[4110-03]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Adminstration

[21 CFR Part 337]

[Docket No. 78N-0036]

EMETIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Tentative Final Order

AGENCY: Food and Drug Administration.

ACTION: Tentative final order.

SUMMARY: This tentative final order contains a monograph establishing conditions under which over-the-counter (OTC) emetic drug products are generally recognized as safe and effective and not misbranded. The Commissioner of Food and Drugs is issuing this tentative final order after considering the report and recommendations of the OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Panel and public comments on the proposed rule that was based on these recommendations. This tentative final order is part of the agency's ongoing review of OTC drug products.

DATE: Objections and/or requests for an oral hearing before the Commissioner by October 5, 1978.

ADDRESS: Written objections and/or requests for oral hearing to the hearing clerk (HFA-305), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of March 21, 1975 (40 FR 12902), the Commissioner, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), published a proposal to establish monographs for over-the-counter (OTC) laxative, antidiarrheal, emetic, and antiemetic drug products, together with the recommendations of the OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Panel (Panel), which is the advisory review Panel responsible for evaluating data on drugs in these categories. Interested persons were invited to submit comments on the propoal within 90 days. For 30 days after the final day for submission of comments, reply comments could be filed with the hearing clerk in response to comments filed in the initial 90-day period.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the office of the hearing clerk, Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857, after deletion of a small amount of trade secret information.

The Commissioner presents his conclusions and recommendations for OTC emetic active ingredients in this document. The conclusions include a restatement of the Panel's recommendations and constitute the Commissioner's adoption of the Panel's findings, as modified by him on the basis of the comments and the Food and Drug Administration's (FDA) independent evaluation of the Panel's report. In addition to substantive modifications in the Panel's findings, the restatement includes changes for clarity and regulatory accuracy, and also include any new data or information that has come to the Commissioner's attention. The Commissioner advises that the conditions included in the monograph on the basis that OTC emetic drug products are generally recognized as safe and effective and are not misbranded (category I) will become effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER. The Commissioner's conclusions for laxative, antidiarrheal, and antiemetic active ingredients will be published in a later issue of the FEDERAL REGISTER.

I. THE COMMISSIONER'S CONCLUSIONS ON THE COMMENTS AND REPLY COMMENTS

A. GENERAL COMMENTS

In response to the proposal, 10 comments and reply comments were received, including 9 comments from drug manufacturers and 1 from a consumer. A summary of these comments and the Commissioner's conclusions are as follows:

1. One comment objected to the Panel's recommendation that the quantity of each active ingredient be stated in OTC drug labeling, on the grounds that section 502(e)(1)(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(e)(1)(A)) provides for quantitative ingredient labeling only for prescription drugs.

The Commissioner agrees that other than for certain specifically named substances the act currently requires quantitative ingredient labeling only for prescription drugs. The tentative final monograph does not require quantitative active ingredient labeling. However, the Commissioner advises that the Panel's recommendation is consistent with that of the National Advisory Drug Committee, which advocates that all OTC drugs be labeled with a quantitative statement of the active ingredients. It is also consistent with the recommendation in 21 CFR 330.1(j) that the labeling of an OTC product contain the quantitative amount of each active ingredient, expressed in terms of the dosage unit stated in the directions for use. Thus, the Commissioner also urges manufacturers to comply voluntarily with this recommendation because of its intrinsic merit.

2. Several comments objected to the Panel's recommendation that all inactive ingredients be listed on the labeling, arguing that such a listing would be meaningless to most consumers, confusing, and misleading.

The Commissioner advises that neither the March 21, 1975 proposed monograph nor the monograph in this tentative final order requires that all inactive ingredients be listed in OTC drug labeling. However, the Commissioner agrees with the Panel's recommendation for full inactive ingredient labeling. Consumers may need to know about the ingredients in OTC drugs because they may be allergic to certain ingredients or unable to tolerate them for other reasons. The Commissioner urges manufacturers to voluntarily list all inactive ingredients, as suggested by the Panel.

3. One comment stated that the proposed monographs violate the objectives and philosophy of the OTC Drug Review in that this Panel appeared to be intent on undermining the concept of self-medication with OTC laxatives, antidiarrheals, antiemetics, or emetics, and that the Panel failed to discharge its obligations.

The comment provides no basis for its allegations and the Commissioner rejects the comment. the Commissioner believes the Panel's recommendations and this tentative final monograph for OTC emetic drug products are fully in accord with the objectives of the OTC Drug Review to develop monographs based on the most up-to-date scientific knowledge and data available.

4. Two comments contend that FDA does not have the authority to establish substantive rules.

This subject was dealt with in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drugs published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), and the Commissioner reaffirms the conclusions stated there. Subsequent court decisions have confirmed the Commissioner's authority to issue substantive regulations by rulemaking. See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F. 2d 688, 696-98 (2d Cir. 1976).

5. Several comments urged a greater role for pharmacists in the sale of OTC drugs. One comment recommended that OTC drugs be available

only through pharmacies, and two suggested that any labeling suggesting consultation with a physician should mention a pharmacist as a viable alternative.

The Commissioner fully discussed these issues in the preamble to the proposal to revise requirements for drug interaction warnings on OTC drugs (see the FEDERAL REGISTER of June 4, 1974 (39 FR 19880)). These views will not be restated here. However, the Commissioner notes that § 330.1(g) requires that labeling for OTC drugs include a warning to seek professional assistance in case of accidental overdose. The pharmacist is one of the health professionals that a consumer might choose to consult.

B. GENERAL COMMENTS ON EMETICS

6. A comment asserted that infants under 1 year of age do not have a developed gag reflex. For infants in this age group, the comment stated that emesis should be attempted only under the supervision of a physician.

The Commissioner concurs that professional advice should be sought before administering ipecac syrup, but disagrees with the contention that a physician must be present when ipecac syrup is administered to an infant under 1 year of age. The existence or nonexistence of a gag reflex in infants has not been positively established, but the issue is irrelevant because ipecac acts directly on the vomiting reflex center in the brain to produce vomiting. More important, the Commissioner believes that the immediate availability of an emetic for use in poisoning (including in infants) is critical because rapid treatment may be the difference between life and death. The Commissioner finds that the proposed § 337.50(c)(1) (21 CFR 337.50(c)(1)) label statement warning persons to seek professional advice before administering ipecac is adequate to protect from irrational use of ipecac syrup in infants.

7. Proposed § 337.50(c)(1) contained the warning "Before using, call physician, Poison Control Center, or hospital emergency room for advice." The Advisory Review Panel on OTC Miscellaneous Internal Drug Products, while reviewing drug products for acute toxic ingestion at its meeting on May 5, 6, and 7, 1978, recommended that the word hospital be deleted from this warning because of the current trend of some emergency rooms being established outside of hospitals and because some hospitals do not have emergency rooms. the Commissioner concurs that the word hospital is not needed in this warning, and proposed § 337.50(c)(1) has been revised accordingly.

8. Proposed § 337.50(c)(2) contained the warning "Do not use in unconscious persons." The Commissioner concludes that the labeling for ipecac syrup should also warn against use in persons who are semiconscious. Proposed § 337.50(c)(2) has been revised accordingly.

9. A comment suggested that the term "gastric lavage" may not be well understood by some consumers. Even if it is understood, the comment expressed doubt that the average consumer would be able to perform the procedure. The comment asserted that the term is not appropriate on consumer labeling and that the labeling of the product should refer the consumer to either a physician or a poison control center.

The Commissioner recognizes that consumers would be unable to perform a "gastric lavage" procedure. Accordingly, the reference to "gastric lavage" has been deleted and instead the consumer is directed to call a physician, Poison Control Center, or emergency room immediately if vomiting does not occur within 20 minutes after a second dose of ipecac syrup is given.

10. At its May 5, 6, and 7, 1978 meeting, the Advisory Review Panel on OTC Miscellaneous Internal Drug Products also recommended that an additional warning be added to the labeling of ipecac syrup, i.e., "Do not administer milk or carbonated beverages with this product." Milk has been reported to reduce the effectiveness of ipecac syrup and carbonated beverages could cause distention of the stomach.

The Commissioner concurs, and proposed § 337.50(c) has been revised accordingly.

11. The Commissioner is aware that activated charcoal is recognized by some people as a general purpose antidote for drug poisoning and that some physicians may recommend its use following use of ipecac syrup. Activated charcoal adsorbs ipecac syrup and may reduce its effectiveness. The Commissioner therefore concludes that a drug interaction statement in the labeling should warn that if both ipecac syrup and activated charcoal are to be used, vomiting must be induced with the ipecac syrup before administering activated charcoal. Proposed § 337.50(d) is added to require such a statement in the "Drug Interaction Precautions" section of the labeling.

12. A comment suggested that labeling information include the need to follow the administration of ipecac with water, because emesis may not occur if the stomach is empty.

The Commissioner agrees that to obtain best results, water should be taken following the administration of ipecac syrup and has revised the directions for use in proposed § 337.50(e) (originally proposed as § 337.50(b)).

II. THE COMMISSIONER'S CONCLUSIONS ON EMETICS

A. GENERAL DISCUSSION

A notice was published in the FEDERAL REGISTER of February 8, 1973 (38 FR 3614) requesting data and information on OTC emetic drugs. No submissions were made. The Commissioner notes that although the Panel received no submissions from the pharmaceutical industry or other sources, it elected to review ipecac syrup as an OTC emetic drug. Based on the Panel review, the comments discussed above, and other data available to him, the Commissioner concludes that ipecac syrup is safe and effective when used in the recommended dose of 1 tablespoonful (15 milliliters (ml)) in persons more than 1 year of age and a dose of 1 teaspoonful (5 ml) to a maximum of 2 teaspoonsful (10 ml) in infants under 1 year of age.

B. SAFETY AND EFFECTIVENESS

An emetic is often used to induce vomiting in poisoning victims, who ingest systemic poisons, to prevent absorption of the chemicals from the gastrointestinal tract. The Commissioner concludes that the most effective and dependable emetic for such use is ipecac syrup and that it is in the interest of the public health for ipecac syrup to be readily available for sale without prescription for the emergency treatment of poisonings.

Ipecac syrup is an official article in the United States Pharmacopeia (U.S.P.) XIX and is prepared from powdered ipecac, which is obtained from the plant *Cephaelis acuminata.* The syrup contains not less than 123 milligrams (mg) and not more than 157 mg of the total ether-soluble alkaloids of ipecac per 100 ml. These alkaloids are emetine and cephaeline, and they act on the vomiting reflex center in the brain to cause vomiting.

An overdose of an ipecac preparation may cause serious poisoning. Thus, existing FDA regulations (21 CFR 201.308(c)) and the conditions to be established in this part 337 limit ipecac syrup to a 30-ml container for OTC sale.

The recommended dose of 1 tablespoonful (15 ml) of ipecac syrup for persons over 1 year of age usually induces vomiting within 20 minutes, but in the event vomiting does not occur by this time, it is recommended that the same dose be repeated once. The ipecac should be recovered by gastric lavage (stomach pumping) if vomiting does not occur after the second dose.

The Commissioner also concludes that labeling for ipecac syrup should identify the product as an emetic (agent to cause vomiting) to be used in case of poisoning and warn the user to call a physician, poison control center,

or emergency room for advice before using the product and to call immediately if vomiting does not occur within 20 minutes after a second dose has been given. To conform with existing FDA regulations (21 CFR 201.308(c)(1)), the warning is to be conspicuously boxed and in red letters. The labeling also warns against the use of ipecac in semiconscious or unconscious persons, or in cases where strychnine, corrosives (alkalies (lye) and strong acids), or petroleum distillates (kerosene, gasoline, paint thinner, or cleaning fluid) have been ingested.

The labeling for all OTC drugs used for oral administration is required to contain the general warning "In case of accidental overdose, seek professional assistance or contact a poison control center immediately." In view of the fact that the labeling for ipecac syrup already requires a warning about contacting a physician, Poison Control Center, or emergency room (see proposed § 337.50(c)(1)), the Commissioner believes that the warning required by § 330.1(g) concerning overdoses would be repetitive and thus will not be required on the labeling for ipecac syrup.

The Commissioner advises that the existing regulation in § 201.308 will be superseded and withdrawn at the time this monograph becomes effective.

REFERENCES

1. Cashman, T. M. and H. C. Shirkey, "Emergency Management of Poisoning," *Pediatric Clinics of North America*, 17:525–534, 1970.

2. "The Pharmacopeia of the United States of America," 19th Rev., The United States Pharmacopeial Convention, Inc., Rockville, Md., p. 266–268, 1975.

3. Robertson, W. O., "Syrup of Ipecac—A Slow or Fast Emetic?," *American Journal of Diseases of Children*, 103:136–139, 1962.

4. "Handbook of Nonprescription Drugs," 5th Ed., American Pharmaceutical Association, Washington, D.C., pp. 57–58, 1977.

The Food and Drug Administration has determined that this document does not contain an agency action covered by 21 CFR 25.1(b) and consideration by the agency of the need for preparing an environmental impact statement is not required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to him (21 CFR 5.1), the Commissioner of Food and Drugs is issuing as a tentative final order new part 337 to read as follows:

PART 337—EMETIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredient

Subpart C—[Reserved]

Subpart D—Labeling

AUTHORITY: Secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 337.1 Scope.

An over-the-counter emetic drug product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this part 337 in addition to each of the general conditions established in § 330.1 of this chapter.

§ 337.3 Definitions.

(a) *Age.* Infant (under 2 years of age), child (2 years to under 12 years of age), and adult (12 years of age and older).

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

Subpart B—Active Ingredient

§ 337.10 Emetic active ingredient.

The active ingredient of the product is powdered ipecac. It is marketed as ipecac syrup, U.S.P. XIX, in the quantity of 1 fluid ounce (30 milliliters) only.

Subpart C—[Reserved]

Subpart D—Labeling

§ 337.50 Labeling of emetic products.

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

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

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

(1) "Call a physician, Poison Control Center, or emergency room for advice before using, and call immediately 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.

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

(3) "Ordinarily, 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."

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

(5) the warning required by § 330.1(g) concerning overdoses is not required on ipecac syrup products.

(d) *Drug interaction precautions.* The labeling of the product contains the following statement under the heading "Drug Interaction Precautions": "Activated charcoal will absorb ipecac syrup. If both activated charcoal and ipecac syrup are to be used, give the activated charcoal only after successful vomiting has been produced by the ipecac syrup."

(e) *Directions.* The labeling of the product contains 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 is repeated once.

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

Interested persons may file written objections and/or request an oral hearing before the Commissioner regarding this tentative final order on or before October 5, 1978. Requests for an oral hearing must specify points to be covered and time requested. All objections and requests shall be submitted (preferably in quadruplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) to the hearing clerk (HFA-305), Food and Drug Administration, Room 4–65, 5600 Fishers Lane, Rockville, Md. 20857, and shall be supported by a brief statement of the grounds therefor. Objections and requests may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the FEDERAL REGISTER.

NOTE.—The Food and Drug Administration has determined that this document will not have a major ecomomic impact as defined by Executive Order 11821 (amended by Executive Order 11949) and OMB Circular A-107. A copy of the economic impact assessment is on file with the hearing clerk, Food and Drug Administration.

Dated: August 25, 1978.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

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