DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 357

[Docket No. 81N-0050]

Drug Products for Over-the-Counter Human Use for the Treatment of Acute Toxic Ingestion; Establishment of a Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of proposed rulemaking that would establish conditions under which over-the-counter (OTC) drug products used for the treatment of acute toxic ingestion are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

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

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

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

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on June 24, 1978 a report of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. FDA regulations (21 CFR 330.10(a)(6))provide that the agency issue in the **Federal Register** a proposed order containing: (1) The monograph recommended by the Panel, which establishes conditions under which OTC drug products for the treatment of acute toxic ingestion are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

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

After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** a tentative final monograph for OTC drug products used for the treatment of acute toxic ingestion 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 notes that the Panel has included in its report a series of labeling recommendations for the use of ipecac syrup as an emetic. (See part III. paragraph A.1.b. below—Ipecac Syrup.) The Panel was aware that ipecac syrup had already been reviewed by the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products and requested that its recommendations regarding ipecac syrup be incorporated in the tentative final monograph (notice of proposed rulemaking) for emetic drug products rather than in the advance notice of proposed rulemaking for drug products for the treatment of acute toxic ingestion which is included in this document. Unfortunately, the report of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products was received too late for the recommendations to be considered in the development of the emetic tentative final monograph (notice of proposed rulemaking) which was published in the **Federal Register** on September 5, 1978 (43 FR 39544). Therefore, FDA will consider that portion of this document which deals with ipecac syrup in promulgating the final rule for emetic drug products.

Ipecac syrup is frequently an integral part of acute toxic ingestion therapy. Additionally, ipecac syrup is marketed with activated charcoal in a kit for acute toxic ingestion. The Panel's recommendations regarding the labeling of ipecac syrup by itself are not incorporated into this advance notice of proposed rulemaking. Rather, this advance notice of proposed rulemaking refers to the tentative final monograph (notice of proposed rulemaking) for OTC emetic drug products (43 FR 39544) for required labeling of ipecac syrup. This advance notice of proposed rulemaking will deal with ipecac syrup only to the extent that it is used in conjunction with other drug products for the treatment of acute toxic ingestion.

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

The agency invites public comment regarding any impact that this rulemaking would have on OTC drug products for the treatment of acute toxic ingestion. Types of impact may include, but are not limited to, the following: Increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing necessary, if any. Comments regarding the impact of this rulemaking on OTC drug products for the treatment of acute toxic ingestion 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 drug products used in the treatment of acute toxic ingestion submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after February 4, 1982, except to the extent that the person

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

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

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

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 6 months after the date of publication of the final monograph in the **Federal Register**. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions which would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered 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 voluntarily comply with the monograph at the earliest possible date.

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

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

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

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

The following FDA employees assisted the Panel: Armond M. Welch, R.Ph., served as the Panel Administrator. Enrique Fefer, Ph. D., served as the Executive Secretary until July 1976, followed by George W. James, Ph. D., until October 1976, followed by Natalia Morgenstern until May 1977, followed by Arthur Auer. Joseph Hussion, R.Ph., served as the Drug Information Analyst unitl July 1976, followed by Anne Eggers, R.Ph., M.S., until October 1977, followed by John R. Short, R. Ph.

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

Carol R. Angle, M.D. (pediatrics)
Jay M. Arena, M.D. (pediatrics)
William A. MacColl, M.D. (pediatrics)
Lynn R. Brady, Ph. D. (pharmacognosy)
Arthur E. Schwarting, Ph. D. (pharmacognosy)
Ralph B. D'Agostino, Ph. D. (statistics)

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products was charged with the review of many categories of drugs; but due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for each drug category. The Panel presents its conclusions and recommendations for drug products used for the treatment of acute toxic ingestion in this document. The review of other categories of miscellaneous internal drug products is being continued by the Panel, and its findings are being published periodically in the **Federal Register**.

The Panel was first convened on January 13, 1975 in an organizational meeting. Meetings at which drug products used for the treatment of acute toxic ingestion were discussed were held on the following dates: March 23 and 24, April 27 and 28, September 21 and 22, November 16 and 17, 1975; March 7 and 8, October 10 and 11, 1976; May 15 and 16, July 9, 10, and 11, 1977; January 28, 29, and 30, March 10, 11, and 12, May 5, 6, and 7, and June 23 and 24, 1978.

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

John B. Johnson requested, and was given, an opportunity to appear before the Panel to express his views on activated charcoal used for the treatment of acute toxic ingestion. No other person requested an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature and submitted data, has listened to additional testimony from an interested person, and has considered all pertinent data and information submitted through June 24, 1978 in arriving at its conclusions and recommendation for OTC drug products used for the treatment of acute toxic ingestion.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel considered OTC drug products for the treatment of acute toxic ingestion with respect to the following three categories:

Category I. Conditions under which OTC drug products used for the treatment of acute toxic ingestion are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC drug products used for the treatment of acute toxic ingestion 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 six active ingredients in drug products for the treatment of acute toxic ingestion and classified two ingredients in Category I, four ingredients in Category II, and no ingredients in Category III.

I. Submission of Data and Information

A. Submission by Firm

Pursuant to the notices published in the Federal Register of November 16, 1973 (39 FR 31696) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on OTC miscellaneous internal drug products, the following firm made a submission for a drug product used for the treatment of acute toxic ingestion.

Firm and marketed product

Bowman Pharmaceuticals, Inc., Canton, OH 44702—Poison antidote kit.

B. Labeled Ingredients Contained in Marketed Products

1. *Ingredients in products submitted to the Panel for review.*

Charcoal, activated
Ipecac syrup

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

Alcohol
Magnesium hydroxide
Potassium arsenite
Tannic acid

C. Classification of Ingredients

1. *Active ingredients.*

Charcoal, activated
Ipecac syrup

2. *Inactive ingredients.* None.

3. *Other ingredients.* No submissions were received for the following ingredients. The Panel has not been able to locate, nor is it aware as a group of experts, of any data, published or unpublished, demonstrated the safety and effectiveness of these ingredients for OTC use in the treatment of acute toxic ingestion. The Panel therefore classifies these ingredients as Category II for this use, and they will not be reviewed in this document.

Alcohol
Magnesium hydroxide
Potassium arsenite
Tannic acid

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179). All of the submitted information is included in one volume which, 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 February 4, 1982, in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. Definitions of Terms

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

1. *Acute toxic ingestion.* An ingestion, within a brief time, of a substance in amounts that could threaten the survival or well-being of an individual.

2. *Adjunct.* An accessory, auxiliary agent, or measure.

3. *Adsorption.* Adhesion of the molecules of a gas, liquid, or dissolved substance to a surface.

4. *Antidote.* A substance used to counteract a poison.

5. *Aspiration.* Inhalation of a foreign substance into the lungs.

6. *Emesis.* Vomiting.

7. *Emetic.* An agent that causes vomiting.

8. *Poison.* A substance ingested within a brief time in amounts that could threaten the survival or well-being of an individual.

9. *Toxic substance.* A poison.

B. General Discussion.

An estimated 2 million accidental poisonings occur in the United States each year (Ref. *1*), and about 60 percent of these poisonings involve children under 5 years of age (Ref. *2*). Therefore, it is obvious that extensive preventive measures are needed to reduce the incidence of accidental poisoning. When ingestion of a toxic substance occurs, means should be available to handle the situation until the patient can be treated by a physician.

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

With the exception of corrosives such as strong acids and alkalies, the emergency treatment of poisoning is aimed at minimizing the absorption of the poison. This can be accomplished by interfering with the absorption of the

poison by the gastrointestinal tract or by removing the poison from the body as quickly as possible.

Upon discovering that a toxic substance has been ingested, a Poison Control Center, emergency medical facility, or physician should be called at once for advice. If medical consultation cannot be obtained immediately, the following procedure should be carried out:

1. The patient should be transported to the medical facility as soon as possible.

2. In most cases the poison should be removed from the patient's stomach immediately by inducing vomiting. However, vomiting should not be induced if the patient: (a) Is semiconscious or unconscious; (b) is having convulsions; (c) has swallowed strychnine, unless advised otherwise by a Poison Control Center, emergency medical facility, or physician; (d) has swallowed petroleum distillates such as kerosene, gasoline, paint thinner, or cleaning fluids, unless advised otherwise by a Poison Control Center, emergency medical facility, or physician; or (e) has swallowed a corrosive poison such as alkali (lye) or strong acid, unless advised otherwise by a physician or emergency treatment facility.

Vomiting may be induced by gently irritating the back of the patient's throat with the blunt end of a spoon or a finger or by using an emetic such as ipecac syrup. In the former method, before the vomiting reflex (gagging) is stimulated, the patient should drink one or two glasses of water (not milk or carbonated beverages) in order to dilute the toxic substance and provide a sufficient volume of gastric contents to be vomited. When retching and vomiting begin, the patient should be placed face down with head lower than hips. This position will prevent the vomitus from being aspirated into the lungs and causing further damage. Unfortunately, this mechanically induced vomiting is usually unsuccessful and incomplete (Ref. *3*).

When using ipecac syrup (not ipecac fluidextract) as an emetic, it should be given in doses of 1 to 2 teaspoonsful (5 to 10 milliliters (mL)) for children under 1 year of age (followed by ½ to 1 glass of water); children over 1 year old and adults should receive 1 tablespoonful (15mL) (followed by 1 to 2 glasses of water). Milk or carbonated beverages should not be used in place of water. If vomiting does not occur after 20 minutes, the dose should be repeated. The subject should be kept upright and ambulatory to speed emesis. A young child may be jiggled to speed emesis. If vomiting does not occur within 20 minutes of the second dose, the advice of a Poison Control Center, emergency medical facility, or physician should again be sought.

Vomiting should not be induced following the ingestion of most petroleum distillates because of the possibility of their being aspirated into the lung (Ref. *4*). However, there may be some cases of petroleum distillate ingestion in which the Poison Control Center, emergency medical facility, or physician will suggest that vomiting be induced.

Vomiting should also not be induced following the ingestion of acidic and alkaline corrosives because regurgitation would increase the damage to the esophagus. Large volumes of water of milk should be ingested to dilute the acidic or alkaline corrosive substances.

Chilling should be prevented by wrapping the patient in blankets, when necessary.

Alcohol in any form should not be given.

Activated charcoal should be given only after the patient vomits or when advised by a health professional. Activated charcoal acts by adsorbing a toxic substance and should not be given prior to the administration of ipecac syrup since it would adsorb the ipecac and negate its emetic action.

Although activated charcoal has a tremendous adsorptive capacity, it should be considered an adjunct for the treatment of an acute toxic ingestion rather than a specific antidote for any one poison. Following the administration of activated charcoal, a physician may still need to use specific antidotes to treat the particular poison.

The major drawback to the use of activated charcoal is its black color which often causes children not to want to ingest it. If spewed, it spots clothes and walls. The Panel, therefore, encourages the development of a palatable formulation which can be more easily administered to children.

Although activated charcoal is an effective, nonspecific adsorbent of a large number of materials, the Panel concurs with the general medical recognition that there is no true "universal antidote" (Ref. *5*). The so-called "universal antidote" recommended in the past consisted of activated charcoal, tannic acid, and magnesium oxide. However, it has been well established that the tannic acid and magnesium oxide have no significant effectiveness and may actually impede the effective ingredient, activated charcoal. The use of burnt toast as a homemade antidote has no merit. This material is not activated charcoal, and it has no significant adsorptive properties (Ref. *5*).

In many cases of accidental poisoning it is not possible to identify the substance ingested; but if the substance is known, the Poison Control Center, emergency medical facility, or physician will want this information along with the container in which the substance was stored to assist in determining the kind and amount of poison ingested and the appropriate treatment.

Although ipecac syrup is the primary mode of treatment of accidental poisoning in children, the Panel considers it rational to market ipecac syrup and activated charcoal in a combination package. The Panel has made specific recommendations in this document for the proper labeling of such a kit to encourage immediate home treatment under the direction of a physician or emergency medical facility.

Every physician treating children should have a supply of ipecac syrup and activated charcoal in his office.

References

(*1*) Arena, J. M., "The Treatment of Poisoning," *Clinical Symposia,* 30:1–47, 1978.

(*2*) National Clearinghouse for Poison Control Centers—Bulletin, U.S. Department of Health, Education, and Welfare, PHS, FDA, Bethesda, MD, February 1978.

(*3*) Arena, J. M., "Poisoning—Toxicology, Symptoms, Treatment," 2d Ed., Charles C. Thomas, Springfield, IL, p. 31, 1970.

(*4*) Arena, J. M., "Poisoning—Toxicology, Symptoms, Treatment," 2d Ed., Charles C. Thomas, Springfield, IL, p. 171, 1970.

(*5*) Done, A. K., "Poison Control," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol, and J. E. Hoover, Mack Publishing Co., Easton, PA, pp. 1830–1831, 1975.

C. Labeling ✱

The Panel has reviewed the labeling claims made for ingredients offered for emergency treatment of acute toxic ingestion and has categorized them as either Category I, Category II, or Category III.

For any labeling to be acceptable, it must include the established name of the drug, an accurate statement of the pharmacological category of the drug, the net quantity of contents, the indications for use, pertinent warnings and contraindications, and the recommended dosage range. Only those indications and warnings listed under the specific ingredient discussions are generally recognized as acceptable at this time.

The Panel believes that all labeling should be clear, concise, and easily readable and understandable by most consumers, including those whose

comprehension is limited. The Panel follows this concept in the development of 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 design labeling which can be read easily by consumers.

The Panel believes that the label should contain the active ingredient by its established name, and the label should state the quantity of the active ingredient in the recommended dosage.

The Panel recommends that drug product labeling contain directions for use which are intended to facilitate the delivery and availability of the active ingredient, and that these directions be prominently displayed on all package labeling.

The Panel agrees with the current OTC labeling regulation on warning statements at 21 CFR 330.1(g) and recommends that labeling for drug products used to treat acute toxic ingestion contain a "Warnings" section which contains the following statement in addition to any drug-specific warnings: "Keep this and all drugs out of the reach of children." The Panel believes that the other warning required by this regulation should not be required for these products, i.e., "In cases of accidental ingestion, seek professional assistance or contact a poison control center immediately."

In order to facilitate administration in emergency situations, activated charcoal should be packaged in containers designed to deliver a minimum of 30 grams (g). The amount of contents should be conspicuously displayed on the front panel of the package label. The person administering the activated charcoal would then have a better idea of the actual amount to give to the patient.

To remove as much of the toxic substance as possible from the stomach, it is essential that vomiting, when indicated, be induced prior to the administration of activated charcoal. If activated charcoal is administered before ipecac syrup, the ipecac will be adsorbed by the activated charcoal and inactivated.

If vomiting does not occur within 20 minutes after the first dose of ipecac syrup, the dose should be repeated. If vomiting does not occur within 20 minutes after the second dose, it is imperative that medical advice be obtained to determine what further procedures should be followed to remove or detoxify the ingested poison.

Labeling for ipecac syrup must contain a warning not to give this drug product if strychnine, corrosive poisons, or petroleum distillates have been ingested unless advised otherwise by a physician or emergency medical facility. The reasons for this warning are contained in the "General Discussion." (See part II. paragraph B. above—General Discussion.)

Milk must not be administered along with ipecac syrup because its coating action on the gastrointestinal tract and its ability to inactivate the ipecac alkaloids through its protein binding action would prevent the ipecac syrup from acting. Carbonated beverages should not be administered with ipecac syrup because they may cause overdistention of the stomach.

III. Categorization of Data

A. Category I Conditions

The following are Category I conditions under which drug products for the treatment of acute toxic ingestion are generally recognized as safe and effective and not misbranded.

1. *Category I active ingredients.*

Charcoal, activated
Ipecac syrup

a. *Charcoal, activated.* The Panel concludes that activated charcoal is safe and effective for OTC use in the treatment of acute toxic ingestion as discussed below.

Wood charcoal is made by burning wood out of contact with the air—the residue obtained consists of nearly pure carbon (Ref. *1*). This process is called destructive distillation. The carbon resulting from destructive distillation can also be obtained from nut shells, animal bones, or other carbonaceous material (Ref. *2*). Charcoal made by this process results in a product with varied adsorptive properties. It is "activated" by treating it with various substances such as steam, air, carbon dioxide, oxygen, zinc chloride, sulfuric acid, phosphoric acid, or a combination of some of these substances at temperatures ranging from 500° to 900° C (Ref. *1*). This treatment produces a very porous, honeycomblike internal structure formed by removing substances previously adsorbed on the charcoal. The internal surface area of activated charcoal averages about 10,000 square feet per g (Ref. *2*).

(1) *Safety.* The Panel concludes that activated charcoal is generally recognized as a safe gastrointestinal adsorbent for ingested poisons when used in the doses noted below.

Activated charcoal has been used since 1960 in uremic patients to reduce the gastrointestinal disturbances of the patient. A dose of 20 to 50 g of activated charcoal was given daily, and no side effects were observed during continuous treatment for 4 to 20 months (Ref. *3*).

Considering the above information and the fact that activated charcoal has been in use for over 150 years (Ref. *4*), the Panel concludes that activated charcoal is generally recognized as a safe gastrointestinal adsorbent for oral administration in the treatment of acute toxic ingestion.

(2) *Effectiveness.* The Panel concludes that activated charcoal is an effective gastrointestinal adsorbent that is widely used for the emergency treatment of acute toxic ingestion of a variety of drugs and toxic agents.

In treating an acute toxic ingestion, activated charcoal should only be used after first contacting a Poison Control Center, emergency medical facility, or a physician. It should generally be restricted to administration following emesis, which is usually induced by the ingestion of ipecac syrup.

Decker, Combs, and Corby (Ref. *5*) have demonstrated in vitro that the adsorption capacity of activated charcoal varies considerably according to the chemical acted on. They found that activated charcoal very efficiently adsorbed high doses of dextroamphetamine sulfate, primaquine phosphate, chlorpheniramine maleate, colchicine, diphenylhydantoin, aspirin, and propoxyphene hyrdochloride. Iodine, phenol, and, to a lesser degree, methyl salicylate were quite well adsorbed. Quinacrine, meprobamate, chlorpromazine, quinine, chloroquine, quinidine, and glutethimide were less efficiently adsorbed by activated charcoal; and inorganic acids, certain alkalies (sodium and potassium hydroxides), and sodium metasilicate (active ingredient in many cleaning preparations) were not adsorbed to any measurable extent. It was observed that the adsorptive capacity did not seem to correlate with chemical structure, although highly ionic substances of low molecular weight, such as cupric copper, ferrous iron, and boric acid, were very poorly adsorbed by activated charcoal. Drugs which are solids and insoluble in acidic aqueous solutions were likewise not adsorbed, e.g., tolbutamide. The insecticides malathion, DDT, and *N*-methylcarbamate were quite poorly adsorbed.

Picchioni, Chin, and Laird (Ref. *6*) list about 30 toxic substances which have been demonstrated to be effectively adsorbed in vivo (in man and animals) by activated charcoal. Some of the more significant ones are aspirin and other salicylates, propoxyphene, amphetamine, acetaminophen, barbiturates (barbital, phenobarbital, pentobarbital, and secobarbital), glutethimide, ethchlorvynol,

chlorpromazine, chlordane, hexachlorophene, kerosene, malathion, mercuric chloride, methyl salicylate, phenylopropanolamine, and strychnine. In addition, Decker (Ref. *7*) mentions the usefulness of activated charcoal in adsorbing tricyclic antidepressants (nortriptyline and imipramine) by interrupting enterohepatic recycling.

Originally it was felt that the activated charcoal and toxic substance complex which was formed in the stomach may possibly dissociate as it passes through the gastrointestinal tract. Recent studies indicate that the competitive effects of other constituents of the gastrointestinal fluids and associated higher pH may cause minimal dissociation to occur during the passage through the gastrointestinal tract (Ref. *7*). However, from a practical standpoint, this effect is inconsequential since it is markedly diminished with increasing doses of activated charcoal (Ref. *7*). It has also been demonstrated that, although the absorption of salicylate, barbiturate, and glutethimide was significantly reduced in rats and dogs, the activated charcoal-drug complexes were not dissociated to any significant extent in the gastrointestinal tract (Ref. *4*).

When possible, activated charcoal should be administered within 30 minutes following ingestion of the toxic substance to achieve significant inhibition of the drug absorption, although it has been shown that charcoal can "catch up" and bind certain poisons which have already passed through the pylorus (the opening through which the stomach contents are emptied into the upper intestine). Considering this, activated charcoal should be administered after ipecac syrup when large amounts of toxic substances have been ingested (Ref. *7*).

Corby, Fiser, and Decker (Ref. *4*) observed that activated charcoal can be a very valuable adjunct in the initial phases of treating acute toxic ingestion of many drugs not only in the emergency room and during the course of treatment in a hospital, but also as a first aid measure in the home.

The Panel recommends that for ease of administration, the activated charcoal be packaged in premeasured units with a minimum quantity of 30 g. If the quantity of the ingested toxic substance is known, it is generally considered that an amount of activated charcoal that is 8 to 10 times the amount of toxic substance should be administered. Otherwise, the recommended dosage of 30 g (6 level tablespoonsful) should be given.

It is obviously important to get as much activated charcoal into the patient as possible and as soon as possible after administration of ipecac syrup has produced vomiting. The Panel is aware of the difficulties in administration of this powdery substance and, therefore, encourages the development of a palatable form, such as a combination of activated charcoal and an inactive vehicle, e.g., carboxymethylcellulose, a highly activated charcoal requiring a lower dose, or coated charcoal particles. If such forms are developed, the adsorption capacity of the labeled dose must be expressed in terms of activated charcoal and determined in vivo.

The Panel recognizes that activited charcoal varies in its adsorptive capacity, but concludes that it is generally recognized as effective in the treatment of acute toxic ingestion.

(3) *Dosage.* The minimum effective dose of activated charcoal varies with the toxic dose of each substance and with several other variables, e.g., retained food, gastric emptying, and solubility. For most compounds, 5 to 10 g of activated charcoal are needed to adsorb 1 g. A theoretical dose of 20 g is required to adsorb the fatal adult dose of 2 g of phenobarbital; 30 g would be required to adsorb the toxic dose of 3 g of salicylates in a preschool child; and 500 g would be required for the fatal adult dose of 50 g of acetaminophen. In view of the wide dose range of activated charcoal and the lack of literature references as to the optimum dose, the Panel recommends that activated charcoal be used in doses, of no less than 30 g (6 level tablespoonsful) mixed with ½ glassful of water. The only upper limit on the amount which can be ingested would be governed by the feasibility of administration.

(4) *Labeling.* The Panel recommends the following labeling for activated charcoal:

(i) *Indication.* "For the treatment of acute poisoning."

(ii) *Warnings.* (*a*) "Before using, call a Poison Control Center, emergency medical facility, or physician for advice." This warning should be conspicuously boxed and in red letters.

(*b*) "Do not use in semiconscious or unconscious persons."

(*c*) "If the patient has received ipecac syrup, do not administer activated charcoal until after the patient has vomited, except under the advice and supervision of a physician.

(iii) *Directions.* "Mix 6 level tablespoonsful (30 g) in ½ glassful (4 ounces) of water. Drink entire contents of glass after mixing."

References

(*1*) Swinyard, E. A., "Gastrointestinal Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol and J. E. Hoover, Mack Publishing Co., Easton, PA, p. 751, 1975.

(*2*) Hawley, G. G., "The Condensed Chemical Dictionary," 8th Revised Ed., Van Nostrand Reinhold Co., New York, p. 168, 1971.

(*3*) Yatzidis, H., "Activated Charcoal Rediscovered," (letter to Editor), *British Medical Journal*, 4:51, 1972.

(*4*) Corby, D. G., R. H. Fiser, and W. J. Decker, "Re-Evaluation of the Use of Activated Charcoal in the Treatment of Acute Poisoning," *Pediatric Clinics of North America*, 17:545–556, 1970.

(*5*) Decker, W. J., H. F. Combs, and D. G. Corby, "Adsorption of Drugs and Poisons by Activated Charcoal," *Toxicology and Applied Pharmacology*, 13:454–460, 1968.

(*6*) Picchioni, A. L., L. Chin, and H. E. Laird, "Activated Charcoal Preparations—Relative Antidotal Efficacy," *Clinical Toxicology*, 7:97–108, 1974.

(*7*) Corby, D. G., and W. J. Decker, "Management of Acute Poisoning with Activated Charcoal," *Pediatrics*, 54:324–328, 1974.

b. Ipecac syrup. The Panel is aware that ipecac syrup has previously been reviewed by the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products and that the FDA is developing the tentative final monograph (TFM) on emetic drug products. This Panel feels that the final monograph for ipecac syrup should contain the following information:

The active ingredients of ipecac syrup are the alkaloids emetine and cephaeline contained in powered ipecac. The product is packaged and marketed as ipecac syrup, United States Pharmacopeia (USP) XIX, in a 1 fluid ounce (30 mL) container or in ½ fluid ounce (15 mL) containers for use in acute toxic ingestion kits.

(1) *Indications.* The labeling of the product contains a statement of the indication under the heading "Indications" that is limited to the phrase "to cause vomiting (emesis) in case of poisoning." This phrase should be conspicuously boxed and in red letters.

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

(i) "Call a Poison Control Center, emergency medical facility, or physician for advice before using and if vomiting does not occur within 20 minutes after a second dose has been given." This warning should be conspicuously boxed and in red letters.

(ii) "Do not use in semiconscious, unconscious, or convulsing persons."

(iii) "This product should not be used if strychnine, corrosives such as alkalies (lye) and strong acids, or petroleum distillates such as kerosene, gasoline, paint thinner, or

cleaning fluid have been ingested, unless advised otherwise by a physician."

(iv) "Do not administer milk or carbonated beverages with this product."

(3) The warning required by the current regulation § 330.1(g) (21 CFR 330.1(g)) concerning overdoses should not be required on ipecac syrup products.

(4) *Drug interaction precautions.* The labeling of the product should contain the following statement under the heading "Drug Interaction Precautions": "Activated charcoal will adsorb the active ingredients of ipecac syrup. If both activated charcoal and ipecac syrup are used, give the activated charcoal only after vomiting has been produced by the ipecac syrup."

(5) *Directions.* The labeling of the product should contain the following statements under the heading "Directions":

(i) *Infants under 1 year of age:* Oral dosage of ipecac syrup is 1 teaspoonful (5 milliliters) to a maximum of 2 teaspoonsful (10 milliliters) followed by ½ to 1 glass of water (4 to 8 ounces) or as directed by a physician. If vomiting does not occur within 20 minutes, the dose should be repeated one.

(ii) *Infants over 1 year of age, children, and adults:* Oral dosage of ipecac syrup is 1 tablespoonful (15 milliliters) followed by 1or 2 glasses of water (8 to 16 ounces) or as directed by a physician. If vomiting does not occur within 20 minutes, the dose should be repeated once.

* 2. *Acute toxic ingestion kit.* The Panel recognizes that it would be in the consumer's interest to establish guidelines for the minimum components of a kit used for the treatment of acute toxic ingestion. It is suggested that the kit contain four containers of 15 mL each of ipecac syrup and two containers of 30 g each of activated charcoal. The activated charcoal containers should be of sufficient size to permit the mixing of 4 ounces of water with the activated charcoal and be equipped with a screw cap so that the mixture can be shaken without spilling.

a. *Labeling.* The following labeling is specific for the outside container of the kit alone:

(1) *Indications.* "For the treatment of acute poisoning."

(2) *Warnings.* (i) "Before using, call a Poison Control Center, emergency medical facility or physician for advice." This warning should be conspicuously boxed and in red letters.

(ii) "Do not use in semiconscious or unconscious persons."

b. *Directions.* (1) "When professional advice is not available, first give ipecac syrup to induce vomiting, after vomiting has occurred give activated charcoal to help adsorb any remaining toxic substance."

(2) In bold-faced print "READ INSTRUCTIONS AT TIME OF PURCHASE AND INSERT PHONE NUMBERS ON LABEL."

(3) "Save the container of the poison."

(4) An area of prominence should be provided to enter the telephone numbers of the Poison Control Center ———, emengency medical facility ———, personal physician ———, and ambulance ———.

B. Category II and Category III Conditions

The ingredients classified as Category II are listed in part I. paragraph C.3. above. The Panel found no Category III conditions. Therefore, Category II and III conditions will not be discussed in this document.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 (see 46 FR 26052; May 11, 1981), the agency advises in this advance notice of proposed rulemaking that subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended by adding to Part 357, a new Subpart A, to read as follows:

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

Subpart A—Drug Products for Over-the-Counter Human Use for the Treatment of Acute Toxic Ingestion

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 A—Drug Products for Over-the-Counter Human Use for the Treatment of Acute Toxic Ingestion

§ 357.1 Scope.

(a) An over-the-counter drug product for the treatment of acute toxic ingestion in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this subpart and each general condition established in § 330.1 of this chapter.

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

§ 357.3 Definitions.

As used in this subpart:

(a) *Acute toxic ingestion.* An ingestion, within a brief time, of a substance in amounts that could threaten the survival or well-being of an individual.

(b) *Emesis.* Vomiting.

(c) *Emetic.* An agent that causes vomiting (emesis).

§ 357.10 Active ingredients for the treatment of acute toxic ingestion.

The active ingredients of the product consist of any of the following when used within the dosage limits established for each ingredient:

(a) Charcoal, activated.

(b) Ipecac syrup.

§ 357.14 Acute toxic ingestion kit.

The kit is a single outer package labeled according to § 357.54 that consists of two 30-gram containers of activated charcoal identified in § 357.10(a) and labeled according to § 357.50 and four 15-milliliter containers of ipecac syrup identified in § 357.10(b) and labeled according to § 357.52. The containers of activated charcoal enclosed within the kit are of sufficient size to permit the addition of 4 ounces (120 milliliters) of water and are equipped with screw top caps to facilitate mixing of the contents.

§ 357.50 Labeling of drug products containing activated charcoal identified in § 357.10(a) for the treatment of acute toxic ingestion.

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

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

phrase: "For the treatment of acute poisoning."

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

(1) "Before using, call a poison control center, emergency medical facility, or physician for advice." This warning should be conspicuously boxed and in red letters.

(2) "Do not use in semiconscious or unconscious persons."

(3) "If the patient has received ipecac syrup, do not administer activated charcoal until after the patient has vomited, except under the advice and supervison of a physician.

(4) The warning required by § 330.1(g) concerning overdoses is not required on products containing activated charcoal.

(d) *Directions.* The labeling of the product contains the following statement under the heading "Directions": "Mix 6 level tablespoonsful (30 grams) in ½ glassful (4 ounces) of water. Drink entire contents of glass after mixing."

§ 357.52 Labeling of drug products containing ipecac syrup identified in § 357.10(b) for the treatment of acute toxic ingestion.

The product contains the labeling identified in proposed § 337.50 for emetic drug products. (See the **Federal Register** of September 5, 1978 (43 FR 39546).)

§ 357.54 Labeling of acute toxic ingestion kit identified in § 357.14 for the treatment of acute toxic ingestion.

In addition to the labeling identified in § 357.50 required on containers of activated charcoal and the labeling identified in § 357.52 required on containers of ipecac syrup, the outer label of the acute toxic ingestion kit bears the following:

(a) *Statement of identity.* The labeling on the outside of the kit contains the established names of the drugs, if any, and identifies the product as an "acute toxic ingestion treatment kit."

(b) *Indications.* The labeling on the outside of the kit contains a statement of the indications under the heading "Indications" that is limited to the following phrase: "For the treatment of acute poisoning."

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

(1) "Before using, call a Poison Control Center, emergency medical facility, or physician for advice." This warning should be conspicuously boxed and in red letters.

(2) "Do not use in semiconscious or unconscious persons."

(3) The warning required by § 330.1(g) concerning overdoses is not required on products containing activated charcoal and ipecac syrup.

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

(1) "When professional advice is not available, first give ipecac to indice vomiting, after vomiting has occurred give activated charcoal to help absorb any remaining toxic substance."

(2) (In bold-faced print) "READ INSTRUCTIONS AT TIME OF PURCHASE AND INSERT PHONE NUMBERS ON LABEL."

(3) "Save the container of the poison."

(e) *Other required statements.* An area of prominence should be provided to enter the telephone numbers of the following: "Poison Control Center ," "emergency medical facility ," "personal physician ," "ambulance ."

Interested persons may, on or before April 5, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before May 5, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 23, 1981.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: December 17, 1981.

Richard S. Schweiker,

Secretary of Health and Human Services.

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