DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 357

[Docket No. 82N-0166]

Orally Administered Drug Products for Relief of Symptoms Associated With Overindulgence in Alcohol and Food for Over-the-Counter Human Use; Establishment of a Monograph

AGENCY: Food and Drug Administration.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of proposed rulemaking that would establish conditions under which over-the-counter (OTC) orally administered drug products for relief of symptoms associated with overindulgence in alcohol and food (drug products for the relief of symptoms of upset stomach due to overindulgence in the conbination of alcohol and food, drug products for the relief of hangover symptoms, and drug products to minimize inebriation or to minimize hangover symptoms) are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by December 30, 1982 and reply comments by January 31, 1983.

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

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

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on August 23, 1981, a report on OTC orally administered drug products for relief of symptoms associated with overindulgence in alcohol and food from the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the **Federal Register** a proposed rule containing (1) the monograph recommended by the Panel, which establishes conditions under which OTC orally administered drug products for relief of symptoms associated with overindulgence in alcohol and food are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

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

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

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

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC orally administered drug products for relief of symptoms associated with overindulgence in alcohol and food. Types of impact may include, but are not limited to cost associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC orally adminstered drug products for relief of symptoms associated with overindulgence in alcohol and food should be accompanied by appropriate documentation.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC orally administerd drug products for relief of symptoms associated with overindulgence in alcohol and food submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after November 1, 1982, except to the extent that the persons submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureaus of Drugs and Biologics (HFD-510) (address above).

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Culter* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979), The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now delegated from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking

process, before the establishment of a final monograph

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

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register.** On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions which would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce. Further, any OTC drug products subject to this monograph which are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In some advance notices of proposed rulemaking previously published in the OTC drug review, the agency suggested an earlier effective date. However, as explained in the tentative final monograph for OTC topical antimicrobial drug products (published in the **Federal Register** of July 9, 1982 (47 FR 29986)), the agency has concluded that, generally, it is more reasonable to have a final monograph be effective 12 months after the date of its publication in the **Federal Register.** This period of time should enable manufacturers to reformulate, relabel, or take other steps to comply with a new monograph with a minimum disruption of the marketplace thereby reducing economic loss and ensuring that consumers have continued access to safe and effective drug products.

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

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

James L. Tullis, M.D., Chairman (appointed December 1979)
John W. Norcross, M.D., Chairman (resigned March 1979)
Ruth Eleanor Brown, R.Ph. (resigned May 1976)
Elizabeth C. Giblin, M.N., Ed. D.
Richard D. Harshfield, M.D. (deceased June 1, 1981)
Theodore L. Hyde, M.D.
Claus A. Rohweder, D.O. (deceased April 13, 1979)
Samuel O. Thier, M.D. (resigned November 1975)
William R. Arrowsmith, M.D. (appointed March 1976)
Diana F. Rodriquez-Calvert, Pharm D. (appointed July 1976)

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

The following FDA employees assisted the Panel: Armond M. Welch, R.Ph., served as the Panel Administrator until July 1979, followed by John R. Short, R.Ph.; Enrique Fefer, Ph. D., served as the Executive Secretary until July 1976, followed by George W. James, Ph. D., until October 1976, followed by Natalia Morgenstern until May 1977, followed by Arthur Auer until October 1978. Roger Gregorio served as the liaison for the Office of New Drug Evaluation beginning November 1978. Joseph Hussion, R.Ph., served as the Drug Information Analyst until July 1976, followed by Anne Eggers, R.Ph., M.S., until October 1977, followed by John R. Short, R.Ph., until July 1979.

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

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

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products was charged with the review of many categories of drugs. Due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents its conclusions and recommendations for OTC drug products for relief of symptoms of upset stomach due to overindulgence in the

combination of alcohol and food, drug products for relief of hangover symptoms, and drug products to prevent inebriation or to minimize or reduce a hangover in this document. The Panel's findings on other categories of miscellaneous internal drug products are being published periodically in the **Federal Register.**

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings which dealt with the topics in this document were held on the following dates: June 6 and 7, August 8 and 9, September 28 and 29, November 15 and 16, December 13 and 14, 1980; January 31, and February 1, March 21, July 10 (telephone conference call), and August 21, 22, and 23, 1981.

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

The following individuals were given an opportunity to appear before the Panel at their own request to express their views on OTC drug products for relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food, drug products for relief of hangover symptoms, and drug products to prevent inebriation or to minimize or reduce a hangover.

William F. Arndt, Jr., M.D.
Allan R. Cooke, M.D.
Leroy J. Honkomp, Ph. D.
Kenneth Klippel
Stanley H. Lorber, M.D.
Sal L. Mercurio, Esq.
Robert Pinco, Esq.
J. Bryan Smith, Ph. D.
Edward B. Truitt, Jr., Ph. D.
Julian E. Villarreal, Ph. D., M.D.
Ralph O. Wallerstein, M.D.
Joseph M. White, M.D.

No person who so requested was denied an opportunity to appear before the Panel to discuss drug products for relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food, drug products for relief of hangover symptoms, and drug products to prevent inebriation or to minimize or reduce a hangover.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent data and information submitted through August 23, 1981, in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations in § 330.10, the Panel's findings with respect to OTC drug products for relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food, drug products for relief of hangover symptoms, and drug products to prevent inebriation or to minimize or reduce a hangover are set out in three categories:

Category I. Conditions under which OTC orally administered drug products for relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food, drug products for relief of hangover symptoms, and drug products to prevent inebriation or to minimize or reduce a hangover are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC orally administered drug products for relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food, drug products for relief of hangover symptoms, and drug products to prevent inebriation or to minimize or reduce a hangover are not generally recognized as safe and effective or are misbranded.

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

The Panel reviewed 16 ingredients for use in treating the symptoms of upset stomach due to overindulgence in the combination of alcohol and food, for the relief of hangover, and to prevent inebriation or to minimize or reduce a hangover. Two ingredients were placed in Category I for use in treating the symptoms of upset stomach due to overindulgence in the combination of alcohol and food. Nine ingredients were placed in Category I and four in Category II for use in the relief of hangovers. Two ingredients were placed in Category III to prevent inebriation or to minimize or reduce a hangover. (The number of ingredients classified does not equal the number of ingredients reviewed because some of the ingredients were reviewed for more than one labeled claim.)

I. Submission of Data and Information

Pursuant to the notices published in the **Federal Register** of November 16, 1973 (38 FR 31696) August 27, 1975 (40 FR 38179) requesting submission of data and information on "hangover remedies" and pursuant to FDA's deferral to this Panel of the "upset stomach" claims from causes other than hyperacidity (44 FR 41607), the following firms made submissions related to drug products for their respective uses as follows:

A. Submissions by Firms

1. *Drug products for relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food.*

Firms, and marketed products

Norwich-Eaton Pharmaceuticals, Norwich, NY 13815; Pepto-Bismol liquid and tablets
Miles Laboratories, Inc., Elkhart, IN 46515; Alka-Seltzer tablets
Warner-Lambert Co., Morris Plains, NJ 07950; Brōmo-Seltzer granules.

2. *Drug products for relief of hangover symptoms.*

Firms, and marketed products

Miles Laboratories, Inc., Elkhart, IN 46515; Alka-Seltzer tablets
Warner-Lambert Co., Morris Plains, NJ 07950; Bromo-Seltzer granules
Lemmon Pharmacal Co., Sellersville, PA 18960; Quick.Over capsules
Cary Corp., St. Helena, CA 94574; Chaser tablets

3. *Drug products to prevent inebriation or to minimize or reduce a hangover.*

Firms, and marketed products

Requa Manufacturing Co., Inc., Greenwich, CT 06830; Requa's activated charcoal capsules
Julius Schmid, Inc., New York, NY 10019; Fructose tablets

B. Ingredients Reviewed by the Panel

1. *Drug products for relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food—Labeled ingredients contained in marketed products submitted to the Panel.*

Acetaminophen
Aspirin [1]
Bismuth subsalicylate
Citric acid [1]
Sodium bicarbonate [1]

2. *Drug products for relief or hangover symptoms—a. Labeled ingredients contained in marketed products submitted to the Panel.*

Acetaminophen
Aspirin [2]

[1] These are the active ingredients in a market package. When immersed in water prior to ingestion, a series of chemical reactions occurs which results in the formation of sodium citrate in solution, sodium acetylsalicylate in solution, and free and dissolved carbon dioxide with a slight excess residual of sodium bicarbonate in solution. For the purposes of this document, only sodium citrate in solution will be discussed for relieving the symptoms of upset stomach due to overindulgence in the combination of alcohol and food.

[2] Aspirin is available as plain aspirin in one submitted product; in another it is present for conversion to sodium acetylsalicylate. Citric acid and sodium bicarbonate are also components of this latter preparation. When the latter preparation is immersed in water prior to ingestion, a series of chemical reactions occurs which results in the formation of sodium citrate in solution, sodium acetylsalicylate in solution, and free and dissolved cabon dioxide with a slight excess of residual sodium bicarbonate in solution. For the purpose of

Aluminum hydroxide
Aluminum hydroxide gel
Caffeine
Citric acid [2]
Magnesium carbonate
Magnesium trisilicate
Niacinamide
Oil of Peppermint
Sodium bicarbonate [2]
Thiamine hydrochloride

b. *Other ingredients.* (Ingredients which appeared in the second **Federal Register** notice dated August 27, 1975 (40 FR 38179) for which no submissions were received.)

Dextrose
Disaccharide
Peat
Thiamine mononitrate
Xylem

3. *Drug products to prevent inebriation or to minimize or reduce a hangover—Labeled ingredients contained in marketed products submitted to the Panel.*

Activated charcoal
Fructose

C. Classification of Ingredients

1. *Drug products for relief of symptoms of upset stomach due to the overindulgence in the combination of alcohol and food*—a. *Active ingredients.*

Bismuth subsalicylate
Sodium citrate in solution

b. *Ingredients reviewed by the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products as published in the* **Federal Register** of July 8, 1977 (42 FR 35346).

Acetaminophen

2. *Drug products for relief of hangover symptoms*—a. *Active ingredients used only in combination.*

Acetaminophen
Aspirin
Aluminum hydroxide
Aluminum hydroxide gel
Caffeine
Magnesium carbonate
Magnesium trisilicate
Sodium acetylsalicylate in solution
Sodium citrate in solution

b. *Inactive ingredients.*

Oil of peppermint

c. *Ingredients reviewed by the Advisory Review Panel on OTC Vitamin, Mineral, and Hematinic Drug Products as published in the* **Federal Register** *of March 16, 1979 (44 FR 16126).* (The Panel is aware that the FDA intends to withdraw this report; nevertheless, it remains a basic scientific reference.) [3]

Niacinamide
Thiamine hydrochloride
Thiamine mononitrate

d. *Other ingredients.* The Panel was not able to locate, nor was it aware of, data demonstrating the safety and effectiveness of the following OTC ingredients when used to relieve hangover symptoms. The Panel, therefore, classifies these ingredients as Category II for this use, and they will not be reviewed further in this document.

Dextrose
Disaccharide
Peat
Xylem

3. *Drug products to prevent inebriation or to minimize or reduce a hangover—Active ingredients.*

Charcoal, activated
Fructose

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons in response to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after November 1, 1982, in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. General Discussion and Definition of Terms

The subject of "upset stomach" has been under review by FDA for quite some time. This claim has been discussed in two previous rulemaking proceedings (antiemetic and antacid). In the tentative final monograph for antimetic drug products (44 FR 41064), FDA specifically deferred the "upset stomach" claim for bismuth-containing compounds to this Panel.

"Upset stomach" was initially denied inclusion in the antacid final monograph in 21 CFR, Part 331 (see 39 FR 19862). Subsequent petitions to amend the monograph to include "upset stomach" were also denied (see 44 FR 41067). After review of the data submitted in the petitions, FDA acknowledged that consumers frequently use the term "upset stomach" to describe symptoms associated with gastric hyperacidity such as "heartburn," "sour stomach," and "acid indigestion." The agency then proposed an amendment to the antacid monograph in the **Federal Register** of September 21, 1979 (44 FR 54731) to allow for claims such as "For the relief of upset stomach associated with heartburn, sour stomach, and acid indigestion." As part of that proposal (44 FR 54732), the agency made the following statement:

> The agency has referred the review of ingredients for the relief of gastrointestinal distress from causes other than gastric hyperacidity to the OTC Advisory Review Panel on Miscellaneous Internal Drug Products. Among ingredients to be reviewed by that Panel are those that are claimed to relieve the symptoms resulting from overindulgence in food and drink.

Based upon the above referral and upon consideration of the data in the submissions received, this Panel decided to review products with claims relating to "upset stomach," "overindulgence in food and drink," "hangover," "preventing inebriation," and "minimizing or reducing a hangover" in this document.

Overindulgence in the combination of alcohol and food can be manifested, in layman's terms, as an "upset stomach" and is sometimes confused with the overlapping symptom of a "hangover" due to overindulgence in alcohol alone. Symptoms of upset stomach due to overindulgence in the combination of alcohol and food can occur within one hour of overindulgence and persist for periods up to 24 hours. Hangover symptoms, however, are not usually manifested until several hours after overindulgence depending on the degree of inebriation. For the purposes of this document the Panel has agreed on the following definitions:

1. *Upset stomach due to overindulgence in the combination of alcohol and food.* A condition which occurs as a result of overindulgence in the combination of alcohol and food and consists of a group of symptoms which includes heartburn, fullness, and nausea.

2. *Hangover.* A condition consisting of a complex of symptoms involving the gastrointestinal, neurologic, and metabolic systems that follows recent acute excessive alcohol ingestion. These symptoms may include nausea, heartburn, thirst, tremor, disturbance of equilibrium, fatigue, generalized aches and pains, headache, dullness, and/or depression or irritability.

this document and the latter formulation, sodium citrate in solution and sodium acetylsalicylate in solution will be considered as the active ingredients for the relief of hangover symptoms.

[3] The withdrawal notice was published in the Federal Register on November 27, 1981 (46 FR 57914).

This document is divided into three parts as follows:

(1) Drug products for relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food.

(2) Drug products for relief of hangover symptoms.

(3) Drug products to prevent inebriation or to minimize or reduce a hangover.

B. Combination Policy

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

> 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 effects; when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel notes that the combination drug products described in this document have been reviewed in accordance with this general combination policy and with FDA's combination guidelines (the availability of which was announced in the **Federal Register** of November 28, 1978 (43 FR 55466)). In addition, the Panel recommends that if a combination of ingredients is intended to treat separate but concurrent conditions, e.g., "upset stomach due to overindulgence in the combination of alcohol and food" and "headache", the labeling of such a combination should convey to the consumer that the product is intended for use only when the concurrent symptoms are present.

C. Labeling

The Panel has carefully reviewed the submitted labeling claims for products promoted for relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food, for relief of hangover symptoms, and to prevent inebriation or to minimize or reduce a hangover and has categorized them into either Category I, Category II, or Category III. The Panel realizes that other terms may be developed to express the same Category I indications; however, only those indications and warnings listed under Category I are generally recognized to be acceptable at this time.

In order for any labeling to be acceptable, it must include (1) the indications for use, (2) pertinent warnings and contraindications, and (3) the recommended dosage.

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

One of the primary functions of this Panel is to attempt to eliminate confusing labeling claims. Some of the labeling either presently used or proposed on currently marketed "upset stomach" and "hangover" drug products is unsupported by scientific data and in some cases misleading. Accordingly, such labeling has been placed in Category II.

The indications for use should be simple and clearly stated. The directions should provide the consumer with enough information for safe and effective use of the product.

The Panel believes that if two ingredients are indistinguishable with regard to effectiveness, it is misleading to claim superiority for one of the ingredients unless supported by scientific data. The Panel understands that its function is not to compare various ingredients in order to determine the OTC drug of choice but to determine only safety and effectiveness for active OTC miscellaneous internal ingredients, as well as proper dosage ranges, warnings, and contraindications.

In the labeling, effectiveness shall not be related to the physical characteristics of the product, except as those characteristics may relate to the action of the active ingredients.

The Panel concurs with the recommendations of the Advisory Review Panel on OTC Antacid Drug Products as published in the **Federal Register** of April 5, 1973 (38 FR 8719) and the agency's regulations in 21 CFR 331.30(b) (4) and (5) that warnings should be included in the labeling of certain drug products containing sodium and magnesium but recommends that the wording be as follows in order to be more meaningful to the consumer:

(1) *For products containing more than 5 mEq of sodium in the maximum recommended daily dosage:* "If you are on a sodium-restricted diet, do not take this product except under the supervision of a physician."

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

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

Because OTC products can be purchased by anyone, it is the view of the Panel that the public may not regard them as products which can result in injurious or potentially serious consequences if used improperly. The public needs to be continually alerted to the idea that these products, like all medicine, carry some risk and should be used with caution. The consumer also should be informed of signs or symptoms of known toxicity requiring discontinuation of the use of the drug.

In addition, the Panel recommends that the drug product labeling contain instructions for the most effective use of the product. These instructions should be displayed prominently on all package labeling.

The Panel recommends that the label should contain a listing of all ingredients and that it should clearly indicate which are active and which are inactive. Active ingredients should be listed by their established names, and the label should state the quantity of the active ingredient per dose.

III. Drug Products for Relief of Symptoms of Upset Stomach Due To Overindulgence in the Combination of Alcohol and Food

A. General Discussion

The Panel has reviewed in detail the diverse symptoms which may occur after the excessive ingestion of alcohol alone or alcohol and food in combination. Although considerable overlap occurs in the symptoms which follow such excesses, the Panel concludes that overindulgence in a combination of alcohol and food produces a distinctive syndrome of

reproducible complaints which is usually different from those experienced from overindulgence in alcohol alone. This syndrome consists primarily of nausea, heartburn, and fullness, although other symptoms may be present.

The development of this overindulgence syndrome from the combination of excessive alcohol and food ingestion has a corollary in clinical medicine. The life-threatening illness, acute pancreatitis, is more likely to follow the ingestion of excessive amounts of alcohol and foods which produce high blood fats than with the excessive ingestion of either agent alone.

The Panel took note of the fact that nausea, heartburn, and fullness which follow overindulgence in the combination of alcohol and food can be produced by a wide range of etiologic factors. For example, nausea may occur in systemic disorders, such as uremia, hypercalcemia, ketoacidosis, or cerebral edema, and in local lesions of the gastrointestinal tract, such as ulcers or neoplasm. Nausea can also be associated with motion sickness, headache, fright, pregnancy, or stress, yet be indistinguishable to the sufferer from the nausea of a more serious origin. As another example, the single symptom of heartburn may often be due to gastric hyperacidity early in a bout of overindulgence, by may be due to acute hyperemia and gastritis several hours later. Thus, the symptoms which follow overindulgence in the combination of alcohol and food may be of different basis than the same symptoms from another cause. A medication which relieves nausea, heartburn, or fullness resulting from one cause may not necessarily provide relief for these symptoms when they are due to another cause.

Consideration of timing is also important. Symptoms which occur immediatley after overindulgence in the combination of alcohol and food can be different from those occurring the next morning. For example, headache is a rare occurrence immediately following such an episode, but frequently occurs the next morning.

The early symptoms, as well as their potential relief, may be further suppressed or confused by the direct effect of alcohol on the central nervous system. Thus, the Panel deemed it important to draw heavily on data from specific clinical trials rather than basing its decisions for effectiveness solely on physiologic probabilities or on empiricism.

1. *Establishment of upset stomach symptom complex as related to overindulgence in the combination of alcohol and food.* The Panel stated previously that for the purposes of this document upset stomach is defined as "a condition which occurs as a result of overindulgence in the combination of alcohol and food and consists of a group of symptoms which includes heartburn, fullness, and nausea." There are two important components in this definition. First, there is the causal factor which, for the purposes of this document, is limited to overindulgence in the combination of alcohol *and* food. The second component in the definition of upset stomach is the symptom complex associated with it. This symptom complex includes heartburn, fullness, and nausea. The Panel decided upon this symptom complex after reviewing the scientific literature and data submitted and listening to oral presentations. Data submitted in references one through seven summarize consumer/patient perception of upset stomach and the frequency of symptoms.

One submission to the Panel contained the results of a combined patient survey and clinical study (Ref. 1). The consumer survey component is relevant to the problem of determining the symptom complex of an upset stomach. Its objective was "to determine which specific terms patients use to describe the presenting symptom 'upset stomach.' " The sample consisted of 285 subjects whose presenting complaint was upset stomach with no known pre-existing gastrointestinal disease.

Each subject was "asked to verbally list all terms that he thought described his 'upset stomach.' " The 285 patients produced 677 terms. These terms consisted of many of the same or overlapping symptoms and were classified by the sponsor into nine categories of symptoms (including a miscellaneous category) "based on the obvious nature of the terms and/or by medical opinion." The eight symptom categories (miscellaneous category excluded) and the percentage of subjects with these symptoms were as follows:

Symptom category	Percent reporting symptom
Gas	56
Nausea	35
Heartburn	37
Pain	26
Acid indigestion	22
Motility	9
Vomiting	3
Upset stomach	4

Ninety-six percent of the subjects had at least one of the symptoms of gas (fullness), heartburn (or acid indigestion), or nausea.

One study did not relate the symptoms of upset stomach to any particular cause such as overindulgence, and so its major contribution is limited to the general discription of the symptom complex of an upset stomach (Ref. 1).

The Panel reviewed the results of three studies (Refs. 2, 3, and 4), whose objective was the determination of the upset stomach symptom complex associated with the overindulgence in food and alcohol. In the first study, which was conducted in Mexico, one of the objectives was to determine whether there is a distinct cluster of symptoms following overindulgence in alcohol and food whch can be distinguished from those clusters of symptoms associated with other conditions (Ref. 2). In this study "more than 600 statements concisely describing subjective experiences of all kinds but associated with gastrointestinal conditions were obtained from many sources." From these, an inventory of 300 questions was finally constructed. These questions were then put to subjects who were divided into five groups as follows:

(1) 40 untreated volunteers (controls),

(2) 11 normal volunteers before and after a heavy meal,

(3) 10 normal volunteers before and after receiving quipazine, a drug known to produce gastrointestinal discomfort,

(4) 18 hospitalized patients with severe drug-induced gastritis, and

(5) 113 hospitalized patients with miscellaneous gastrointestinal disorders.

The statistical method of cluster analysis was applied to the study subjects, and is consistently separated the subjects who had the heavy meal from the other groups. Further, the statistical method of discriminant analysis was employed, and it correctly classified all subjects who had the heavy meal. Next, factor analysis was used to characterize the pattern of the overindulgence sysmptons. The symptom categories (or clusters) which increased by at least 25 percent after the meal from those given before the meal were as follows:

Symptom category (cluster)	Post meal percent positive response
Fullness	90
Dry mouth	90
Headache	64
Sluggishness	55
Belching	50

Symptom category (cluster)	Post meal percent positive response
Nausea	36
Stomach ache	36
Feeling of needing air	36
Rumbling sensation	27

Another study was a consumer survey of 143 male subjects, all of whom had experienced upset stomach within the past six months (Ref. 3). Of the respondents, 53 percent listed overindulgence in the combination of food and drink, and another 27 percent listed overeating alone, as the cause of upset stomach. The survey subjects were given a list of 33 symptoms compiled from the symptoms used in the Mexico study. These 33 symptoms were considered to provide the greatest discrimination. The subjects were asked to check those symptoms that they usually experienced when they had an upset stomach and for which they took medication. There were 12 symptom categories in which symptoms sere reported as being experienced by 30 percent or more of the subjects as follows:

Symptom category	Percent reporting symptom
Fullness[1]	72
Heartburn/burning	65
Passing of gas	64
Headache[1]	62
Stomach ache[1]	60
Belching[1]	57
Rumbling sensation[1]	54
Thirsty/dry mouth[1]	51
Sluggishness[1]	50
Taste repeat	46
Nausea[1]	39
Bitter/acid aftertaste	30

[1] These symptom categories also appeared with high frequency in the Mexico study (Ref. 2).

The Panel reviewed a clinical study in which 64 subjects from the group of 143 males of the previous survey were given a heavy meal accompanied by alcoholic beverages to induce an upset stomach (Ref. 4). Of the 12 symptoms listed above, all except headache are clearly related to the gastrointestinal tract, and, during the course of this study, all 11 of those appeared with at least a 50 percent frequency. Specifically, 60 of the 64 subjects (94 percent) had fullness, 33 (52 percent) had nausea, and 33 (52 percent) had heartburn (Ref. 5).

The results of one consumer survey (Refs. 6 and 7) and one clinical trial (Ref. 8) were also reviewed. The objective of the consumer survey was "to determine the specific symptoms that consumers perceive as comprising the condition known and commonly referred to as the 'upset stomach.' " Data were collected by an independent market research firm through personal interviews with adult men and women (18 to 75 years old) who claimed to have suffered from an upset stomach at least once in the 6 months immediately preceding the date of the interview. Respondents were selected by the shopping center intercept survey technique at 10 geographically dispersed high traffic shopping centers throughout the continental United States. There were approximately 40 interviews per center with a total of 432 interviews in all.

Respondents were asked what they perceived to be the cause of their last upset stomach. Multiple causes could be given. Thirty-one percent (133 subjects) stated overeating and/or overdrinking as the cause, and 35 percent (151 subjects) cited "food that was disagreeable" as the cause. In total, 59 percent (257 subjects) stated either overindulgence in alcohol and/or food and/or eating food that was disagreeable as the cause. Each respondent also was asked to indicate all symptoms usually experienced when suffering an upset stomach. This was accomplished using a closed-end questionnaire consisting of 17 comprehensive symptoms. The symptom list was developed utilizing the marketing experience of the sponsor and the consumer research data contained in studies discussed above (Refs. 1, 2, and 3).

The statistical technique of cluster analysis was applied to the results of the survey in order to extract individual symptoms or groups of symptoms which were statistically distinguishable from other symptoms or groups of symptoms (Refs. 9 and 10). These distinguishable individual symptoms or groups of symptoms were called clusters. When the cluster analysis was applied to the subjects with upset stomach caused by overindulgence (133 subjects), or to the subjects with upset stomach caused by eating disagreable food (151 subjects), or to the combination of these two groups (257 subjects), four distinct clusters emerged. In each of these three conditions there were separate clusters for heartburn, fullness, and nausea. The fouth cluster, cosisting of symptoms such as headache, feeling sluggish, diarrhea, and dry mouth, can be called a cluster of associated symptoms. This delineation of the symptoms into four clusters, i.e., heartburn, fullness, nausea, and the associated conditions, was similar to clusters proposed in one of the consumer surveys (Ref. 6) before the application of the satistical procedure of cluster analysis. The analysis (Ref. 7) acted as a confirmation of the proposed structure in one of the consumer surveys (Ref. 6).

At least 30 percent of the respondents in each of the three subject groups given above (i.e., upset stomach caused by overindulgence, or eating disagreeable food, or both) reported having symptoms in the categories of heartburn, fullness, or nausea. Over 80 percent reported symptoms in at least one of these three symptom categories (Ref. 11).

A clinical study by Berkowitz (Ref. 8) consisted of 132 normal, healthy, nonalcoholic, adult volunteers who partook of a large meal which included wine, champagne, and cordials. Ninety-one of the subjects developed symptoms of upset stomach. Seventy-three percent of these had fullness, 55 percent had nausea, and 53 percent had heartburn. A cluster analysis was perfomed on all the symptoms reported (nausea, fullness, heartburn, belching, bitter or acid taste, stomach pain/cramps, passing gas/wind, or other). As was the case in the consumer survey when four clusters were extracted from the data, the symptom categories of heartburn, fullness, and nausea were distinguished clearly from one another and from the remaining symptoms and associated conditions. Ninety-five percent of the subjects had at least one of these three symptoms, i.e., heartburn, fullness, or nausea (Ref. 7).

On the basis of its review of the above clinical studies and consumer surveys, the Panel concluded that there is a significant target population for whom upset stomach due ot overindulgence in the combination of alcohol and food consists predominently of a group of symptoms which includes heartburn, fullness, and nausea.

2. *Clinical study guidelines.* In order to evaluate the date from clinical trials designed to investigate the effectiveness of drugs for relieving the symptoms of upset stomach due to overindulgence in the combination of alcohol and food, the Panel decided upon the following criteria: (1) The study must be placebo-controlled and double-blind, (2) The upset stomach reported by the study subjects must be related to overindulgence in the combination of alcohol and food, and (3) A significant number of subjects (e.g., at least 90 percent) must report symptoms in at least one of the symptom categories of heartburn, fullness, and nausea and the other two symptom categories must be reported by a substantial number (e.g., at least 30 percent) of the subject.

3. *Effectiveness criteria.* The major effectiveness variable should be a

variable measuring "overall" relief from the upset stomach. The data for this variable can be obtained by having the subjects categorize their overall relief (e.g., into one of the four categories of excellent, good, fair, and poor or none), or by having the subjects rate relief separately for each individual symptom and then combine these ratings for an overall rating (e.g., by averaging). A statistically significant difference (p less than or equal to 0.05) between drug and placebo on the overall relief variable is needed to establish the effectiveness of a drug for relieving the symptoms of upset stomach due to overindulgence in the combination of alcohol and food.

In order to justify the claim of relief for any specific symptom (i.e., for relief of heartburn, fullness, or nausea), analysis for the specific symptom must be performed and the difference between the drug and placebo must be statistically significant.

4. *Combination products and concurrent symptoms.* The Panel believes that there exists a significant target population of individuals who, in addition to having an upset stomach due to overindulgence in the combination of alcohol and food, also experience a headache or other minor aches and pains. With the exception of combining two or more salicylate-containing ingredients (due to potential salicylate toxicity), the Panel recommends that any Category I ingredient used to relieve the symptoms of upset stomach due to overindulgence in the combination of alcohol and food may be combined with any Category I internal analgesic used to relieve minor aches and pains for relieving the concurrent symptoms; if the analgesia is aspirin, the preparation should be appropriately buffered so that the final dosage form at least meets the buffering capacity required of an antacid final dosage form.

A combination product should be labeled as follows: "For the relief of upset stomach due to overindulgence in the combination of food and drink, when accompanied by a headache or other minor aches and pains."

References

(1) Comment 31–11370, Docket No. 78N–0263, Dockets Management Branch.

(2) Villarreal, J., et al., "Discrimination and Characterization of the Cluster of Symptoms Resulting from overindulgence in Food and Drink," unpublished study and related materials, OTC Volumes 170123 (Appendix 2), 170132, 170189 (Section III.D.2.), 170204 (Tab 369), and 170212.

(3) Hurley, F. L., and J. M. White, "Consumer Definition of Upset Stomach," unpublished study and related materials, OTC Volumes 170123 (Appendix 4), 170189 (Section III.D.2.), and 170196 (Tab 151).

(4) White, J. M., et al., "Clinical Study of Experimentally Produced Upset Stomach and Its Treatment," unpublished study and related materials, OTC Volumes 170123 (Appendix 5), 170132, 170189 (Section III.D.2.), 170205 (Tab 390), and 170212.

(5) Letter from Miles Laboratories, Inc., dated September 18, 1980 (Exhibit B), Panel Administrator's File (OTC Volume 17LPAII).

(6) Consumer survey conducted by Norwich-Eaton Pharmaceuticals included in OTC Volume 170187 (pp. 4–6).

(7) OTC Volume 170206.

(8) Berkowitz, J. M., "Bismuth Subsalicylate in Excessive Alcohol/Food Intake," unpublished study and related materials, OTC Volumes 170206 (pp. 7–9) and 170208 (pp. 11–15).

(9) "SAS (Statistical Analysis System) User's Guide," 1979 Ed., SAS Institute. Inc., Raleigh, NC, 1979.

(10) Johnson, S. C., "Hierarchal Clustering Schemes," *Psychometrika*, 32:241–254, 1967.

(11) Letter from Norwich-Eaton Pharmaceuticals, dated August 29, 1980, Panel Administrator's File (OTC Volume 17LPAII).

B. Category I Conditions

The following are Category I conditions under which drug products for relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food are generally recognized as safe and effective and not misbranded.

1. *Category I active ingredients.*
Bismuth subsalicylate
Sodium citrate in solution

a. *Bismuth subsalicylate.* The Panel concludes that bismuth subsalicylate is generally recognized as safe and effective in the dosage noted below for OTC use in relieving symptoms of upset stomach due to overindulgence in the combination of alcohol and food.

(1) *Safety.* The Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic and Antiemetic Drug Products in its report published in the **Federal Register** of March 21, 1975 (40 FR 12930) found bismuth subsalicylate to be safe for use as an antidiarrheal preparation in a dose of 0.6 to 2.0 grams (g) taken three to four times daily. Based on the data submitted for the claim of relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food, this Panel finds the manufacturer's recommended dose of 0.525 g of bismuth subsalicylate given up to eight times daily at intervals of at least ½ to 1 hour between doses to be safe because this limits the maximum daily dose to 4.2 g.

This Panel has considered reports of many cases of bismuth encephalopathy occurring in France and Australia (Ref. 1). Those reactions followed chronic administration of various bismuth preparations at very high doses. The bismuth preparations implicated in those reports were all of French origin. There have been no new cases of bismuth encephalopathy reported from Australia since Australia ceased the importation of bismuth from France (Ref. 2). A communication by the manufacturer (Ref. 3) further points out that no cases of bismuth encephalopathy have been reported in the United States and, furthermore, bismuth subsalicylate has never been implicated by any source as having caused a case of bismuth-related encephalopathy. It is also noted from this communication that several studies have failed to show bismuth absorption in humans; no bismuth was detected by the tests employed in the blood or urine of any subjects. Based upon this evidence, the Panel concludes that bismuth subsalicylate does not present a risk of bismuth encephalopathy when administered at the dosage recommended below.

The Panel is aware of a report in *The Medical Letter* on *Drugs and Therapeutics* (Ref. 4) which cites the theoretical possibility that if the maximum dose (240 milliliters (mL)) of a bismuth subsalicylate preparation for the treatment of diarrhea were consumed with large daily doses of a salicylate-containing internal analgesic (e.g., the amount of aspirin for the treatment of arthritis), the plasma salicylate concentrations would be likely to rise to toxic levels. The Panel also shares this concern and has given due consideration to the maximum daily dose of salicylate of 3.04 g (4 g aspirin) recommended by the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (hereafter referred to as the Internal Analgesic Panel). The recommended daily dose of salicylate in the bismuth subsalicylate preparation submitted to this Panel (but not reviewed by the Internal Analgesic Panel) is 2.144 g of salicylate (25 percent of the salicylate content contributed by ingredients other than bismuth subsalicylate). According to the manufacturer's recommended dosage intervals (8 times daily, every ½ to 1 hour), the maximum amount of salicylate can be consumed within 3½ hours. This works out to an hourly dose of 612.6 milligrams (mg) which exceeds the maximum salicylate dose recommended by the Internal Analgesic Panel which is 1,500 mg of aspirin over a 3-hour period (42 FR 35490) or an average of 500 mg/hour (equivalent to 381 mg/hour of salicylate). In a recent study conducted by Pickering et al. (Ref. 5) using the same preparation according to the dosage recommended by the

manufacturer (as cited above), an average peak plasma salicylate level of 137 micrograms per milliliter (μg/mL) (13.7 mg/100 mL) was reported, which is considerably less than the average level (20 mg/100 mL) at which ototoxicity (tinnitus—ringing in the ears) may appear (42 FR 35362 and 35364). In addition, *The Medical Letter on Drugs and Therapeutics* (Ref. 4) reported that the administration of 60 mL of this same bismuth subsalicylate preparation to 6 normal adult volunteers produced peak plasma salicylate concentrations of 40 μg/mL (4 mg/100 mL) which is comparable to the plasma concentration achieved with the usual analgesic doses of aspirin. The Panel, therefore, does not consider salicylate toxicity to be a problem when bismuth subsalicylate is administered alone because of the acute, self-limiting disorder (upset stomach due to overindulgence in the combination of alcohol and food) being treated; but, because of the possibility of concomitant use of bismuth subsalicylate with other salicylates, the warning regarding ringing in the ears is indicated. The Panel, therefore, recommends that the following warning be included in the labeling of any bismuth subsalicylate preparation: "This product contains salicylates. If taken with other salicylate-containing preparations, such as aspirin, and ringing in the ears occurs, discontinue use."

Additionally, *The Medical Letter on Drugs and Therapeutics* (Ref. 4) stated that such high plasma salicylate levels (resulting from the concurrent administration of bismuth subsalicylate and salicylate-containing internal analgesics) could lead to enhanced effects of anticoagulants causing bleeding, could inhibit the activity of uricosuric drugs, and could increase the methotrexate toxicity in patients who are taking such a medication.

A presentation was made to the Panel by Joseph M. White, M.D. (Ref. 6), a consultant for Miles Laboratories, in which he discussed the significance of the possible interaction of salicylates with certain prescription drugs, i.e., anticoagulants and drugs for the treatment of diabetes, gout, and arthritis, as proposed by the Internal Analgesic Panel in the **Federal Register** of July 8, 1977 (42 FR 35493). This Panel concurs with his conclusions that a warning prohibiting the concomitant use of salicylates and anticoagulants is justified. The Panel also concurs that a warning relating to the other three types of drugs, i.e., for diabetes, gout, and arthritis, need not be included in the labeling of preparations marketed only for the acute, self-limiting condition discussed here (upset stomach due to overindulgence in the combination of alcohol and food). The Panel, therefore, recommends that the following warning be included in the labeling of products containing bismuth subsalicylate and intended to relieve upset stomach due to overindulgence in the combination of alcohol and food: "If taking oral medication for anticoagulation (thinning of the blood), consult a physician before taking this product."

The Panel concludes that bismuth subsalicylate is safe for OTC use when administered at a dose of 0.525 g to be repeated no more frequently than every ½ to 1 hour with a maximum daily dose not to exceed 4.2 g (8 doses) and when labeled with the warnings described below.

(2) *Effectiveness.* Three randomized, placebo-controlled, double-blind studies were reviewed (Refs. 7, 8, and 9). Investigators were Jesse M. Berkowitz, M.D. (Ref. 7), John H. Newsom, M.D. (Ref. 8), and Charles S. Davis, M.D., Ph. D (Ref. 9). The latter two studies have design faults, but are supportive of the effectiveness claim.

Berkowitz studied 132 normal, healthy, nonalcoholic adult volunteers, 18 to 63 years of age of both sexes. These subjects participated in a randomized, placebo-controlled, double-blind, parallel clinical trial in which they were instructed to fast for a 6-hour period immediately preceding the study. In the study, subjects were provided unlimited food and drink (champagne, wine, cordials) in a dinner party atmosphere. Of the 132 subjects, 91 developed one or more symptoms of gastrointestinal distress that required medication. Forty-three subjects took one or more doses of the bismuth subsalicylate formulation as cited above (0.525 g per dose) ½ to 1 hour apart up to a maximum of 8 doses, and 48 subjects took 1 or more doses of a placebo formulation.

Subjects were instructed to record the symptoms, degree of discomfort (none, mild, moderate, or severe), and the time of onset for each of the following symptoms: stomach queasiness/nausea, sense of fullness/bloated feeling, heartburn, belching, stomach pain/cramps, passing gas/wind, bitter or acid taste in mouth, and "others."

In addition, for each dose of medication during the study period, the subjects filled in the time taken and relief obtained (none, poor, good, or excellent). At the end of the study (24 hours after subjects arrived at study site), the subjects were asked to give their subjective evaluation of the overall relief obtained (none, poor, good, or excellent) from their treatment.

The subjects who took the bismuth subsalicylate formulation reported significantly better overall relief than did the subjects who took the placebo (p less than 0.01). Ninety-one percent of those who took bismuth subsalicylate and 56 percent of those who took the placebo reported good or excellent overall relief. (Statistical technique employed was the chi square test.)

Statistical analyses (Mantel-Haenszel test and the chi square test) showed that subjects taking the bismuth subsalicylate got significantly greater relief than subjects taking the placebo for the specific symptoms of nausea (p less than 0.01), fullness (p less than 0.01), and heartburn (p less than 0.01). Baseline symptom severity (i.e., before medication) was considered in the analyses. Further, the time to relief analyses (life table techniques) showed that bismuth subsalicylate provided significantly faster relief than the placebo for nausea (p less than 0.01), fullness (p less than 0.01), and heartburn) (p less than 0.01). The number of subjects who experienced these individual symptoms by treatment groups were as follows:

	Treatment Group		
	Bismuth subsalicylate	Placebo	Total
Nausea	22	28	50
Fullness	29	37	66
Heartburn	26	22	48

The Newsom study (Ref. 8) was a randomized, placebo-controlled, double-blind, multiple crossover study involving 48 adult subjects suffering from episodes of "indigestion" or "acute gastrointestinal discomfort" which was defined as a symptom complex consisting of two or more of the following symptoms occurring during or after the ingestion of food: nausea, heartburn, upper-abdominal pain, flatulence and eructation (belching), sense of fullness, and a feeling of abdominal distension. There was no record of whether or not alcohol was ingested. Subjects were not in any study or controlled setting during the episodes, but took the medication during their normal daily routine.

Each subject was treated for six episodes, three with a bismuth subsalicylate formulation (as cited above) and three with a placebo formulation. For each episode treated, the subjects recorded the time of onset, identified the specific symptoms present, and rated the overall severity

(mild, moderate, or severe) on the case report form. Further, the severity of each symptom was rated at 15 and 30 minutes following each dose. Up to 8 doses could be taken at 30 minute intervals if needed. Additionally, if relief was obtained, the subject was asked to specify the time it was noted.

For the overall relief of symptoms, independent of the time to relief, there was a uniformly higher proportion of relief for the episodes treated with bismuth subsalicylate than for the episodes treated with placebo. This trend held in all severity categories (mild, moderate, and severe). However, the differences were not statistically significant (p equals more than 0.05, but less than 0.10). Analysis of time to overall relief (by the Bernard and Van Elteran test) did attain a statistically significant difference between the bismuth subsalicylate and the placebo (p less than 0.005).

For individual symptoms, bismuth subsalicylate was statistically superior to the placebo for both the mean severity score over the 4-hour time period (up to 8 doses at half hour intervals) and for the time to relief for the symptoms of nausea, fullness, and heartburn.

The number of episodes in which subjects treated these individual symptoms with placebo and with bismuth subsalicylate is as follows:

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	Bismuth subsalicylate	Placebo	Total
Nausea	53	56	109
Fullness	83	91	174
Heartburn	88	75	163

In order to perform the analysis on the treatment of separate symptoms, episodes were considered the basic units of analysis and not the individual subjects. This ignores the fact that subjects contributed variable total numbers of episodes, that the number of bismuth subsalicylate-treated and placebo-treated episodes contributed by a given subject were not always equal, and that the episodes were not independent of other episodes.

The Davis study (Ref. 9) was a randomized, placebo-controlled, double-blind study which involved 626 families. Each family was given a medication (bismuth subsalicylate formulation (as cited above) or placebo formulation (in a ratio of two bismuth to one placebo) and instructed to use it for minor gastrointestinal upsets (upset stomach) which might occur within the 2-week period following enrollment in the study.

In the 625 families, 141 individuals had upset stomach; of these, 97 were treated with bismuth subsalicylate and 44 with placebo. Statistical analysis of the five ordered relief categories (complete, good, fair, slight, and none) showed a statistically significant advantage for the bismuth subsalicylate treatment (p equals 0.04 for a two-sided test). When the relief categories were divided into "success" (complete or good) and "failure" (fair, slight, or none), the difference between the bismuth subsalicylate and placebo groups still favored the bismuth group, but now was not statistically significant (p equals 0.123 for a two-sided test).

The Panel concludes that the "overall" effectiveness of bismuth subsalicylate has been demonstrated in relieving the symptoms of upset stomach due to overindulgence in the combination of alcohol and food. In addition, it has been demonstrated to be effective in relieving the specific symptoms of nausea, fullness, and heartburn due to overindulgence in the combination of alcohol and food.

(3) *Dosage.* The Panel has determined that a dose of 0.525 g of bismuth subsalicylate to be given at intervals no more frequent than every ½ to 1 hour for a total daily dose of 4.2 g (8 doses) is safe and effective for relief of the symptoms of upset stomach due to overindulgence in the combination of alcohol and food.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients intended to relieve symptoms of upset stomach due to overindulgence in the combination of alcohol and food. (See part III. paragraph B.2. below—*Category I labeling.*) In addition, the Panel recommends the following warnings: "This product contains salicylates. If taken with other salicylate-containing preparations, such as aspirin, and ringing in the ears occurs, discontinue use. If taking oral medication for anticoagulation (thinning of the blood), consult a physician before taking this product."

Data submitted have demonstrated the effectiveness of bismuth subsalicylate in relieving the specific symptoms of nausea, heartburn, and fullness due to overindulgence in the combination of alcohol and food and, therefore, these symptoms may be included in the indication as stated under Category I labeling. (See part III. paragraph B.2. below—*Category I labeling.*)

References

(1) Anonymous, "Mental Illness Due to Bismuth Salts," *Japan Medical Gazette,* pp. 8–9, February 20, 1976.

(2) Buge, A., et al., "Correlations Evolutives: Cliniques Electroencephalographiques, Tomodensitometriques et Toxicologiques, Dan Cinq Cas D'Encephalopathies Bismuthiques," *La Semaine Des Hopitaux De Paris,* 55:1466–1472, 1979.

(3) OTC Volume 170208 (p. 5).

(4) Anonymous, "Salicylate in Pepto-Bismol," *The Medical Letter on Drugs and Therapeutics,* 22:63, 1980.

(5) Pickering, L. K., et al., "Absorption of Salicylate and Bismuth in Children and Adults from a Bismuth Subsalicylate Containing Compound (Pepto-Bismol)," unpublished study (forwarded to FDA by letter dated February 24, 1981), Panel Administrator's File (Volume 17LPAII).

(6) White, J. M., "Drug Interactions," OTC Volumes 170213 and 170214.

(7) Berkowitz, J. M., "Bismuth Subsalicylate in Excessive Alcohol/Food Intake," OTC Volume 170208 (pp. 11–15).

(8) Newsom, J. H., "Evaluation of Bismuth Subsalicylate in Relieving Symptoms of Indigestion," OTC Volume 170208 (pp. 15–17).

(9) Davis, C. S., "The Effectiveness of Pepto-Bismol in Gastrointestinal Upsets," OTC Volume 170208 (pp. 18–19).

b. *Sodium citrate in solution.* The Panel concludes that sodium citrate in solution is generally recognized as safe and effective in the dosage noted below for OTC use in relieving symptoms of upset stomach due to overindulgence in the combination of alcohol and food.

Two of the preparations which the Panel reviewed for this indication are combination drug products which contain, in addition to an analgesic, citric acid and sodium bicarbonate in a dry form. One preparation is formulated as effervescent granules, and the other as an effervescent tablet. When either preparation is immersed in water, a series of chemical reactions occurs which results in the formation of sodium citrate in solution and free and dissolved carbon dioxide, with a slight excess of residual sodium bicarbonate in solution. The slight excess of sodium bicarbonate is included in the formulation to ensure that the above chemical reaction progresses to completion. For treating the symptoms of upset stomach due to overindulgence in the combination of alcohol and food, the Panel considers sodium citrate in solution to be the only active ingredient.

(1) *Safety.* The Advisory Review Panel on OTC Antacid Drug Products concluded that the citrate ion (available as citric acid or salt) is safe in a maximum daily dose limit of 8 g as published in the **Federal Register** of April 5, 1973 (38 FR 8724). This Panel is unaware of any safety problems associated with the ingestion of citrate ion, and believes that the Antacid Panel's daily limits of 100 mEq of

sodium for persons 60 years of age or older and 200 mEq of sodium for persons under 60 years of age is more realistic than using the citrate ion as the upper limit and adopts these limits for calculating the amounts of sodium citrate. The Panel, therefore, concludes that sodium citrate is safe in a daily dose of up to 8.6 g (100 mEq of sodium) for persons 60 years of age or older and up to 17.2 g (200 mEq of sodium) for persons under 60 years of age. If there is another source of sodium in a combination drug product, the dose of sodium citrate must be reduced proportionally.

(2) *Effectiveness.* Sodium citrate was reviewed by the Advisory Review Panel on OTC Antacid Drug Products and was found to be effective for use as an antacid (38 Fr 8724).

This Panel has been presented with another claim for sodium citrate, i.e., upset stomach due to overindulgence in the combination of food and drink. In support of this claim, White et al. (Ref. 1) conducted a study comparing the effectiveness of a sodium acetylsalicylate and sodium citrate combination to aspirin tablets, an antacid, and a placebo. This was a placebo-controlled, parallel sample study on 64 subjects who were randomly assigned to one of the medication groups. The subjects were separated into 4 groups of 16. Each group, on different dates, was encouraged to overeat a variety of rich and spicy foods while consuming alcoholic beverages of their own choosing. A symptom questionnaire, which was completed 5 times during the course of the 14-hour and 15-minute study protocol, included 11 upset stomach symptoms: fullness, heartburn/burning, passing of gas, stomach ache, belching, rumbling sensation, thirsty/dry mouth, sluggishness, taste repeat, nausea, and bitter/acidic aftertaste. Average severity scores for each subject were computed and analysis of variance was applied comparing the four treatments for each time period. Significant differences (p equals 0.004) among treatments were found for the final measurement (45 minutes after medication on the morning after overindulgence), which was the primary point of measurement. Duncan's Multiple Range test showed the combination of sodium acetylsalicylate and sodium citrate significantly better than placebo (p equals 0.05) or aspirin (p equals 0.05) at the final measurement. Also, there was no significant difference between aspirin and placebo.

On the basis of this study, collateral studies (Ref. 2), proven antacid capacity (21 CFR Part 331), and long history of use, the Panel concludes that sodium citrate in solution has demonstrated an "overall" effectiveness in relieving the symptoms of upset stomach due to overindulgence in the combination of alcohol and food.

(3) *Dosage.* The Panel recommends that sodium citrate be given in divided doses and that the daily dose not exceed 8.6 g (100 mEq of sodium) for persons 60 years of age or older and 17.2 g (200 mEq of sodium) for persons under 60 years of age. If there is another source of sodium in a combination drug product, the dose of sodium citrate must be reduced accordingly.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients intended for relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food. (See part III. paragraph B.2. below—*Category I labeling.*) In addition, the Panel recommends the following statements:

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

(ii) *Directions.* "If you are 60 years of age or older, the maximum daily dose should not exceed —— of this drug." (Space to be filled in with the number of dosage units which will not exceed 100 mEq of sodium in a daily dose as specified under "Dosage.")

References

(1) White, J. M., et al., "Clinical Study of Experimentally Produced Upset Stomach and Its Treatment," unpublished study, OTC Volumes 170123 (Appendix 5), 170132, 170189 (Section III.D.2.), 170205 (Tab 390), and 170212.

(2) OTC Volume 170189.

2. *Category I labeling.* The Panel recommends the following Category I labeling for drug products which contain ingredients that are generally recognized as safe and effective for relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food, as well as any ingredient-specific labeling statements discussed previously:

Indications. "For the relief of upset stomach due to overindulgence in the combination of food and drink." Throughout this document the Panel has used the phrase "overindulgence in the combination of alcohol and food" to emphasize that alcohol is the more important of the two elements in terms of symptoms generated. The Panel has not followed through with this wording in the indication to be used on product labeling because it believes that the phrase "overindulgence in the combination of food and drink" is more acceptable to the consumer. It is also assumed by the Panel that the consumer will know that "drink" means an alcoholic beverage.

If any or all of the major individual symptoms (i.e., nausea, heartburn, and fullness) are also demonstrated to be relieved by a particular drug product (e.g., bismuth subsalicylate), those symptoms relieved may also be included in the labeling following the term "upset stomach." For example, if all these symptoms are shown to be relieved, the labeling could be as follows: "For the relief of upset stomach associated with nausea, heartburn, and fullness due to overindulgence in the combination of food and drink."

C. Category II Conditions

The following are Category II conditions under which drug products intended to relieve the symptoms of upset stomach due to overindulgence in the combination of alcohol and food are not generally recognized as safe and effective or are misbranded.

1. *Category II active ingredients.* None.

2. *Category II labeling.* The Panel concludes that the following labeling claims are misleading or unsupported by scientific data. Therefore, the following claims and other related terms are classified as Category II labeling:

a. "Upset stomach." (unqualified as to cause)

b. "Fast relief," "quick relief," or any other term which nonspecifically relates to the speed of action.

c. "Upset stomach with headache from overindulgence." (no explanation as to what item in which one overindulged)

D. Category III Conditions

There are no Category III conditions.

IV. Drug Products for Relief of Hangover Symptoms

General Discussion

The word "hangover" is commonly used to describe noxious feelings encountered several hours after the sporadic ingestion of large amounts of alcohol. This syndrome involves a temporary metabolic disturbance affecting many organ systems of the body, most notably the central nervous system, gastrointestinal system, and endocrine system. A hangover is generally differentiated from alcoholism, an entirely different disorder encountered with chronic alcohol ingestion and the resulting pathological organ damage. This Panel has

considered only the treatment of the sporadic episode of overindulging in alcohol. The Panel has reviewed the literature and found approximately 30 symptoms used in describing "hangover" (Refs. 1 through 5).

Collins (Ref. 1), in measuring performance effects on simulated tasks during alcohol intoxication and hangover, used a questionnaire to measure severity of an assortment of hangover symptoms which included the following: "throwing up, stomachache, hungry, headache, loose bowels, tight bowels, muscle aches, shaking, dizzy, feel hot, feel confused, eyes burn, backache, nose runs, nervous, tired, dry mouth, feel sad or depressed, ringing in ears, hurts to move, thirsty, nauseated, heartburn."

In a review article, Anylian, Dorn, and Swerdlow (Ref. 2) reported the results of a series of tests conducted in Finland which attempted to define hangover by using the subjective feelings of "fatigue, headache, dizziness, nausea, thirst, tension, depression, and general malaise," and the objective signs of "paleness, tremor, perspiration, nystagmus (involuntary eye movement), vomiting, and general appearance." This paper cited three other studies in which hangover symptoms were measured. Khan, Jensen, and Krogh (Ref. 3) in comparing pyritinol and placebo in preventing hangover, used the following symptoms: "vomiting, loss of appetite, heartburn, lassitude, continued thirst, palpitation, weakness of joints, respiratory difficulties, sleeplessness, giddiness, headache, fatigue, sweating, disturbed balance and gait, pallor, tremor, nystagmus, general malaise, anxiety and depression." Chapman (Ref. 4), in attempting to predictably induce hangover for experimental studies, used the following symptoms: "thirst, fatigue, drowsiness, trouble in sleeping, general malaise, nausea, loss of appetite, dizziness or feelings of faintness, headache, depression, and anxiety." Damrau and Liddy (Ref. 5), in attempting to demonstrate that congeners play an important role in the production of hangover, used the following symptoms: "headache, bad breath, gastric irritation, fatigue, dizziness and desensitization of the taste sensations."

To the Panel's knowledge no study has been performed delinating the frequency of these symptoms in a large population. Therefore, the Panel developed a list of the most frequently occurring hangover symptoms mentioned in the five studies cited above (Refs. 1 through 5). These symptoms reflect disturbances in the gastrointestinal, neurologic, and endocrine systems and consist of nausea, heartburn, thirst, tremor, disturbance of equilibrium, fatigue, generalized aches and pains, headache, dullness, and/or depression or irritability.

The Panel has reviewed remedies for relief of hangover symptoms in a different manner from those remedies intended for relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food. For the latter, the Panel required results of clinical studies to demonstrate effectiveness, but for hangover remedies, no studies were deemed necessary. The hangover symptom complex is complicated and reflects multiple body disturbances. Based upon the Panel's background in clinical medicine, it concluded that a hangover can be manifested by a wide variety of signs and symptoms of varying frequency and severity usually appearing several hours after overindulgence in alcohol.

Over the years, people have found it convenient to treat their generalized hangover symptoms with internal analgesics for headache, antacids for gastric distress, and caffeine for the fatigue or dullness. The Panel, therefore, concludes that it would be logical to allow consumers to self-treat hangover symptoms with various combinations of analgesics, antacids, and stimulants. The Panel recommends that preparations intended as hangover remedies contain a combination of ingredients from two or more of these drug categories so that consumers can choose the product which contains the ingredients needed to treat the symptoms they are experiencing. Because these ingredients have been extensively reviewed by other panels for treating the diffferent symptoms that comprise a hangover, the Panel considers it unnecessary to require clinical studies that demonstrate effectiveness. The Panel does require that these combinations conform to FDA's combination policy and combination guidelines. (See part II. paragraph B. above—*Combination Policy.*)

The Panel required clinical studies for remedies intended to relieve the symptoms of upset stomach due to overindulgence in the combination of alcohol and food because it believes that this condition is not as clearly understood by consumers as is the hangover syndrome. Moreover, the symptoms of upset stomach due to overindulgence in the combination of alcohol and food have been difficult to identify, even by experts in the field. This Panel required prolonged discussions and reviews before arriving at a classification of symptoms that appears reproducible and characteristic. Furthermore, the Panel is not aware of any Category I ingredient which would relieve two of the three symptoms established by the Panel, i.e., nausea and fullness. The Panel, therefore, concludes that the effectiveness of any single ingredient intended to relieve symptoms of an upset stomach due to overindulgence in the combination of alcohol and food must be demonstrated by the use of clinical trials. The use of empiricism or reasonable probabilities was not deemed adequate.

1. *Formulation criteria.* The Panel has identified no product or single ingredient which is unique in relieveing the symptoms of a hangover. Based upon this fact and the above discussion, the Panel recommends that a hangover drug product contain a combination which may include analgesics, antacids, and/or stimulants as long as the preparation meets all of the following criteria:

a. The combination must contain Category I ingredients from at least two of the following drug categories: analgesics (a final dosage form containing aspirin would have to at least meet the buffering capacity required of an antacid final dosage form), antacids, and stimulants.

b. Each of the ingredients, and any combination of ingredients (if applicable) must meet the conditions of the appropriate monographs with the exceptions as specified in paragraph 3. below—*"Use of buffered aspirin and an antacid in gastric distress."*

c. The product must conform with FDA's combination policy and combination guidelines.

If these criteria are met and the product does not contain any active ingredients other than Category I analgesics, antacids, or stimulants, the Panel considers such a product to be rational and effective for relieving hangover symptoms.

2. *Combination products for relief of hangovers.* The Panel has reviewed the following four combination products for the relief of hangover symptoms:

a. Aspirin, citric acid, and sodium bicarbonate (when immersed in water and ingested contains sodium acetylsalicylate in solution and sodium citrate in solution as the active ingredients),

b. Acetaminophen, citric acid, and sodium bicarbonate (when immersed in water and ingested contains acetaminophen and sodium citrate in solution as the active ingredients),

c. Aspirin, caffeine, aluminum hydroxide, and magnesium carbonate, and

d. Acetaminophen, aspirin, caffeine, magnesium trisilicate, magnesium carbonate, and aluminum hydroxide gel.

The panel concludes that each combination satisfies the criteria of effectiveness established by the Panel. However, combinations c. and d. require additional acid neutralizing capacity to meet requirements of the antacid monograph.

The Panel emphasizes that although the consumer may desire an antacid for what he describes as heartburn, acid indigestion, or sour stomach, the condition existing in a hangover state usually is not due to hyperacidity. It is more likely due to acute gastritis (inflamed gastric mucosa) and the antacid would be necessary to protect the mucosa from normal gastric acid secretion.

3. *Use of buffered aspirin and an antacid in gastric distress.* the Advisory Review Panel on OTRC Internal Analgesic and Antirheumatic Drug Products, in its report published in the **Federal Register** of July 8, 1977 (42 FR 35386 and 35471), recommended against the combination of aspirin and an antacid for use in gastric distress. This Panel differs with that Panel's recommendation and bases its conclusion in favor of combining aspirin with antacids (as long as the final dosage form at least meets the buffering capacity required of an antacid final dosage form) for use in conditions of gastric distress for the following reasons:

Acetylsalicylic acid (aspirin) has been shown to cause an increase in blood loss from the gastrointestinal tract. Aspirin is a weak acid and is lipid-soluble in its undissociated dorm, which facilitates its absorption into the gastric mucosa. The presence of aspirin in gastric mucosal cells results in an abnormal permeability and subsequent back diffusion of gastric acid which in turn results in an increased potential for mucosal erosions and bleeding. In the presence of strong buffers, aspirin is converted to sodium acetylsalicylate which is water-soluble and lipid-insoluble. In this form it is not absorbed by the cells of the gastric mucosa in amounts significant enough to cause gastric erosion. Studies of an effervescent alkaline solution containing sodium acetysalicylate have demonstrated that there is no increase in fecal blood loss (Ref. 6), no gastric erosions are seen on gastrocamera examination (Ref. 7), and the mucosal barrier of dogs remains intact (Ref. 8). Concommitant administration of alcohol had no affect on the gastric mucosa of dogs, whereas aspirin combined with alcohol showed an increase in blood loss (Ref. 8).

The Advisory Review Panel on OTC Antacid Drug Products in its report published in the **Federal Register** of April 5, 1973 (38 FR 8721) concluded that

> . . . unbuffered aspirin causes greqter visible gastric mucosal damage and more gastrointestinal blood loss than strongly buffered aspirin in solution, which causes little or none of these experimental forms of damage. However, the actual clinical condition of major gastrointestinal hemorrhage associated with aspirin ingestion has been seen with both unbuffered and strongly buffered aspirin in solution. There is inadequate evidence to establish whether the risk of clinically major gastrointestinal hemorrhage is less with strongly buffered aspirin in solution than with unbuffered aspirin.

The internal Analgesic Panel in its report published in the **Federal Register** of july 8, 1977 (42 FR 35471), concluded

> * * * that there is evidence that highly buffered aspirin solutions will reduce, but not eliminate the acute gastric erosions and occult blood loss produced by the local effects of aspirin in experimental animals and individuals with no predisposing gastrointestinal disease. However, there is no valid clinical evidence to support the claim that highly buffered aspirin for solution has significantly less potential to induce major gastrointestinal hemorrhage in patients with preexisting gastrointestinal lesions which the Panel believes includes mechanisms other than the acid-mediated local mechanisms involved in the production of occult bleeding in normal subjects.

That Panel also stated: "Furthermore, based on current knowledge of high risk groups such as individuals who drink alcohol excessively, the benefit to risk ratio for individuals with symptoms of gastric distress, particularly with concomitant headache, does not warrant the use of aspirin in any dosage form."

This Panel, with its experience in hematology, has reviewed the current literature and considered expert testimony (Ref. 9) and concludes that evidence indicates that sodium acetylsalicylate does not cause gastric erosions or appreciable increased blood loss. The Panel also concludes that evidence implicating sodium acetylsalicylate as a cause of major gastrointestinal hemorrhage has been based on occasional isolated reports in which there is no proven causal relationship.

The effects of aspirin on the mechanisms of hemostasis were reviewed because it has been suggested that mechanisms other than acid reflux might cause gastrointestinal hemorrhage. When a blood vessel is served, a complex series of interactions ensues, i.e., localized vasoconstriction, platelet adhesion at the wound site, platelet aggregation, release of internal platelet materials, formation of a platelet plug, formation of a fibrin network, and, finally, dissolution of the fibrin clot by the action of plasmin and other means. Aspirin has an inhibitory effect on prostaglandin synthesis, which in turn inhibits secretion of adenosine diphosphate from platelets and their aggregation. However, adenosine diphosphate is present in abundance from other sources where tissue or vacular damage occurs, and so the net effect is minimal in healthy persons. O'Laughlin et al. (Ref. 10) studied the effects of acute and chronic aspirin use on gastric bleeding time in humans using endospic punch biopsies and observed the time it took for bleeding to stop. This study demonstrated that aspirin in the dose administered had no measurable effect on the bleeding time of gastric mucosa.

The synergism between the effects of aspirin and alcohol to induce gastrointestinal bleeding was explored by the Panel. At low concentrations, alcohol stimulates acid secretion. Davenport (Ref. 11) observed that severe damage occurred to the gastric mucosa of dogs treated with a mixture of aspirin, hydrochloric acid, and 8 to 10 percent alcohol; however, no back diffusion of acid or bleeding occurred when the solution contained a combination of buffered sodium acetylsalicylate and alcohol. Leonards (Ref. 12) administered large amounts of alcohol to normal subjects and compared fecal blood loss after alcohol alone and after a combination of alcohol and buffered sodium acetylsalicylate. Adding buffered aspirin produced no increase in fecal blood loss. Another study also demonstrated that a combination of alcohol and buffered sodium acetylsalicylate did not cause gastrointestinal bleeding (Ref. 13).

It should be noted that chronic alcoholism is well known to cause gastrointestinal hemorrhage for various reasons and that no claims of effectiveness of sodium acetylsalicylate in relief of symptoms of chronic alcoholism are recognized.

The Panel has reviewed sodium acetylsalicylate as an agent to provide symptomatic relief of a hangover defined by the Panel as overindulgence in alcohol producing symptoms which include nausea, heartburn, thirst, tremor, disturbance of equilibrium, fatigue, generalized aches or pains, headache, dullness, and/or depression or

irritability, and has found this ingredient to be safe and effective in relief of those symptoms subject to relief by an analgesic. In addition, the combination of sodium citrate and sodium acetylsalicylate to treat a hangover is rational and justified because the alkaline buffering ability of sodium citrate enables aspirin to become dissolved and remain dissolved as sodium acetylsalicylate, thus protecting the gastric mucosa from the erosive effects caused by the combination of aspirin, gastric acidity, and alcohol.

4. *Category I labeling for OTC drug products that provide relief from hangover symptoms.* The Panel offers the following discussion and recommendations of Category I labeling claims for drug products which are considered safe and effective for relief of hangover symptoms and are not misbranded. A drug manufacturer shall include all of the hangover symptoms (from the Panel's definition of hangover) which the active ingredients in the formulation would normally be expected to relieve (e.g., if one of the ingredients is an analgesic, the symptoms of "headache" and/or "generalized aches and pains" shall be included).

Any additional labeling information (e.g., warnings, drug interaction precaution) which is specific to the individual ingredients would come from the respective monographs (i.e., analgesic (21 CFR Part 343), antacid (21 CFR Part 331), and stimulant (21 CFR Part 348); only the antacid monograph is final at this time). With regard to warnings, for those products marketed only for the condition "relief of hangover" the following exceptions are recommended to the warning statements as published in the July 8, 1077 **Federal Register** (42 FR 35493–4) for internal analgesics, the June 4, 1974 **Federal Register** (39 FR 19876) for antacids, and the June 13, 1978 **Federal Register** (43 FR 25602) for stimulants:

Any labeling pertaining to children (except the warning to keep the medication out of the reach of children) is not applicable due to the nature of the condition being treated.

a. *For products that include a salicylate.* (1) That portion of § 343.50(c)(1)(i) that reads, "Adults: Do not take this product for more than 10 days," is not applicable and should be deleted because of the acute nature of the condition being treated. The resultant warning would read, "If symptoms persist, or new ones occur, consult your physician."

(2) That portion of § 343.50(c)(3)(ii) that reads, "or other symptoms," (regarding ringing in the ears) should be deleted because it is too vague. The resultant warning would read, "Stop taking this product if ringing in the ears occurs."

(3) The entire warning in § 343.50(c)(3)(iv) that reads, "*Caution.* Do not take this product if you have stomach distress, ulcers, or bleeding problems except under the advice and supervision of a physician," is not applicable and should be deleted because the hangover syndrome involves stomach distress.

(4) Revision of the warning regarding the concurrent use of certain prescription medications (§ 343.50(c)(3)(v)) has been discussed earlier in this document. (See part III. paragraph B.1.a. above—*Bismuth subsalicylate*). This reasoning also applies to hangover remedies and the resultant wording should read, "*Warning:* If taking medication for anticoagulation (thinning of the blood), consult a physician before taking this product."

(5) That portion of § 343.50(c)(6) that reads, "except under the advice and supervision of a physician," (regarding an allergic reaction to the salicylate portion of choline, magnesium, and sodium salicylate) should be deleted because if one is allergic to the ingredient, then one should not take the product. The resultant warning would read, "Do not take this product if you are allergic to salicylates, such as aspirin."

(b) *For products that contain acetaminophen.* (1) The warning in § 343.50(c)(5)(i) that reads, "Do not exceed recommended dosage because severe liver damage may occur," is not applicable and should be deleted because of the temporary nature of the condition being treated.

(2) That portion of § 343.50(c)(1)(i) that reads, "Adults: Do not take this product for more than 10 days," is not applicable and should be deleted because of the temporary nature of the condition being treated. The resultant warning would read, "If symptoms persist, or new ones occur, consult your physician."

c. *For products that contain antiacids.* (1) The portion of § 331.30(b)(1) that reads, "or use the maximum dosage of this product for more than 2 weeks," is not applicable and should be deleted because of the temporary nature of the condition being treated. The resultant warning would read, "Do not take more than (maximum recommended daily dosage, broken down by age groups if appropriate, expressed in units such as tablets or teaspoonsful) in a 24-hour period, except under the advice and supervision of a physician."

(2) The warning in § 331.30(b)(2) that reads, "May cause constipation," for use with products which cause constipation in 5 percent or more of the persons who take the maximum recommended dosage is not applicable and should be deleted because of the temporary nature of the condition being treated.

(3) The warning in § 331.30(b)(3) that reads, "May have a laxative effect," for use with products which cause laxation in 5 percent or more of persons who take the maximum recommended dosage is not applicable and should be deleted because of the temporary nature of the condition being treated.

d. *For products that contain stimulants.* That portion of § 340.50(c)(2) that reads, "If fatigue or drowsiness persist continuously for more than 2 weeks, consult a physician," is not applicable and should be deleted because of the temporary nature of the condition being treated. The resultant warning would read, "For occasional use only."

5. *Category II labeling.* The Panel concludes that the following labeling claims are misleading or unsupported by scientific data. Therefore, the following claims and other related terms are classified as Category II labeling:

a. "For the relief of overindulgence."

b. "Fast relief," "quick relief," or any other term which nonspecifically relates to the speed of action.

6. *Category III labeling.* The Panel could identify no labeling claims for which available data are insufficient to permit final classification at this time.

References

(1) Collins, W. E., "Performance Effects of Alcohol Intoxication and Hangover at Ground Level and at Simulated Altitude," *Aviation Space and Environmental Medicine,* 51:327–335, 1980.

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(3) Khan, M. A., K. Jensen, and H. J. Krough, "Alcohol-Induced Hangover: A Double-Blind Comparison of Pyritinol and Placebo in Preventing Hangover Symptoms," *Quarterly Journal of Studies on Alcohol,* 34:1195–1201, 1973.

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(6) Leonards, J. R., and G. Levy, "Reduction or Prevention of Aspirin-Induced Occult Gastrointestinal Blood Loss in Man," *Clinical Pharmacology and Therapeutics,* 10:571–575, 1969.

(7) Hurley, J. W., "Direct Observations of the Gastric Mucosa in the Presence of

Acetylsalicylate at Different pH Levels," report to Miles Laboratories, Inc., OTC Volume 170196 (Tab 152).

(8) Davenport, H. W., "Gastric Mucosal Hemorrhage in Dogs. Effects of Acid, Aspirin and Alcohol," *Gastroenterology*, 56:439–449, 1969.

(9) OTC Volume 170212.

(10) O'Laughlin, J. C., et al., "Does Aspirin Prolong Bleeding from Gastric Biopsies in Man?" unpublished report. OTC Volume 170200 (Tab 265).

(11) Davenport, H. W., "Ethanol Damage to Canine Oxyntic Glandular Mucosa," *Proceedings of the Society for Experimental Biology and Medicine*, 126:657–662, 1967.

(12) Leonards, J. R., "The Effect of Alcohol and Alka-Seltzer on Gastrointestinal Blood Loss," report to Miles Laboratories, Inc., OTC Volume 170197 (Tab 195).

(13) Bouchier, I. A. D., and H. S. Williams, "Determination of Faecal Blood-Loss After Combined Alcohol and Sodium Acetylsalicylate Intake," *Lancet*, 1:178–180, 1969.

V. Drug Products To Prevent Inebriation or To Minimize or Reduce a Hangover

A. General Discussion

In addition to products submitted for relief of "upset stomach due to overindulgence in food and drink" and for relief of "symptoms of hangover," the Panel reviewed preparations which had claims of "minimizing or reducing the symptoms of hangover" and "to prevent alcoholic intoxication." Because the claims for these products were preventive in nature, the Panel decided to review them separately.

Activated charcoal is the only ingredient reviewed with the claim of minimizing or reducing the symptoms of a hangover. The Panel believes that congeners in alcoholic beverages contribute to a hangover and realizes that activated charcoal has been demonstrated in vitro to adsorb congeners but no clinical studies have been submitted. The Panel classified this ingredient in Category III and recommends that clinical studies be performed to demonstrate that activated charcoal minimizes the symptoms of a hangover.

Fructose is the only active ingredient reviewed by the Panel with the claim of preventing alcoholic intoxication. The Panel believes that the term "inebriation" is more familiar to the public and, therefore, has used this term throughout this document. The Panel has classified fructose in Category III.

B. Category I Conditions

The following are Category I conditions under which drug products intended to prevent inebriation or to minimize or reduce the symptoms of a hangover are generally recognized as safe and effective and not misbranded.

1. *Category I active ingredients.* None.

2. *Category I labeling.* Although there are no Category I active ingredients, the Panel recommends the use of Category I labeling for Category III ingredients.

a. *To prevent inebriation:* "To minimize inebriation."

b. *To minimize or reduce a hangover*—(1) "To minimize the symptoms of a hangover caused by alcoholic beverages."

(2) "For minimizing the symptoms of a hangover caused by alcoholic beverages."

(3) "An aid in minimizing the symptoms of a hangover caused by alcoholic beverages."

C. Category II Conditions

The following are Category II conditions under which drug products intended to prevent inebriation or to minimize or reduce a hangover are not generally recognized as safe and effective or are misbranded.

1. *Category II active ingredients.* None.

2. *Category II labeling.* The Panel considers the claims listed below and any related claims to be unsupported by scientific data and, therefore, are classified as Category II.

a. *To prevent inebriation*—(1) "For the inebriation."

(2) "For the prevention of alcholic inebriation."

b. *To minimize or reduce a hangover.*—(1) "For the prevention (or reduction) of the symptoms of a hangover caused by alcoholic beverages."

(2) "An aid in preventing (or reducing) the symptoms of a hangover caused by alcoholic beverages."

D. Category III Conditions

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

1. *Category III active ingredients*—a. *To prevent inebriation—Fructose.* The Panel concludes that fructose is safe for OTC use in the dose noted below, but data are insufficient to demonstrate its effectiveness in minimizing inebriation. The Panel has placed an "prevention" claims in Category II because the Panel is unaware of any evidence that any ingredient can entirely prevent inebriation.

(1) *Safety.* Fructose, also known as levulose or fruit sugar, is usually obtained from the inversion of aqueous solutions of sucrose and the subsequent separation from glucose. A component of honey, fructose is sweeter that sucrose and is readily absorbed from the gastrointestinal tract, but not as rapidly as dextrose (Refs. 1, 2, and 3).

One text considers fructose to be safe in oral dose of up to 150 g per day in divided doses of 2 to 25 g (Ref. 2). The author notes that large oral doses may cause abdominal pain and diarrhea and that fructose should not be given to person with a fructose intolerance. Persons with methyl alcohol poisoning should not be given fructose, because it enhances the oxidation of the methyl alcohol to formaldehyde. As fructose is rapidly removed from the blood, it has little effect on blood-sugar concentration, except that diabetics metabolize it to dextrose to a greater extent that do nondiabetics. Furthermore, it does not require insulin for its metabolism (Ref. 2).

Fructose has been used as in intervenous infusion (500 mL of a 40-percent solution) in grossly intoxicated individuals to accelerate the metabolism of the alcohol (Ref. 4).

The Panel, therefore, concludes that the ingestion of up to 4 g of fructose (2 g followed by 2 g in 30 minutes), as recommended by the manufacturer, is generally recognized as safe for OTC use.

(2) *Effectiveness.* All the studies available to the Panel involved the investigation of the effect of fructose on lowering blood-alcohol levels. In a study by Pawan (Ref. 5), 12 normal, healthy male volunteers ingested 30 g doses of fructose along with alcohol (0.5 ethanol per kilogram body weight) and the rates or slopes of the decrease in plasma alcohol concentrations for up to 4.5 hours after the ingestion were compared to the rates obtained when the alcohol was ingested along with a control of pure lemon juice. Fructose was reported to produce a "significant increase of 18–40 percent" in the rate of alcohol metabolism over the control (no level of significance was reported). Eight of the 12 subjects repeated the above experiment, but took the fructose 30 minutes after the ingestion of the alcohol. The fructose "increased the rate of metabolism of alcohol by 15–30 percent." No statement about statistical significance of this result was reported. The above experiments were performed for other sugars (glucose, galactose, and sucrose) on different days. Only sucrose showed any increase in the rate of alcohol metabolism. It was, however, only "very slight."

In a small-scale, controlled, pilot experiment, Feldman (Ref. 6) performed two crossover studies involving four subjects (two males and two females). In the first study, no significant difference was found between the use of

10 g of fructose and 10 g of sucrose in reducing blood-alcohol levels for up to 1 hour after consumption of 1 ounce of 80 proof vodka and a glass of water. In the second study, the subjects were again given 1 ounce of 80 proof vodka and a glass of water. In ths study there was a highly significant difference (p less than 0.001) between the use of 2 g of fructose in a lozenge form (dissolved in the mouth) versus the use of no other active ingredient in reducing blood-alcohol levels for up to 1 hour after the drink.

In another small-scale experiment, involving a total of 20 subjects, Molomut (Ref. 7) performed two crossover studies investigating the effects of glucose, a 1-g fructose lozenge swallowed directly, and two 1-g fructose lozenges dissolved in the mouth when taken simultaneously with 80 proof vodka (43 mL) on blood-alcohol levels measured at 30- and 60-minute intervals after ingestion of the alcohol. While the investigator claimed an effect in favor of dissolving the fructose lozenge in the mouth, as compared to swallowing it directly, the data at 30- and 60-minute intervals are inconsistent and no clear interpretation of the data can be made.

In another crossover study, Albanese (Ref. 8) used 9 subjects to compare the effect of a 1-g fructose tablet versus the use of a placebo tablet (both to be dissolved in the mouth) just prior to administration of 80 proof vodka (0.5 mL/kg). While fructose had a better reduction of blood-alcohol levels than did the placebo, the difference in reduction was not statistically significant (p greater than 0.05). Albanese also investigated the effectiveness of one fructose tablet on two doses of vodka. (twice the amount cited above) and the effectiveness of fructose when given 30 minutes after the ingestion of the vodka. The sample sizes and variations displayed in the latter two studies made it impossible to reach any conclusions.

An additional controlled study was performed by Brown et al. (Ref. 9) to test the effectiveness of fructose when administered as an intravenous infusion (500 mL of a 40-percent solution) in treating patients with acute alcoholic intoxication. Nineteen patients were used in the experiment which covered a 15-month period. Normal saline was used as the control. The investigators reported the rate of decrease in the blood-ethanol levels of the patients receiving fructose to be approximately 25 percent greater than that obtained from the normal saline controls. This was statistically significant with a one-sided test (p equals 0.05). They concluded that:

In unconscious patients, where the possibility of drug overdosage, head injury, or other acute medical emergency may coexist, intravenous fructose may help to reveal any underlying pathological condition by shortening the period of alcoholic intoxication. In patients who are simply inebriated, 200 g of intravenous fructose may usefully shorten their stay in a casualty department by a few hours, depending on the initial ethanol level.

This study was later commented on by Hessov (Ref. 10), who stated that such a high dose of fructose (200 g) over such a short period of time (30 minutes) could have at least three unfavorable effects and further complicate the coexisting conditions mentioned above.

The above studies indicate that fructose given with a drink of alcohol may have an effect in lowering blood-alcohol levels, but the data are insufficient for the Panel to determine what practical clinical significance the blood level lowering has in minimizing inebriation. The Panel is unaware of any evidence that any ingredient can entirely prevent inebriation and therefore has placed any "prevention" claims in Category II.

(3) *Proposed dosage.* The Panel recommends the dosage, as recommended by the manufacturer, of 2 g of fructose administered either just prior to drinking or within 30 minutes following such ingestion, followed by an additional 2 g taken 30 minutes after the first dose, if necessary.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients intended to minimize inebriation. (see part V. paragraph B.2.a.—*Category I labeling.*)

(5) *Evaluation.* The Panel concludes that fructose is generally recognized as safe for OTC use in the dosage noted above, but data are insufficient to demonstrate its effectiveness in minimizing inebriation. The Panel recommends that clinical studies be performed to demonstrate what practical clinical significance the lowering of blood-alcohol levels has in minimizing inebriation.

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(9) Brown, S. S., J. A. H. Forrest, and P. Roscoe, "A Controlled Trial of Fructose in the Treatment of Acute Alcoholic Intoxication," *Lancet,* 2:898–900, 1972.

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b. *To minimize or reduce a hangover—Charcoal, activated.* The Panel concludes that activated charcoal is safe for OTC use in the doses noted below, but data are insufficient to demonstrate its effectiveness in minimizing the symptoms of a hangover. The Panel has placed claims for "reduction" in Category II because activated charcoal is only intended to work prior to getting a hangover.

(1) *Safety.* The Panel has previously reviewed this ingredient in its reports on OTC Digestive Aid Drug Products, Deodorants for Internal Use Drug Products, and OTC Drug Products for the Treatment of Acute Toxic Ingestion. In each case, it has found activated charcoal to be safe for OTC use in the dosages recommended. The Panel's recommended dosage in the Acute Toxic Ingestion report is 30 g as a one-time dose, whereas the dosage was limited to 10 g per day in both the Digestive Aid and Deodorants for Internal Use reports. The 7-day limit of use as a digestive aid was because, if symptoms lasted that long, a physician should be consulted to identify the underlying cause, whereas, chronic administration was allowed for use as a deodorant for internal use because of the long-term condition being treated.

(2) *Effectiveness.* Activated charcoal is known to adsorb many gases, organic and inorganic compounds, and toxins. Activated charcoal is claimed to minimize or reduce a hangover by adsorbing the congeners in the alcoholic beverage. In order to show that activated charcoal is effective in minimizing a hangover, it must first be shown that hangovers are caused by the congeners in the alcoholic beverage. Congeners are materials, other than ethanol and water, in alcoholic beverages which give the beverage its unique color, aroma, and taste (Ref. 1).

It has been established that the congener content varies from one

alcoholic beverage to another; bourbon contains the most and vodka contains the least (not much more than synthetic ethanol) (Refs. 1 and 2). The congeners measured in each of these studies are acetaldehyde, ethyl formate, ethyl acetate, methanol, *n*-propanol, isobutanol, and isoamyl alcohol (the latter three being the primary constituents of fusel oil). In most of the beverages tested isoamyl alcohol and ethyl acetate constituted more than 70 percent of the total congeners present (Ref. 2).

Although the Panel was unable to find studies in which activated charcoal was given to subjects to determine what effect it would have in minimizing a hangover, one in vitro study does demonstrate the ability of activated charcoal to adsorb congeners. Damrau and Goldberg (Ref. 3) performed the study in which a mixture of 86 proof whiskey and 0.1 N hydrochloric acid (to simulate stomach contents) was subjected to activated charcoal in a ratio of 1 g per 60 mL of whiskey. Total congener content was determined following 1 hour of agitation. As a control a separate mixture of whisky and hydrochloric acid was agitated and measured for congeners. Results indicated that "significant amounts" of the congeners were removed (36 percent fusel oils, 82.6 percent acetaldehyde, 93.8 percent furfural, and 31.3 percent ethyl acetate). The investigators cited a clinical study conducted by Damrau and Liddy (Ref. 4) in which they conducted a crossover clinical study to test the effects of 80 proof whiskey (high congener content) and prefiltered 80 proof vodka ("virtually no congeners") in a 2-ounce dose with the intention of producing a hangover the day following administration of the beverage. Damrau and Liddy found the whiskey to produce the following "after-effects": halitosis, gastric irritation, headache, dizziness, and fatigue. These effects occurred in 6 to 27 percent of those consuming whiskey, but only headache and gastric irritation occurred in 2 percent of those ingesting vodka. No raw data were given for this study. Damrau and Goldberg (Ref. 3) concluded from the above results (Res. 3 and 4) that "activated charcoal appears to be a useful agent for reducing the congeneric material from whiskey" and that "whiskey with less congeneric material should lessen hangover symptoms."

In order to determine whether the congener content of alcoholic beverages is the primary contributing factor to a hangover, the Panel reviewed a number of additional studies. Chapman (Ref. 5) found in testing 91 subjects that when vodka and bourbon were consumed in amounts equivalent to 1.5 mL of ethanol per kg of body weight, this level was the minimal dose which consistently produced hangover symptoms. An ethanol dose of 1.0 mL/kg (10 subjects) and 1.25 mL/kg (10 subjects) did not consistently produce the symptoms, and a dose of 1.75 mL/kg (11 subjects) did not increase the proportion of hangovers reported, but did increase the incidence of undesirable behavior. Concentrating on the results of the 1.5 mL/kg group (60 subjects), Chapman found that when using a scale of 0 to 7 (0 for no hangover and 7 for the most severe possible) 20 of the 30 subjects who received bourbon reported a definite hangover (rating of 2 or more) as compared with 13 of the 30 who received vodka. He also reported that 10 of the 30 who received bourbon noted a severe hangover (ratings greater than 3), and only 1 of 30 who received vodka noted a severe hangover. Chapman concluded that the dose of the ethanol (1.5 mL/kg) is crucial in consistently producing hangover symptoms (50 percent of the subjects when vodka or bourbon ws administered at a ethanol dose of 1.5 mL/kg). He also concluded that "subjects in our culture, drinking relatively large amounts of bourbon, experienced a greater incidence and severity of hangover than they did after drinking equivalent amounts of alcohol as vodka."

Brusch et al. (Ref. 6) in a crossover study administered bourbon, rum, gin, and vodka in amounts equivalent to 3 ounces of ethyl alcohol mixed with sufficient water to produce a total of 12 ounces to 20 subjects (not described as to heavy, moderate, or non-drinkers). For this test, the authors concluded that, "our results indicate that there are definite differences produced by some spirits and that these differences are probably produced by the congeners they contain." Although the authors report that hangover was based on subjective and objective finding, no data is given for the various beverages consumed. The data are so incomplete that no analysis can be made.

Murphree, Price, and Greenberg (Ref. 7), in reporting on the effect of alcoholic beverage congeners on the incidence of nystagmus (involuntary eye movement) during intoxication, demonstrate a more prolonged nystagmus when a congener-fortified vodka (32 times as much congeners as the bourbon) is administered than when bourbon containing the same amount of ethanol is administered. They also cite published studies in which moderate differences were reported favoring vodka (low congener content) over whiskey (high congener content) (Refs. 4 and 6) but make the following comment regarding these studies: "Limitation of the observations employed in these studies to highly subjective and impressionistic evaluations, and the absence of objective measurements of any kind, render the reported conclusions suggestive but something less then convincing."

An unpublished study by Collins and Chiles (Ref. 8) also references the studies conducted by Damrau and Liddy (ref. 4) and Brusch et al. (Ref. 6) and states that their "experimental approaches make the results less than convincing (e.g., Damrau and Liddy administered only 2 ounces of alcohol to nondrinkers or moderate social drinkers and obtained what they referred to as an 'unexpected' relatively high percentage of hangover effects)." Collins and Chiles (Ref. 8) performed a study to determine the effects of alcohol on the performance of simulated tasks. In a crossover experiment, 11 subjects were exposed to a series of tasks to determine the effect on hangover of consuming bourbon, vodka, and placebo (tests also performed to determine effect while inebriated). During the period from 8:00 p.m. to 12:00 p.m. (midnight) subjects were given four large drinks (each containing one-fourth of the total bourbon and vodka consumed—1.62 mL of ethanol per kg of body weight) with 1 hour to finish each drink. All the subjects consuming bourbon and vodka indicated drunkenness at a midnight testing session and two of the subjects who were given the placebo were rated "slightly drunk" at the same midnight session. The next morning, strong hangover symptoms occurred for both types of alcoholic beverages, with vodka showing a slightly higher rating (increased degree of hangover) over placebo than did bourbon, but performance on the various tasks was not significantly affected. The authors concluded that for the morning after "there were no significant impairments due to alcohol and no congener vs. noncongener differences." While subjects reported significant hangover symptoms, there were no statistical differences between the effects of bourbon and vodka on any of the hangover ratings (in fact, vodka, the noncongener beverage, produced numerically higher overall hangover scores than did bourbon). This study was performed to determine the effects of hangover on pilots' "8-hour rule" (no member may act as a crewmember of a civil aircraft within 8 hours after the consumption of any alcoholic beverage).

The authors concluded that while the results of this study do not contradict the "8-hour rule," they should be interpreted with caution.

A placebo-controlled, crossover study was conducted by Ylikahri et al. (Ref. 9), in which 23 medical students were given either ethanol (1.5 g per kg body weight) or water (placebo) over a 3-hour period in order to produce a hangover the next morning. This study determined various metabolites of ethanol over a 21-hour period in an attempt to relate them to degrees of intoxication (subjective and physical signs) and hangover (subjective and physical signs). Subjective feelings for intoxication and hangover were graded by the subject and objective physical signs for these conditions were graded by the observer. Blood samples were taken at 0, 2, 4, 8, 12, 14, 15, 16, 18, and 21 hours and analyzed for lactate, acetaldehyde, ethanol, ketone bodies, blood glucose, free fatty acids, and triglyceride.

Results indicated that a hangover begins when the blood-alcohol concentration begins to decrease and that the most severe hangover was found 14 hours after the initiation of a 3-hour drinking episode. Ethanol had disappeared from the blood at about 14 hours. No difference was demonstrated in the acetaldehyde level between the groups with severe (group I) and mild hangovers (group II) and the concentration of acetaldehyde showed no correlation with the intensity of hangover at any time. Lactate concentration was found to reach a maximum at 16 hours after the start of drinking, when the hangover was still severe. There were no differences in lactate concentration between groups I and II, and there was no significant correlation between lactate concentration and clinical symptoms and signs of the hangover. The highest levels of free fatty acids occurred at the time of maximal hangover, and the mean concentration of free fatty acids in group I was significantly higher than in group II (p less than 0.05). Ketone bodies were found to be at the highest concentration 16 hours after the start of drinking (when the mean hangover was severe). Ketonemia was somewhat greater in group I than in group II, but the difference was not statistically significant. No correlation could be found between the ketone body concentration and the severity of the hangover. The authors observed that the states of intoxication and hangover are not clearly separated by any subjective symptom or physical sign. They also state that this study clearly indicates that hangover can be induced by pure ethanol in a dose of 1.5 g/kg body weight and that this will result in moderate alcohol intoxication which leads to a feeling of severe hangover in half of the subjects. The authors concluded that, although there seems to be some correlation between the free fatty acid levels and the intensity of hangover, this certainly is not the cause; it is probably secondary to the anxiety state associated with hangover. The following additional comments were made by the authors:

> Thus the present results suggest that hangover is not caused by major metabolic changes induced by ethanol oxidation, but is perhaps more attributable to pharmacological effects on central nervous system and hormonal homeostasis. However, the symptoms of hangover are multiple and variable, which suggests multiple pathogenic mechanisms. Thus, it seems probable that hangover has no single cause, but that the syndrome is due to a combination of neural, hormonal and metabolic effects, the relative importance of which is not known (Ref. 9).

Information was also available to the Panel by means of a convincing presentation by E. B. Truitt, Ph. D. (Ref. 10).

The Panel concludes that, even though the results from various studies described above are conflicting, congeners do contribute to the cause of a hangover. But data are insufficient to demonstrate the effectiveness of activated charcoal in minimizing the symptoms of a hangover.

(3) *Proposed Dosage.* The Panel recommends a dosage, as recommended by the manufacturer, of 1,600 mg taken before, during, or immediately after consumption of alcoholic beverages, with the maximum 24-hour dose not to exceed 10 g.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients intended to minimize the symptoms of a hangover. (See part V, paragraph B.2.b. above—*Category I labeling.*)

(5) *Evaluation.* The Panel concludes that activated charcoal is safe for OTC use in the doses stated above, but data are insufficient to demonstrate its effectiveness in minimizing the symptoms of a hangover. The Panel recommends that clinical studies be performed to demonstrate such effectiveness.

References

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(9) Ylikahri, R. H., et al., "Metabolic Studies on the Pathogenesis of Hangover," *European Journal of Clinical Investigations,* 4:93–100, 1974.

(10) Truitt, E. B., presentation made to the OTC Miscellaneous Internal Panel on August 23, 1981, Panel Administrator's File (OTC Volume 17L:PAII).

2. *Category III labeling.* None.

List of Subjects in 21 CFR Part 357

Over the counter drugs.

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

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended by adding in Part 357, a new Subpart J, to read as follows:

* * * * *

Subpart J—Orally Administered Drug Products for Relief of Symptoms Associated with Overindulgence in Alcohol and Food

Sec.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

Subpart J—Orally Administered Drug Products for Relief of Symptoms Associated With Overindulgence in Alcohol and Food

§ 357.901 Scope.

(a) An over-the-counter drug product for the relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food, for the relief of hangover symptoms, to minimize inebriation, or to minimize hangover symptoms, in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this subpart and each general condition established in § 330.1.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter 1 of Title 21 unless otherwise noted.

(c) References to Part 343 are to the proposed monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products published in the **Federal Register** of July 8, 1977 (42 FR 35346).

(d) References to Part 340 are to the tentative final monograph for OTC stimulant drug products published in the **Federal Register** of June 13, 1978 (43 FR 25544).

§ 357.903 Definitions.

As used in this subpart:

(a) *Upset stomach due to overindulgence in the combination of alcohol and food.* A condition which occurs as a result of overindulgence in the combination of alcohol and food and consists of a group of symptoms which includes heartburn, fullness, and nausea.

(b) *Hangover.* A condition consisting of a complex of symptoms involving the gastrointestinal, neurologic, and metabolic system that follows recent acute excessive alcohol ingestion. The symptoms may includes nausea, heartburn, thirst, tremor, disturbances of equilibrium, fatigue, generalized aches and pains, headache, dullness, and/or depression or irritability.

§ 357.910 Active ingredients for the relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food.

The active ingredients of the product consist of the following in the dosage limits established for each ingredient in § 357.950(d):

(a) Bismuth subsalicylate.

(b) Sodium citrate in solution.

§ 357.912 Active ingredients for the relief of hangover symptoms.

The active ingredients of the product consist of the following when used only in combination as provided in § 357.920(b) and in the dosage limits established for each ingredient in the respective OTC drug monographs:

(a) Any analgesic active ingredient identified in Part 343.

(b) Any antacid active ingredient identified in Part 331.

(c) Any stimulant active ingredient identified in Part 340.

§ 357.914 Active ingredients to minimize inebriation. [Reserved]

§ 357.916 Active ingredients to minimize hangover symptoms. [Reserved]

§ 357.920 Permitted combinations of active ingredients.

(a) *Combinations of ingredients for the relief of the symptoms of upset stomach due to overindulgence in the combination of alcohol and food.* (1) Bismuth subsalicylate identified in § 357.910(a) may be combined with any nonsalicylate analgesic active ingredient identified in Part 343.

(2) Sodium citrate in solution identified in § 357.910(b) may be combined with any analgesic active ingredient identified in Part 343, provided that if the product contains aspirin identified in Part 343, the finished product meets the acid neutralizing requirements of § 331.10.

(b) *Combinations of ingredients for the relief of hangover symptoms.* The combination contains active ingredients from at least two of the three drug categories identified in § 357.912 provided the product is labeled according to § 357.952. If the product contains aspirin, the finished product must meet the acid neutralizing requirements of § 331.10. The combination of ingredients must also meet the conditions of the respective drug monographs, except as otherwise noted in this subpart.

§ 357.950 Labeling of drug products for the relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "food and drink overindulgence reliever."

(b) *Indications.* The labeling of the product contains a statement of indications under the heading "Indications" that is limited to following phrases:

(1) *For products containing the ingredients identified in § 357.910.* "For the relief of upset stomach due to overindulgence in the combination of food and drink."

(2) *Alternative indication—For products containing bismuth subsalicylate identified in § 357.910(a).* "For the relief of upset stomach associated with" (select one or more of the following: "nausea," "heartburn," and "fullness") "due to overindulgence in the combination of food and drink."

(3). *For combination products identified in § 357.920(a).* "For the relief of upset stomach due to overindulgence in the combination of food and drink, when accompanied by a headache or other minor aches and pains."

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

(1) *For products containing bismuth subsalicylate identified in § 357.910(a).* (i) "This product contains salicylates. If taken with other salicylate-containing preparations, such as aspirin, and ringing in the ears occurs, discontinue use."

(ii) "If taking oral medication for anticoagulation (thinning of the blood), consult a physician before taking this product."

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

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(1) *For products containing bismuth subsalicylate identified in § 357.910(a).* Adult oral dosage is 0.525 grams to be given at intervals no more frequently than every ½ to 1 hour for a total daily dose of 4.2 grams (8 doses).

(2) *For products containing sodium citrate in solution identified in § 357.910(b).* For adults under 60 years of age the oral daily dosage should not exceed 17.2 grams sodium citrate (200 milliequivalents of sodium) in divided doses. For adults 60 years of age and over the oral daily dosage should not exceed 8.6 grams sodium citrate (100 milliequivalents of sodium) in divided doses. If there is another source of sodium in the product, the dose of sodium citrate must be reduced accordingly. In addition, the labeling contains the following statement: "If you are 60 years of age or older, the maximum daily dose should not exceed —— of this drug." (Space to be filled in the the number of dosage units which will not exceed 100 milliequivalents of sodium in a daily dose.)

§ 357.952 Labeling of drug products for the relief of hangover symptoms.

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

(b) *Indications.* The labeling of the product contains a statement of indications under the heading "Indications" that is limited to the following: "For the relief of" (select all symptoms applicable to the product: "heartburn" (antacids), "fatigue" (stimulants), and/or "headache and generalized aches and pains" (analgesics)) "associated with a hangover."

(c) *Warnings.* The labeling of the drug product contains the applicable warnings under Parts 331, 340, and 343 with the following exceptions:

(1) *General exception.* Labeling warnings in Parts 331, 340, and 343 that pertain to children should be excluded.

(2) *Exceptions to Part 331 warnings.* (i) The warning in § 331.30(b)(1) should be revised to state "Do not take more than (maximum recommended daily dosage, broken down by age groups if appropriate, expressed in units such as tablets or teaspoonsful) in a 24-hour period, except under the advice and supervision of a physician."

(ii) The warning in § 331.30(b)(2) should be excluded from the labeling.

(iii) The warning in § 331.30(b)(3) should be excluded from the labeling.

(iv) The warning in § 331.30(b)(4) should be revised to state "If you are on a sodium-restricted diet, do not take this product except under the supervision of a physician."

(v) The warning in § 331.30(b)(5) should be revised to state "If you have kidney disease, do not take this product except under the supervision of a physician."

(3) *Exceptions to Part 340 warnings.* The warning in § 340.50(c)(2) should be revised to state "For occasional use only."

(4) *Exceptions to Part 343 warnings.* (i) The warning in § 343.50(c)(1)(i) should be revised to state "If symptoms persist or new ones occur, consult your physician."

(ii) The warning in § 343.50(c)(3)(ii) should be revised to state "Stop taking this product if ringing in the ears occurs."

(iii) The warning in § 343.50(c)(3)(iv) should be excluded from the labeling.

(iv) The warning in § 343.50(c)(3)(v) should be revised to state "If taking medication for anticoagulation (thinning of blood), consult a physician before taking this product."

(v) The warning in § 343.50(c)(6) should be revised to state "Do not take this product if you are allergic to salicylates, such as aspirin."

(vi) The warning in § 343.50(c)(5)(i) should be excluded from the labeling.

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(1) *For products containing any analgesic ingredient identified in § 357.912(a).* The labeling of the product contains the dosage and any applicable directions identified in Part 343.

(2) *For products containing any antacid ingredient identified in § 357.912(b).* The labeling of the product contains the dosage and any applicable directions identified in Part 331.

(3) *For products containing any stimulant ingredient identified in § 357.912(c).* The labeling of the product contains the dosage and any applicable directions identified in Part 340.

§ 357.954 Labeling of drug products to minimize inebriation.

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

(b) *Indications.* The labeling of the product contains a statement of indications under the heading "Indications" that is limited to the following phrase: "To minimize inebriation."

(c) *Warnings.* [Reserved]

(d) *Directions.* [Reserved]

§ 357.956 Labeling of drug products to minimize hangover symptoms.

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

(b) *Indications.* The labeling of the products contains a statement of indications under the heading "Indications" that is limited to the following phrases:

(1) "To minimize the symptoms of a hangover caused by alcoholic beverages."

(2) "For minimizing the symptoms of a hangover caused by alcoholic beverages."

(3) "An aid in minimizing the symptoms of a hangover caused by alcoholic beverages."

(c) *Warning.* [Reserved]

(d) *Directions.* [Reserved]

Interested persons may, on or before December 30, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in the brackets in the heading of this document. Comments replying to comments may also be submitted on or before January 31, 1983. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: September 22, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

[FR Doc. 82–27054 Filed 9–30–82; 8:45 am]

BILLING CODE 4160–01–M