel.
Purdue Frederick Co., Norwalk, CO 06856.	Parelixir Liquid.
A. H. Robins Co., Richmond, VA 23220.	Donnagel, Donnagel-PG.
William H. Rorer, Inc., Fort Washington, PA 19034.	Parapectolin.
The Upjohn Co., Kalamazoo, MI 49001.	Kao-Con, Kaopectate.
USV Pharmaceutical Corp., Tuckahoe, NY 10707.	Bacid.
Wyeth Laboratories, Inc., Philadelphia, PA 19101.	Kalpec, Kaomagma, Polymagma, Polymagma Tablets.

B. LABELED INGREDIENTS CONTAINED IN SUBMITTED PRODUCTS

Alumina powder, hydrated
Aminoacetic acid
Atropine sulfate
Attapulgite, activated
Bismuth subnitrate
Bismuth subsalicylate
Calcium carbonate, precipitated
Calcium hydroxide
Carboxymethylcellulose
Charcoal, Activated
Homatropine methylbromide
Hyoscyamine sulfate
Kaolin
Lactobacillus acidophilus
Lactobacillus bulgaricus
Opium powder
Opium, tincture of
Paregoric (camphorated tincture of opium)
Pectin
Phenyl salicylate, (salol)
Potassium carbonate
Rhubarb fluidextract
Scopolamine hydrobromide (hyoscine hydrobromide)
Zinc phenolsulfonate

In addition, the panel reviewed the following ingredient: polycarbophil.

C. DIARRHEA AND THE USE OF OTC ANTIDIARRHEAL PRODUCTS

Diarrhea may be defined as the excretion of stools with increased frequency and an increased weight and water content (Ref. 1). Healthy adults may have up to three stools per day (Ref. 2); and the water content may vary from 60 to 85 percent. Individuals with diarrhea excrete more than 200 grams of stool per day containing 60 to 95 percent water (Ref. 1). The major factor contributing to diarrhea is the excess water. It is remarkable that only 80 to 120 milliliters of water are excreted daily in the stool, when one considers that normal daily fluid intake is approximately 2 liters and normal secretions into the digestive tract account for an additional 7 liters. This indicates the extreme efficiency of the normal digestive tract in absorbing water and that excretion of only a few hundred milliliters of water in the stools will contribute to diarrhea.

Water absorption is thought to occur passively in the gut as a result of the absorption of solutes (ions as sodium, potassium, chloride, bicarbonate, etc., and simple products of digestion as glucose, amino acids, etc.). Thus, any condition that interferes with or inhibits normal solute absorption secondarily disturbs water absorption and may result in diarrhea. In a recent excellent review, the pathophysiology of diarrheal states is described and correlated with clinical conditions (Ref. 1). The multiple causes of diarrhea include bacterial and viral infections, parasitic infestations, lack of adequate digestive enzymes, pathological conditions of the intestinal mucosa, various metabolic and hormonal disturbances, increased gastrointestinal motility resulting in decreased transit time, and various surgical operations upon the digestive tract.

Diarrhea, unassociated with fever or blood in the stool, but sometimes associated with symptoms such as loss of appetite, abdominal cramps, nausea and vomiting is common. The Panel concludes that this type of diarrhea for which relief may be sought in OTC antidiarrheal products is a self-limiting disorder and usually lasts about 2 days. The Panel believes that OTC antidiarrheal products provide only symptomatic relief and are most effective in the mildest types of diarrhea.

The Panel has therefore adopted the following definitions:

(1) *Diarrhea.* Abnormally frequent passage of watery stools, self limiting (24 to 48 hours) usually with no identifiable cause.

(2) *Antidiarrheal.* An agent that is effective for the treatment of diarrhea.

REFERENCES

(1) Phillips, S. F., "Diarrhea: A Current View of the Pathophysiology," Gastroenterology, 63:495–518, 1972.

(2) Connell, A. M., C. Hilton, G. Irvine, J. E. Lennard-Jones, and J. J. Misiewicz, "Variation of Bowel Habit in Two Population Samples," British Medical Journal, 2:1095–1099, 1965.

D. LABELING OF ANTIDIARRHEAL PRODUCTS

1. *Indications.* The indications for use of an antidiarrheal should be simple and clearly stated. If the product is taken for specific indications such as to decrease the frequency of bowel movements, or to increase the bulk of the stool, the label should so state. The directions for use should be clear and provide the user a reasonable expectation of the results anticipated from use of the product. Statements of indications for use should be specific and confined to the conditions for which the product is recommended. No reference should be made, or implied, regarding the alleviation or relief of symptoms unrelated to the condition that is an indication for use of the product.

2. *Ingredients.* The label should state in metric units the quantity of each active ingredient contained in the recommended dose, e.g., teaspoonfuls, tablets, etc.

A product containing more than 1.0 mEq (23 mg) sodium per maximum daily dose should be labeled as to the sodium content per dosage unit. Furthermore, if the product contains more than 15 mEq (345 mg) sodium in the maximum recommended daily dose, the label should state:

Do not use this product except under the advice and supervision of a physician if you are on a low salt diet.

And in addition.

Do not use this product except under the advice and supervision of a physician if you have kidney disease.

If the product contains more than 25 mEq (975 mg) potassium in the maximum recommended daily dose, labeling should state: "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

If the product contains more than 50 mEq (600 mg) magnesium in the maximum recommended daily dose, the labeling should state: "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

The Panel strongly recommends that all inactive ingredients be listed with or without a statement of their quantity.

3. *Directions for use.* The label should contain a clear statement of the usually effective, minimal and maximal dose per time interval broken down by age groups, and if appropriate, may be followed by the statement "except under the advice and supervision of a physician."

4. *Warnings.* The Panel concurs with the regulation (21 CFR 369.20) containing the general warning statement for diarrhea preparations which states:

WARNING—Do not use for more than 2 days or in the presence of high fever or in infants or children under 3 years of age unless directed by a physician.

In addition, the label of antidiarrheal products containing belladonna preparations and preparations of its alkaloids shall also contain the specific warnings for these agents as discussed below for anticholinergics in Category III as antidiarrheals.

Opium-paregoric and other habit-forming drugs should contain the labeling requirements as provided in the regulation (21 CFR 329.10) as discussed below for opiates in Category I as antidiarrheals. The label should clearly state that if diarrhea is associated with high fever, the patient should see a physician.

E. Classification of Active Ingredients

The Panel reviewed all active ingredients which were the subject of submissions made to the Panel. Additionally, the Panel reviewed polycarbophil brought to their attention by the Food and Drug Administration. The Panel considered all pertinent data and information in arriving at its conclusions and recommendations.

In accordance with the regulation (21 CFR 330.10), the Panel's findings with respect to these ingredients are set forth in three categories:

I. Conditions under which antidiarrheal products are generally recognized as safe and effective and are not misbranded.

II. Conditions under which antidiarrheal products are not generally recognized as safe and effective or are misbranded.

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

The Panel recommends the following for each category of drugs:

1. That the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient to classify such conditions either as generally recognized as safe and effective and not misbranded or as not being generally recognized as safe and effective or would result in misbranding (Category III) be permitted to remain in use for 2 years after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel.

F. Review of Active Ingredients

In considering the active ingredients in antidiarrheal products, the Panel elected to classify ingredients on the basis of the usually accepted pharmacologic categories of the ingredient in providing relief from diarrhea, i.e., adsorptives, anticholinergics, astringents, opiates, and other active ingredients. Like laxative products, the Panel found that many antidiarrheal products contain more than one active ingredient. Some of these combinations are considered irrational because one or more of the active ingredients is considered too small to contribute significantly to the overall effectiveness of the product. The Panel finds it difficult to substantiate the claims of effectiveness of some antidiarrheal products.

1. *Conditions under which antidiarrheal products are generally recognized as safe and effective and are not misbranded.* After carefully reviewing all data available to the Panel, the following antidiarrheal ingredients were classified as safe and effective and not misbranded:

OPIATES

Opium powder
Opium, tincture of
Paregoric (camphorated tincture of opium)

POLYCARBOPHIL

(a) *Active ingredients classified as opiates*—(1) *Opium powder, tincture of opium, paregoric (camphorated tincture of opium).* The Panel concludes that opiates are safe and effective in the amounts usually taken orally: adults 15 to 20 milligrams opium per unit dose; children (6 to 12 years) 5 to 10 milligrams opium per unit dose or adults 1.5 to 2.0 milligrams morphine per unit dose; children (6 to 12 years) 0.5 to 1.0 milligram morphine per unit dose 1 to 4 times a day in antidiarrheal products for use not to exceed 2 days.

The Panel concurs that preparations containing less than 100 milligrams opium per 100 milliliters should be exempt from the federal requirements (21 CFR 329.20(a)) for prescription of narcotics: *"Provided,* That the preparations * * * contain one or more nonnarcotic active medicinal ingredients in sufficient proportion to confer upon the preparation valuable medicinal qualities other than those possessed by the narcotic drug alone." These preparations should be sold over-the-counter unless limited by state or local laws.

The opiates are generally recognized as effective antidiarrheals at the dose equivalent to 15 to 20 milligrams of opium or 1.5 to 2.0 milligrams of morphine. Morphine increases rhythmical segmenting contractions of both the small intestine and the colon with inhibition of propulsive movements (Ref. 1). The delayed colonic emptying affords clinical relief but may actually retard recovery from infectious (shigellosis) diarrhea (Ref. 2).

The resulting high intraluminal pressure, a possible precursor of diverticular disease, is considered a contraindication to the chronic use of opiates in persons with disorders of gut motility (Ref. 3).

LABELING

In addition to the general warnings required of all antidiarrheals (See labeling statements above for antidiarrheal products), the labeling of products containing opium and its alkaloids should meet the labeling requirements in 21 CFR 329.10 for habit forming drugs which states the following:

WARNING.—May be habit forming.

REFERENCES

(1) Adler, H. F., A. J. Atkinson and A. C. Ivy, "Effect of Morphine and Dilaudid on the Ileum and of Morphine, Dilaudid and Atropine on the Colon of Man," Archives of Internal Medicine, 69:974–85, 1942.

(2) Dupont, H. L. and R. B. Hornick, "Lomotil Therapy of Induced Shigellosis," Clinical Research, 21:598, 1973.

(3) Read, A. E., "Anti-diarrheal Agents," Practitioner, 206:69–76, 1971.

(b) *Other active ingredients*—(1) *Polycarbophil.* The Panel concludes that polycarbophil is safe and effective in amounts usually taken orally (4 to 6 grams per day) in antidiarrheal preparations (or when used as a laxative). The pediatric dose is 0.5 to 1.0 gram for infants not more than 2 years; 1 to 1.5 grams for children (2 to 5 years); and 1.5 to 3.0 grams for children over 5 years.

Polycarbophil, a hydrophilic polyacrylic resin (polyacrylic acid cross-linked with divinyl glycol), is insoluble in water, dilute acids, dilute alkalis, and common

organic solvents. It has a marked capacity for binding water and absorbs about 60 times its original weight. This property is the basis for its use as an internal hydrosorptive agent.

The seemingly paradoxical utilization of this hydrosorptive agent in the treatment of both diarrhea and constipation is based on its modifying effect on abnormal fecal consistency. In diarrheal states, the hydrophilic agent absorbs free fecal water forming a gel in the lumen of the intestine that is incapable of absorbing water at normal rates, and produces formed stools. In constipation, the agent retains water intraluminally and opposes dehydrating forces in the bowel. The water-retaining capacity of polycarbophil is considerably greater than that of methylcellulose or psyllium mucilloid. The degree of hydrophilia (cc/gm) of polycarbophil in synthetic intestinal juice is about 120 while for psyllium, methylcellulose, agar-agar, and carbo gum the values are 30, 36, 14, and 22, respectively.

In animal studies, polycarbophil has been shown to be free of toxicity, to be nonabsorbable, to have no effect on digestive enzymes, to have no influence on nutritional status, and to be metabolically inactive.

Clinical studies in patients with both acute and chronic diarrhea have demonstrated the effectiveness of polycarbophil as an antidiarrheal.

COMMENT

The Panel is of the opinion that there is a great need for more Category I antidiarrheal ingredients and urges industry to develop additional safe and effective antidiarrheal agents.

REFERENCES

(1) Grossman, A. J., R. C. Batterman and P. Leifer, "Polyacrylic Resin: Effective Hydrophilic Colloid for the Treatment of Constipation," Journal of the American Geriatric Society, 5:187–192, 1957.

(2) Roth, J. L. A., "Effects of Polycarbophil as Enteral Hydrosorbent in Diarrhea," American Journal of Digestive Diseases, 5:965–971, 1960.

(3) Pimparker, B. D., F. F. Paustian, J. L. A. Roth and H. L. Bockus, "Effect of Polycarbophil on Diarrhea and Constipation," Gastroenterology, 40:397–404, 1961.

(4) Rutledge, M. L., M. M. Willner and J. T. King, "Calcium Polycarbophil in Acute Childhood Diarrhea," Clinical Pediatrics, 2:61–63, 1963.

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

2. *Conditions under which antidiarrheal products are not generally recognized as safe and effective or are misbranded.* After careful review of all data submitted as well as additional evidence provided by the Food and Drug Administration and the results of a literature search, the Panel found there is no scientific or even sound theoretical basis for claimed efficacy of a number of ingredients used in OTC antidiarrheal preparations. The Panel concludes that the ingredients, labeling, and combination drugs involved should be removed from the market unless further scientific testing supports their use. In addition, the Panel concludes that it is neither truthful nor accurate to make claims regarding multiple indications for some single ingredients or to claim enhanced effectiveness and/or safety in some combinations of ingredients.

The Panel concludes that the following ingredients, labeling, and combination drugs involved should be removed from the market as antidiarrheals unless and until further scientific testing supports their use:

ASTRINGENT

Rhubarb fluidextract

OTHER CLAIMED ACTIVE INGREDIENTS

Aminoacetic acid (glycine)
Potassium carbonate
Scopolamine hydrobromide (hyoscine hydrobromide)

LABELING CLAIMS FOR SPECIFIC COMBINATIONS

Anticholinergic
Antacid

a. *Claimed active ingredient classified as an astringent—(1) Rhubarb Fluidextract.* The Panel recognizes that Chinese rhubarb (*Rheum officinale*) contains derivatives which are related to active laxative agents, but concludes there is no reliable scientific evidence to permit classification of this plant derivative as an antidiarrheal.

Chinese rhubarb contains several hydroxymethyl-anthraquinone derivatives which are chemically similar to those found in aloe, cascara sagrada, and senna. In addition to these anthraquinone type compounds, rhubarb also contains astringent ingredients such as rheotannic acid and gallic acid. The Panel found no reliable scientific data that evaluated the influence of these astringents on the laxative action of the anthraquinone ingredients (Refs. 1 and 2). Moreover, there are no dose response studies in man that establish an effective and safe dose for Chinese rhubarb. It is the Panel's opinion that the claim of Chinese Rhubarb acting as a laxative in high doses due to its anthraquinone like compounds, and as an antidiarrheal in low doses due to its astringent properties, is unfounded and represents misbranding.

In the case of Chinese rhubarb, the Panel's concern with safety relates only to the known side effects common with all anthraquinones. American rhubarb, which is used extensively in foods, is devoid of anthraquinone derivatives (Ref. 1). It is the opinion of the Panel that Chinese rhubarb in small amounts is inactive as an antidiarrheal, but may contribute to flavoring.

REFERENCES

(1) AMA Drug Evaluations, 1st Ed., American Medical Association, Chicago, IL, p. 597, 1970.

(2) Sollmann, T., A Manual of Pharmacology, 8th Ed., W. B. Saunders, Inc., Philadelphia, p. 211, 1957.

b. *Other claimed active ingredients in antidiarrheal preparations—(1) Aminoacetic acid (glycine).* The Panel concludes that aminoacetic acid (glycine) is safe in the amounts (400 to 800 milligrams daily) taken orally in antidiarrheal preparations but there is no evidence to establish efficacy in diarrhea.

Aminoacetic acid was reviewed by the OTC Antacid Panel, which found glycine to be safe in the amounts usually taken orally (5 grams per day) in antacid preparations (Ref. 1). Animal toxicity studies report excess glycine (10 percent glycine diet) leads to the accumulation of fat in the liver and slower growth rate (Ref. 2).

Aminoacetic acid is described in the National Formulary and other textbooks as a dietary supplement or antacid (Ref. 3 and 4). The Panel recognizes that the small amount of glycine used in antidiarrheal preparations may be included for palatability or as a pharmaceutical necessity. It is the scientific opinion of the Panel that there is no justification to claim glycine an active antidiarrheal ingredient.

REFERENCES

(1) "Proposal Establishing a Monograph for OTC Antacid Products," published in the FEDERAL REGISTER of April 5, 1973 (38 FR 8714).

(2) Arnstein, H. R. V., "The Metabolism of Glycine," Advances in Protein Chemistry, 9:17–18, 1954.

(3) The National Formulary, 13th Ed., American Pharmaceutical Association, Washington, D.C., p. 38–39, 1970.

(4) Wilson, C. W., et al., The Textbook of Oragnic Medicinal and Pharmaceutical Chemistry, 5th Ed., J. B. Lippincott, Philadelphia, p. 803–804, 1966.

(2) *Potassium carbonate.* The Panel concludes that potassium carbonate is safe in amounts usually taken orally in antidiarrheal preparations (3 to 6 grams per day), but there is no evidence that it possesses an antidiarrheal effect.

Although claimed as an active antidiarrheal ingredient, it is the Panel's opinion that potassium carbonate is an inactive ingredient and should be so regarded. The Panel is unaware of any evidence indicating potassium carbonate has antidiarrheal properties. Products containing potassium carbonate should list on the label the available potassium in a recommended dose of the product. If significant amounts are present, specific warnings should be made for patients with renal disease.

REFERENCE

(1) OTC Volume 090005.[1]

(3) *Scopolamine hydrobromide (hyoscine hydrobromide).* The Panel concludes there is insufficient evidence that scopolamine hydrobromide exerts an antidiarrheal effect.

Scopolamine hydrobromide differs quantitatively from atropine in its antimuscarinic action. Scopolamine has more pronounced effects on the central nervous system, ciliary body, iris and various secretory glands while atropine is more effective in reducing intestinal tone and motility (Ref. 1). There is, therefore, little or no rationale for the use of scopolamine in the treatment of diarrhea. The use of the related anticholinergics, atropine sulfate, homatropine methylbromide, and hyoscyamine sulfate is discussed below.

REFERENCES

(1) Innes, I. R. and M. Nickerson, "Drugs Inhibiting the Action of Acetylcholine on Structures Innervated by Postganglionic Parasympathetic Nerves (Antimuscarinic or Atropinic Drugs)," The Pharmacological Basis of Therapeutics, 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Company, New York, p. 524–548, 1970.

(c) *Labeling claims for specific combinations*—(1) *Claims for combinations of anticholinergic with opiates.* The Panel concludes that claims for enhanced effectiveness of the opiates through combination with atropine or its derivatives is not supported clinically or theoretically, since large and potentially toxic doses of the anticholinergics are required for partial suppression of the increased tone of the ileum and colon induced by morphine (Ref. 1). For example, the addition, in a non-OTC drug, of atropine at only 1/20 of the usual effective dose (0.025 mg./tablet) to diphenoxylate is widely recognized as an example of additive toxicity without additive therapeutic benefit (Ref. 2).

REFERENCES

(1) Adler, H. F., A. J. Atkinson and A. C. Ivy, "Effect of Morphine and Dilaudid on the Ileum and of Morphine, Dilaudid and Atropine on the Colon of Man," Archives of Internal Medicine, 69:974–85, 1942.

(2) Rosenstein, G., M. Freeman, A. Standard and N. Weston, "Warning: The Use of Lomotil in Children," Pediatrics, 51:132–133, 1973.

(2) *Claims for combinations of antidiarrheals with antacids.* Some antidiarrheal combination products contain various amounts of effective antacid ingredients as calcium carbonate, calcium hydroxide and hydrated alumina powder, as well an antidiarrheal ingredients. It is well known that many effective antacids including those listed above when given in adequate doses for antacid therapy will sometimes cause mild constipation. The fact that these agents may cause constipation when used in antacid therapy, does not constitute a rational basis for the claim that these agents are also effective antidiarrheals. In addition, there is no known relationship between gastric secretion and constipation. Thus, the Panel is of the opinion that it is not rational concurrent therapy for a significant portion of the population for the label to claim both antacid and antidiarrheal properties if the antidiarrheal claim is supported by a nonantidiarrheal ingredient.

(3) *Conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the active ingredients listed below:

ADSORBENTS

Attapulgite, activated
Charcoal, activated
Kaolin
Pectin

ANTICHOLINERGICS

Atropine sulfate
Homatropine methylbromide
Hyoscyamine sulfate

ASTRINGENTS

Alumina powder, hydrated
Bismuth salts
Calcium hydroxide
Phenyl salicylate (salol)
Zinc phenolsulfonate

OTHER CLAIMED ACTIVE INGREDIENTS

Calcium carbonate
Lactobacilli
  Acidophilus
  Bulgaricus
Sodium carboxymethylcellulose

LABELING CLAIMS FOR SPECIFIC INGREDIENT

Bismuth subsalicylate

The Panel believes it reasonable to allow 2 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If data regarding adequate effectiveness and safety are not obtained within 2 years, however, the ingredients listed in this category should no longer be marketed as active antidiarrheal ingredients in over-the-counter products but may be permitted as inactive ingredients if the amount employed is shown to be free of pharmacologic or toxic effect and contributes to the pharmaceutical formulation of the product. Some ingredients may be present in products in quantities which are pharmacologically inactive by virtue of being subclinical doses. In these cases, the ingredients may be included for pharmaceutical necessity or convenience, such as improving the stability or palatability of the product. However, it is the opinion of the Panel that if an ingredient was originally claimed by the sponsor to be active, it cannot then also be claimed inactive and included for formulation purposes unless the following are documented: The absolute necessity for inclusion in the pharmaceutical formulation, the safety of the quantity in the finished product, and the inactivity of the quantity in the finished product.

The Panel strongly recommends that all inactive ingredients be listed with or without a statement of their quantity, since the consumer may need to know for a variety of reasons, the ingredient in a product. However, the product cannot be promoted on the basis of its inactive ingredients, nor can the label emphasize the inclusion of the inactive ingredients.

The Panel has given careful consideration to the types of studies and types of data to be required for removing a claimed active antidiarrheal ingredient from Category III and placing it in Category I. (See paragraph I below for data required for antidiarrheal ingredient evaluation.) In general, to demonstrate effectiveness, the design of the study should have a sound scientific basis (e.g., a randomized, double-blind study comparing claimed active ingredients to placebo), the clinical trial should be carefully controlled (e.g., consideration given to selection of subjects representative of general population as well as diet, activity, travel, etc., of subjects being studied), and quantitative measurement of various parameters appropriate for the claimed effects of the ingredients (e.g., stool frequency, stool volume, stool weight, stool water content, stool consistency, etc.). To demonstrate safety, appropriate toxicological studies in experimental animals (preferably primate) and man are required as outlined elsewhere.

(a) *Claimed active ingredients classified as adsorbents*—(1) *Attapulgite, activated.* The Panel concludes activated attapulgite is safe in the amounts taken orally (e.g., 6 to 9 grams per 24 hour period) but there is insufficient evidence to classify it as an effective antidiarrheal.

Attapulgite is a naturally occurring aluminum magnesium silicate, similar to kaolin. It is inert and, presumably, nontoxic when administered orally (Ref. 1). In experimental animals, no LD_{50} could be obtained at 900 times the clinical dose. There have been few clinical studies on the safety or efficacy of attapulgite (Refs. 2 and 3). One well-controlled study showed that a combination of attapulgite and pectin was more effective than a placebo of unknown composition (Ref. 4). The claimed action of attapulgite is apparently due to its adsorptive properties (Ref. 5), i.e., adsorption of bacteria, toxins, etc.

DATA PERTINENT FOR EFFECTIVENESS

The Panel recognizes that attapulgite is generally recognized as safe in the amounts taken orally, but adequate data to establish effectiveness are lacking. Additional in vivo and in vitro studies are needed to establish that the primary mechanism of action is that of adsorption. Additionally, well-designed and carefully controlled clinical studies are necessary to establish the effectiveness of attapulgite when compared to placebo and/or an effective antidiarrheal. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) Gaubert, Y., "A New Intestinal Adsorbent Medication," Quest. Medical, 17:990–994, 1964 (French).

(2) Caroli, J. and J. Plessier, "Clinical Study of Attapulgite," Semaine des Hospitaux de Paris, 40:1685–1689, 1964.

(3) Barr, M., "Activated Attapulgite," Journal of the American Pharmaceutical Association, 19:85–87, 1958.

(4) Vernon, W. G., Attapulgite Efficacy Study included in OTC Volume 090133.

(5) Bartell, P., W. Peirzchala and H. Tint, "The Adsorption of Enteroviruses by Activated Attapulgite," Journal of the American Pharmaceutical Association (Scientific Edition), 49:1–4, 1960.

(2) *Charcoal, activated.* The Panel concludes activated charcoal to be safe in the amounts taken orally, but believes there is a lack of acceptable clinical evidence to establish its effectiveness as an antidiarrheal agent.

Activated charcoal powder is the residue obtained by the destructive distillation of wood pulp, suitably treated to increase its adsorptive power. Important characteristics of activated charcoal that contribute to its adsorptive capacity are small particle size, large total surface area, and low mineral content. The only generally accepted medicinal use for activated charcoal is as an antidote in poisoning (Ref. 1), although it may also

prove useful in the treatment of acute hepatic failure (Ref. 2). In regard to its use as an antidote, the adsorbent has been amply demonstrated to bind a number of chemicals within the gastrointestinal tract and thus, prevent their absorption (Ref. 1). Since activated charcoal in the form of tablets or capsules is sometimes recommended for the management of various gastrointestinal disorders such as flatulence and diarrhea (Ref. 3), it is significant to point out that activated charcoal powder has been demonstrated to be much more effective as an adsorbent than activated charcoal tablets (Ref. 4).

DATA PERTINENT FOR SAFETY AND EFFECTIVENESS

The Panel concurs that activated charcoal is a potent adsorptive agent but there are no partially controlled or controlled clinical studies to establish the effectiveness of activated charcoal as an antidiarrheal agent. Effectiveness should be tested in well-controlled clinical trials comparing activated charcoal with a placebo and/or a known effective antidiarrheal. Dose response data should be established, and, if determined, the effects of an effective dose on the gastrointestinal absorption of various drugs commonly used in small doses (e.g. cardiac glycosides, alkaloids and synthetic estrogens) should be determined. Additionally, data are needed to determine whether activated charcoal contains benzpyrene or methylcholanthrene type carcinogens. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) Picchioni, A. L., "Activated Charcoal: A Neglected Antidote," Pediatric Clinics of North America, 17:535–543, 1970.

(2) Gazzard, B. G., et al., "Charcoal Haemoperfusion in the Treatment of Fulminant Hepatic Failure," Lancet, 1:1301–1307, 1974.

(3) Riese, J. A. and F. Damrau, "Use of Activated Charcoal in Gastroenterology: Value for Flatulence and Nervous Diarrhea," Journal of the American Geriatrics Society, 12:500–502, 1964.

(4) Tsuchiya, T. and G. Levy, "Drug Adsorption Efficacy of Commercial Activated Charcoal Tablets in vitro and in Man," Journal of Pharmaceutical Sciences, 61:624–625, 1972.

(3) *Kaolin.* The Panel concludes kaolin is safe in the amounts taken orally (e.g. 12 to 24 grams per dose), but there is insufficient evidence to classify it as an effective antidiarrheal at this time, nor are there data to establish a dose response relationship.

Kaolin is a native hydrated aluminum silicate, powdered and freed from gritty particles. It is a clay and occurs as a soft white or yellowish white powder. Kaolin is considered to act as an adsorbent and protectant and has been used for over 200 years. It is available only in combination with pectin, or with one or more other antidiarrheals. Kaolin Mixture with Pectin, N.F., is a suspension which contains 20 percent kaolin and 1 percent pectin (Ref. 1). The usual dose is 30 milliliters (6 grams of kaolin, 300 milligrams of pectin). Adequately controlled clinical studies demonstrating the effectiveness of kaolin alone or in combination with pectin are not available. It is considered that kaolin adsorbs some toxins, bacteria, and viruses and is said to provide a protective coating for the intestinal mucosa (Ref. 2). In addition to adsorbing bacteria and various toxins, kaolin may act to increase the resistance of flow by solidifying the colonic contents, although this has not been demonstrated. As with the absorption of some drugs, and with vitamins such as thiamine, thus prolonged use may not be advisable (Refs. 3 and 4). A kaolin pectin mixture has been reported to interfere with the gastrointestinal absorption of the antibiotic lincomycin (Ref. 5).

A recent unpublished study submitted to the Panel provided data on the effectiveness of kaolin, pectin, the combination of both, and placebo (water) on a variety of diarrheagenic models in the squirrel monkey (Ref. 5). The dose of active ingredient used was comparable to that recommended for adult humans and based on milliliters per square meter of body surface area. Thus, the dose for a 0.9-kilogram squirrel monkey with a body surface of 0.10 square meter was 3.44 milliliters of kaolin and pectin combination given 3 times daily. The experimental models used to induce diarrhea included (a) A diarrheagenic diet, consisting of oranges, carrots, cabbage ad lib and prune juice instead of drinking water; (b) cholera toxin, in 3 doses; a low dose of 500 mg/kg, a medium dose of 2 gm/kg, and a high (lethal in 48 hours) dose of 4 gm/kg; (c) castor oil, 4 ml/kg; (d) phenolphthalein, 100 mg/kg; (e) methyl prostaglandin E_2, 0.4 mg/kg; (f) bile (beef, dehydrated), 2 gm/kg; and (g) lactulose.

In most of the models studied, it was shown that kaolin, pectin, or the combination of both was more effective in reducing the total number of stools or the number of loose and liquid stools than the placebo. The consistency of the stool was determined by simple observation only. In many of the models, the observed effects can probably be explained by the absorption of the diarrheagenic agent by the kaolin and pectin. In the diarrheagenic diet model, there was no change in the total number of stools but the number of loose and liquid stools was reduced by kaolin and pectin. In some of the models studied, the diarrheagenic agent did not increase the total number of stools as compared to control periods but the number of loose and liquid stools was increased.

The Panel accepts the results of these studies but questions the relevance of the experimental models to human disease states.

DATA PERTINENT FOR EFFECTIVENESS EVALUATION

The claim that kaolin acts as an adsorbent and protectant should be tested in man using kaolin alone and compared to other known adsorbents. Clinical effectiveness in treatment of diarrhea should be documented by well-designed and controlled clinical trials to test the effectiveness of kaolin alone and comparisons made with placebo and/or a known effective antidiarrheal. Additional information is needed regarding the interaction of kaolin with other drugs such as cardiac glycosides, antibiotics, alkaloids and vitamins. (See paragraph I below for data pertinent for effectiveness evaluation.)

REFERENCES

(1) The National Formulary, 13th Ed., American Pharmaceutical Association, Washington, DC, p. 388, 1970.

(2) AMA Drug Evaluations, 1st Ed., "Antidiarrheals," American Medical Association, Chicago, p. 579, 1971.

(3) Mann, G. V. and F. J. Stare, "Nutritional Needs in Illness and Disease," Journal of the American Medical Association, 142: 409–419, 1950.

(4) Messerli, N., "The Influence of the Addition of Adsorbents to the One-Sided Diet in the Production of Avitaminosis," Archives et Internationales Physiologie de Biochemie, 19:103–114, 1922.

(5) Hansten, P. D., Drug Interactions, 2nd Ed., Lea and Febiger, Philadelphia, p. 131, 1973.

(6) OTC Volume 090121.[1]

(4) *Pectin.* The Panel concludes pectin is safe in amounts taken orally (e.g. 300 milligrams, 3 to 4 times per day), but there is insufficient evidence to establish its effectiveness, nor are there data to establish a dose response relationship.

Pectin is a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. It consists chiefly of partially methoxylated polygalacturonic acids. Pectin yields not less than 6.7 percent of methoxy groups and not less than 74 percent of galacturonic acid calculated on a dried basis. Pectin dissolves in 20 parts of water; the resulting colloidal solution is viscous and opalescent, and acid in reaction (Refs. 1 and 2). The mechanism of action of pectin in diarrhea is unknown (Ref. 3). It has been claimed that pectin produces beneficial results because it is an adsorbent and protective agent (Ref. 4). It has also been claimed the beneficial effects are due to lowering the pH by galacturonic acid (Refs. 5 and 6). When fed to healthy human subjects, only a small amount is recovered in the feces because pectin is decomposed in the colon by bacterial action (Ref. 7). In patients with diarrhea, much larger amounts may be eliminated unchanged.

The effectiveness of pectin in various diarrheagenic models in squirrel monkeys has been discussed in the section on kaolin.

DATA PERTINENT FOR EFFECTIVENESS

The Panel finds insufficient evidence to establish the claimed mechanism of action of pectin as an antidiarrheal agent, i.e. an adsorbent and protective agent. This claim should be tested in man. The effect of pectin on intraluminal pH also has not been well documented. There are no controlled clinical trials substantiating the effectiveness of pectin alone in the treatment of diarrhea in man. Pectin is usually given in combination with

kaolin or other antidiarrheal agents. Effectiveness of pectin should be tested against a placebo in well-controlled clinical trials. A comparison should also be made with a known effective antidiarrheal. If pectin acts by physically altering the suspension of kaolin or otherwise enhancing the effect of other antidiarrheals, this should be documented and the dose-ratio established. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) The National Formulary, 13th Ed., American Pharmaceutical Association, Washington, D.C., p. 525–526, 1970.

(2) Swinyard, E. A., "Demulcents, Emollients, Protectives and Adsorbents, Antiperspirants and Deodorants, Absorbable Hemostatics, Astringents, Irritants, Sclerosing Agents, Caustics, Keratolytics, Antiseborrheics, Melanizing and Demelanizing Agents, Mucolytics, and Certain Enzymes," The Pharmacological Basis of Therapeutics, 4th Ed., Edited by Goodman, L. S. and A. Gilman, MacMillan Co., New York, p. 990, 1970.

(3) Howard, P. J. and C. A. Tompkins, "Pectin-Agar for Diarrhea in Infants and the Newborn: A Rational, Simple and Effective Treatment," Journal of the American Medical Association, 114:2355–2358, 1940.

(4) Olsen, A. G., "Pectin Therapy and Pectin Types," American Journal of Digestive Diseases, 7:515–519, 1940.

(5) Haynes, E., C. A. Tompkins, G. Washburn and M. Winters, "Bactericidal Action of Pectin," Proceedings of the Society of Experimental Biology and Medicine, 36:839–840, 1937.

(6) Steinhaus, J. E. and C. E. Georgi, "The Effect of Pectin, Galacturonic Acid and Alpha Methyl Galaturonate Upon the Growth of Enterobacteriaceae," Journal of Infectious Diseases, 69:1–6, 1941.

(7) Werch, S. C. and A. C. Ivy, "A Study of the Metabolism of Ingested Pectin," American Journal of Diseases of Children, 62:499–511, 1941.

(b) *Claimed active ingredients classified as anticholinergics.* The Panel concludes that some anticholinergic drugs are effective in reducing gastrointestinal motility when given in doses which are equivalent to 0.6 to 1.0 milligram of atropine sulfate. However, neither atropine sulfate nor any other anticholinergic drug is safe when given in such doses. Further, the effectiveness of such a small dosage (e.g., 1/100 of the effective atropine dose) of these anticholinergic drugs as contained in present combination of OTC antidiarrheal products is not established. Since the safety and effectiveness is not satisfactorily established for OTC use, the Panel recommends that antidiarrheal products containing anticholinergics when given in doses which are equivalent to 0.6 to 1.0 milligram of atropine sulfate be available only by prescription.

(1) *Atropine sulfate.* The Panel concludes there is insufficient evidence to establish the safety and effectiveness of atropine sulfate.

Atropine sulfate and related belladonna alkaloids significantly reduce the tone and motility of the gastrointestinal tract by producing parasympathetic blockade (Ref. 1). This effect is especially prominent since sympathetic nerve impulses play little or no part in the regulation of intestinal motility and muscle tone. Normal subjects and some patients with gastrointestinal disease exhibit reduced motor activity in the stomach, small and large intestine following full therapeutic doses (0.6–1.0 milligram) subcutaneously or orally (Refs. 1, 2 and 3). However, there is insufficient evidence that the small quantities of anticholinergic agents in antidiarrheal products contribute in any way to effectiveness. Atropine toxicity is well established; children are particularly susceptible. Although doses of 500 milligrams have been survived, as little as 10 milligrams have been fatal (Ref. 1).

(2) *Homatropine methylbromide.* The Panel concludes that there is insufficient evidence to establish the safety and effectiveness of homatropine methylbromide at this time.

Homatropine methylbromide is a quaternary ammonium derivative of belladonna alkaloid which possesses most of the pharmacologic and toxic properties of atropine (Refs. 1, 4, and 5). It is approximately ½ as potent as atropine, and it is claimed to be only 1/50 as toxic as atropine (Ref. 1), although this claim is not well documented (Ref. 1).

(3) *Hyoscyamine sulfate.* The Panel concludes there is insufficient evidence to establish the safety and efficacy of hyoscyamine sulfate.

Atropine is a racemic mixture of equal parts of *d*- and *l*-hyoscyamine. The *l*-form is more potent than *d*-hyoscyamine. Hyoscyamine sulfate is entirely in the *l*-form and is, therefore, nearly twice as potent as atropine sulfate in its antimuscarinic effects (Ref. 1).

LABELING

The Panel concurs with the required warning statements for belladonna preparations in the regulations (21 CFR 369.20) which states in part:

WARNING.—Not to be used by persons having glaucoma or excessive pressure within the eye, or by elderly persons (when undiagnosed glaucoma or excessive pressure within the eye occurs most frequently), or by children under 6 years of age, unless directed by a physician. Discontinue use if blurring of vision, rapid pulse, or dizziness occurs. Do not exceed recommended dosage. Not for frequent or prolonged use. If dryness of the mouth occurs, decrease dosage. If eye pain occurs, discontinue use and see your physician immediately as this may indicate undiagnosed glaucoma.

Because of occurrence of severe atropine poisoning in young children, belladonna preparations for OTC use should not contain more than 0.5 milligram atropine equivalent per 15 milliliters or per 15 grams of final preparation.

DATA PERTINENT FOR SAFETY AND EFFECTIVENESS

The Panel concurs that anticholinergic drugs can be effective in the treatment of diarrhea when administered under the supervision of a physician. The Panel's primary concern is that of safety when anticholinergic drugs are included in OTC antidiarrheal products in quantities that contribute to the antidiarrheal effect of the product. Accordingly, if the safety and effectiveness is not satisfactorily established for OTC use, the Panel recommends that antidiarrheal products containing anticholinergics be available only by prescription. It must be demonstrated by carefully controlled clinical trials that anticholinergic drugs used in OTC antidiarrheals are safe and contribute to the effectiveness of the combination products. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) Innes, I. R. and M. Nickerson, "Drugs Inhibiting the Action of Acetylcholine on Structures Innervated by Postganglionic Parasympathetic Nerves (Antimuscarinic or Atropinic Drugs)," The Pharmacological Basis of Therapeutics, 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, p. 524–548, 1970.

(2) Bachrach, W. H., "Anticholinergic Drugs: Survey of the Literature and Some Experimental Observation," American Journal of Digestive Diseases, 3:743–799, 1958.

(3) Ingelfinger, F. J., "The Modification of Intestinal Motility by Drugs," New England Journal of Medicine, 229:114–122, 1943.

(4) Hadfield, W. A., Jr., "The Effect of Homatropine Methylbromide on Human Gastrointestinal Motor Activity," Gastroenterology, 28:642–655, 1955.

(5) Cahen, R. L. and K. Tvede, "Homatropine Methylbromide: A Pharmacological Revaluation," Journal of Pharmacology and Experimental Therapeutics, 105:166–177, 1952.

(c) *Claimed active ingredients classified as astringents.* Astringents are locally acting drugs that precipitate protein. They are thought to act by reducing cell membrane permeability without cell destruction. A number of organic chemicals and certain metallic ions such as those of zinc and aluminum are said to have astringent properties in high dilution. Many antidiarrheal drugs are claimed to have an astringent action. The Panel was unable to find evidence to support this claim or to demonstrate that astringent properties confer effectiveness in diarrhea.

(1) *Alumina powder, hydrated.* The Panel agrees with the OTC antacid Panel that hydrated alumina powder is safe in the amounts usually taken orally for antacid therapy (Ref. 1). Doses used for antacid therapy sometimes cause constipation (Ref. 2).

The fact that hydrated alumina powder sometimes causes constipation when used in adequate doses in antacid therapy does not constitute a rational basis for the claim that the agent is also an effective antidiarrheal.

The Panel is unable to find any studies that evaluate aluminum compounds as a single agent for the treatment of acute diarrhea. Nor could any dose-response data relative to the constipating effect be located.

The inclusion of alumina gel in antidiarrheal preparations to maintain kaolin or attapulgite in suspension and allow greater surface area for absorption may be a reasonable formulation or pharmaceutical necessity but does not

justify the claim that it is an active ingredient.

DATA PERTINENT FOR EFFECTIVENESS

It must be demonstrated in man that alumina powder is an effective antidiarrheal by well-controlled clinical comparisons made with a known effective antidiarrheal and a placebo. If found effective, dose-response data should be obtained. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation).

REFERENCES

(1) "Proposal Establishing a Monograph for OTC Antacid Products," published in the FEDERAL REGISTER of April 5, 1973 (38 FR 8714).

(2) AMA Drug Evaluations, 1st Ed., American Medical Association, Chicago, p. 575, 1971.

(2) *Bismuth salts (Bismuth subnitrate, bismuth subsalicylate).* The Panel concludes that the bismuth subsalicylate is safe in amounts taken orally (0.6 to 2.0 grams of bismuth subsalicylate, 3 to 4 times per day) but there is insufficient evidence to establish effectiveness at this time. There is some question of the safety of bismuth subnitrate. The manufacturer's maximum recommended dose would provide about 5.6 grams for adults and 0.475 gram for children (3 to 6 years old) in 4 hours. Methemoglobinemia in infants has been reported in the literature due to the absorption of nitrates from bismuth subnitrate (Refs. 1 and 2) contraindicating its use in children under 2 years.

Bismuth salts appear to be poorly absorbed from the gastrointestinal tract; several studies report the absence of detectable bismuth in the urine of human subjects given high doses or used over long periods of time. The ingestion of 30 to 45 milliliters of a liquid bismuth subsalicylate preparation (equivalent to ingesting 5.5 to 8.25 grains (349 to 523.5 mg) of salicylic acid) yielded blood salicylate levels that ranged from barely detectable to 6.2 mg/100 ml.

Data supporting the effectiveness of bismuth in diarrhea are questionable. A ligated calf intestine model was used to study the effect of one bismuth compound on fluid formation by *E. coli*. Fluid production in the intestinal segment with *E. coli* and drug was less than with *E. coli* alone, but the relationship of this model to common diarrhea in humans is unclear. When the drug was administered in vivo to calves with diarrhea, the results indicated that the drug was not effective.

The products are said to provide a coating action. However, two unpublished studies using animals and two using a "gastro-camera" on human subjects failed to demonstrate any clear evidence of a coating action on the mucosa. Reports attempting to document a coating action for bismuth utilizing a technique of pretreatment with bismuth probably are not applicable, as it can be postulated that the majority of consumers do not use bismuth compounds "prophylactically."

Several clinical trials attempted to document effectiveness of the bismuth compounds in diarrhea. One clinical trial utilized a double-blind technique with a control drug in patients suffering from diarrhea secondary to foreign travel. However, the outcome measurements were based on the patient's subjective opinions of relief (good, excellent, poor, none) with no attempt to standardize the criteria for these responses. Interpretation of the results was difficult. Objective parameters as stool frequency and consistency before and after treatment were not carefully measured (Ref. 3).

LABELING

Special labeling should indicate that stools may become dark with use of any bismuth compound.

Bismuth subnitrate is contarindicated for use in infants under the age of 2 because of the known risk of methemoglobinemia.

DATA PERTINENT FOR EFFECTIVENESS

Data to date suggest bismuth salts may be effective in mild diarrhea, but the claim needs confirmation by testing in a well-controlled clinical trial using objective parameters to indicate response (e.g. number of stools, water content). Bismuth salts should be compared to nonsalicylate containing bismuth salts in order to determine the contribution of salicylate to effectiveness. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) "Accumulation of Nitrate," National Academy of Sciences, Washington, DC, p. 46-75, 1972.

(2) Gleason, M. N., et. al., Clinical Toxicology of Commercial Products: Acute Poisoning, 3rd Ed., Williams and Wilkins, Baltimore, MD, p. 24, 1969.

(3) OTC Volume 090120.[1]

(3) *Calcium hydroxide.* The Panel concludes that calcium hydroxide is safe in the amounts taken orally in antidiarrheal products, but there is no evidence of its effectiveness as an antidiarrheal agent.

Calcium hydroxide solution, commonly known as lime water, is claimed useful for its antacid properties and for buffering purposes (Ref. 1). The constipating effects of calcium when used as an antacid in moderate doses are well known. However, there is no evidence of effectiveness in the treatment of diarrhea. Calcium hydroxide has been included in multiple ingredient antidiarrheal preparations to provide "temporary relief of gastric discomfort due to overeating and other dietary indiscretions." The Panel is of the opinion that it is not rational concurrent therapy for a significant portion of the population for the label to claim both antacid and antidiarrheal activity if the antidiarrheal claim is supported by a nonantidiarrheal antacid ingredient. (See antidiarrheals discussion above for Category II claims.)

DATA PERTINENT FOR EFFECTIVENESS

Data are needed on mechanism(s) of action and a dose-response relationship. Effectiveness should be tested in well-controlled clinical trials comparing calcium hydroxide with placebo. Comparison should also be made with a known effective antidiarrheal. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) *The Pharmacopeia of the United States of America,* 18th Revision, The United States Pharmacopeial Convention, Inc., Washington, DC, pp. 93-94, 1970.

(4) *Phenyl salicylate (salol).* The Panel concludes that phenyl salicylate is safe in the small amounts taken orally in antidiarrheal preparations, but there is no evidence that it is an effective antidiarrheal.

Phenyl salicylate is no longer listed in the United States Pharmacopeia or National Formulary. The antiseptic utility of salol depended largely on its hydrolysis to phenol and salicylic acid (Ref. 1). However, the decomposition is uncertain or very slow and the absorption of phenol is so rapid that effective concentration of the drug in the alimentary tract is questionable (Ref. 2). The amount of phenol available in salol antidiarrheal preparations is considerably below the 1 to 2 percent phenol solution accepted as bacteriostatic. Giving larger doses of salol could possibly result in phenol poisoning (Ref. 3).

DATA PERTINENT FOR EFFECTIVENESS

Data are needed on mechanism(s) of action and a dose-response relationship. Effectiveness should be tested in well-controlled, double-blind clinical trials of the antidiarrheal effect of phenyl salicylate (salol) alone and, if desired, in combination as compared with placebo. Comparison should also be with a known effective antidiarrheal. Additionally, measurement of blood salicylate at one hour after dose administration is needed to document the absorption of salicylate. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) The United States Dispensatory and Physicians' Pharmacology, 26th Ed., Edited by Osol, A., R. Pratt and M. D. Altshule, J. B. Lippincott Co., Philadelphia, PA, p. 899, 1967.

(2) OTC Volume 090053.[1]

(3) Gleason, M. N., et al., Clinical Toxicology of Commercial Products: Acute Poisoning, 3rd Ed., The Williams and Wilkins Co., Baltimore, p. 113, 1969.

(5) *Zinc phenolsulfonate.* The Panel concludes that zinc phenolsulfonate is safe in the small amounts usually taken in antidiarrheal preparations, but no evidence exists to establish effectiveness.

The maximal daily adult dose of zinc phenolsulfonate in antidiarrheal products is approximately 400 milligrams. If all of the phenol from zinc phenolsulfonate in antidiarrheal products were absorbed, the amount would be approximately 136 milligrams in a maximum daily adult dose. This figure is well below the reported fatal dose of 1.5 grams (Ref. 1). Therefore, the ingredient seems safe in the small amounts used in antidiarrheal products.

There is no evidence in the scientific literature or modern standard reference texts to establish the effectiveness of zinc phenolsulfonate in the treatment of diarrhea. The sparse information about zinc phenolsulfonate in older editions of textbooks describes the compound as an astringent for topical application to indolent ulcers and subacute inflammation of the nasopharynx or vagina (Ref. 2).

DATA PERTINENT FOR EFFECTIVENESS

The Panel finds zinc phenolsulfonate safe in the amounts usually taken orally. Effectiveness should be tested in well-controlled, double-blind clinical trails of the antidiarrheal effect of zinc phenolsulfonate alone and, if desired, in combination as compared with placebo. Comparison should also be made with a known effective antidiarrheal. In addition, data are needed on mechanism(s) of action and dose-response relationship. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) Gleason, M. N., et al., Clinical Toxicology of Commercial Products: Acute Poisoning, 3rd Ed., Williams and Wilkins, Baltimore, MD, p. 153, 1969.

(2) The Dispensatory of the United States of America, 25th Ed., Edited by Osol, A. and G. E. Farrar, J. B. Lippincott Co., Philadelphia, p. 1519, 1955.

(d) *Other claimed active ingredients*—(1) *Calcium carbonate.* The Panel concludes that calcium carbonate is safe in the amounts taken orally for antacid therapy, but can find no evidence that it is an effective antidiarrheal.

The OTC antacid Panel concluded calcium carbonate to be an effective antacid, with the recommendation that not more than 8 grams be taken per day (Ref. 1). The recommendation was based on the knowledge that calcium ingestion can lead to hypercalcuria in some instances. In some individuals, this dose of calcium carbonate can case constipation (Ref. 2).

The claimed effectiveness of calcium carbonate in acute, self-limiting diarrhea rests on its known constipating effects when used as an antacid in doses of 2 to 4 grams 4 times daily. The Panel could find no dose-response data relative to the constipating effect that could be used to establish dosage as an antidiarrheal. The Panel concludes the constipating effect sometimes observed with effective antacid therapy is not a rational basis for claimed efficacy as an antidiarrheal.

DATA PERTINENT FOR EFFECTIVENESS

Data are needed on mechanism(s) of action and a dose-response relationship. Effectiveness should be tested in well-controlled clinical trials comparing calcium carbonate with placebo. Comparison should also be with a known effective antidiarrheal. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) "Proposal Establishing a Monograph for OTC Antacid Products," published in the FEDERAL REGISTER of April 5, 1973, (38 FR 8714).

(2) AMA Drug Evaluations, 2nd Ed., American Medical Association, Chicago, p. 787, 1973.

(3) *Lactobacillus acidophilus and bulgaricus.* The Panel concludes that lactobacillus acidophilus and lactobacillus bulgaricus are safe in the amounts taken orally in antidiarrheal preparations, but finds inadequate evidence to support their effectiveness as antidiarrheal agents.

In the past 60 years well over 200 papers have reported on the use of *lactobacillus acidophilus* and *lactobacillus bulgaricus* in the treatment of diarrhea. Despite the proliferation of studies the very few controlled studies more often show lack of effectiveness than any antidiarrheal effect. The many clinical trials reported are not only uncontrolled but usually ignore the well-defined evidence that establishment of lactobacillus as the dominant fecal flora requires the administration of large amounts (240 to 400 gm) per day of an appropriate carbohydrate such as lactose or dextrin. Dominant colonization, in fact, can be induced by such carbohydrate alone without supplemental lactobacilli (Refs. 1, 2 and 3). Colonization is virtually impossible in the presence of antibiotic therapy; this fact is theoretically inconsistent with the use of lactobacilli to attempt control of antibiotic diarrhea.

The Panel has been informed that additional clinical studies are in progress. In view of this, the Panel finds it appropriate to place lactobacillus in Category III.

DATA PERTINENT FOR EFFECTIVENESS

The clinical efficacy of lactobacillus should be established in a well-controlled, double-blind study in diarrhea of two or more types. The stool frequency, weight, volume, pH and dominant flora should be included in the evaluation of response of well-matched groups receiving lactobacilli, lactobacilli plus carbohydrate, carbohydrate alone and placebo. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) Cheplin, H. A. and L. F. Rettger, "Studies on Intestinal Implantation of Bacillus acidophilus," Proceedings of the Society of Experimental Biology and Medicine, 17:192–195, 1920.

(2) Conn, H. O. and M. H. Floch, "Effect of Lactulose and Lactobacillus acidophilus on the Fecal Flora," American Journal of Clinical Nutrition, 23:1588–1594, 1970.

(3) Macbeth, W. A. A. G., E. H. Kass and W. V. McDermott, Jr. "Treatment of Hepatic Encephalopathy by Alteration of Intestinal Flora with Lactobacillus acidophilus," Lancet, 1:399–403, 1965.

(3) *Sodium carboxymethylcellulose.* The Panel concludes that sodium carboxymethylcellulose is safe in the small amounts usually taken orally in antidiarrheal products (200 milligrams 2 to 4 times per day) but that there is insufficient evidence to establish effectiveness as an antidiarrheal agent.

Sodium carboxymethylcellulose is a semisynthetic cellulose derivative which was previously evaluated as a bulk laxative. It is categorized in several texts as a thickening agent to increase the viscosity of various solutions (Refs. 1 and 2). The Panel surmises that increase in the viscosity of the diarrheal fluid and the possible adsorptive qualities might be the rationale for inclusion in an antidiarrheal product. However, the Panel was unable to locate any studies substantiating the effectiveness of carboxymethylcellulose in the treatment of diarrhea at any dose.

DATA PERTINENT FOR EFFECTIVENESS

The Panel finds sodium carboxymethylcellulose safe in the amounts usually taken orally and would encourage studies to determine effectiveness of a potentially useful antidiarrheal preparation. Effectiveness should be tested in well-controlled clinical trials comparing sodium carboxymethylcellulose with placebo. Comparison should also be made with a known effective antidiarrheal. In addition, data are needed on mechanism(s) of action and dose-response relationship. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) The Pharmacopeia of the United States of America, 18th Rev., The United States Pharmacopeial Convention, Inc., Washington, D.C., p. 593–594, 1970.

(2) Wilson, C. O., O. Gisvold and R. F. Doerge, Textbook of Organic Medicinal and Pharmaceutical Chemistry, 5th Ed., J. B. Lippincott, Co., Philadelphia, pp. 789, 1966.

(e) *Labeling claims for specific ingredient—Bismuth subsalicylate.* The Panel concludes that claims that bismuth produces a protective coating that corrects the symptoms of upset stomach, indigestion and nausea are unfounded. The use of a single ingredient for dual or multiple symptoms must be appropriate and rational therapy for a significant proportion of the population. In the case of bismuth subsalicylate, claims of effectiveness for the treatment of a number of symptoms such as nausea, indigestion, upset stomach, etc., in addition to the primary claim as an antidiarrheal, may be rational provided the medication is proven to be effective against each symptom, and there is a significant target population having such concurrent symptoms to justify its use, as for example, individuals suffering from travel related symptoms such as those commonly occurring in the "Turista" syndrome.

DATA PERTINENT FOR EFFECTIVENESS EVALUATION

The Panel concurs with the conclusions of the OTC Antacid Panel in a proposal published in the FEDERAL REGISTER of April 5, 1973 (38 FR 8714) that such claims (nausea, indigestion, upset stomach, etc.) "* * * provide evidence of

effectiveness consisting of statistically valid clinical trials in relieving each of these symptoms for which a claim is made." (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

G. PRODUCTS CONTAINING MULTIPLE ANTIDIARRHEAL INGREDIENTS

1. *General Statements* a. The Panel has followed the regulation (21 CFR 330.10(a)(4)(iv)) which states:

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 direction for use, and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

b. The Panel concludes that, in general, the fewer the ingredients, the safer and more rational the therapy. The Panel believes that the interests of the consumer are best served by exposing the user of OTC drugs to the fewest ingredients possible at the lowest possible dosage regimen consistent with a satisfactory level of effectiveness.

c. The Panel concludes that OTC drugs should contain only such inactive ingredients as are necessary for pharmaceutical formulation.

2. *Requirement of significant contribution.* The Panel has determined that each claimed active ingredient in the combination must make a significant contribution to the claimed effect. In the absence of data showing the minimum dose necessary to achieve the intended antidiarrheal effect, the amount of ingredient present in antidiarrheal products must be at least equal to the currently accepted minimum dose level for such active ingredients as set forth elsewhere in this document.

The Panel found it impossible to develop a formula for establishing a level below the minimum effective dose level for an ingredient as a single entity at which it could reliably be stated that each antidiarrheal ingredient would make a contribution to a combination drug product. This may be possible with other agents as antacid combination products where the contribution of each antacid can be determined by chemical titration. Antidiarrheals are believed to have a minimum effective dose below which there are few measurable responses. The Panel recognizes that it is possible that some ingredients may be proved to contribute to the effectiveness of a combination product in amounts below the generally recognized minimum effective daily dose. However, because of the numerous variables involved (e.g., differing modes of action, etc.), the Panel could not select one lower level of an active ingredient which may be assumed to be effective in a combination product.

Moreover, the Panel could not establish the percentage of contribution that an active ingredient must make to the effectiveness of the product in order for that contribution to be considered "significant."

The Panel concluded that where a combination product is permitted, as discussed below, it is sufficient to demonstrate in well-controlled clinical trials (Section I below—Data Required for Antidiarrheal Ingredient Evaluation) that each of the ingredients makes a statistically significant contribution to the claimed effect. As long as "statistical significance" is shown, the Panel concludes that a contribution toward antidiarrheal effect will also have been shown to be clinically "significant."

3. *Safety and effectiveness.* In its consideration of active ingredients the Panel reviewed the safety and effectiveness of all the combinations submitted. However, the Panel could not place any combination reviewed in Category I because of a lack of sufficient information concerning the safety and/or effectiveness of such ingredients as contained in the submitted combinations.

The Panel considers it important that the minimum effective dose be established for each ingredient in a combination product.

4. *Single active ingredients.* OTC drugs containing safe and effective single ingredients are preferred to those having multiple active ingredients because of the reduced risks of toxic effects, synergistic effects, allergic and/or idiosyncratic reactions, and possible unrecognized and undesirable drug interaction(s).

It is an established medical principle to give only those medications, preferably as single entities, necessary for the safe and effective treatment of the patient. This principle applies equally to self-medication. To add needlessly to the patient's medication increases the risk of adverse reactions.

5. *Limitation of ingredients in antidiarrheal combination products.* Given the paucity of effective antidiarrheal agents and the multiplicity of pathologic mechanisms causing common diarrhea, the Panel finds it difficult to define or restrict the total number of ingredients. However, in keeping with its conclusion that the fewer the ingredients the safer the combination, Category I combinations will be limited to 2 ingredients.

6. *Active ingredients not reviewed by the Panel.* Each claimed active ingredient must be an ingredient that has been reviewed by the Panel. If a product contains an active ingredient that has not been reviewed by the Panel and consequently not found in this document, such ingredient is automatically classified as a Category II ingredient, i.e., it is not generally recognized as safe and/or effective. Appropriate animal and human testing and prior approval by the Food and Drug Administration is required before a product containing such an ingredient may be marketed.

7. *Review of submitted combination products.* The Panel considered only those combination products submitted pursuant to the notice published in the FEDERAL REGISTER of February 8, 1973 (38 FR 3614) and included above in paragraph A. The Panel recognizes that other combination products may be in the market place but it has either no knowledge of such products, or insufficient data with respect to such products to make a reasonable judgment of safety and/or effectiveness.

Accordingly, the Panel recommends that any new combination, or any presently marketed combination not submitted to this Panel be evaluated through the new drug procedures, or be the subject of an appropriate petition to the Commissioner to review or amend the OTC antidiarrheal monograph.

8. *Combinations containing nonantidiarrheal ingredients.* Products combining antidiarrheal ingredient(s) with other ingredients having nonantidiarrheal pharmacologic effects are considered irrational, unless it can be shown that there is a significant target population requiring concurrent treatment of symptoms that require antidiarrheal(s) and nonantidiarrheal(s) in combination. The common symptoms of gastroenteritis would support the rationale of combining an antidiarrheal with an antiemetic or an agent for the treatment of gastritis but no such effective combination has been found.

Nonantidiarrheal ingredient(s) may be present as inactive ingredients in antidiarrheal products as an aid to formulation or to palatability. However, the presence of such ingredient(s) must not be emphasized or identified as active ingredients in the labeling or in the advertisement of such product(s).

9. *Classification of submitted combinations.* Within the categories defined by the Panel the combinations submitted for review are classified as follows:

ORAL DOSAGE FORMS

Category I combinations

None yet designated.

Category II combinations

a. Bismuth subsalicylate, phenyl salicylate (salol), and zinc phenolsulfonate.

b. Bismuth subsalicylate, precipitated calcium carbonate, and aminoacetic acid (glycine, glycocol).

c. Kaolin, pectin, hyoscyamine sulfate, atropine sulfate, scopolamine (hyoscine) hydrobromide, and powdered opium.

d. Kaolin, pectin, hyoscyamine sulfate, atropine sulfate, and scopolamine (hyoscine) hydrobromide.

e. Bismuth subnitrate, rhubarb fluidextract, potassium carbonate, and calcium hydroxide.

f. Activated attapulgite, pectin, and hydrated alumina powder.

g. Paregoric, pectin, and kaolin.

h. Kaolin, hydrated alumina powder, and pectin.

i. Tincture of opium, homatropine methylbromide, and pectin.

Category III combinations

a. Lactobacillus acidophilus and sodium carboxymethylcellulose.

b. Lactobacillus acidophilus and lactobacillus bulgaricus.

c. Activiated attapulgite and pectin.

d. Kaolin and pectin.

e. Tincture of opium and pectin.

f. Kaolin and hydrated alumina powder.

RECTAL DOSAGE FORMS

None yet designated.

10. *Ingredients included in Category I combinations.* Since there are presently no acceptable Category I combinations the Panel is setting forth guidelines whereby present and future Category I ingredients may reasonably be considered for a Category I combination. The Panel recommends:

a. The combination be limited to 2 Category I active antidiarrheal ingredients.

b. Each ingredient in the subject combination must be present within the dosage range for a Category I antidiarrheal ingredient, as set forth elsewhere in this document. The Panel recommends that the Food and Drug Administration designate additional Category I antidiarrheal agents as appropriate safety and efficacy data become available.

c. The specific combination of ingredients must be an approved Category I combination. Since there are no Category I combinations presently designated, the Panel recommends that the Food and Drug Administration designate such combinations as appropriate safety and efficacy data become available.

11. *Criteria for Category II combination products.* A combination is classified by the Panel as a Category II product, i.e., one that is not generally recognized as safe and effective, if any of the following apply:

a. The combination contains 3 or more active antidiarrheal ingredients.

b. The combination contains any ingredient that is above the maximum dosage set for such agent as listed elsewhere in this document or in the future designated by the Food and Drug Administration for an antidiarrheal agent.

c. The combination contains any active antidiarrheal ingredient that has not been reviewed by the Panel and accordingly not listed in this document or in the future designated by the Food and Drug Administration.

12. *Criteria for Category III combination products.* A combination is classified as a Category II combination if any of the following apply:

a. If any Category I ingredient is below the minmum dosage range set by the Panel elsewhere in this document for such respective ingredient.

b. If 1 or more ingredient(s) are Category III ingredients, as set forth elsewhere in this document for single active antidiarrheal ingredients.

13. *Reclassification requirements for Category III combinations to Category I combinations.* a. For any Category III combination found in paragraph 9 where one or both ingredients fall below the minimum effective level as set forth elsewhere in this document for such individual ingredient(s), tests must be performed to substantiate the effectiveness of any such ingredient. The Panel recommends that such testing be pursued under the NDA procedures or petition to the Agency for appropriate modification of the monograph to permit such lower dosages.

b. (1) Any combination that contains one or both ingredients in Category III, as set forth elsewhere in this document, must be tested to satisfy Category I requirements for each such ingredient.

(2) Two Category I ingredients in a combination not found in paragraph 9 must be petitioned to the Agency for an appropriate amendment to the monograph or proceed through the NDA procedures.

14. *Combinations containing nonantidiarrheal ingredients.* Products combining antidiarrheal ingredient(s) with other ingredients having nonantidiarrheal pharmacologic effects are considered irrational, unless it can be shown that there is a significant target population requiring concurrent treatment of symptoms that require antidiarrheal(s) and nonantidiarrheal(s) in combination.

Nonantidiarrheal ingredient(s) may be present as inactive ingredients in antidiarrheal product as an aid to formulation or to palatability. However, the presence of such ingredient(s) must not be emphasized or identified as active ingredients in the labeling or in the advertisement of such product(s).

H. INACTIVE INGREDIENTS

When antidiarrheal products contain inactive ingredients, the Panel recommends that the inactive ingredients be listed on the label with or without the amounts contained in a recommended dose. The availability of sodium, potassium, and magnesium in the maximum recommended daily dose should be stated on the label. (See labeling discussion above for antidiarrheal products.) If significant amounts are present, special warnings on the label should be provided (as indicated previously in this document) for patients with heart disease and renal disease or those on a low salt diet.

I. DATA PERTINENT FOR ANTIDIARRHEAL INGREDIENT EVALUATION

The Panel has given considerable thought to the problem of demonstrating that an antidiarrheal is safe and effective. When a drug is available for widespread use, as in OTC products, its safety and effectiveness must be well documented by toxicological data, data on the absorption, distribution, fate and excretion of the drug, the pharmacological effects of the drug, and the mechanism of action. The drug should also meet certain effectiveness standards.

The Panel recommends that information such as the following be obtained in the categories of data when relevant and pertinent to the drug under study: Toxicological data, absorption, distribution, fate, and excretion (ADFE) data, mechanism of action. The drug should standards.

1. *Toxicological data.* A variety of toxicological data can be obtained to demonstrate that an antidiarrheal is safe. Manufacturers are not expected to obtain all of the following data, but are expected to obtain those data relevant to the unanswered questions regarding the safety of their products. The Panel recommends that data such as the following be obtained in animal studies and in clinical studies in man. Certain data on human subjects, such as lethal doses and chronic toxicity, will be available only from poison control centers, hospitals, medical centers, or medical examiners. However, the Panel considers such data important and attempts should be made to obtain them.

(a) *Preclinical animal studies.* (1) The oral LD_{50} established in no less than two animal species.

(2) Determinations of histologic and biochemical alterations in animals given lethal doses acutely or low doses chronically.

(3) Studies of teratogenicity and embryolethality. Studies of effects on fertility, delivery, and nursing offspring may also be indicated.

(b) *Clinical studies.* (1) Biochemical tests of liver and renal function and measurement of serum electrolytes after a therapeutic dose.

(2) Chronic toxicity studies in man, especially in relation to altered function and cytological changes of the mucosa of the intestinal tract of man.

(3) Adverse drug reactions should be well documented. Substantial effort should be made to have physicians document side effects, especially those of a serious nature as indicated.

(4) Minimal lethal dose by single oral ingestion and in divided doses when such data are available from accidental or deliberate overdosing.

(5) Maximal tolerated dose from single oral ingestion, or divided multiple oral ingestions, when such data are available from accidental or deliberate overdosing.

2. *Absorption, distribution, fate, and excretion (ADFE) as determined by currently accepted methods.* Since ADFE bears directly on the safety of drugs and occasionally on the mechanism of action of antidiarrheals, appropriate data should be provided for all active ingredients and their active metabolic products. The methods for obtaining these data are established and are not different from those used in the study of ADFE of other drugs. Data such as the following would provide sufficient information regarding ADFE. Manufacturers are not expected to obtain all of the following data, but are expected to obtain those data relevant to the unanswered questions regarding ADFE of their products:

a. The percentages of various oral doses of the drug which are absorbed in man.

b. The percentages of various oral doses of the drug which are excreted in the urine in man.

c. The percentages of various oral doses of the drug which are excreted in breast milk.

d. The metabolic fate in man of absorbed but unexcreted drug.

e. The fate of unabsorbed drug in man.

f. The net bioavailability of the drug in man.

g. The ingredients and metabolic products associated with fecally excreted drug and/or its unabsorbed intraluminal biotransformation products.

h. The ingredients and metabolic products associated with renally excreted drug and/or its renally excreted biotransformation product.

3. *Effects.* The Panel recognizes that the mechanism of action of many safe and effective drugs is unknown. Nevertheless, data should be provided which serve to elucidate the pharmacologic effects of antidiarrheals. For example, if they are claimed to be adsorptive agents, adsorption must be documented. If the claim is based upon the effects of an anticholinergic action on motility, appropriate methods should be used that will demonstrate the effects of the agent on intestinal or colonic motility. In addition, it is recommended that data such as the following be obtained. Manufacturers are not expected to obtain all of these data, but are expected to obtain those data relevant to the unanswered questions regarding the mode of action of their products:

a. Effects of oral drug on jejunal secretion and the flux of ions and water at the levels of jejunum, ileum, proximal and distal colon.

b. Effects of the oral drug on the absorption of actively transported ions, sugars, and amino acids.

c. Effects of the oral drug on the absorption of carbohydrate, protein, lipids and fat-soluble vitamins.

d. Effects of the oral drug on the absorption of other drugs.

e. Effects of the oral drug on secretion of gastrointestinal enzymes and hormones.

f. Effects on intestinal smooth muscle such as contractility and electromyographic changes.

4. *Effectiveness standards.* The effectiveness of antidiarrheal agents can be tested using patients with diarrheal disorders as occur in travel and commonly referred to as "Turista", or in institutionalized patients where periodic epidemic mild diarrhea may occur, or in outpatient clinics and pharmacies where pediatric and adult patients are frequently seen with diarrheal problems and in specific situations such as radiation diarrhea. Although antidiarrheal agents can be tested in both human and animal models where diarrhea has been induced, i.e., cholera model, the Panel questions the relevance of these to human disease states as related to nonspecific common diarrhea. Antidiarrheals may be of a number of different types. When the antidiarrheal product contains more than one active ingredient, the double-blind, Latin square, design is particularly suited for testing the effectiveness of individual ingredients as well as comparing their effect against that of placebo. When it is impossible or impractical to devise an acceptable placebo, the antidiarrheal ingredient may be compared with another acceptable agent and studied in parallel groups. When experimental models of induced diarrhea are used, each subject can serve as his own control, but the period of study should be sufficiently long to clearly demonstrate differences.

Specific parameters that can be measured quantitatively to determine the effectiveness of an antidiarrheal agent include many of those used for determining the effectivenes of a laxative agent. For an antidiarrheal agent, the following parameters would be considered appropriate for assessing the effectiveness of the agent. Manufacturers are not expected to obtain all of the following data, but are expected to obtain those data relevant to the unanswered questions regarding the effectiveness of their products:

a. *Frequency.* The Panel recognizes that frequency of stool evacuation is quite variable among normal, healthy individuals and may range from three bowel movements per day to three per week. Frequency should be expressed in number of evacuations per unit time such as 24 hours or per week, etc.

b. *Volume.* The volume of stool evacuated during a unit time period is easy to determine and is usually expressed in milliliters or cubic centimeters per 24 hours or other time period. Average normal is 150 ml/24 hours.

c. *Weight.* Weight of stool is expressed in grams per 24 hours or other unit time period. Weight is independent of consistency and important in determining the effectiveness of antidiarrheals. Average normal is 110 to 130 grams per 24 hours.

d. *Water content.* Water content of the feces is usually expressed as percent water. Excess water excretion is the hallmark of diarrhea and important in evaluating the effectiveness of antidiarrheals. Average normal is 60 to 85 percent. Since hydrophilic agents may decrease stool frequency and percent water content but actually increase the daily excretion of water and electrolytes, the combined information is particularly relevant to the effect of antidiarrheal in young children.

Because of the large variation in the water content of normal stools, measurement on stool water content for each subject before, during and after treatment become very important.

e. *Consistency.* Consistency should be evaluated in some objective manner in addition to the subject's sensation of ease of passage or the observer's description of the stool as liquid, soft, hard, etc. Since major changes in the consistency of stool (and other materials) may occur with little change in either percent water or total stool weight, the Panel recommends a quantitative determination of consistency. There are few rheologic studies of colonic content (Refs. 1 and 2) but instrumentation used to quantitate the consistency of compounds, such as bread doughs, various pastes, and soils might be appropriate. If a tube viscometer is used, consistency is expressed in terms of shear rate and if a penetrometer is used, consistency is expressed in terms of kilogram per square centimeter.

f. *Fecal solids.* Fecal solids are usually expressed in grams per 24 hours. Average normal is 25 grams/24 hours.

g. *Bulk density.* Bulk density is expressed as unit weight per unit volume, usually grams per cubic centimeter, and is determined by drying a known volume to a constant weight at 105° C. Bulk density is an important parameter in determining the effectiveness of bulk-forming laxatives. Average normal is 0.15 to 0.18 gm/cc.

h. *Transit time.* Transit time may be expressed by either the "time method" or the "distance method" by use of nonabsorbable markers such as polyethylene glycol, nonabsorbable color dyes such as carmine, and nonabsorbable radioactive materials such as chromium. In addition, inert colored plastic beads have been used as a marker to determine transit time. The use of some markers, such as carmine dye, is associated with considerable "streaming" and should be taken into account when markers are used to separate treatment periods. Average normal is 40 to 60 hours for complete transit of the digestive tract.

i. *Fecal excretion rate.* Fecal excretion rate is expressed in weight per unit time, usually grams per hour. Average normal fecal excretion rate is 6 grams per hour.

j. *Stool electrolytes, bile salts, etc.* Feces contain a number of substances that might be appropriate to measure in evaluating antidiarrheal agents. Stool electrolytes, particularly sodium, potassium and chloride, may be markedly altered by diarrhea and losses may be actually increased by antidiarrheals such as hydrophilic agents.

REFERENCES

(1) Picologlou, B. F., P. D. Patel, and P. S. Lykoudis, "Biorheological Aspects of Colonic Activity: Part I. Theoretical Considerations," Biorheology, 10:431–440, 1973.

(2) Picologlou, B. C., P. D. Patel and P. S. Lykoudis, "Biorheological Aspects of Colonic Activity: Part II. Experimental Investigation of Rheological Behavior of Human Feces," Biorheology, 10:441–446, 1973.

III. ANTIEMETICS

Pursuant to the notice published in the FEDERAL REGISTER of February 8, 1973 (38 FR 3614) requesting the submission of data and information on OTC antiemetic drugs, the following firms made submissions relating to the indicated products:

A. DATA AND INFORMATION SUBMISSIONS

FIRM	MARKETED PRODUCTS
Pfizer Pharmaceuticals, New York, NY 10017	Bonine.
William H. Rorer, Inc., Fort Washington, PA 19034.	Emetrol.
Searle Laboratories, Chicago, IL 60680	Dramamine, Dramamine Liquid.
Norwich Pharmaceutical Co., Norwich, NY 13815.	Pepto-Bismol Liquid, Pepto-Bismol Tablets.

B. THE LABELED INGREDIENTS CONTAINED IN SUBMITTED PRODUCTS

Aminoacetic acid (glycine, glycocol)
Bismuth subsalicylate
Dimenhydrinate
Meclizine hydrochloride
Orthophosphoric acid
Phenylsalicylate (salol)
Sugar (invert)
Zinc phenolsulfonate

The Panel also undertook a review of the following: Cyclizine hydrochloride.

C. EMESIS AND THE USE OF OTC ANTIEMETICS

Severe nausea, and the realization that one is about to vomit, is one of the more dreadful conditions suffered by man. Motion sickness accompanied by nausea and vomiting is not unusual and may be prevented effectively by a number of antihistamine-like drugs available in OTC antiemetic products. Motion sickness occurs when visual and vestibular stimuli are not in accord, particularly when the head rotates in two axes simultaneously. Some individuals are more resistant to motion sickness than others, but none is immune. Travel aboard ship, in airplanes, or even in automobiles may induce motion sickness. OTC antiemetics are also needed for other causes of nausea and vomiting as in patients undergoing chemotherapy or radiation therapy for malignancy, and episodic vomiting of childhood.

D. CLASSIFICATION OF ACTIVE INGREDIENTS

The Panel reviewed all active ingredients which were the subject of submissions made to the Panel pursuant to the standards for safety, effectiveness, and truthful labeling.

In accordance with the regulation (21 CFR 330.10), the Panel's findings with respect to these ingredients are set forth in three categories:

I. Conditions under which antiemetic products are generally recognized as safe and effective and are not misbranded.

II. Conditions under which antiemetic products are not generally recognized as safe and effective or are misbranded.

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

The Panel recommends for each class of drugs:

1. That the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient to classify such conditions either as generally recognized as safe and effective and not misbranded or as not being generally recognized as safe and effective or would result in misbranding (Category III) be permitted to remain in use for 2 years after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel.

E. REVIEW OF ACTIVE INGREDIENTS

All active ingredients which were the subject of submissions made to the Panel were carefully reviewed. The Panel considered all pertinent data and information available to the Panel in arriving at its conclusions and recommendations.

1. *Conditions under which antiemetic products are generally recognized as safe and effective and are not misbranded.* The following antiemetic ingredients were classified as safe and effective and not misbranded:

BENZHYDRYL PIPERAZINE ANTIHISTAMINES

Cyclizine
Meclizine

DIMENHYDRINATE

(a) *Benzhydryl piperazine antihistamines*—(1) *Cyclizine and Meclizine.* The Panel concludes that cyclizine and meclizine are safe and effective in the amounts taken orally (meclizine, for adults 25 to 50 milligrams once daily; and cyclizine, 50 milligrams up to 4 times daily and for children 6 to 12 years 25 mg up to 3 times daily) in antiemetic products for the treatment of nausea and vomiting of motion sickness.

Meclizine is a member of the benzhydryl piperazine group of antihistamine compounds which also includes cyclizine. Chemically, these compounds differ from other antihistamines in that the alkylamino group exists as a ring structure.

An extensive literature is available to support the conclusion that meclizine is effective and safe in the management of motion sickness (Refs. 1 through 5). The drug has a relatively long duration of action and is reported to afford 24-hour protection against the symptoms of motion sickness (Refs. 3 and 4).

Meclizine is relatively free of side effects when administered in therapeutic doses, although sedation (drowsiness) sometimes occurs and may be troublesome in those persons who drive automobiles or operate other machinery. Containers of OTC meclizine tablets are labeled to warn of this potential hazard.

In 1966, the Food and Drug Administration acting on the recommendation of an Ad Hoc Advisory Committee, required relabeling of the OTC products containing meclizine and cyclizine to include the following warning:

Not for use by women who are pregnant or who may become pregnant, unless directed by a physician, since this drug may have the potentiality of injuring the unborn child.

This labeling warning was prompted by concern that the drug may have teratogenic or embryolethal potential. The Panel has carefully reviewed more recent epidemiological data, the previous report of the FDA Ad Hoc Advisory Committee, and the position of the American Teratology Society regarding the limitations of extrapolating animal data to man (Ref. 6). The Panel concluded that the scientific data do not warrant a need to restrict the use of meclizine or cyclizine or require the labeling to include a pregnancy warning, but reevaluation may be needed as additional data become available.

The Panel reviewed data on 50,282 pregnant women of which 1,014 had used meclizine during the early stages of pregnancy. Data showed that the incidence of malformation of the offspring of the 1,014 women was not statistically increased over that of the other 49,268 pregnant women not using meclizine, but who had used other drugs during pregnancy. Further, the Panel had indirect evidence that meclizine is not embryocidal and that the incidence of specific teratogenicity (e.g., cleft palate) was actually less in the data compiled from the use of meclizine in human pregnancies than that which might have been expected from the previous underlying animal studies which had led to the pregnancy warning (Ref. 7).

LABELING

A claim should be made only for the effectiveness of benzydryl piperazine group in the treatment of nausea and vomiting due to motion sickness. Claims for effectiveness for the treatment of nausea and vomiting of other causes have not been proven. The label should carry the warning that this drug can produce drowsiness and persons taking it should be cautioned regarding driving automobiles or operating heavy machinery or equipment. Specific warnings should also cite its anticholinergic action and patients with glaucoma or enlargement of the prostrate gland should be cautioned regarding taking this OTC product other than under the direction of a physician. For cyclizines the label should also contain the following warning:

Do not give to children under 6 years of age except under the advice and supervision of a physician.

For meclizine, the label should also contain the following warning:

Do not give to children under 12 years of age except under the advice and supervision of a physician.

REFERENCES

(1) Chinn, H. I., et al., Evaluation of Drugs for Protection Against Motion Sickness Aboard Transport Ships, Journal of the American Medical Association, 160:755–760, 1956.

(2) Arner, O., H. Diamant, L. Goldberg and G. Wrange, "Antihistamines in Sea Sickness," Archives Internationales de Pharmacodynamie et de Therapie, 117:404–418, 1958.

(3) Handford, S. W., T. E. Cone, H. I. Chinn and P. K. Smith, "Drugs Preventing Motion Sickness at Sea," Journal of Pharmacology and Experimental Therapeutics, 111: 447–453, 1954.

(4) Chinn, H. I., S. W. Handford, P. K. Smith, T. E. Cone, Jr., R. F. Redmond, J. V. Maloney and C. M. Smythe, "Evaluation of

Some Drugs in Seasickness," Journal of Pharmacology and Experimental Therapeutics, 108:69–79, 1953.

(5) Franks, J. J., L. J. Milch and E. V. Dahl, "Prevention of Airsickness with Meprobamate," Journal of the American Medical Association, 181:263–264, 1962.

(6) Staples, R. E., "Teratogens and the Delaney Clause," Science, 185:813–814, 1974.

(7) Shapiro, S., Boston Children's Medical Center, Testimony Before OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Panel, October 11, 1974.

(b) *Other active ingredient—Dimenhydrinate.* The Panel concludes that 50 to 100 milligrams dimenhydrinate is safe and effective in the amounts usually taken orally in antiemetic products (200 mg to 400 mg daily in 4 divided doses) for the treatment of nausea and vomiting associated with motion sickness. The dosage for children 2 to 5 years of age is 12.5 to 25 mg up to 3 times daily and for children 6 years and over 25 to 50 mg up to 3 times daily.

Dimenhydrinate is the 8-chlorotheophyllin salt of the antihistamine diphenhydramine. Since introduction in 1949, the effectiveness of dimenhydrinate against seasickness and airsickness has been repeatedly demonstrated. Dimenhydrinate is relatively free of side effects when administered in recommended doses, although drowsiness sometimes occurs and may prove troublesome in individuals driving an automobile or operating other types of machinery.

LABELING

A claim should be made only for the effectiveness of dimenhydrinate in the treatment of nausea and vomiting due to motion sickness. The Panel is unaware of the existence of acceptable scientific data relating to claims for effectiveness in the treatment of nausea and vomiting from other causes. Such additional claims have not been proven.

The label should carry the warning that this drug can produce drowsiness and persons taking it should be cautioned regarding driving automobiles or operating heavy machinery or equipment. Specific warnings should also cite its anticholinergic action and patients with glaucoma or enlargement of the prostate gland should be cautioned regarding taking this OTC product other than under the direction of a physician.

REFERENCES

(1) Gay, L. N. and P. E. Carliner, "The Prevention and Treatment of Motion Sickness. I. Seasickness," Science, 109:359, 1949.

(2) Chinn, H. I. and P. K. Smith, "Motion Sickness," Pharmacological Reviews, 7:33–82, 1955.

2. *Conditions under which antiemetic products are not generally recognized as safe and effective or are misbranded.* The Panel found that there was no scientific or even sound theoretical basis for claimed effectiveness of a number of ingredients used in OTC antiemetic products. The Panel concludes that it is misleading to make claims regarding multiple indications for use of single ingredients when no evidence exists to support such claims.

The Panel further concludes that the following ingredient, should be removed from the market as an antiemetic agent unless and until further scientific testing supports its use:

INDIVIDUAL ACTIVE INGREDIENT

Aminoacetic acid (glycine, glycocol)

(a) *Individual active ingredient*—(1) *Aminoacetic acid (glycine, glycocol).* The Panel concludes that aminoacetic acid is safe in the amounts usually taken orally in antidiarrheal products, but there is no evidence to support its effectiveness as an antiemetic agent.

The Panel can find no evidence to support the claim that glycine (identified in the Antacid Monograph) alone or in combination is an effective antiemetic or antinauseant. The claim that glycine is effective for the relief of "nausea," "indigestion," "gas," "fullness," "bloating," "pressure," and "upset stomach" is not supported by any carefully controlled clinical studies. Since hyperacidity is not a known cause of vomiting there is no sound theoretical or scientific basis to indicate that the addition of glycine to antiemetics would offer relief of the indicated symptoms.

3. *Conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the active ingredients listed below:

Bismuth subsalicylate
Phenyl salicylate (salol)
Phosphorated carbohydrate
Zinc phenolsulfonate

The Panel believes it reasonable to allow 2 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If data regarding adequate effectiveness and safety are not obtained within 2 years, however, the ingredients listed in this category should no longer be marketed as active ingredients in over-the-counter products but may be permitted as inactive ingredients if the amount employed is necessary for the pharmaceutical formulation of the product. Some ingredients may be present in products in quantities which are pharmacologically inactive by virtue of being subclinical doses. In these cases the ingredients may be included for pharmaceutical necessity such as improving the stability or palatability of the product. However, it is the opinion of the Panel that if an ingredient was originally claimed by the sponsor to be active, it cannot then also be claimed inactive and included for formulation purposes unless the following are documented: The absolute necessity for inclusion in the pharmaceutical formulation, the safety of the quantity in the finished product, and the inactivity of the quantity in the finished product.

The Panel has given careful consideration to the types of studies and types of data to be required for removing a claimed active antiemetic ingredient from Category III and placing it in Category I. See data required below for antiemetic ingredient evaluation. In general, to demonstrate effectiveness, the design of the study should have a sound scientific basis (e.g., a randomized, double-blind, cross-over study comparing claimed active ingredients to placebo), the clinical trial should be carefully controlled (e.g., consideration given to selection of subjects representative of general population as well as diet, activity, travel, etc. of subjects being studied), and quantitative measurement of various parameters appropriate for the claimed effects of the ingredient. To demonstrate safety, appropriate toxicological studies in experimental animals (preferably primate) and man are required as outlined elsewhere.

(a) *Bismuth subsalicylate.* The Panel concludes that bismuth subsalicylate is safe in the amounts usually taken (1 to 4 grams) orally. However, the Panel concludes that there is insufficient evidence to establish effectiveness of bismuth subsalicylate as an antiemetic.

Evidence available to the Panel indicates that emesis in dogs induced by 15 ml of ipecac syrup can be controlled effectively by pretreatment with 0.35 gm/kg of bismuth subsalicylate in a liquid preparation (Ref. 1). In human subjects, 1 ounce of a bismuth preparation was no better than 1 ounce of water in preventing emesis which had been induced by a dose of 15 ml of ipecac syrup.

Studies evaluating the effectiveness of bismuth compounds for "upset stomach" or "nausea" suffer from the vague definitions of these complaints. Bismuth compounds appear to control the uncomfortable feelings accompanying low doses of ipecac syrup, but whether pretreatment with bismuth (subsalicylate) followed by ipecac is an appropriate model for the consumer's "upset stomach" is debatable. It is difficult to postulate any effect of any drug on distention symptoms induced by overeating, unless it affects gastric emptying time, the tone of the stomach wall or intragastric pressure. However, bismuth subsalicylate has been promoted for use to treat symptoms such as "indigestion", "gas", "full stomach", etc. The Panel concurs with the Commissioner of Food and Drugs when he noted in the tentative final order establishing the Antacid monograph published in the FEDERAL REGISTER of November 12, 1973 (38 FR 31260), that some of these symptoms are vague, and most are poorly understood (Ref. 2).

LABELING

Special labeling should indicate that stools may become dark with use of any bismuth compound.

DATE PERTINENT FOR EFFECTIVENESS

Bismuth is not promoted as an antimotion sickness agent, thus, motion sickness models would not be appropriate for this agent.

Vomiting induced by the oral administration of ipecac, pepper sauce, mustard, or potassium chloride are suggested models for the claim of antiemesis. The investigator using these models should ensure that patients not be pretreated with bismuth.

A model must be developed that approximates the upper gastrointestinal symptoms produced by food intolerance, and it must produce these sensations with some reliability and measure of objectivity. The Panel is unable to define such claims as "upset stomach," and "distention". Accordingly, the Panel cannot appropriately suggest a model to test the effectiveness of bismuth for such claims.

The Panel concurs with the conclusions of the OTC antacid Panel set forth in the proposal published in the FEDERAL REGISTER of April 5, 1973 (38 FR 8714) that such claims provide evidence of effectiveness. The evidence should consist of statistically valid clinical trials to support each of the respective claims. (See paragraph G below for data pertinent for antiemetic ingredient evaluation.)

REFERENCES

(1) OTC Volume 090123.[1]

(2) "Tentative Final Order for Antacid Products," published in the FEDERAL REGISTER of November 12, 1973 (38 FR 31260).

(b) *Phenyl salicylate (salol).* The Panel concludes that salol is safe in the amounts usually taken orally in OTC products, but there is no evidence to support its effectiveness as an antiemetic agent.

The Panel can find no evidence to support the claim that salol alone or in combination is an effective antiemetic or antinauseant. The claim that phenyl salicylate is effective for the relief of "nausea," "indigestion," "gas," "fullness," "bloating," "pressure," and "upset stomach" is not supported by any carefully controlled clinical studies.

DATA PERTINENT FOR EFFECTIVENESS

Well-controlled, double-blind clinical trials are needed to compare the antiemetic effect of phenylsalicylate, alone and if desired in combination, as compared with placebo and with an effective antiemetic. Documentation is needed of the blood salicylate levels 1 hour after ingestion. The response should be evaluated by objective changes in frequency of vomiting. Careful experimental design, definition of terms and matching of subjects is needed to assess the effect on subject complaints of malaise and nausea. (See paragraph G below for data pertinent for antiemetic ingredient evaluation.)

(c) *Phosphorated carbohydrate (levulose-dextrose-ortho-phosphoric acid).* The Panel concludes that phosphorated carbohydrate is safe in the amounts usually taken (8 to 18 grams) orally. However, the Panel concludes that there is insufficient evidence to establish effectiveness of phosphorated carbohydrate as an antinauseant-antiemetic.

Phosphorated carbohydrate preparation consists of a solution containing invert sugar (a mixture of equimolar amounts of levulose and dextrose obtained by hydrolysis of sucrose) and phosphoric acid which is used to adjust the pH of the solution to a range of 1.5 to 1.6.

A mechanism that has been cited in support of the belief that a carbohydrate-phosphoric acid mixture relieves nausea and vomiting is its potential to inhibit gastric emptying as a consequence of inhibition of gastric peristalsis and a reduction in gastric tone. It has been reported that the high osmotic pressure exerted by concentrated solutions of simple sugars (monosaccharides) inhibits gastric emptying through an action on duodenal osmoreceptors which are sensitive to high osmotic pressures (Ref. 1). However, a positive correlation between an increase in gastric emptying time and relief of nausea and vomiting has not been established.

Only a few clinical studies have been reported on the use of a carbohydrate-phosphoric acid preparation for the management of nausea and vomiting. Most of these were either uncontrolled or partially controlled investigations (Refs. 2 through 4). In the only double-blind clinical investigation, the study was poorly designed (Ref. 5).

DATA PERTINENT FOR EFFECTIVENESS

The Panel concludes that well-controlled, properly designed clinical studies are needed to establish the effectiveness of the carbohydrate-phosphoric acid solution for the control of nausea or vomiting. (See paragraph G below for data pertinent for anti-emetic ingredient evaluation.)

REFERENCES

(1) Van Liere, E. J., D. W. Northrup and J. C. Stickney, "The Effect of Glucose on the Mobility of the Stomach and Small Intestine," Gastroenterology, 7:218–223, 1946.

(2) Bradley, J. E., L. Proutt, E. R. Shipley and R. H. Oster, "An Evaluation of Carbohydrate-Phosphoric Acid Solution in the Management of Vomiting", Journal of Pediatrics, 38:41–44, 1951.

(3) Crunden, A. B., Jr. and W. A. Davis, "The Oral Use of a Phosphorated Carbohydrate Solution in Nausea and Vomiting of Pregnancy," American Journal of Obstetrics and Gynecology, 65:311–313, 1953.

(4) Tebrock, H. E. and M. M. Fisher, "Nausea and Vomiting: Evaluation of an Orally Administered Phosphorated Carbohydrate Solution," Medical Times, 82: 271–275, 1954.

(5) Agerty, H. A., "A Phosphorated Carbohydrate Solution for the Prevention of Motion Sickness," Adult and Child, 1:66, 1960.

(d) *Zinc phenolsulfonate.* The Panel concludes that zinc phenolsulfonate is safe in amounts usually taken orally in OTC products, but there is no evidence to support its effectiveness as an antiemetic agent.

The Panel can find no evidence to support the claim that zinc phenolsulfonate alone or in combination in OTC products is an effective antiemetic or antinauseant. The claim that zinc phenolsulfonate is effective for the relief of "nausea," "indigestion," "gas," "fullness," "bloating," "pressure," and "upset stomach" is not supported by any carefully controlled clinical studies.

DATA PERTINENT FOR EFFECTIVENESS

Well-controlled, double-blind clinical trials are needed to compare the antiemetic effect of zinc phenolsulfonate, alone and if desired in combination, as compared with placebo and with an effective antiemetic. The response should be evaluated by objective changes in frequency of vomiting. Careful experimental design, definition of terms, and matching of subjects is needed to assess the effect on subject complaints of malaise and nausea. (See paragraph G below for data pertinent for antiemetic ingredient evaluation.)

F. PRODUCTS CONTAINING MULTIPLE ANTIEMETIC INGREDIENTS

1. *General statements.* a. The Panel noted the regulation (21 CFR 330.10(a)(4)(iv)) which states: "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 direction for use, and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population."

b. The Panel concludes that, in general, the fewer the ingredients, the safer and more rational the therapy. The Panel believes that the interests of the consumer are best served by exposing the user of OTC drugs to the fewest ingredients possible at the lowest possible dosage regimen consistent with a satisfactory level of effectiveness.

c. The Panel further concludes that OTC drugs should contain only such inactive ingredients that are necessary for pharmaceutical formulation.

2. *Requirement of significant contribution.* The Panel has further determined that each claimed active ingredient in the combination must make a significant contribution to the claimed effect. In the absence of data showing the minimum dose necessary to achieve the intended antiemetic effect, the amount of ingredient present in antiemetic products must be at least equal to the currently accepted minimum dose range for such active ingredients as set forth elsewhere in this document.

The Panel found it difficult to quantitate the contribution of each antiemetic ingredient in combinations, as is possible with antacid combination products, for example, where the contribution of each antacid can be determined by chemical titration. Further, the minimum effective dose may vary considerably with the cause of the vomiting. The Panel recognizes that it is possible that some ingredients may be proved to contribute to the effectiveness of a combination product in amounts below the generally recognized minimum effective daily dose.

The Panel concluded that where a combination product is permitted, it is sufficient to demonstrate in well-controlled clinical trials that each of the ingredients makes a statistically significant contribution to the claimed effect.

As long as "statistical significance" is shown, the Panel concludes that a contribution toward antiemesis will also have been shown.

3. *Single active ingredients.* OTC drugs containing safe and effective single ingredients are preferred to those having multiple active ingredients because of the reduced risks of toxic effects, synergistic effects, allergic and/or idiosyncratic reactions, and possible unrecognized and undesirable drug interaction(s).

It is an established medical principle to give only those medications, preferably as single entities, necessary for the safe and effective treatment of the patient. This principle applies equally to self-medication. To add needlessly to the patient's medication increases the risk of adverse reactions.

4. *Active ingredients not reviewed by the Panel.* Each claimed active ingredient must be an ingredient that has been reviewed by the Panel. If a product contains an active ingredient that has not been reviewed by the Panel and consequently not found in this document, such ingredient is automatically classified as a Category II ingredient, i.e., it is not generally recognized as safe and/or effective. Appropriate animal and human testing and prior approval by the Food and Drug Administration is required before a product containing such an ingredient may be marketed.

5. *Review of submitted combination products.* The Panel considered only those combination products submitted pursuant to the notice published in the FEDERAL REGISTER of February 8, 1973 (38 FR 3614) and included above in paragraph —. The Panel recognizes that other combination products may be in the marketplace but it has either no knowledge of such products, or insufficient data with respect to such products to make a reasonable judgment of safety and/or effectiveness.

Accordingly, the Panel recommends that any new combination, or any presently marketed combination not submitted to this Panel be evaluated through the new drug procedures, or be the subject of an appropriate petition to the Commissioner to review or amend the OTC antiemetic monograph.

6. *Category II combination product.* The Panel concludes that combinations of bismuth subsalicylate, aminoacetic acid, phenyl salicylate, and zinc phenolsulfonate are safe in the amounts usually taken orally in OTC combination products, but there is no evidence that each of these four ingredients makes a significant contribution to the claimed antiemetic action of such combination.

Further, because any combination containing a Category II ingredient is classified as a Category II combination, the above combination is deemed a Category II product.

G. DATA PERTINENT FOR ANTIEMETIC INGREDIENT EVALUATION

When a drug is available for widespread use, as in OTC products, its safety and effectiveness must be well documented by toxicological data, data on the absorption, distribution, fate, and excretion of the drug, the pharmacological effects of the drug, and the mechanism of action. The drug should also meet certain effectiveness standards. The Panel recommends that information such as the following be submitted when relevant and pertinent to the drug under study: Toxicological data, absorption, distribution, fate, and excretion (ADFE) data, pharmacological effects, and effectiveness standards.

1. *Toxicological data.* A variety of toxicological data can be obtained to demonstrate that an antiemetic is safe. Manufacturers are not expected to obtain all of the following data, but are expected to obtain those data relevant to the unanswered questions regarding the safety of their products. The Panel recommends that data such as the following be required in preclinical animal studies and in clinical studies in man. Certain data on humans, such as lethal doses and chronic toxicity, will only be available from poison control centers, hospitals, medical centers, or medical examiners. However, the Panel considers such data important and attempts should be made to obtain them.

(a) *Preclinical animal studies.* (1) The oral LD_{50} should be established in several animal species.

(2) Determinations must be made to detect histologic and biochemical alterations in animals given lethal doses acutely or low doses chronically.

(3) Studies of teratogenicity and embryolethality are necessary. Studies of effects on fertility, delivery, and nursing offspring may also be indicated.

(b) *Clinical studies in man.* (1) Biochemical tests of liver and renal function and measurement of serum electrolytes after a therapeutic dose.

(2) Chronic toxicity studies in man.

(3) A clear record of unwanted drug effects. Substantial effort should be made to have physicians document side effects, especially those of serious nature.

(4) Minimal lethal dose by single oral ingestion and in divided doses when such data are available from accidental or deliberate overdosing.

(5) Maximal tolerated dose from single oral ingestion, or divided multiple oral ingestions, when such data are available from accidental or deliberate overdosing.

2. *Absorption, distribution, fate and excretion (ADFE) as determined by currently accepted methods.* Since ADFE bears directly on the safety of drugs and occasionally on the mechanism of action, appropriate data should be provided for all active ingredients and their metabolic products. The method for obtaining these data are established and are not different from those used in the study of other drugs. Data such as the following would provide sufficient information regarding ADFE. Manufacturers are not expected to obtain all of the following data, but are expected to obtain these data relevant to the unanswered questions regarding ADFE of their products:

a. The percentages of various oral doses of the drug which are absorbed in man.

b. The percentages of various oral doses of the drug which are excreted in the urine in man.

c. The metabolic fate in man of absorbed but unexcreted drug including studies on placental transfer and breast milk excretion.

d. The fate of unabsorbed drug in man.

e. The net bioavailability of the drug in man.

f. The ingredients and metabolic products associated with fecally excreted drug and/or its unabsorbed intraluminal biotransformation products.

g. The ingredients and metabolic products associated with renally excreted drug and/or its renally excreted biotransformation product.

3. *Effects.* The Panel recognizes the lack of physiological data on the gastrointestinal receptors and effectors of emesis and the related difficulty in establishing the mechanism of action of agents acting on either the central or autonomic nervous system or directly affecting gastric motility or tone. However, data should be provided which serve to elucidate the pharmacologic effects of antiemetic agents. The Panel recommends that data such as the following be obtained. Manufacturers are not expected to obtain all of the following data, but are expected to obtain those data relevant to the unanswered questions regarding pharmacologic effects of their products:

a. Effects of oral drug on nausea and vomiting.

b. Effects of oral drug on cardiovascular system (blood pressure and heart rate).

c. Effects of oral drug on autonomic nervous system.

d. Duration of oral drug effects.

e. Effects on drowsiness and the central nervous system.

4. *Effectiveness standards.* Motion sickness, which may occur when visual and vestibular stimuli are not in accord, may be induced by a number of techniques. Unusual motion patterns in which the head is rotated in two axes simultaneously will produce motion sickness in anyone; some individuals are more resistant than others, but none is immune. Motion sickness may also be induced when the body is stationary and the individual looks at a motion picture film as seen from an airplane doing acrobatics or a roller coaster ride (Ref. 1). Thus, a number of experimental models are available to test the effectiveness of antiemetic agents advocated for nausea and vomiting resulting from motion sickness. Both normal individuals and subjects with known susceptibility to motion sickness could be tested.

The threshold of stimulus (duration in time, rotation rate in r.p.m., and acceleration rate) to induce motion sickness should be determined before and after the test drug is administered to determine degree of effectiveness and duration of time of protection from motion sickness. Comparisons should be made

using the double-blind technique, with placebo and a known effective agent such as scopolamine. Manufacturers are not expected to obtain all of the data listed above, but are expected to obtain those data relevant to the unanswered questions regarding the effectiveness of their products. The effectiveness of drugs in vomiting due to causes other than motion sickness requires well-controlled clinical trials in homogenous groups of subjects with vomiting of relatively specific types such as that of radiation sickness, epidemic food or chemical poisoning, post-operative vomiting, epidemic gastroenteris, etc.

The experimental design for testing effectiveness of antiemetic may be of a number of different types. When the antiemetic product contains more than one active ingredient, the double-blind, Latin square, cross-ver design is particularly suited for testing the effectiveness of individual ingredients as well as comparing their effect against that of placebo. When it is impossible or impractical to devise an acceptable placebo, the antiemetic ingredient may be compared with another acceptable agent and studied in parallel groups. When experimental models of induced diarrhea are used, each subject can serve as his own control, but the period of study should be sufficiently long to clearly demonstrate differences.

REFERENCES

(1) Brown, J. L., Best and Taylor 9th Ed., Edited by John R. Brobeck, Chap. 8; p. 60–61, Williams & Wilkins, 1973.

IV. EMETICS

Pursuant to the notice published in the FEDERAL REGISTER of February 8, 1973 (38 FR 3614) requesting the submission of data and information on OTC emetic drugs, no submissions were made. Although the Panel received no submissions from the pharmaceutical industry or other source, it elected to review ipecac syrup as an OTC emetic drug.

A. CLASSIFICATION OF ACTIVE INGREDIENTS INTO CATEGORIES

The Panel reviewed one ingredient pursuant to the standards for safety, effectiveness and truthful labeling. In accordance with the regulation (21 CFR 330.10), the Panel's findings are set forth below:

B. REVIEW OF ACTIVE INGREDIENT

1. *Conditions under which emetic products are generally recognized as safe and effective and not misbranded.* The following ingredient was classified as safe and effective and not misbranded:

IPECAC SYRUP

The Panel concludes that ipecac syrup is safe and effective when used in the recommended dose of 15 milliliters in persons above 1 year of age and 5 to a maximum 10 milliliters in infants under 1 year.

An emetic is often used to induce vomiting in poisoning victims, who ingest systemic poisons, in order to prevent absorption of the chemicals from the gastrointestinal tract. The Panel believes that the most effective and dependable emetic for use in the home is ipecac syrup.

Ipecac syrup is prepared from powered ipecac, which is obtained from the plant Cephaelis ipecacuanha. The syrup contains the emetic alkaloids emetine and cephaeline. These emetic principles probably act both centrally and locally in the gastrointestinal tract to cause vomiting. An overdose of an ipecac preparation may cause serious poisoning.

The recommended effective and safe emetic dose of ipecac syrup for persons over 1 year of age is 15 milliliters. This dose usually induces vomiting within 20 minutes, but in the event emesis does not occur by this time, it is recommended that a similar dose be repeated once. The ipecac should be recovered by gastric lavage if emesis does not occur after the second dose. The OTC product container should not contain more than 30 milliliters of ipecac syrup.

LABELING

Labeling should identify the product as an "emetic to induce emesis (vomiting) in case of poisoning" and state the following:

(1) Before using, call physician, Poison Control Center, or hospital emergency room for advice. (2) Do not use in unconscious persons. (3) *Caution:* If emesis (vomiting) does not occur after a repeated dose or after the first dose if a second dose is not given, the ipecac should be recovered by gastric lavage. (4) Ordinarily, this drug should not be used if strychnine, corrosive [alkalies (lye) and strong acids], or petroleum distillates (kerosene, gasoline, paint thinner, or cleaning fluid) have been ingested.

REFERENCES

(1) Cashman, T. M. and H. C. Shirkey, "Emergency Management of Poisoning," Pediatric Clinics of North America, 17:525–534, 1970.

(2) The Pharmacopeia of the United States of America, 18th Rev., The United States Pharmacopeial Convention, Inc., Washington, D.C., Mack Printing Co., Easton, Pa., p. 345, 1970.

(3) Robertson, W. O., "Syrup of Ipecac—A Slow or Fast Emetic?," American Journal of Diseases of Children. 103:136–139, 1962.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 404)) and under authority delegated to him (21 CFR 2.120), the Commissioner of Food and Drugs proposes that Subchapter D be amended by adding new Parts 334, 335, 336 and 337 to read as follows:

PART 334—LAXATIVE PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
334.1 Scope.
334.3 Definitions.

Subpart B—Active Ingredients

Sec.
334.10 Bulk forming laxatives.
334.12 Hyperosmotic laxatives.
334.14 Lubricant laxatives.
334.16 Saline laxatives.
334.18 Stimulant laxatives.
334.20 Stool softener laxatives.
334.22 Miscellaneous laxatives.
334.30 Combinations of laxative active ingredients.
334.31 Laxative combination criteria.
334.32 Permitted active ingredient combinations.
334.35 Combination with nonlaxative active ingredients.

Subpart C—[Reserved]

Subpart D—Labeling

334.50 Labeling of laxative products.
334.52 Bulk forming laxatives.
334.54 Hyperosmotic laxatives.
334.56 Lubricant laxatives.
334.58 Saline laxatives.
334.60 Stimulant laxatives.
334.62 Stool softner laxatives.
334.64 Miscellaneous laxative.
334.80 Professional labeling.

AUTHORITY: Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–42 as amended, 1055–56 as amended by 72 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371), and Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243, as amended (5 U.S.C. 553, 554, 702, 703, 704)).

Subpart A—General Provisions

§ 334.1 Scope.

An over-the-counter laxative product in a form suitable for oral or rectal administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

§ 334.3 Definitions.

As used in this part:

(a) *Adequate liquid intake.* The ingestion of a full glass (8 oz.) of liquid with each dose.

(b) *Age (dosage) range.* Infant (not more than 2 years), child (2 years and over but not more than 12 years), and adult (12 years and over).

(c) *Bulk forming laxative.* An agent that promotes the evacuation of the bowel by increasing bulk volume and water content of the stools.

(d) *Constipation.* Infrequent or difficult bowel movement.

(e) *Hyperosmotic laxative.* An agent that attracts water into the stool.

(f) *Laxative.* Any agent used for the relief of constipation.

(g) *Lubricant laxative.* An agent that lubricates the contents of the intestinal tract, promoting easier bowel movements.

(h) *Oral Dosage.* The dosage range (minimum and maximum amounts) that is generally recognized as safe and effective by mouth.

(i) *Rectal dosage.* The dosage range (minimum and maximum) that is generally recognized as safe and effective by rectum.

(j) *Saline laxative.* An agent that increases water in the intestine thereby promoting bowel movement.

(k) *Short-term use.* Use of a laxative for no longer than a 1 week period.

(l) *Stimulant laxative.* An agent that promotes bowel movement by one or more direct actions on the intestine.

(m) *Stool softener laxative.* An agent that penetrates and softens the stool.

Subpart B—Active Ingredients

§ 334.10 Bulk forming laxatives.

The active ingredients of the product consist of the following when used within the dosage limit established for each ingredient:

(a) *Bran, dietary.* Usual oral dosage is 6 gm to 14 gm daily accompanied by adequate liquid intake; however, no upper dosage limitation is indicated.

(b) *Cellulose derivatives, semi-synthetic (methylcellulose, sodium carboxymethylcellulose).* Adult oral dosage is 4 gm to 6 gm daily accompanied by adequate liquid intake. Children over 6 years oral dosage is 1 gm to 1.5 gm daily accompanied by adequate liquid intake.

(c) *Karaya (sterculia gum).* Oral dosage is 5 gm to 10 gm daily accompanied by adequate liquid intake.

(d) *Malt soup extract.* Adult oral dosage is 12 gm to 64 gm daily accompanied by adequate liquid intake. Infants (not more than 2 years) oral dosage is 6 gm to 32 gm daily accompanied by adequate liquid intake.

(e) *Polycarbophil.* Adult oral dosage is 4 gm to 6 gm daily accompanied by adequate liquid intake. Infants (not more than 2 years) oral dosage is 0.5 gm to 1.0 gm, children (2 to 5 years) oral dosage is 1.0 gm to 1.5 gm, children (6 to 12 years) oral dosage is 1.5 gm to 3.0 gm accompanied by adequate liquid intake.

(f) *Psyllium preparations [Plantago seed, plantago ovata husks, psyllium (hemicellulose), psyllium hydrophyllic mucilloid (psyllium hydrocolloid), psyllium seed, psyllium seed (blond), psyllium seed husks].* Adult oral dosage is 2.5 gm to 30 gm daily accompanied by adequate liquid intake. Children 6 to 12 years oral dosage is 1.25 gm to 15.0 gm daily accompanied by adequate liquid intake. No pediatric dose for under 6 years.

§ 334.12 Hyperosmotic laxatives.

The active ingredients of the product consists of the following when used within the dosage limit established for each ingredient:

(a) *Glycerin.* Adult rectal dosage is 3 gm suppository or 5 ml to 15 ml enema. Children under 6 years rectal dosage is 1 gm to 1.5 gm suppository or 2 ml to 5 ml enema.

(b) *Sorbitol.* Adult rectal dosage is 120 ml as a 25 to 30 percent weight/volume solution. Children 2 years and older rectal dosage is 30 ml to 60 ml as a 25 to 30 percent weight/volume solution.

§ 334.14 Lubricant laxatives.

The active ingredients of the product consists of the following when used within the dosage limit established for the ingredient:

(a) *Mineral oil, plain.* Adult oral dosage is 15 ml to 45 ml and children over 6 years oral dose is 10 ml to 15 ml taken only at bedtime; adult rectal dosage is 120 ml and children 3 years and older rectal dose is 60 ml.

(b) *Mineral oil, emulsion.* Adult oral dosage is 15 ml to 45 ml of mineral oil component of emulsion administered orally twice daily with the first dose taken on arising and the second dose taken at bedtime and neither dose at mealtimes; and children over 6 years oral dosage is 0.25 ml and 5 ml of mineral oil component of emulsion administered orally twice daily with the first dose taken on arising and the second dose taken at bedtime and neither dosage at mealtimes.

§ 334.16 Saline laxatives.

The active ingredients of the product consists of the following when used within the dosage limit established for each ingredient:

(a) *Magnesium citrate.* (1) Adult oral daily dosage taken in divided doses is 11 gm to 18 gm (77 to 126 mEq magnesium ion). Children 2 to 5 years oral daily dosage is 2.5 gm to 5 gm and children 6 years and older oral daily dosage is 5 gm to 10 gm taken in divided doses.

(2) Magnesium citrate products may be formulated in combinations with sequestering agents, citric acid and anhydrous sodium citrate, to allow magnesium to be held in solution as a complex. Citric acid and anhydrous sodium citrate are not laxative agents and shall not be claimed as active ingredients on the labeling.

(b) *Magnesium hydroxide.* Adult oral daily dosage taken in divided doses is 2.4 gm to 4.8 gm (82 to 164 mEq magnesium ion). Children 2 to 5 years oral daily dosage is 0.4 gm to 1.2 gm and children 6 years and older oral daily dosage is 1.2 gm to 2.4 gm taken in divided doses.

(c) *Magnesium sulfate.* Adult oral daily dosage taken in divided doses is 10 gm to 30 gm (81 to 243 mEq magnesium ion). Children 2 to 5 years oral daily dosage is 2.5 gm to 5 gm and children 6 years and older oral daily dosage is 5 gm to 10 gm taken in divided doses.

(d) *Phosphate salts (combined sodium biphosphate, sodium phosphate, disodium phosphate and monosodium phosphate).* Total adult oral daily combined amount is 9.6 gm to 19.2 gm [210 to 420 mEq (biphosphate ion)] sodium biphosphate, 3.6 gm to 7.2 gm [40 to 80 mEq (phosphate ion)] sodium phosphate, 1.9 gm to 3.8 gm [40 to 80 mEq (phosphate ion)] disodium phosphate, and 8.3 gm to 16.6 gm [208 to 415 mEq (phosphate ion)] monosodium phosphate. Total adult rectal single combined amount is 19.2 gm [420 mEq (biphosphate ion)] sodium biphosphate, 7.2 gm [80 mEq (phosphate ion)] sodium phosphate, 3.8 gm [80 mEq (phosphate ion)] disodium phospate and 16.6 gm [415 mEq (phosphate ion)] monosodium phosphate. The usual oral dosage for children 5 to 10 years of age is ¼ adult dosage of phosphate salts; for children over 10 years usual oral dosage is ½ adult dosage of phosphate salts. The usual rectal dosage for children over 2 years is ½ adult dosage of phosphate salts.

§ 334.18 Stimulant laxatives.

The active ingredients of the product consists of the following when used within the dosage limit established for each ingredient:

(a) *Aloe.* Adult oral dosage is 120 mg to 250 mg daily. Children 6 to 8 years oral dosage is 40 mg to 80 mg daily. Adolescent 8 to 15 years oral dosage is 80 mg to 120 mg daily. No pediatric dosage under 6 years.

(b) *Bisacodyl.* Adult oral dosage is 5 mg to 15 mg and children over 3 years oral dose is 5 mg at bedtime in enteric coated dosage form. Adult rectal suppository dosage is 10 mg and children under 2 years 5 mg.

(c) *Cascara sagrada preparations (aromatic cascara fluidextract, cascara sagrada bark, cascara sagrada fluidextract, cascara sagrada extract, casanthranol).* (1) Adult oral daily dosage of aromatic cascara fluidextract is 2 ml to 6 ml. Infants (not more than 2 years) oral daily dose is 1 ml to 2 ml.

(2) Adult oral daily dosage of cascara sagrada bark is 300 mg to 1.0 gm.

(3) Adult oral daily dosage of cascara sagrada fluidextract is 0.5 ml to 1.5 ml.

(4) Adult oral daily dosage of cascara sagrada extract is 200 mg to 400 mg.

(5) Adult oral daily dosage of casanthranol is 30 mg to 90 mg.

(6) For all Cascara sagrada preparations the usual infant dose is ¼ adult dose; usual childhood dose is ½ adult dose.

(d) *Castor oil.* Adult oral dosage is 15 ml to 60 ml in a single dose. Infants not more than 2 years oral dosage is 1 ml to 5 ml in a single dose. Children 2 years and over but not more than 12 years oral dosage is 5 ml to 15 ml in a single dose.

(e) *Danthron.* Adult oral dosage is 75 mg to 150 mg daily. No pediatric dosage for children under 12 years.

(f) *Dehydrocholic acid.* Adult oral dosage is 750 mg to 900 mg daily in divided doses. No pediatric dosage for children under 12 years.

(g) *Phenolphthalein (white phenolphthalein, yellow phenolphthalein).* Adult oral dosage is 30 mg to 270 mg daily in single or divided dose. Children 2 to 5 years oral dosage is 15 mg to 30 mg in single or divided dose. Children 6 years to 12 years oral dosage is 30 mg to 60 mg in single or divided dose.

(h) *Senna preparations (senna leaf powder, senna fluidextract, senna fruit extract, senna syrup, sennosides A & B crystalline, senna pod concentrate).* (1) Adult oral daily dosage of senna leaf powder is 2 gm in a single dose.

(2) Adult oral daily dosage of senna fluidextract is 2 ml in a single dose.

(3) Adult oral daily dosage of senna fruit extract is 3.4 gm to 4 gm in a single dose.

(4) Adult oral daily dosage of senna syrup is 8 ml in a single dose.

(5) Adult oral daily dosage of sennosides A and B is 12 mg to 36 mg in a single dose.

(6) Adult oral dosage of senna pod concentrate is 0.6 gm to 1.0 gm per dose 1 to 4 times daily.

(7) The usual childhood dose of senna preparations is ⅛ adult dose for infants (not more than 2 years), ¼ adult dose for children 1 to 5 years, and ½ adult dose for children 6 to 12 years.

§ 334.20 Stool softener laxatives.

The active ingredients of the product consist of the following when used within the dosage limit established for each ingredient:

(a) *Dioctyl calcium sulfosuccinate.* Adult oral dosage is 50 mg to 360 mg daily. Infants (not more than 2 years) oral dosage is 25 mg daily. Children 2 years and over but not more than 12 years oral dosage is 50 to 150 mg daily.

(b) *Dioctyl pitassium sulfosuccinate.* Adult rectal dosage is 50 mg to 250 mg daily. Children 2 years and over but not more than 12 years rectal dosage is 100 mg daily.

(c) *Dioctyl sodium sulfosuccinate.* Adult oral dosage is 50 mg to 360 mg daily. Infants (not more than 2 years) oral dosage is 20 to 25 mg daily. Children 2 years and over but not more than 12 years oral dosage is 50 to 125 mg daily.

§ 334.22 Miscellaneous laxative.

The active ingredient of the product consists of the following when used within the dosage limit established: (a) *Released carbon dioxide from combined sodium biphosphate anhydrous, sodium acid pyrophosphate and sodium bicarbonate.* Adult rectal dose is 1.2 gm to 1.5 gm sodium biphosphate anhydrous, 0.04 gm to 0.05 gm sodium acid pyrophosphate and 1.0 gm to 1.5 gm sodium bicarbonate releasing approximately 230 ml carbon dioxide per moistened suppository. No pediatric dosage for childern under 12 years. The suppository is moistened by placing under a water tap for about 30 seconds or by immersing in a cup of water for at least 10 seconds prior to rectal insertion.

§ 334.30 Combinations of active laxative ingredients.

The active laxative ingredients of the product consist of the combination of ingredients permitted in § 334.32 within the dosage range for such active ingredients established in § 334.10, 334.12, 334.14, 334.16, 334.18 or § 334.20 and meet the laxative combination criteria established in § 334.31.

§ 334.31 Laxative combination criteria.

(a) The sum of the percentages of the effective range dosage (EDR) determined in paragraph (b) of this section for each active ingredient in the combinations permitted in § 334.32 shall not exceed 100 percent.

(b) The method used for determining the EDR percentage value of each active ingredient is as follows:

$$\frac{\text{L max d}-\text{EDR (min)}}{\text{EDR (max)}-\text{EDR (min)}}100 = \%\ \text{EDR of each ingredient}$$

where:

(1) L max d is the labeled maximum daily dosage for the product,

(2) EDR (min) is the effective range dosage minimum of the monograph, and EDR (max) is the effective range dosage maximum of the monograph for the active ingredient established in this Subpart B of such ingredient established in §§ 334.10, 334.12, 334,14, 334.16, 334.18 or 334.20.

§ 334.32 Permitted active ingredient combinations.

(a) *Oral dosage forms.* (1) Dioctyl calcium sulfosuccinate and danthron.

(2) Dioctyl sodium sulfosuccinate and casanthranol.

(3) Dioctyl sodium sulfosuccinate and danthron.

(4) Dioctyl sodium sulfosuccinate and phenolphthalein.

(5) Cascara sagrada and aloe.

(6) Cascara sagrada and magnesium hydroxide.

(7) Cascara sagrada and phenolphthalein.

(8) Malt soup extract and blond psyllium seed.

(9) Malt soup extract and blond psyllium seed husks.

(10) Mineral oil and casanthranol.

(11) Mineral oil and cascara sagrada.

(12) Mineral oil and cascara sagrada fluidextract.

(13) Mineral oil (emulsified) and magnesium hydroxide.

(14) Mineral oil and phenolphthalein.

(15) Mineral oil and psyllium seed.

(16) Plantago ovata husk and methylcellulose.

(17) Psyllium and senna concentrate.

(18) Senna concentrate and dioctyl sodium sulfosuccinate.

(19) Sodium carboxymethylcellulose and dioctyl sodium sulfosuccinate.

(b) *Rectal dosage forms.* (1) Glycerin and dioctyl potassium sulfosuccinate.

(2) Sorbitol and dioctyl potassium sulfosuccinate.

§ 334.35 Combinations with nonlaxative active ingredients.

(a) The antacid ingredient, sodium bicarbonate, identified in § 331.11(k) (1) of this chapter may be combined with monosodium phosphate identified in § 334.16(c) for purposes of product formulation (effervescence) but is not an active ingredient when used for this purpose.

Subpart C—[Reserved]

Subpart D—Labeling

§ 334.50 Labeling of laxative products.

(a) *Indications.* (1) The labeling shall identify the product as a "laxative" for the "short-term relief of constipation." The appropriate definition(s) describing the action of the active ingredient(s) as set forth in § 334.3 shall appear on the label. Products combining 2 laxative ingredients with differing modes of action shall identify both modes of action in the labeling of the product.

(2) Products containing magnesium hydroxide may be labeled as both an antacid and a laxative. No claims of superior laxation on the basis of the antacid properties shall be made.

(3) Rectal suppository products releasing carbon dioxide shall describe the mode of action as a gentle pressure in the rectum from expanding gas thereby promoting bowel movement.

(b) *Directions for use.* The labeling of the product contains the recommended dosage and appropriate directions identified under §§ 334.10, 334.12, 334.14, 334.16, 334.18, 334.20 or 334.22, under the heading "Directions," per time interval, e.g., every 4 hours, or other time period, e.g., once daily or at bedtime broken down by age groups if appropriate followed by "or as directed by a physician."

(c) *Warnings.* The labeling of the product contains the appropriate warning(s) under §§ 334.52, 334.54, 334.56, 334.58, 334.60, 334.62, or 334.64 and the following general warning(s) under the heading "Warnings", which may be combined with warnings for specific ingredients to eliminate duplicative words or phrases so the resulting warning is clear and understandable:

(1) "Do not use this product when abdominal pain, nausea, or vomiting are present."

(2) "If you have noticed a sudden change in bowel habits that persist over a period of 2 weeks, consult a physician before using a laxative."

(3) "This product should not be used for a period of longer than 1 week except under the advice and supervision of a physician."

(4) For products containing more than 15 mEq (345 mg) sodium in the maximum recommended daily dose:

(i) "Do not use this product except under the advice and supervision of a physician if you are on a low salt diet."

(ii) "Do not use this product except under the advice and supervision of a physician if you have kidney desease."

(5) For products containing more than 25 mEq (975 mg) potassium in the maximum recommended daily dose: "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

(6) For products containing more 50 mEq (600 mg) magnesium in the maximum recommended daily dose: "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

(d) *Drug interaction precautions.* The labeling of the product, where appropriate under §§ 334.52, 334.56 or 334.62, contains drug interaction precautions, under the heading "*Drug Interaction Precautions.*"

(e) *Statement of sodium content.* A product containing more than 1.0 mEq (23 mg) sodium per maximum daily dose shall be labeled as to the sodium content per dosage unit.

§ 334.52 Bulk forming laxatives.

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

(1) *"Caution:* Drink a full glass (8 oz.) of liquid with each dose."

(2) For products containing karaya (sterculia gum): "Drink a full glass (8 oz.) of liquid immediately with each dose."

(b) *Drug interaction precautions.* For products containing cellulose derivatives: "This product may combine with certain other drugs. Do not take this product if you are presently taking salicylates or a prescription drug."

§ 334.54 Hyperosmotic laxatives.

The labeling of the product contains the following warnings under the heading *"Warnings":*

(a) For products containing glycerin:

(1) "For rectal use only and not for oral use. Large doses of glycerin if taken orally can lead to serious toxic effects."

(2) *"Caution:* Glycerin administered rectally may produce in some individuals rectal discomfort or a burning sensation."

(b) For products containing sorbitol: "For rectal use only."

§ 334.56 Lubricant laxatives.

The labeling of the product contains the following warnings under the heading *"Warnings":*

(a) For products containing mineral oil (plain) to be used orally:

(1) *"Caution:* To be taken only at bedtime. Do not administer orally to infants or to children under 6 years of age, to pregnant women, to bedridden or aged patients, to persons with difficulty in swallowing, to persons having recent episode of vomiting or regurgitation, or to persons having abdominal pain."

(2) *Drug Interaction precaution.* "Do not take this product if you are presently taking a stool softener laxative."

(b) For products containing mineral oil (emulsion) to be used orally:

(1) *"Caution:* Do not administer orally to infants or to children under 6 years of age, to pregnant women, to bedridden or aged patients, to persons with difficulty in swallowing, to persons having recent episodes of vomiting or regurgitation, or to persons having abdominal pain."

(2) *Drug interaction precaution.* "Do not take this product if you are presently taking a stool softener laxative."

§ 334.58 Saline laxatives.

The labeling of the product contains the following warnings under the heading *"Warning":*

(a) "For occasional use only. Serious side effects from prolonged use or overdosage may occur."

(b) For products containing magnesium citrate solution: "Store this product in a cold place (refrigerator temperature) to retard decomposition."

(c) For products containing phosphates:

(1) "Do not take this product except under the advice and supervision of a physician if you have kidney disease."

(2) For oral preparations: "Do not give to children under 6 years of age except under the advice and supervision of a physician."

(3) For rectal preparations: "Do not give to children under 2 years of age except under the advice and supervision of a physician."

§ 334.60 Stimulant laxatives.

The labeling of the product contains the following warnings, under the heading *"Warnings":*

(a) For all products containing stimulant laxatives:

(1) *"Caution:* Prolonged or continued use of this product can lead to laxative dependency and loss of normal bowel function."

(2) "Serious side effects from prolonged use or overdose can occur."

(3) "This product should be used only occasionally, but in any event no longer than daily for 1 week, except on the advice of a physician."

(b) For products contains bisacodyl:

(1) "Do not chew."

(2) "Do not give to children under 3 years of age or to persons who cannot swallow without chewing."

(3) *"Caution*—Do not take this product within 1 hour after taking an antacid and/or milk."

(4) "This product may cause abdominal discomfort, faintness, rectal burning and mild cramps."

(5) "Store in a cool place at temperatures not above 86° F (30° C)."

(c) For products containing castor oil:

(1) "For the treatment of isolated episodes of constipation."

(2) "Do not take this product on a daily basis except under the advice and supervision of a physician."

(3) *"Caution:* Castor oil affects the small intestine and regular use may cause excessive loss of water, and body salts, which can have debilitating effects".

(d) For products containing phenolphthalein: *"Caution:* If a skin rash appears, do not use this product or any other preparation containing phenolphthalein."

§ 334.62 Stool softener laxatives.

(a) For all products containing stool softener laxatives the labeling of the product contains the following warnings, under the heading *"Warnings": "Caution:* This product should be used only occasionally but in any event no longer than daily for 1 week."

(b) Drug interaction precaution: "Do not take this product if you are presently taking a prescription drug or mineral oil."

§ 334.64 Miscellaneous laxative.

For products providing for release of carbon dioxide from a rectal suppository dosage form the labeling of the product contains the following warnings under the heading *"Warnings":*

(a) "For rectal use only."

(b) "Do not lubricate with mineral oil or petrolatum jelly prior to rectal insertion."

(c) "Rectal bleeding or failure to evacuate may indicate a serious condition and a physician should be consulted."

§ 334.80 Professional labeling.

The labeling of the product provided to health professionals (but not to the general public):

(a) For products containing phosphates:

(1) "Do not use in patients with megacolon, as hypernatremic dehydration may occur. Use with caution in patients with impaired renal functions as hyperphosphatemia and hypocalcemia may occur."

(2) Shall provide the total dose of sodium in mEq (mg) per standard dose.

(b) For products containing mineral oil:

(1) May contain as an additional indication, "For the preparation of the colon for x-ray and endoscopic examination."

(2) Shall contain the following: "Side effects with the proper use of mineral oil are few. However, with chronic use and particularly with excess dosage, laxation, anal leakage and dermatologic reactions may occur. Owing to its property as a lipid solvent, liquid paraffin (mineral oil) may interfere with the absorption of provitamin A, vitamin A, and vitamin D leading to impairment of calcium and phosphorus metabolism. This occurs only under conditions of chronic usage. Administration of mineral oil may lower prothrombin levels, probably secondary to impaired vitamin K absorption, and regular use in pregnancy may predispose to hemorrhagic disease of the newborn. Because of possible interference with nutrition, mineral oil should not be ingested in close proximity to meals. These side effects occur very rarely and then only with chronic and abusive use."

(c) For products containing castor oil: May contain as an additional indication, "For the preparation of the colon for x-ray and endoscopic examination."

(d) For products containing karaya (sterculia gum):

(1) "Warnings: Rare cases of allergic reactions and urticaria caused by karaya have been reported."

(2) "Inadequate fluid intake may cause large bowel obstructions."

(e) For products containing senna: may contain as additional indication, "For the preparation of the colon for x-ray and endoscopic examination."

(f) For products containing bisacodyl: May contain additional indications, "For use in preparation of the patient for surgery or for preparation of the colon for x-ray and endoscopic examination."

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

Subpart A—General Provisions

Sec.
335.1 Scope.
335.3 Definitions.

Subpart B—Active Ingredients

335.10 Antidiarrheal active ingredients.

Subpart C—[Reserved]

Subpart D—Labeling

335.50 Labeling for antidiarrheal products.

AUTHORITY: Federal Food, Drug and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–42 as amended, 1055–56 as amended by 72 Stat. 919 and 72 Stat. 948; (21 U.S.C. 321, 352, 355, 371), and Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243, as amended; (5 U.S.C. 553, 554, 702, 703, 704))).

Subpart A—General Provisions

§ 335.1 Scope.

An over-the-counter antidiarrheal product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

§ 335.3 Definitions.

As used in this part:

(a) *Diarrhea.* The abnormally frequent passage of watery stools, self limiting (24–48 hours) usually with no identifiable cause.

(b) *Antidiarrheal.* An agent that is effective for the treatment of diarrhea.

Subpart B—Active Ingredients

§ 335.10 Antidiarrheal active ingredients.

The active ingredient of the product consists of the following when used within the dosage limit established for each ingredient:

(a) *Opiates—opium powder, tincture of opium, paregoric (camphorated tincture of opium).* (1) Adult oral dosage equivalent to 15 mg to 20 mg opium per unit dose or 1.5 mg to 2.0 mg of morphine per unit dose 1 to 4 times a day not to exceed 2 days use. Children 6 to 12 years oral dosage equivalent to 5 mg to 10 mg opium per unit dose or 0.5 mg to 1.0 mg morphine per unit dose 1 to 4 times a day not to exceed 2 days use.

(2) Shall apply to antidiarrheal products pursuant to the requirements identified in § 329.20(a) of this chapter.

(b) *Polycarbophil.* Adult oral dosage is 4 gm to 6 gm daily. Infants (not more than 2 years) oral dosage is 0.5 gm to 1.0 gm daily. Children 2 to 5 years oral dosage is 1 gm to 1.5 gm daily and over 5 years oral dosage is 1.5 gm to 3.0 gm daily.

Subpart C—[Reserved]

Subpart D—Labeling

§ 335.50 Labeling of antidiarrheal products.

(a) *Indications.* The labeling shall identify the product as an "antidiarrheal" for the treatment of diarrhea.

(b) *Directions for use.* The labeling of the product contains the recommended dosage and appropriate directions identified under § 335.10, under the heading "Directions", per time interval, e.g., every 4 hours or other time period, e.g., twice daily, broken down by age groups if appropriate, followed by "except under the advice or supervision of a physician."

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

(1) "Do not use for more than 2 days or in the presence of high fever, or in infants or children under 3 years unless directed by a physician."

(2) Products containing opiates (opium powder, tincture of opium, paregoric (camphorated tincture of opium)) shall contain the labeling requirements identified in § 329.10 of this chapter.

(3) For products containing more than 15 mEq (345 mg) sodium in the maximum recommended daily dose:

(i) "Do not use this product except under the advice and supervision of a physician if you are on a low salt diet."

(ii) "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

(4) For products containing more than 25 mEq (975 mg) potassium in the maximum recommended daily dose: "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

(5) For products containing more than 50 mEq. (600 mg) magnesium in the maximum recommended daily dose: "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

(d) *Statement of sodium content.* A product containing more than 1.0 mEq (23 mg) sodium per maximum daily dose shall be labeled as to the sodium content per dosage unit.

PART 336—ANTIEMETIC PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
336.1 Scope.

Subpart B—Active Ingredients

336.10 Antiemetic active ingredients.

Subpart C—[Reserved]

Subpart D—Labeling

336.50 Labeling for antiemetic products.

AUTHORITY: Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–42 as amended, 1055–56 as amended by 72 Stat. 919 and 72 Stat. 948; (21 U.S.C. 321, 352, 355, 371), and Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243, as amended (5 U.S.C. 553, 554, 702, 703, 704))).

Subpart A—General Provisions

§ 336.1 Scope.

An over-the-counter antiemetic product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

Subpart B—Active Ingredients

§ 336.10 Antiemetic active ingredients.

The active ingredients of the product consists of the following when used within the dosage limit established for each ingredient.

(a) *Cyclizine.* Adult oral dosage is 50 mg to 200 mg daily. Children 6 to 12 years oral dosage is 25 mg up to 3 times daily.

(b) *Dimenhydrinate.* Adult oral dosage is 200 mg to 400 mg daily in 4 divided doses. Children 2 to 6 years oral dosage is 12.5 mg to 25 mg up to 3 times daily and children over 6 years oral dosage is 25 mg up to 3 times daily.

(c) *Meclizine.* Adult oral dosage is 25 mg to 50 mg once daily.

Subpart C—[Reserved]

Subpart D—Labeling

§ 336.50 Labeling of antiemetic products.

(a) *Indications.* The labeling shall identify the product as a "antiemetic" for the "treatment of nausea and vomiting associated with motion sickness."

(b) *Directions for Use.* The labeling of the product contains the recommended dosage and appropriate directions identified under § 336.10, under the heading "Directions", per time interval or other time period, (e.g., 4 times daily), broken down by age groups if appropriate, followed by "except under the advice or supervision of a physician."

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

(1) "Drowsiness sometimes occurs while taking this product." "Do not operate motor vehicles or other machinery while taking this product."

(2) "Do not take this product in the presence of glaucoma or enlargement of the prostate gland, except under the advice and supervision of a physician."

(3) For products containing cyclizine: "Do not give to children under 6 years of age except under the advice and supervision of a physician."

(4) For products containing meclizine: "Do not give to children under 12 years of age except under the advice and supervision of a physician."

PART 337—EMETIC PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
337.1 Scope.

Subpart B—Active Ingredient

337.10 Emetic active ingredient.

Subpart C—[Revised]

Subpart D—Labeling

337.50 Labeling for emetic products.

AUTHORITY: Federal Food, Drug and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–42 as amended, 1055–56 as amended by 72 Stat. 919 and 72 Stat. 948; (21 U.S.C. 321, 352, 355, 371), and Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243, as amended; (5 U.S.C. 553, 554, 702, 703, 704))).

Subpart A—General Provisions

§ 337.1 Scope.

An over-the-counter emetic product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

Subpart B—Active Ingredients

§ 337.10 Emetic active ingredient.

The active ingredient of the product consists of the following when used within the dosage limit established:

(a) *Ipecac syrup.* (1) Oral dosage is 15 ml above 1 year of age. Infants under 1 year of age oral dosage is 5 ml to maximum 10 ml. If emesis (vomiting) does not occur within 20 minutes, a similar dose is repeated once.

(2) The OTC product container shall not contain more than 30 ml of ipecac syrup.

Subpart C—[Reserved]

Subpart D—Labeling

§ 337.50 Labeling of emetic products.

(a) *Indications.* The labeling shall identify the product as an "emetic" to "induce vomiting (emesis) in case of poisoning."

(b) *Directions for use.* The labeling of the product contains the recommended dosage and appropriate directions identified under § 336.10, under the heading "Directions", followed by "except under the advice or supervision of a physician".

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

(1) "Before using, call physician, Poison Control Center, or hospital emergency room for advice."

(2) "Do not use in unconscious persons."

(3) "*Caution:* If vomiting (emesis) does not occur after a repeated dose or after the first dose if a second dose is not given the ipecac should be recovered by gastric lavage."

(4) "Ordinarily, this drug should not be used if strychnine, corrosives such as alkalies (lye) and strong acids, or petroleum distillates such as kerosene, gasoline, paint thinner, or cleaning fluid have been ingested."

Interested persons are invited to submit their comments in writing (preferably in quintuplicate) regarding this proposal on or before June 19, 1975. Such comments should be addressed to the Office of the Hearing Clerk, Food and Drug Administration, Room 4–65, 5600 Fishers Lane, Rockville, MD 20852, and may be accompanied by a memorandum or brief in support thereof. Additional comments replying to any comments so filed may also be submitted on or before Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: March 11, 1975.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

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