Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before January 15, 1986, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before March 17, 1986. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on March 17, 1986. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: December 31, 1984.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

[FR Doc. 85-680 Filed 1-14-85; 8:45 am]

BILLING CODE 4160-01-M

federal register

Tuesday
January 15, 1985

Part IX

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 341

Cold, Cough Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Over-the-Counter Nasal Decongestant Drug Products

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 76N-052N]

21 CFR Part 341

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Over-the-Counter Nasal Decongestant Drug Products

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) nasal decongestant drug products (drug products used for relieving the symptom of nasal congestion caused by acute or chronic rhinitis) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal deals only with nasal decongestant drug products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by May 15, 1985. New data by January 15, 1986. Comments on the new data by March 17, 1986. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determination by May 15, 1985.

ADDRESS: Written comments, objections, new data, or requests for oral hearing 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, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products, together with the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthamatic Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. Interested persons were invited to submit comments by December 8, 1976. Reply comments in response to comments filed in the initial comment period could be submitted by January 7, 1977.

In a notice published in the **Federal Register** of March 21, 1980 (45 FR 18400), the agency advised that it had reopened the administrative record for OTC cold, cough, allergy, bronchodilator, and antiasthamatic drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch after the date the administrative record previously had officially closed. The agency concluded that any new data and information filed prior to March 21, 1980 should be available to the agency in developing a proposed regulation in the form of a tentative final monograph.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. Data and information received after the administrative record was reopened have also been put on display in the Dockets Management Branch. In response to the advance notice of proposed rulemaking, 16 manufacturers, 2 manufacturers' associations, 4 consumers, the staff members of one bureau of a government agency, 19 health care professionals, and 5 health care professional societies submitted comments on nasal decongestants. One manufacturer submitted a reply comment. Copies of the comments received are on public display in the Dockets Management Branch.

FDA is issuing the tentative final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products in segments. This document on nasal decongestant drug products is the fourth segment to be published. The first segment, on anticholinergic drug products and expectorant drug products, was published in the **Federal Register** of July 9, 1982 (47 FR 30002). The second segment, on bronchodilator drug products, was published in the **Federal Register** of October 26, 1982 (47 FR 47520). The third segment, on antitussive drug products, was published in the **Federal Register** of October 19, 1983; 48 FR 48576). The fifth segment, on antihistamine drug products, is being published elsewhere in this issue of the **Federal Register**. A subsequent segment on combination drug products and general comments will be published in a future issue of the **Federal Register**.

The advance notice of proposed rulemaking, which was published in the **Federal Register** on September 9, 1976 (41 FR 38312), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) the FDA states for the first time its position on the establishment of a monograph for OTC nasal decongestant drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC nasal decongestant drug products.

This tentative final monograph would amend Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations in Part 341 (as set forth in the tentative final monograph on anticholinergic drug products and expectorant drug products that was published in the **Federal Register** of July 9, 1982 (47 FR 30002)) in Subpart A, by adding in § 341.3, new paragraphs (h) and (i); in Subpart B, by adding new § 341.20; and in Subpart C, by adding new § 341.80, and by adding in § 341.90, new paragraphs (m) and (n). This proposal constitutes FDA's tentative adoption of the Panel's conclusion and recommendations on OTC nasal decongestant drug products, as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

The OTC procedural regulations (21 CFR 330.10) have been revised to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). (See the **Federal Register** of September

29, 1981; 46 FR 47730.) The Court in *Cutler* held that the OTC drug review regulations were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision has been deleted from the regulations, which 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" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead 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 at the tentative final monograph stage.

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 that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced into interstate commerce unless they are the subject of an approved new drug application (NDA). Further, any OTC drug products subject to this monograph that 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 the advance notice of proposed rulemaking for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products (published in the **Federal Register** of September 9, 1976 (41 FR 38312)), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products will have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and have their products in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of August 9, 1972 (37 FR 16029) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products recommended that phenylpropanolamine preparations be classified in Category I for nasal decongestant use at adult oral dosages equivalent to these phenylpropanolamine hydrochloride dosages: 25 milligrams (mg) every 4 hours or 50 mg every 8 hours not to exceed 150 mg in 24 hours (see 41 FR 38420; September 9, 1976). Similarly, the Advisory Review Panel on OTC Miscellaneous Internal Drug Products recommended that phenylpropanolamine hydrochloride be classified as Category I for appetite control use in adult oral dosages of 25 to 50 mg, not exceeding 150 mg daily. (See 47 FR 8484; February 26, 1982.) However, FDA became aware of reports of studies, made available after the Panels' reports had been submitted, indicating that certain dosages of phenylpropanolamine cause blood pressure elevation. These studies were discussed in the preamble to the advance notice of proposed rulemaking for OTC weight control drug products (47 FR 8466–8468). At that time, the agency specifically requested comments and information on the extent to which phenylpropanolamine induces or aggravates hypertension and interacts with medications that inhibit prostaglandin synthesis.

Numerous comments on the recommended phenylpropanolamine dosage levels and related issues have been submitted to FDA in both the OTC weight control and the OTC nasal decongestant rulemakings. Because the issues concerning the safety of phenylpropanolamine for weight control use and for nasal decongestant use are closely related, the agency has decided to address these issues in the **Federal Register** publication to be published in the near future. Therefore, phenylpropanolamine preparations will not be categorized or further discussed in this tentative final monograph for OTC nasal decongestant drug products.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on Nasal Decongestant Drug Products

1. One comment stated that there is no evidence that "so-called nasal

decongestants" are of any clinical value. No data or published references were submitted or cited to support this statement.

The Panel reviewed the scientific literature and data submissions, listened to testimony from interested parties, and considered all other available data and information before categorizing OTC nasal decongestant active ingredients. The Panel classified in Category I those active ingredients for which it had appropriate supportive data to establish general recognition of safety and effectiveness. In addition, the Panel placed in Category III those active ingredients for which it did not have sufficient data to establish safety and effectiveness. Additional data must be submitted on these Category III ingredients before they can be generally recognized as safe and effective. The agency believes that those ingredients which have been categorized as safe and effective do have clinical value for the indications listed in this tentative final monograph.

2. One comment disagreed with the Panel's recommendation that claims such as "most recommended by doctors" be placed in Category II because such claims are difficult to substantiate. The comment contended that "difficulty in substantiating does not imply inability to substantiate." Thus, according to the comment, the Panel's reasoning justifies placing this type of claim in Category III. More importantly, the comment argued, this type of claim is not specifically related to safety or effectiveness. If this type of statement were true, the comment contended, banning its use is an inappropriate prior restraint and in violation of the First Amendment to the Constitution.

The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. Two principal conditions examined during the review are allowable ingredients and allowable labeling. The FDA has determined that it is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in OTC drug products. Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of covered products by lay persons. OTC drug monographs establish allowable labeling for the following items: product statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action.

The agency believes terms such as "most recommended by doctors" are unrelated to the characteristics of the drugs in question and, therefore, do not relate in a significant way to the drugs' safe and effective use. Accordingly, the term "most recommended by doctors" is outside the scope of the OTC drug review. The agency emphasizes that even though terms such as "most recommended by doctors" are outside the scope of the OTC drug review, they are subject to the prohibitions in section 502 of the act (21 U.S.C. 352) relating to labeling that is false of misleading. Such statements or terms will be evaluated by the agency on a product-by-product basis, under the provisions of section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading.

Moreover, any statement or term that is outside the scope of the monograph, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information. However, statements and terms outside the scope of the monograph may be included elsewhere in the labeling, provided they are not false or misleading.

3. One comment stated that two nasal decongestants should not be taken simultaneously and recommended that the labeling should be clear on this matter. The comment did not further elaborate on its statement.

The agency believes that the comment is referring to two different drug products, each containing a nasal decongestant, for similar uses. The proposed labeling for nasal decongestants in this tentative final monograph specifically requires that the product's principal intended use, i.e., "nasal decongestant" be stated in the labeling. Further, all products containing a nasal decongestant will bear similar indications for use. By reading the label, the consumer should understand that two different drug products containing nasal decongestants are intended to treat the same symptoms and should not be taken simultaneously. The agency, therefore, believes that two nasal decongestants contained in different products will not inadvertently be taken simultaneously because the proposed labeling for nasal decongestants is explicit enough to inform the consumer of the proper use of these drugs. In addition, the agency is unaware of any data that indicate that the proposed labeling for nasal decongestants is inadequate to prevent the inadvertent use of two nasal decongestants simultaneously. (Note: the combination of two nasal decongestants in the same product will be discussed in the combinations segment of the tentative final monograph in a future issue of the Federal Register.)

B. Comments on the Switch of Prescription Nasal Decongestants to OTC Status

4. Several comments agreed with the Panel's classification of oxymetazoline hydrochloride and xylometazoline hydrochloride as Category I OTC topical nasal decongestants. Other comments were opposed to the OTC availability of these ingredients for various reasons. Several comments stated that the habituation and rebound congestion caused by these drugs contraindicated their OTC availability. One comment petitioned the FDA to remove oxymetazoline hydrochloride nasal spray and nasal solution from the OTC market because it is a new drug and the subject of a new drug application which limits its introduction into interstate commerce as a prescription only product. Another comment stated that the use of a xylometazoline hydrochloride nasal spray was the probable cause of a specific incident of severe cardiac upset.

The agency's position regarding the marketing status of ingredients recommended for OTC use which had previously been limited to prescription use is contained in the Code of Federal Regulations at 21 CFR 330.13(b)(2). This regulation explains that such ingredients placed in Category I by a Panel may be marketed OTC following publication of the Panel's proposed monograph subject to the risk that the Commissioner may not accept the Panel's recommendation and may instead adopt a different position that may require relabeling, recall, or other regulatory action. Because the Panel considered oxymetazoline hydrochloride safe, it recommended that this drug, previously available only by prescription prior to publication of the Panel's report in the Federal Register, be reclassified to permit OTC use. Because oxymetazoline has been placed in Category I and the Panel's report has been published without an agency dissent, a manufacturer may market the drug OTC, prior to promulgation of a final monograph, subject to the risk that the Commissioner may subsequently adopt a position different from the Panel's recommendation.

The agency recognizes the problem of rebound congestion associated with the use of topical nasal decongestants. Rebound congestion occurs when

topical nasal decongestants are used too frequently and for too long a period of time. The nasal mucous membranes become more congested and edematous as the drug's vasoconstrictor effect subsides. This effect leads to continued use of the drug and perpetuation of the rebound phenomenon. The Panel also addressed this problem and recommended that all nasal drops and sprays be labeled to limit use to not more than 3 days so as to discourage prolonged use. The Panel also recommended labeling that advised the consumer to consult a doctor if symptoms persisted after 3 days of use. (See § 341.80(b)(1)(ii), 41 FR 38423.) Although aware that continued use of these drugs might result in rebound congestion, the Panel thought that the clinical and marketing data it reviewed showed these drugs to be safe and effective when used according to label directions. Therefore, the Panel concluded that the drug should be available for OTC use.

From the information available, the agency cannot determine the cause of the cardiac upset reported in one of the comments. However, it is reported in the literature that the imidazolines (a class of drugs which includes naphazoline hydrochloride, oxymetazoline hydrochloride, and xylometazoline hydrochloride) may cause arrhythmias, presumably due to coronary vasoconstriction (Ref. 1). Because of these effects, the imidazolines should be used sparingly and with caution in infants, young children, and patients with cardiovascular disease (Refs. 1 and 2).

Studies of the effect of the imidazolines on the intestinal smooth muscle of the rabbit and on the cardiovascular system of the cat showed that the pharmacological action of these drugs, particularly oxymetazoline, is strong (Ref. 3). Nasal decongestants that are administered orally are known to be capable of producing systemic effects. Consequently, the Panel recommended a warning to persons with high blood pressure, heart disease, diabetes, or thyroid disease not to take the drug except under the advice and supervision of a physican. (See § 341.80(b)(2)(iii), 41 FR 38423.) A warning that the product should be used very cautiously in patients with hyperthyroidism, coronary artery disease, hypertension, and diabetes mellitus has also been required for prescription topical nasal decongestants containing oxymetazoline and xylometazoline for over 10 years (Refs. 4 and 5). Because the Panel believed that absorption of the drug into the general circulation was negligible following topical use, the Panel did not recommend a similar warning statement; therefore, the above warning was not required for these products marketed on an OTC basis pursuant to § 330.13 following publication of the Panel's report.

The agency believes that use of these drugs in a generally healthy person is safe, but is concerned that systemic effects can occur in small children or in persons with cardiovascular disease as a result of absorption from the gastrointestinal tract if an excessive amount of the drug is swallowed. Because some of the drug is often swallowed when nose drops and sprays are administered, systemic effects such as those occurring from an orally administered dose can occur. Because of the possibility of generalized vasoconstriction and tachycardia, persons with hypertension, heart disease, diabetes, or hyperthyroidism should only use nasal decongestants as directed by a doctor (Refs. 1, 2, 4, 5, and 6).

Use of these drugs can also produce effects which could alter the balance of insulin and glucose in a diabetic patient (Refs. 6 and 7). Additionally, because of the vascular problems which frequently accompany diabetes, diabetic patients should consult a doctor before using topical nasal decongestants.

Because of the potential side effects that topical nasal decongestants can produce, the agency believes that, in the interest of safety, the warning proposed by the Panel in § 341.80(b)(2)(iii) for oral nasal decongestants shoul also apply to all topical nasal decongestants (except topical inhalants). Based on the Panel's review of data showing that the topical inhalants (propylhexedrine and l-desoxyephedrine) produce little or no significant vasopressor side effects (41 FR 38402 and 38407), the agency proposes to exclude topical inhalants from this warning requirement. Therefore, in this tentative final monograph, the warning as stated in § 341.80(c)(1)(i)(c) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor," will be applicable to all oral nasal decongestants, and a similar warning in § 341.80(c)(2)(iii)(*b*) "Do not use this product if you have heart disease, high blood pressure * * *" will be applicable to all topical nasal decongestants except topical inhalants. The agency also proposes to restrict the use of oxymetazoline hydrochloride and xylometazoline hydrochloride in children under 6 years of age. (See comment 28 below.)

The agency believes that the above warning and limitation of the product to 3 days use will provide for the safe use of these ingredients as OTC topical nasal decongestants.

References

(1) "AMA Drug Evaluations," 4th Ed., American Medical Association, New York, p. 454, 1980.

(2) Harvey, S.C., "Sympathomimetic Drugs," *in* "Remington's Pharmaceutical Sciences," 16th Ed., edited by A. Osol, et al., Mack Publishing Co., Easton, PA pp. 818–819, 1980.

(3) Mujic, M., and J.M. Van Rossum, "Comparative Pharmacodynamics of Sympathomimetic Imidazolines; Studies on Intestinal Smooth Muscle of the Rabbit and the Cardiovascular System of the Cat," *Archives Internationales de Pharmacodynamie et de Therapie*, 155:432–449, 1965.

(4) Copy of FDA approved labeling from NDA 11–919, in OTC Volume 04NTFM, Docket No. 76N–052N, Dockets Management Branch.

(5) Copy of FDA approved labeling from NDA 14–717, in OTC Volume 04NTFM, Docket No. 76N–052N, Dockets Management Branch.

(6) "New Drugs," American Medical Association, Chicago, pp. 211–212, 1965.

(7) "Clinical Pharmacology; Basic Principles in Therapeutics, 2d Ed., Macmillan Publishing Co., Inc., New York, p. 192, 1978.

C. Comments on Specific OTC Nasal Decongestant Active Ingredients

5. One comment stated that there is concern about camphor poisoning in children (Refs. 1 and 2) and recommended that the camphor content of OTC nasal decongestant products (topical inhalants) be limited to less than 0.75 gram (g)/30 grams (g) or to less than 2.5 percent (weight/volume). The comment stated that there is no evidence that warning statements deter childhood poisoning, but concluded that this lower concentration would reduce the risk of serious accidental poisoning while still permitting an adequate concentration of camphor.

The Panel concluded that camphor is safe when applied topically or as an inhalant at specific concentrations, but that there were insufficient data to permit final classification of its effectiveness when labeled for use as a nasal decongestant (41 FR 38406). For adults and children 2 to under 12 years of age, the Panel recommended that camphor should be used in the form of a 5-percent ointment preparation, a 7-percent solution for steam inhalation, or a lozenge containing 0.02 to 15 mg camphor. Following publication of this Panel's recommendations on camphor,

the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel) also reviewed camphor for topical use. The Miscellaneous External Panel concluded that OTC products containing a concentration of camphor greater than 2.5 percent have a low benefit-to-risk ratio and recommended that camphor be limited in OTC drug products for external use to less than 2.5 percent. The Miscellaneous External Panel also recommended that the quantity of camphor in a package be limited to a total of 360 mg per package and that camphor be marketed in a child-proof container to deter accidental poisoning of children (45 FR 63875).

In the **Federal Register** of September 21, 1982 (47 FR 41716), the agency published a final rule establishing that camphorated oil drug products (historically marketed primarily as topical counterirritants or liniments) are misbranded and are new drugs. The agency also initiated a recall of camphorated oil products to the retail level. In the **Federal Register** of September 26, 1980 (45 FR 63874), the agency announced that it was treating the data and information on camphor received from the Miscellaneous External Panel as a petition to reopen the administrative record on cold, cough, allergy, bronchodilator, and antiasthmatic drug products. The agency granted this petition by allowing those data and information to be included in the administrative record for these drug products. This notice served to inform interested persons of the existence of these recommendations and also invited persons or firms to submit any comments they may have. This reopening of the administrative record related only to the ingredient camphor in OTC drug products.

The agency's position on the safety of camphor containing products for topical application has been stated in the tentative final rule for OTC external analgesic drug products in the **Federal Register** of February 8, 1983 (48 FR 5854). In that document, the agency concluded that, at this time, there is no need to limit camphor content to 360 mg per package and that the camphor content will be limited to 11 percent or lower. The agency's position as stated in that document is hereby incorporated into this nasal decongestant rulemaking.

To date, no new data have been submitted to support the effectiveness of camphor as a nasal decongestant and at this time, camphor will remain in Category III as a nasal decongestant.

References

(1) Aronow, R.J., "Camphor Poisoning," *Journal of the American Medical Association*, 235:1260, 1976.

(2) Phelan, W.J., "Camphor Poisoning: Over-the-Counter Dangers," *Pediatrics*, 57:428–431, 1976.

6. One comment objected to the Panel's limiting eucalyptol, menthol, and thymol to lozenge and mouthwash dosage forms when these ingredients are used as "oral (topical) nasal decongestants." The comment contended that this limitation is arbitrary because viscous syrups and compressed tablets are just as effective as mouthwashes and lozenges. The comment recommended that "oral (topical) dosage" forms of eucalyptol, menthol, and thymol include any oral dosage form which is topically effective and which can be formulated to contain the same concentrations of these ingredients that are allowed for lozenges.

The comment's use of the term "oral (topical) nasal decongestant" apparently refers to dosage forms such as mouthwashes, lozenges, and compressed tablets, which are all used topically in the mouth, rather than swallowed, for a nasal decongestant effect. Compressed tablets and lozenges are solid dosage forms which can be used topically in the same manner and the site of application would be the same for compressed tablets, lozenges, and mouthwashes. The agency agrees that compressed tablets could also be included as a dosage form for eucalyptol, menthol, and thymol, when used as oral (topical) nasal decongestants intended to be dissolved in the mouth rather than swallowed, once the ingredients in this dosage form have been classified in Category I. The agency points out that eucalyptol, menthol, and thymol are all Category III ingredients, which, although found safe by the Panel, lack adequate data to demonstrate effectiveness as topical or inhalant nasal decongestants. Data to demonstrate effectiveness are required in order to permit final classification of these ingredients in the monograph for this use.

The comment's suggestion to allow viscous syrups as topical dosage forms in the mouth is not accepted because the agency is not aware of any data on viscous syrups containing eucalyptol, menthol, or thymol that are used as oral (topical) nasal decongestants. Interested persons are invited to submit data on viscous syrups containing these ingredients that are used as oral (topical) nasal decongestants in the mouth.

7. A comment representing the views of the staff of the Bureau of Consumer Protection of the Federal Trade Commission (FTC) requested that the active ingredients eucalyptol, menthol, and thymol used as a nasal decongestant or antitussive in a mouthwash dosage form be classified as Category II. The comment pointed out that after more than 4 months of adjudicative hearings, during which voluminous evidentiary records consisting of thousands of pages of expert testimony and exhibits were thoroughly examined for a marketed product with labeling and advertising claims that the product cured or prevented colds or sore throat, or lessened the severity or incidence of colds, cold symptoms, or sore thoats by killing germs (Ref. 1), the FTC determined that 0.91 mg of eucalyptol per milliliter (mL) of product (mg/mL), 0.42 mg/mL menthol, and 0.63 mg/mL thymol in a mouthwash solution are insufficient in concentration to provide relief for the symptoms of the common cold, including nasal congestion and cough. Expert medical and scientific witnesses testified that the process of gargling with a mouthwash containing these ingredients does not allow the ingredients to reach the critical areas of the body they need to reach to relieve the symptoms of a cold, nor do the ingredients penetrate the infected cells where the action of the cold viruses would be taking place.

The comment stated that the FTC's conclusion, after examining the records and hearing expert testimony, was consistent with the Panel's findings that there are no well-controlled studies documenting the effectiveness of eucalyptol, menthol, and thymol when usd in a mouthwash dosage form as a nasal decongestant or an antitussive. The comment pointed out that the FTC's opinion and supporting evidence were not available to the Panel during its deliberations. Therefore, the comment requested that the FDA review the FTC's opinion and the supporting evidence and use them as a basis to classify eucalyptol, menthol, and thymol in Category II for use as a nasal decongestant or antitussive in a mouthwash dosage form.

The response in this document addresses only the nasal decongestant use of these ingredients. The antitussive use will be addressed in a future issue of the **Federal Register**. The agency has reviewed the FTC's opinion and supporting evidence (Ref. 1). Medical and scientific experts testified at the FTC hearing that there is an absence of literature showing that the combination

of eucalyptol, menthol, and thymol in a mouthwash dosage form is effective in preventing colds and alleviating cold symptoms such as nasal congestion and cough. These experts in the fields of respiratory and infectious diseases, virology, pharmocology, and microbiology further stated, based upon their knowledge in their respective areas, that it is doubtful that these ingredients would be effective in treating symptoms of the common cold.

Although the Panel did not have access to the FTC's opinion and supporting evidence, it did review the St. Barnabas study, which was one of the studies discussed during the FTC hearing (Ref. 2). The St. Barnabas study was undertaken to demonstrate the effect of rinsing and gargling twice daily with an aqueous mixture of 0.91 mg/mL eucalyptol, 0.42 mg/mL menthol, and 0.63 mg/mL thymol on the incidence, duration, and severity of the common cold and its symptoms. It was a 4-year subjective study in over 4,800 schoolchildren. The experts who testified at the FTC hearing agreed that the deficiencies in the design and execution of the study precluded any meaningful interpretation of the results. The FTC concluded that the design and execution of the tests heavily biased the results in favor of the manufacturer, and therefore the tests could not support the advertising claims. The Panel concluded that although the study was not well-controlled and could not be considered proof of effectiveness, the results did reveal milder nasal symptoms and cough symptoms in individuals using the medicated mouthwash as compared with these symptoms in individuals using the placebo. Because this study did not demonstrate the effectiveness of the individual nasal decongestant ingredients, the Panel recommended that data to demonstrate effectiveness of each ingredient alone be required in accordance with its guidelines for testing OTC nasal decongestant drug products (41 FR 38415). Because safety was not at issue, and the data suggested the possibility that the combination of eucalyptol, menthol, and thymol was effective as a nasal decongestant in a mouthwash dosage form, the Panel believed that a Category III classification was justified.

At the tentative final monograph stage, FDA usually proposes Category II status for an ingredient only if there is a potential safety problem or if there are essentially no data to support the ingredient's effectiveness for its purported use. Although medical and scientific experts testified for the FTC that it is unlikely that eucalyptol, menthol, and thymol in a mouthwash would be effective as a nasal decongestant, they also stated that the studies that were done contained defects which made the results inconclusive. In view of the inconclusive results caused by deficiencies in the studies, the agency does not believe it appropriate at this time to classify the drugs as "ineffective," i.e., Category II, without allowing interested parties the opportunity to develop a well-controlled study that might demonstrate the drugs' effectiveness. Therefore, the agency is proposing that eucalyptol, menthol, and thymol in a mouthwash dosage form as a nasal decongestant remain in Category III in this tentative final monograph.

In the final monograph, any ingredient that has not been found to be safe and effective will be classified as "nonmonograph" and may not be legally marketed. To date, there have been no new data submitted to support the effectiveness of eucalyptol, menthol, and thymol in a mouthwash dosage form as a nasal decongestant, and if adequate data are not submitted before establishment of a final monograph, these ingredients for this use will be classified as "nonmonograph."

References

(1) Comment No. C0126, Docket No. 76N–0052, Dockets Management Branch.

(2) "The Effect of Listerine Antiseptic on the Incidence, Severity, and Duration of the Common Cold. A 4-Year Study," draft of unpublished paper in OTC Volume 040278, section 3.a. (referred to as the St. Barnabas Study in Comment No. C0126.)

8. One comment (Ref. 1) submitted new data from four controlled clinical studies (Refs. 2 through 5) on the effectiveness of 1-desoxyephedrine, alone and in combination with aromatics (camphor, menthol, methyl salicylate, bornyl acetate, and lavender oil), as a topical nasal decongestant (administered by a nasal inhaler). The comment requested Category I status for 1-desoxyephedrine based on the new data (Refs. 2 through 5), data submitted to the Panel (Refs. 6 and 7), and the manufacturer's marketing experience.

The agency has reviewed the data and concludes that they are adequate to reclassify this ingredient in Category I as a topical nasal decongestant. The combination of 1-desoxyephedrine and aromatics will be addressed in the combinations segment of the cold, cough, allergy, bronchodilator, and antiasthmatic tentative final monograph in a future issue of the **Federal Register.**

The agency's evaluation of study numbers 74–10A, 74–30, 74–58, and 70–24 (Refs. 2 through 4, and 6 and 7) showed significant decongestion of the nostrils treated with 1-desoxyephedrine and the combination of 1-desoxyephedrine and aromatics, when compared to baseline measurements or placebo. Study 75–45 (Ref. 5) showed that 1-desoxyephedrine did not cause rebound congestion within a 7-day period. Based on the data, the agency proposes an adult dosage of two inhalations in each nostril not more often than every 2 hours from an inhaler that delivers in each 800 mL of air 0.04 to 0.15 mg of 1-desoxyephedrine. In keeping with the guidelines established by the Panel (41 FR 38333), the agency proposes a dosage for children 6 to under 12 years of age of one-half of the adult dosage, i.e., one inhalation in each nostril not more often than every 2 hours from an inhaler that delivers in each 800 mL of air 0.04 to 0.15 mg of 1-desoxyephedrine. The data demonstrate that this ingredient does not cause rebound nasal congestion within a 7-day period. Therefore, the use of 1-desoxyephedrine as a topical nasal decongestant should be limited to not more than 7 days rather than the 3-day limit for other topical nasal decongestants that cause rebound congestion.

The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (Ref. 8).

References

(1) Comment Nos. C0111, CR0003, and SUP015, Docket No. 76N–0052, Dockets Management Branch.

(2) Connell, J.T., "Nasal Decongestant Delta-'P' Method," draft of unpublished study (74–10A), in Comment No. C0111, Docket No. 76N–0052, Dockets Management Branch.

(3) Connell, J.T., "Inhaler," draft of unpublished study (74–30), in Comment No. C0111, Docket No. 76N–0052, Dockets Management Branch.

(4) Connell, J.T., "Inhaler," draft of unpublished study (74–58), in Comment No. C0111 (Volume 4), Docket No. 76N–0052, Dockets Management Branch.

(5) Connell, J.T., "Nasomucosal Rebound Delta-P," draft of unpublished study (75–45), in Comment No. C0111 (Volume 4), Docket No. 76N–0052, Dockets Management Branch.

(6) Turgeon, R.F., "Vick Inhaler," draft of unpublished study (70–24), dated February 11, 1971, in OTC Volume 040298.

(7) Memo to Burke, W.E., from E.B. Cohen, "Vick Inhaler: Vick Rhinorhemeter Study-Maine Research" (Supersedes Study 70–24 dated February 11, 1971), in OTC Volume 040298.

(8) Letter from W.E. Gilbertson, FDA, to G.F. Hoffnagle, Vicks Health Care Division of Richardson-Merrell, Inc., coded LET072, Docket No. 76N–052N, Dockets Management Branch.

9. One comment reported two cases in which use of nose drops containing phenylephrine hydrochloride had caused a permanent loss of the sense of

taste and smell. The comment recommended a warning statement in the labeling of these products which alerts consumers to the possibility of such an adverse reaction.

No data were submitted with the comment; however, the agency has reviewed both the Panel's discussion on the safety of phenylephrine hydrochloride (41 FR 38399) and its recommended warnings for nasal decongestants (41 FR 38422). The Panel concluded that phenylephrine hydrochloride is generally recognized as safe for use as a nasal decongestant, and it did not make any reference to the type of adverse reaction cited in the comment. Accordingly, no warning statement was recommeded.

The agency is concerned about the possibility of any adverse effects resulting from the use of drug products, and it routinely reviews and evaluates reports of those adverse reactions which are submitted. FDA's "Annual Adverse Reaction Summary Listing" for the period from 1969 to 1981 does include one reported case of parosmia (any disease or disorder of the sense of smell) that occurred in 1977 (Ref. 1). However, this case and the two cases cited in the comment are not adequate evidence to show a relationship between the permanent loss of the sense of taste and smell and the use of OTC nasal decongestant drops containing phenylephrine hydrochloride. Therefore, based upon the limited amount of information available on this type of adverse reaction, the agency does not consider it necessary at this time to require a warning statement, as the comment requested. The agency invites interested persons to submit additional comments and data on this type of adverse reaction.

Reference

(1) Department of Health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listings," pertinent pages for the years 1969 through 1981, in OTC volume 04NTFM, Docket No. 76N-052N, Dockets Management Branch.

10. One comment questioned the studies used by the Panel to substantiate the effectiveness of phenylephrine hydrochloride as an oral nasal decongestant. The comment stated that numerous unpublished studies, which split evenly between mild successes and total failures, were quoted by the Panel, and in the one study (Ref. 1) published in an academically acceptable journal, no efficacy was seen even with doses higher than usually recommended. In addition, the comment cited two references which questioned the oral bioavailability of phenylephrine hydrochloride (Refs. 2 and 3). The comment recommended that phenylephrine hydrochloride not be used as an oral nasal decongestant.

The Panel concluded that phenylephrine hydrochloride was effective as an oral nasal decongestant after a thorough review of published and unpublished studies, oral and written submissions by manufacturers, and evaluations of clinical and marketing experience. The published study referred to by the comment (Ref. 1) is discussed in comment 11 below. The Panel was aware of one of the references that the comment cited as questioning the oral bioavailability of phenylephrine hydrochloride (Ref. 3), and cited this reference is discussing the safety of phenylephrine hydrochloride (41 FR 38399). This study is not relevant to the effectiveness of phenylephrine hydrochloride, but does confirm the potentiation of the effect of oral phenylephrine by a monoamine oxidase inhibitor.

The agency has reviewed the information cited by the comment, the Panel's recommendations, and all of the supporting data and concludes that, based on the studies cited by the Panel, information on clinical use and marketing experience, and the Panel's expertise in evaluating the clinical and marketing experience of this ingredient, there is sufficient basis to determine the phenylephrine hydrochloride is generally recognized as effective for OTC use as an oral nasal decongestant. The comment's recommendation is therefore not accepted.

References

(1) Rodgers, J.M., E.B. Reilly, and H.A. Bickerman, "Physiologic and Pharmacologic Studies on Nasal Airway Resistance," *Clinical Pharmacology and Therapeutics*, 14:146, 1973.

(2) Innes, I.R., and M.L. Nickerson, "Norepinephrine, Epinephrine, and the Sympathomimetic Amines," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L.S. Goodman and A. Gilman, the Macmillan Co., New York, pp. 477–494, 1975.

(3) Elis, J., et al., "Modification by Monoamine Oxidase Inhibitors of the Effect of Some Sympathomimetics on Blood Pressure," *British Medical Journal*, 2:75–78, 1967, in OTC Cough/Cold Reference Volume E, Docket No. 76N-0052, Dockets Management Branch.

11. One comment stated that a reference to a study by Rodgers, Reilly, and Bickerman (Ref. 1) cited by the Panel in three different places (in part VIII. paragraph B.d. on page 38400, in part VIII. paragraph B.e. on page 38401, and in part VIII. paragraph B.h. on page 39403) was incorrect in that the cited information was not contained in that particular reference.

The agency has reviewed the Panel's discussions on pages 38399 through 38403 and agrees with the comment that the study by Rodgers, Reilly and Bickerman (Ref. 1) does not contain the information cited by the Panel on page 38399, nor is the agency aware of what reference should have been cited there. Nevertheless, this omission does not have a bearing on the tentative status of phenylephrine hydrochloride for oral and topical use as a nasal decongestant.

The agency has determined, however, that the information in the discussions on pages 38401 and 38403 is supported in another study by Bickerman (Ref. 2) that was reviewed by the Panel and cited on page 38401. The information on pages 38401 and 38403 that was attributed to the study by Rodgers, Reilly, and Bickerman (Ref. 1) should be attributed to the Bickerman Study (Ref. 2).

References

(1) Rodgers, J.M., E.B. Reilly, and H.A. Bickerman, "Physiologic and Pharmacologic Studies in Nasal Airway Resistance," (abstract), *Clinical Pharmacology and Therapeutics*, 14:146, 1973.

(2) Bickerman, H.A., "Physiologic and Pharmacologic Studies on Nasal Airway Resistance (R^N). Current Research Methodology in the Evaluation of Proprietary Medicines. Cold and Allergy Preparations," *in* "Conference Proceedings of the Research and Scientific Development Committee of the Proprietary Association," The Proprietary Association, New York, pp. 60–72, 1971.

12. One comment claimed that certain OTC inhalant nasal decongestant products containing propylhexedrine have the capability of producing a "high" and therefore have a potential for abuse. The comment included a 1976 newspaper article which described six deaths traced to the abuse of propylhexedrine.

The Panel reviewed the data submitted on propylhexedrine and concluded that it was safe and effective for OTC use (41 FR 38402). In the dosage range recommended by the Panel, propylhexedrine has a wide margin of safety and relative freedom from toxic effects. Harvey (Ref. 1) describes propylhexedrine as a volatile indirect sympathomimetic amine that does not have central excitatory effects or addiction liability. It has a decongestant effect on the nasal mucous membrane and acts as a vasoconstrictor when inhaled once or twice through each nostril. It is considered safe for self-medication by adults, but children should not have unsupervised access to

a propylhexedrine inhaler. Side effects of propylhexedrine include rebound congestion, headache, and, in rare instances, an increase in blood pressure (Ref. 1). The Panel pointed out that 100 mg oral doses of propylhexedrine alone induce a 17- to 23-millimeter (mm) rise in blood pressure and reflex bradycardia in normal adults but no overt symptoms or euphoria, palpitation, or dry mouth (41 FR 38402).

The agency agrees with the Panel's conclusion that propylhexedrine has a wide margin of safety in the dosage range recommended for use by adults and children 6 to under 12 years of age (0.40 to 0.50 mg in two inhalations per nostril). The Panel pointed out that "the risk of misuse and/or abuse is minimized by restriction on the types of pharmacologic agents in available OTC products, limitations on dosage and concentration of active drug, and adequate and explicit directions for use coupled with appropriate warnings" (41 FR 38332).

The agency routinely reviews and evaluates reports of adverse reactions resulting from the use of OTC drug products. Annual adverse reaction summaries, compiled for the years 1969 to 1981 (Ref. 2), show that, of 21 cases of adverse reactions reported during this 12-year period for the two products mentioned by the comment, 7 cases involved the misuse of propylhexedrine in an inhaler. The six propylhexedrine-related deaths referred to by the comment occurred among individuals, most of whom had a history of drug abuse, who knowingly misused the drug. The agency is concerned about the possibility of any adverse effects resulting from the use of OTC drug products, but it also recognizes that a number of substances in the marketplace can be and are abused by some individuals. The few isolated reports on the abuse of propylhexedrine (the latest one was reported to the agency in 1977) do not indicate a widespread problem. The agency believes that propylhexedrine should be available as an inhalant nasal decongestant because it is safe and effective, when used as instructed in the labeling.

References

(1) Harvey, S.C., "Sympathomimetic Drugs," *in* "Remington's Pharmaceutical Sciences," 16th Ed., edited by A. Osol, et al., Mack Publishing Co., Easton, PA, p. 830, 1980.

(2) Department of Health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listing," pertinent pages for the years 1969 through 1981, in OTC Volume 04NTFM, Docket No. 76N-052N, Dockets Management Branch.

13. Several comments strongly disagreed with the Panel's recommendation that pseudoephedrine preparations be available OTC as nasal decongestants. One comment agreed with the Panel's recommendation. The comments that objected to the OTC status of pseudoephedrine stated that pseudoephedrine causes tachyphylaxis fatigue of the beta-response mechanism and urinary retention; side effects, although rarely severe or fatal, occur frequently; pseudoephedrine is a stimulant and overuse may be very damaging; and unrestricted availability to the public may be dangerous.

The agency agrees with the Panel's recommendation that pseudoephedrine preparations (pseudoephedrine hydrochloride and pseudoephedrine sulfate) are safe and effective as oral nasal decongestants for OTC use. The comments did not submit any data in support of their reasons for objecting to the OTC status of pseudoephedrine.

It has been reported in the literature that tachyphylaxis, a condition in which effectiveness of a drug decreases after rapidly repated doses, can occur with ephedrine and its isomeric forms (i.e., d- and l-ephedrine, and d- and l-pseudoephedrine) (Refs. 1, 2, and 3). However, the agency concludes that this should not be a problem if the drug is used according to labeling directions.

Roth et al. (Ref. 4) reported that side effects of patients treated with a single oral dose of 60 mg of pseudoephedrine were minimal. Of 20 patients, 2 experienced mild elevations in pulse rate, 1 developed a moderate elevation in pulse rate, 1 experienced mild elevations in pulse rate and diastolic blood pressure, 1 developed palpitations and a slight increase in pulse rate, 2 reported tiredness, and 3 reported a light-headed feeling. Empey et al. (Ref. 5) noted that side effects were of little problem in patients taking 60 mg of pseudoephedrine three times a day. In this study, pseudoephedrine and an antihistamine were tested separately, in combination, and compared with a placebo. One patient reported dryness of the mouth when taking pseudoephedrine alone, and one patient reported excessive sweating, but there were no reports of nervousness or palpitations. The authors stated that the lower incidence of drowsiness reported with the combination, as compared with the antihistamine alone, might reflect a slight stimulant effect from pseudoephedrine; however, stimulation was not reported by anyone taking pseudoephedrine alone. In its report, the panel cited a study which indicated that mild side effects, such as drowsiness, nausea, insomnia, and headache, can occur with the use of pseudoephedrine (Ref. 6). However, these side effects are not severe and would not warrant the elimination of pseudoephedrine from the OTC marketplace. Pseudoephedrine preparations have been marketed OTC safely for many years.

The use of pseudoephedrine, as with most other sympathomimetic drugs, may cause an increase in blood pressure when taken with monoamine oxidase inhibitors. Therefore, the Panel recommended a drug interaction precaution for oral nasal decongestants in § 341.80(b)(2)(iv) (redesignated as § 341.80(c)(1)(i)(*d*) in this tentative final monograph) to warn against the use of the product when taking a prescription drug for high blood pressure or depression without first consulting a doctor. (See comment 23 below.)

Because of the vasoconstrictive properties of sympathomimetic drugs, persons suffering from urinary retention, especially elderly men with an enlarged prostate, could experience increased difficulty in urinating (Refs. 7 and 8). Males with an enlargd prostate shoud only use these drugs under the supervision of a physician. Therefore, the agency has determined that this condition will be added to the warning proposed by the Panel in § 341.80(b)(2)(iii) which appears as § 341.80(c)(1)(i)(*c*) in this tentative final monograph. This warning will read as follows: "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." (NOTE: The part of the warning concerning "difficulty in urination due to enlargement of the prostate gland" is not necessary for products labeled for use only in children under 12 years of age. That part of the warning is not applicable to children and its presence in the labeling would tend to distract parents from label warnings which are important. Accordingly, the revised warning for products labeled for use in children only, "Do not give this product to children who have heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor," has been added to the tentative final monograph in § 341.80(c)(1)(ii)(*c*)). The directions for use and appropriate warnings will inform the consumer of the proper use of the product. Based on these considerations, the agency concludes that pseudoephedrine will remain available as an OTC nasal decongestant.

References

(1) Innes, I.R., and M. Nickerson, "Norepinephrine, Epinephrine, and the Sympathomimetic Amines," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L.S. Goodman and A. Gilman, Macmillan Publishing Co., New York, pp. 500–501, 1975.

(2) Patil, P.N., A. Tye, and J.B. Lapidus, "A Pharmacological Study of the Ephedrine Isomers," *Journal of Pharmacology and Experimental Therapeutics*, 148:158–168, 1965.

(3) Aviado, D.M., Jr., A.L. Wnuck, and E.J. DeBeer, "Cardiovascular Effects of Sympathomimetic Bronchodilators, Epinephrine, Ephedrine, Pseudoephedrine, Isoproterenal, Methoxyphenamine and Isoprophenamine," *Journal of Pharmacologh and Experimental Therapeutics*, 122:406–417, 1958.

(4) Roth, R.P., et al., "Nasal Decongestant Activity of Pseudoephedrine, "*Annals of Otology, Rhinology and Laryngology*, 86:235–241, 1977.

(5) Empey, M.B., et al., "A Double-Blind Crossover Trial of Pseudoephedrine and Triprolidine Alone and in Combination, for the Treatment of Allergenic Rhinitis," *Annals of Allergy*, 34:41–46, 1975.

(6) Arbesman, C.E., and R.J. Ehrenreich, "New Drugs in the Treatment of Allergies," *New York State Journal of Medicine*, 61:219–299, 1961.

(7) Innes, I.R., and M. Nickerson, "Norephinephrine, Epinephrine, and the Sympathomimetic Amines," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L.S. Goodman and A. Gilman, Macmillan Publishing Co., New York, pp. 505–507, 1975.

(8) Harvey, S.C., "Sympathomimetic Drugs," *in* "Remington's Pharmaceutical Sciences," 16th ED. edited by A. Osol, et al., Mack Publishing Co., Easton, PA, pp. 818–820, 1980.

D. Comments on Dosages for OTC Nasal Decongestants

14. One comment stated that there was an inconsistency between the dosage for naphazoline hydrochloride recommended by the Panel in § 341.20(b) and the warning for that ingredient in § 341.80(b)(6). The comment explained that in § 341.20(b) there is no dosage instruction for the use of a 0.05-percent solution in children under 12 years of age. However, § 341.80(b)(6) states that the 0.05-percent solution is not to be given to children under 6 years of age. Because the ages 6 to under 12 years are not mentioned in § 341.80(b)(6), the comment recommended that the warning in § 341.80(b)(6) should state that the 0.05-percent solution is not to be given to children under 12 years of age or, as an alternative, that dosage instructions for the 0.05-percent solution for children 6 to 11 years of age be included in § 341.20(b).

The agency agrees that the warning recommended by the Panel in § 341.80(b)(6) should be revised for clarity. The dosage instructions as stated in § 341.20(b) specify that 0.05 percent naphazoline hydrochloride is for adult use only, and that a 0.025-percent solution is to be used for children 6 to under 12 years of age. However, the warning in § 341.80(b)(6) states that the 0.05-percent solution is for adult use and should not be used in children under 6 years of age. As the comment points out, the warning in § 341.80(b)(6) neglects to mention children in the 6- to under 12-year age group. In § 341.3(a) of the advance notice of proposed rulemaking (41 FR 38419), an adult has been defined as any person 12 years of age and older. The agency has deleted the first part of the Panel's warning in § 341.80(b)(6), "For adult use only," because the product directions will specify that the 0.05-percent solution should be used only in adults. Therefore, the warning in § 341.80(b)(6) (redesignated as § 341.80(c)(2)(iv) in this document) will be revised to read as follows:

For products containing naphazoline hydrochloride identified in § 341.20(b)(6) at a concentration of 0.05 percent: "Do not use this product in children under 12 years of age because it may cause sedation if swallowed."

15. One comment proposed that § 341.20(d)(2) be revised so that an "aqueous solution" is not specified in the formulation of phenylephrine hydrochloride as a topical nasal decongestant. The comment stated that all other portions of the monograph avoid specifying inactive ingredients and that specifying an inactive ingredient was not consistent with the intent of the OTC drug review. The comment also stated that if an "aqueous solution" was specified in the formulation of phenylephrine hydrochloride to assure against the potential problem of lipid pneumonia, which can occur from the accidental aspiration of oil-based nose drops, then an appropriate limitation should be incorporated into the monograph to protect against this possibility. The comment suggested limiting the product form to "non-oil-based drops or sprays."

The purpose of the OTC drug review process is to determine the safety and effectiveness of OTC drugs. If an active ingredient is safe, but the product's inactive ingredient formulation results in an unsafe product, it was the responsibility of the Panel to address those ingredients which make the product unsafe. As the comment observes, oil-based drops or sprays may be aspirated into the lungs and may cause lipid pneumonia (Refs. 1 and 2). The Panel recognized this problem and concluded that nasal drops and sprays can only be generally recognized as safe and effective for OTC use when they are formulated as aqueous solutions. Because the designation "non-oil-based" solutions could also include types of solutions that are non-aqueous, the agency believes that a more explicit term than "non-oil-based" is necessary. Therefore, the comment's suggestion is not accepted. The phrase "aqueous solution" will remain in the topical nasal decongestant dosage for drops and sprays in § 341.20(a), (b), (c), (d)(2), and (h) (redesignated as § 341.80(d)(2)(ii)(*a*), (iii)(*a*), (iv)(*a*), and (vii)(*a*) in this document).

References

(1) Crofton, J., and A. Douglas, "Respiratory Diseases," Blackwell Scientific Publications, Oxford, England, pp. 142–150, 1969.

(2) Martin, E.W., "Hazards of Medication," 2d Ed., J.B. Lippincott Co., Philadelphia, pp. 206–207, 1978.

16. One comment (Ref. 1) stated that the Panel's recommended dosage of phenylephrine hydrochloride in § 341.20(d)(2) inadvertently allows an unnecessarily wide variation in dosage and unnecessarily restrains product formulation. The dosage allowed by the Panel is two or three sprays per nostril of a 0.25 to 0.5 percent aqueous solution. The comment stated that no effort was made to define the quantity of drug that is to be delivered in each spray; that the amount of drug delivered by a spray container can vary significantly from one container to another depending on the design and dimensions of the nozzle orifice; that container shape and fill-level also affect the amount of product delivered; that the Panel's recommendation does not limit the drug delivery system to a spray container like the one currently in common use and as a result any kind of spray mechanism could be used with even greater variability. The comment added that for all drugs in the monograph, except topical nasal decongestants, the dosages are given in concise statements of the quantity of drug to be delivered and requested that manufacturers should be permitted to formulate at percentages below 0.25 or above 0.50 as long as the total drug delivery is within the dosage range proposed by the comment. The comment submitted data to support a dosage range of 0.80 to 1.80 mg of phenylephrine hydrochloride per nostril every 4 hours.

The comment raises a number of valid points. The dosages recommended for nasal drops and sprays are not absolute amounts and are variable; however, the

Panel reviewed numerous studies on nasal drops and sprays which showed that there is a wide range of safety with these drugs. Nasal sprays and drops have been available for years, and the data that have been accumulated on these products show that the concentrations and dosages recommended by the Panel are safe and effective. Thus, although there may be some variation in the amount of drug delivered from various droppers or spray containers, the amount of drug delivered will be within the safe and effective range. The study submitted by the comment was designed to quantitatively determine the amount of phenylephrine hydrochloride delivered with one spray from a commercial nasal spray squeeze bottle. The data did not show that the measured amount of drug was either a safe or effective dose. The comment's suggestion for a milligram dosage is not accepted, and dosages for nasal drops and sprays will continue to be defined in terms of concentration.

Reference

(1) Comment No. C0135, Docket No. 76N-0052, Dockets Management Branch.

17. One comment requested that 1 percent phenylephrine hydrochloride for OTC use as a topical nasal decongestant be placed in Category I as safe and effective. The comment pointed out that the Panel recommended Category I status for aqueous solutions of phenylephrine hydrochloride in concentrations of 0.125, 0.25, and 0.5 percent. Although a submission on 1 percent phenylephrine was made, the Panel did not categorize this concentration. Two studies were submitted with the comment to document the safety and effectiveness of 1 percent phenylephrine hydrochloride (Ref. 1). The comment pointed out that nasal decongestant drops containing 1 percent phenylephrine hydrochloride have been marketed OTC for 40 years.

The agency has reviewed the two studies submitted to support the comment's request to place 1 percent phenylephrine hydrochloride in Category I for OTC use as a topical nasal decongestant. The results of the studies showed no significant difference in effectiveness between 0.5 and 1 percent concentrations of phenylephrine hydrochloride. Nasal irritation and side effects such as headache, nausea, dizziness, nasal edema, and erythema occurred with both 0.5 and 1 percent concentrations; but the differences in side effects between the two groups were not statistically significant. However, the data did suggest that the 1-percent concentration seemed more likely to induce rebound congestion. Therefore, the agency is proposing that 1 percent phenylephrine hydrochloride be classified in Category I as a topical nasal decongestant and that the product be labeled for adult use only. Additionally, because of a possible rebound effect with continued use of the 1-percent concentration of phenylephrine hydrochloride, the agency is proposing the following warning in § 341.80(c)(2)(v) for the 1-percent concentration of phenylephrine hydrochloride. "Frequent use of this product may cause nasal congestion to recur or worsen."

The agency's detailed comments and evaluation on the data are on file in the Dockets Management Branch (Ref. 2).

Reference

(1) Comment No. C0125, Docket No. 76N-0052, Dockets Management Branch.

(2) Letter from W.E. Gilbertson, FDA, to E.J. Hiross, Sterling Drug, Inc., coded LET081, Docket No. 76N-052N, Dockets Management Branch.

18. Several comments agreed with the Panel's recommendation to make 60 mg pseudoephedrine preparations available on an OTC basis. (Previously, oral nasal decongestants containing 60 mg pseudoephedrine were available only on a prescription basis. Preparations containing 30 mg pseudoephedrine have been available on an OTC basis for many years.) However, two of the comments expressed concern over the 24-hour dosage limit of 360 mg for pseudoephedrine preparations recommended by the Panel. Both of these comments recommended a dosage of 60 mg pseudoephedrine every 4 to 6 hours for a maximum of 240 mg per 24 hours rather than the 60 mg every 4 hours not to exceed a maximum of 360 mg in 24 hours recommended by the Panel. Because the maximum daily dose for the prescription 60-mg pseudoephedrine preparations was 240 mg per 24 hours, the comments argued that it does not seem reasonable to recommend a 360-mg maximum daily dose for OTC pseudoephedrine preparations.

One of the comments submitted data on the pharmacokinetics of pseudoephedrine, indicating that a 240-mg maximum dose per 24 hours may be a more appropriate dose for OTC use of 60-mg pseudoephedrine preparations (Ref. 1). In addition, information was submitted from a study showing that increasing the 24-hour dosage to 360 mg did not present a clinical advantage. The comment concluded that the risk-to-benefit ratio favors limiting the dosage to 240 mg per day.

The agency concluded from these comments and data that a dosage of 60 mg of pseudoephedrine every 4 hours might lead to accumulation of the drug and eventually marked side effects, and that a daily dosage in excess of 240 mg might be associated with significant side effects without additional therapeutic benefit. Therefore, the agency published a notice in the **Federal Register** of September 30, 1980 (45 FR 64709) changing the dosage of pseudoephedrine to 60 mg every 6 hours with a maximum 24-hour dose of 240 mg.

Three drug manufacturers subsequently submitted a petition containing new data to prove that if a 240-mg/24-hour limit is observed, a dosing interval of every 6 hours confers no added safety benefit relative to a more flexible interval of every 4 to 6 hours (Ref. 2). The petition included information on the pharmacokinetic behavior of pseudoephedrine, a review of adverse drug reactions related to pseudoephedrine, and eight studies (Refs. 3 through 10). The companies supported reduction of the maximum adult dosage of pseudoephedrine from 360 to 240 mg in 24 hours, but requested that the agency adopt a dosage interval of 60 mg every 4 to 6 hours. The petitioners also requested an extension of the May 1, 1981 effective data for compliance with the revised dosage limitations that had been set forth in the September 30, 1980 notice. In the **Federal Register** of May 5, 1981 (46 FR 25144), the agency stayed until further notice the May 1, 1981 effective date for the revised dosage interval of 60 mg every 6 hours until the new data had been reviewed. The requirement for revised labeling reflecting the maximum daily OTC dosage of 240 mg for adults and corresponding maximum daily OTC dosages for children was not stayed, but became effective on May 1, 1981.

The agency has determined that the pharmacokinetic data show that the major determinant of the half-life of pseudoephedrine is urinary pH and that the half-life varies from 4 to 8 hours in normal individuals who are representative of the population at large. The agency notes that only two of the eight studies are relevant to the issue of whether the frequency of administration of pseudoephedrine is a factor in the incidence of side effects (Refs. 3 and 4). The Kuntzman study (Ref. 3) demonstrates the influence of urinary pH on the half-life of pseudoephedrine. When urinary pH is decreased, plasma half-life of pseudoephedrine is decreased markedly. In contrast, when urinary pH is increased, plasma half-life increases. The Brater study (Ref. 4)

confirms Kuntzman's findings. After reviewing the new data, the agency finds that there is sufficient evidence to show the efficacy of a total daily dose of 240 mg of pseudoephedrine and that it is reasonable to project similar plasma levels, whether this total daily dose is given as 60 mg every 4 to 6 hours or as 60 mg every 6 hours. The agency, therefore, agrees with the comment that a more flexible adult dosage schedule for pseudoephedrine of 60 mg every 4 to 6 hours, not to exceed 240 mg daily, should be permitted. The dosage and directions for use of pseudoephedrine in § 341.80(d) (1) (ii) of the tentative final monograph will reflect this proposed revision. The dosages for children will also reflect the proposed change in dosage interval. The agency's comments on the data are on file in the Dockets Management Branch (Ref. 11).

References

(1) Comment No. C0112, Docket No., 76N–0052, Dockets Management Branch.

(2) Citizen Petition, Docket No. 76N–052N, Dockets Management Branch.

(3) Kuntzman, R.G., et at., "The influence of urinary pH on the plasma half-life of pseudoephedrine in man and dog and a sensitive assay for its determination in human plasma," *Clinical Pharmacology and Therapeutics*, 12:62–67, 1971, in Citizen Petition, Docket No. 76N–052N, Dockets Managment Branch.

(4) Brater, D.C., et al., "Renal excretion of pseudophedrine," *Clinical Pharmacology and Therapeutics*, 28:690–694, 1980, in Citizen Petition, Docket No. 76N–052N, Dockets Management Branch.

(5) Roth, R.P., et al., "Nasal Decongestant Activity of Pseudoephedrine," *Annals of Otology, Rhinology and Laryngology*, 86:235–242, 1977, in Citizen Petition, Docket No. 76N–052N, Dockets Managmeent Branch.

(6) Yacobi, A., et al., "Evaluation of Sustained-Action Chlorpheniramine-Pseudoephedrine Dosage Forms in Humans," *Journal of Pharmaceutical Sciences*, 69:1077–1081, 1980, in Citizen Petition, Docket No. 76N–052N, Dockets Management Branch.

(7) Bright, T.P., et al., "Selected Cardiac and Metabolic Responses to Pseudoephedrine with Exercise," draft of unpublished study from Dow Chemical Co., in Citizen Petition, Docket No. 76N–052N, Dockets Management Branch.

(8) Empey, D.W., et al., "Dose-Response Study of the Nasal Decongestant and Cardiovascular Effects of Pseudoephedrine," *British Journal of Clinical Pharmacology*, 9:351–358, 1980, in Citizen Petition, Docket No. 76N–052N, Dockets Management Branch

(9) Bye, Co., et al., "A Comparison of Plasma Levels of L (+) Pseudoephedrine Following Different Formulations, and their Relation to Cardiovascular and Subjective Effects in Man," *European Journal of Clinical Pharmacology*, 8:47–53, 1975, in Citizen Petition, Docket No. 76N–052N, Dockets Management Branch.

(10) Perkins, J.G., "A Bioavailability and Safety Study Comparing Actifed® Sustained-Action (SA) Capsules to Actifed Immediate-Release (IR) Tablets," *Current Therapeutic Research*, 28:650–668, 1980, in Citizen Petition, Docket No. 76N–052N, Dockets Management Branch.

(11) Letters from W.E. Gilbertson, FDA, to K.V. Crean, Buroughs-Wellcome Co., A.S. Davidson, Schering Corp., and R.L. Selman, Dow Chemical Co., coded LET077, LET078, and LET079, Docket No. 76N–052N, Dockets Management Branch.

19. One comment suggested deleting from § 341.20(c), § 341.20(d)(2), and § 341.20(h) of the Panel's recommendations the provision that topical nasal decongestant drug products containing oxymetazoline hydrochloride, phenylephrine hydrochloride, or xylometazoline hydrochloride, when administered to children 2 to under 6 years of age, should be used only in the form of nose drops and not in the form of nasal sprays. The comment stated that the Panel based this provision on the contention that a spray is difficult to use in a small nostril. The comment argued that while there may be a problem if the same nosepiece is used for both adult's and children's sprays, this problem could be resolved by using a nosepiece especially designed for the smaller nostril of children 2 to 6 years of age.

As noted in the comment, the only reason given in the Panel's report for not permitting the use of nasal decongestant sprays in children 2 to under 6 years of age is that "the spray is difficult to use in the small nostril" (41 FR 38420). The agency agrees with the comment that manufacturers should be permitted to modify the nosepiece of a nasal decongestant spray so that it can be used in a small nostril. The agency also believes that the use of a nasal spray in certain instances may be easier and more acceptable than the use of drops, especially when the obvious problems of administering drops to children in the 2- to under 6-year age range are taken into consideration.

Nasal decongestant ingredients such as phenylephrine hydrochloride have been marketed OTC for use in children in a nasal spray dosage form for many years without reports of significant adverse reactions directly attributable to the use of the spray (Ref. 1) However, the agency has concluded that oxymetazoline hydrochloride and xylometazoline hydrochloride should not be used in children under 6 years of age in any dosage form. These drugs are long-acting, potent vasoconstrictors and can cause side effects. It is often difficult to measure a correct dose of a topical nasal decongestant in a small child, and the child may inadvertently receive an excessive dose by swallowing the administered medication. Therefore, the agency believes that in the interest of safety, oxymetazoline hydrochloride and xylometazoline hydrochloride should not be used in children under 6 years of age unless directed by a doctor. (See comment 29 below.) The statement recommended by the Panel in § 341.20(c), (d)(2), and (h) "Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril" will not be included in this tentative final monograph. The agency is proposing that the dosage instruction for the use of oxymetazoline hydrochloride and xylometazoline hydrochloride in children under 6 years of age be deleted from § 341.20 (c) and (h) and placed in professional labeling in § 341.90 (m) and (n). The directions for phenylephrine hydrochloride in § 341.80(d)(2)(v)(*4*) of this tentative final monograph have been revised to include the use of drops or sprays for children 2 to under 6 years of age.

Additionally, the Panel did not address topical nasal decongestants in a jelly dosage form, although these products are presently marketed. The agency has concluded that a jelly should not be used in children under 6 years of age. A jelly must be placed in the nose and then inhaled well back into the nasal passages. The small nostril of a child under 6 years of age could make insertion of a proper amount of nasal decongestant jelly very difficult, and a safe or effective dose may not be achieved. Other topical dosage forms, such as sprays or drops would be more acceptable for use by a child under 6 years of age. Therefore, for children under 6 years of age, the agency is restricting the use of any topical nasal decongestant formulated as a jelly unless directed by a doctor. This restriction has been added to the appropriate "Directions" sections of the monograph.

Reference

(1) Department of Health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listing," pertinent pages for the years 1969 through 1981, in OTC Volume 04NTFM, Docket No. 76N–052N, Dockets Management Branch.

E. Comments on OTC Nasal Decongestant Labeling and Warnings

20. One comment urged that every manufacturer of a nasal decongestant drug product be required to label the product as a "nasal decongestant" instead of as a "decongestant" as many such products are labeled. Also, the comment pointed out that the consumer

often mistakenly thinks that decongestant means expectorant and therefore may self-medicate with the wrong drug.

The agency agrees that a nasal decongestant drug product should be clearly labeled as such instead of simply as a "decongestant". Under § 341.80(a) of this tentative final monograph, nasal decongestant drug products would be required to use the term "nasal decongestant" as the statement of identity.

21. Several comments pointed out that OTC drug products containing oral nasal decongestants may be labeled and marketed for use only in pediatric populations. The comments argued that the warning statement proposed by the Panel, i.e., "Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor . . .," applies only to adults and should not be required on products labeled strictly for use in children. The comments recommended that an exempting statement should be added to the monograph under § 341.50(c) stating, "Warnings which are inappropriate for children's products may be eliminated in the labeling of products containing dosage instructions for children only."

The agency does not agree that the drug interaction precaution recommended by the Panel in § 341.80(b)(2)(iv) concerning prescription antihypertensives and antidepressants containing a monoamine oxidase inhibitor should be deleted from the labeling of pediatric products. Hypertension and depression do occur in children (Refs. 1, 2, and 3). Pediatric dosages for antihypertensives are provided in a widely recognized pediatric text; however, antidepressants containing a monoamine oxidase inhibitor are not widely accepted for pediatric use and pediatric dose ranges have not been established (Refs. 4 and 5). Nevertheless, a physician might prescribe either of these drugs for children. Accordingly, this drug interaction warning will be required in the labeling of all oral nasal decongestants. (Note: The agency is proposing to simplify this warning statement, which will appear in this document as § 341.80(c)(1)(i)(*d*), to read as follows: "*Drug interaction precaution.* Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor." (See comment 22 below.))

The agency is not adding an exempting statement to the monograph as suggested by the comment. However, a portion of one warning concerning "difficuly in urination due to enlargement of the prostate gland" has been deleted for products labeled for use in children only (see comment 13 above). Additionally, warnings for products which are labeled specifically for children 2 to under 12 years of age have been reworded to reflect the administration of the products by adults rather than self administration. Warnings for products which are labeled for both adults and children have also been proposed in the tentative final monograph.

References

(1) Loggie, J.M.H., "Hypertension," *in* "Textbook of Pediatrics," edited by W.E. Nelson, 11th Ed., W.B. Saunders Co., Philadelphia, pp. 1353–1361, 1979.

(2) Forman, M.A., W.H. Hetznecker, and J.M. Dunn, "Psychopharmacology," *in* "Textbook of Pediatrics," edited by W.E. Nelson, 11th Ed., W.B. Saunders Co., Philadelphia, pp. 93–95, 1979.

(3) Etteldorf, J.N., "Noninfectious Disorders of the Urinary System," *in* "Pediatric Therapy," 4th Ed., edited by H.C. Shirkey, C.V. Mosby Co., St. Louis, pp. 722–725, 1972.

(4) Shirkey, H.C., "Table of Drugs," *in* "Pediatric Therapy," 4th Ed., edited by H.C. Shirkey, C.V. Mosby Co., St. Louis, pp. 1150–1152, 1972.

(5) Rapoport, J.L., and E. Mikkelsen, "Antidepressants," *in* "Pediatric Psychopharmacology: The Use of Behavior Modifying Drugs in Children," edited by J.S. Werry, Brunner/Mazel, New York, pp. 208–233, 1978.

22. Two comments suggested that the Panel's recommended drug interaction precaution for oral nasal decongestant drug products should be deleted from § 341.80(b)(2)(iv) of the monograph. This precaution is "Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor except under the advice and supervision of a physician." One comment argued that terms such as "antihypertensive," "antidepressant," and "monoamine oxidase inhibitor" are highly technical; that only a small percentage of the population is likely to understand this warning; and that including such a warning in the labeling of an OTC drug is contrary to the well-established principle that unnecessary or confusing precautions tend to dilute the significance of all instructions in the labeling and, hence, should be avoided. The other comment contended that it is the responsibility of the physician to instruct each patient who is taking a monoamine oxidase inhibitor on the proper means of avoiding the possible adverse reactions that can be associated with the use of this type of drug.

The agency agrees with the comment that the Panel's proposed drug interaction precaution may not be readily understood by all consumers. However, it considers a warning of this type necessary to alert consumers because antihypertensive and antidepressant drugs are widely prescribed. To simplify this precautionary statement the agency is proposing to substitute the term "high blood pressure" for the term "antihypertensive" and the term "depression" for "antidepressant." The agency also believes that the words "monoamine oxidase inhibitor" would be confusing to consumers and need not be included in the precautionary statement to convey the intended message. Accordingly, § 341.80(b)(2)(iv) (redesignated in this tentative final monograph as § 341.80(c)(1)(i)(*d*)) will be amended to read as follows: "*Drug interaction precaution.* Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor."

23. Two comments stated that the claim "relieves sinus pressure" should be in Category I rather than in Category III. One comment (Ref. 1) submitted the results of a survey conducted among sinus headache sufferers who were asked about the nature of their symptoms, i.e., whether facial pressure and/or facial congestion were present. Of 428 respondents who mentioned facial pressure 65.9 percent also mentioned facial congestion; of 380 respondents who mentioned facial congestion, 74.2 percent also mentioned facial pressure; and 704 (72.5 percent) of 971 patients taking medication to relieve the congestion of sinus headache also expected it to relieve sinus pressure. The comment concluded that consumers use the term "pressure" synonymously with "congestion." The second comment stated that the Panel's recommendations are conflicting because the Panel placed in Category I those claims relating to the relief of congestion and the promotion of sinus drainage. However, claims relating to relief of sinus pressure were placed in Category III. The comment did not submit any data in support of its position but concluded that it is a simple fact that relief of congestion and promotion of sinus drainage will relieve sinus pressure.

The agency has reviewed the survey data, including a statistical evaluation (Ref. 1), to determine whether the data support the comment's contention that "congestion" and "pressure" are synonymous terms to consumers. The details of the survey are insufficient to

support any definitive conclusions. However, it seems likely that the terms "sinus pressure" and "sinus congestion" are closely associated in the minds of consumers. "Webster's New Collegiate Dictionary" (Ref. 2) defines "pressure" as "the application of force to something by something else in direct contact with it." "Congestion" is defined as "[concentration] in a small or narrow space" (Ref. 3). "Congestion" is also defined as "excessive or abnormal accumulation of blood in a part" (Ref. 4). Using these definitions, it would follow that congestion is logically thought to be the cause of pressure. If an area (e.g., the sinuses) is congested, then whatever is causing the congestion is likely to exert pressure on the boundaries of the area. It would then follow that if congestion were relieved, pressure would be relieved also. Therefore, the agency has decided to expand the Category I indications for nasal decongestants proposed by the Panel in § 341.80(a)(9) and (10) (redesignated as § 341.80(b)(2) (iv) and (v) in this tentative final monograph). The revised indications will read as follows:

(iv) "Helps decongest sinus openings and passages; relieves sinus pressure."

(v) "Promotes nasal and/or sinus drainage; relieves sinus pressure."

References

(1) Comment No. C0056, Docket No. 76N-0052, Dockets Management Branch.

(2) "Webster's New Collegiate Dictionary," G.&C. Merriam Co., Springfield, MA, 1979, s.v. "pressure."

(3) "Webster's New Collegiate Dictionary," G.&C. Merriam Co., Springfield, MA, 1979, s.v. "congestion."

(4) "Dorland's Illustrated Medical Dictionary," 25th Ed., W.B. Saunders Co., Philadelphia, 1974, s.v. "congestion."

24. Several comments objected to the Panel's recommended warning in § 341.80(b)(ii) for topical nasal decongestants: "Do not use this product for more than 3 days . . . ." The comments contended that rebound congestion does not begin to appear until more than 7 days after starting use, that the basis for the warning is the assumption that the product will not be used according to label directions, and that the Panel cited no data to support the 3-day limitation. The comments added that "AMA Drug Evaluations" (Ref. 1) states that nasal decongestants should be used for periods not exceeding 10 to 15 days. One comment recommended that the warning be changed to limit use to no more than 10 days, and the other comments requested deletion of the warning entirely.

The agency disagrees with the comments. The comments have not submitted any data which prove that rebound congestion does not appear until after more than 7 days of use. Furthermore, individuals may respond differently to nasal congestion (Ref. 2). An individual's psychological state can affect the occurrence and degree of rebound congestion (Ref. 3 and 4).

The Panel reviewed several references (Refs. 3, 5, and 6) which provided a basis for the 3-day warning. Messek (Ref. 5) reported the occurrence of rebound congestion 90 to 120 minutes after the use of a nasal decongestant. Another nasal decongestant produced rebound congestion 6 hours after use. Rudiger (Ref. 3) reported rebound congestion approximately 4 hours after use. Biesalski (Ref. 6) found that a nasal decongestant caused rebound congestion after 5 hours. These data show that nasal decongestants can produce rebound congestion after a short period of use. Therefore, it cannot be categorically stated that rebound congestion does not begin to appear until more than 7 days after starting use of a nasal decongestant as one comment contended.

The Panel recognized that "because of the remarkable degree of nasal decongestion which follows topical application of these agents, there is a tendency on the part of patients to administer nasal decongestants too frequently and for too long a period of time." Prolonged use of topical nasal decongestants may be accompanied by a rebound phenomenon in which the initial vasoconstriction is followed by vasodilation and congestion. Thus, continued use can intensify nasal congestion. Because of the nasal congestion caused by the rebound effect, there is a tendency for an individual to habitually use a nasal decongestant. Therefore, the Panel concluded that a warning to discourage use beyond several days is necessary. The Panel reviewed references concerning persistent nasal congestion caused by the habitual use of nasal decongestants for varying periods of time, ranging from 6 to 23 months (Refs. 7 and 8). Because of the Panel's concern about the problem of rebound congestion leading to prolonged usage of nasal decongestants, it recommended a 3-day limitation on the use of these products. In addition, in order to further curb the continuous use of topical nasal decongestants, the Panel recommended that a physician be seen if symptoms persist for more than 3 days.

The agency concludes that the 3-day warning is justified in view of the above discussion. Therefore, the 3-day warning in § 341.80(b)(1)(ii) (redesignated as § 341.80(c)(2) (iii)(*a*) and (vi)) is appropriate for topical nasal decongestants except 1-desoxyephedrine which has a 7-day limit (see comment 8 above.) In addition, the agency has revised the format of the "Warnings" section in § 341.80(b) (redesignated as § 341.80(c) is this tentative final monograph) for clarity and to conform to the format of recently published monographs.

References

(1) "AMA Drug Evaluations," 2d Ed., Publishing Sciences Group, Acton, MA, p. 469, 1973.

(2) Harris, H.H., "Comparative Study of Decongestive Effectiveness of Oxymetazoline Hydrochloride in Rhinitis," *EENT Digest*, 46:41–43, 1967.

(3) Rudiger, W., "Investigations of the passability of air through the nose under the effect of a new vasoconstricting agent," (English translation), ("Ensaios sobre a permeabilidade nasal ao ar com o em prego de nova substancia vasoconstritora"), *HNO Wegweiser*, 7:77–80, 1958.

(4) Connell, J.T., "Effectiveness of Topical Nasal Decongestants," *Annals of Allergy*, 27:541–546, 1969.

(5) Messek, H., "The Effect of Different Vasoconstrictors on Various Qualities of the Nasal Mucosa," (English translation), ("Die Wirkung verschiedener Vasokonstriktoria auf einige Qualitaten der Nasenschleimhaut"), *Monatsschrift fur Ohrenheilkunde und Laryngo-Rhinologie*, 96:294–306, 1962.

(6) Biesalski, P., and K. Marquardt, "Treatment of Rhinitis of Early Childhood. Thermoelectric Studies on Decongestant Nasal Drugs," (English translation), "Zur Behandlung der Rhinitis im fruhen Kindesalter. Thermoelektrische Untersuchungen an abschwellenden Nasenmitteln"), *Schweizerische Medizinische Wochenschrift.*, 89:510–512,1959.

(7) Putnam, L.E., and R.P. Herwick, "Privine Dependence of Two Years Duration," *Journal of the American Medical Association*, 130:702–703, 1946.

(8) Thomas, J.W., and U. Fabiano, "Privine Sensitivity: A Report of Eight Cases," *Southern Medical Journal*, 39:658–664, 1946.

25. One comment proposed that the Panel's recommended warning statement for topical nasal decongestants in § 341.80(b)(1)(i) "Do not exceed recommended dosage because symptoms may occur such as burning, stinging, sneezing, or increase of nasal discharge" be required only if the active ingredient is administered topically as a drop or spray directly to the nasal mucosa. The comment contended that requiring this warning for other dosage forms is unnecessary and is not supported by available data.

The agency disagrees with the comment's contention that this warning is unnecessary for dosage forms other than those administered topically as a drop or spray. Topical nasal decongestants may be administered as

drops, sprays, jellies, or inhaled vapors. The comment did not specify which other dosage forms should not be required to be labeled with the warning recommended by the Panel § 341.80(b)(1)(i); nor did the comment submit any data to show that this warning statement is unnecessary for other dosage forms of topical nasal decongestants.

The agency believes that this warning statement should apply to all topical nasal decongestant active ingredients administered as a drop, spray, jelly, or in an inhalant dosage form. Evaluation of the studies reviewed by Panel on propylhexedrine reveals that slight stinging occurred in some cases (41 FR 38402). Because nasal decongestants when used in all of these forms, i.e., drops, sprays, inhalants, and jellies, are administered to the nasal mucosa through the nostrils, the warning statement regarding burning, stinging, sneezing, or increase in nasal discharge is appropriate on these dosage forms. Therefore, the comment is not accepted. This warning, which has been revised to read: "Do not exceed recommended dosage because burning, stinging, sneezing, or increase of nasal discharge may occur," will be required for all dosage forms of topical nasal decongestants.

26. One comment suggested that the Panel's recommended warning statement for topical nasal decongestants in § 341.80(b)(1)(ii) "Do not use this product for more than 3 days. If symptoms persist, consult a physician," should apply only if the nasal decongestant is administered topically as a drop or spray. The comment also recommended that other forms to topical administration, such as via a "lozenge or mouthwash," should appropriately use the "7-day warning" recommended by the Panel for oral nasal decongestants in § 341.80(b)(2)(ii).

The agency agrees with the Panel that topical nasal decongestants administered as a drop or spray should not be used for more than 3 days because rebound congestion is likely to occur with prolonged use. Nasal decongestants in lozenges and mouthwashes are considered to be topical nasal decongestants; however, their route of administration is different from that of ingredients administered in a drop or spray. Lozenges and mouthwashes introduce the nasal decongestant through the oral cavity and the nasopharynx. Because of this difference in routes of administration, topical nasal decongestants in lozenges and mouthwashes are unlikely to cause rebound congestion. The Panel recommended the camphor, thymol, menthol/peppermint oil, and eucalyptol/eucalptus oil be used as topical nasal decongestants in lozenges and mouthwashes. The Panel's review of these active ingredients indicates that rebound congestion does not occur with these ingredients. The ingredients in the lozenges and mouthwashes are of a different pharmacologic group from those in topical nasal decongestants administered in drop or spray dosage forms. In view of this, it would be reasonable to conclude that use of the nasal decongestants recommended by the Panel for use in lozenges and mouthwashes for a longer period than 3 days would not result in rebound congestion.

The agency concludes that, although nasal decongestants in lozenges and mouthwashes are considered to be topically administered, the specific warning statement concerning 3-day use should not apply in the labeling of these specific topical nasal decongestants and agrees with the comment that it may be more appropriate to require the use of the "7-day warning" as stated in § 341.80(b)(2)(ii) (redesignated as § 341.80(c)(1)(*b*) in this document). The agency points out that none of the ingredients listed above are included in the tentative final monograph; hence, no revisions are currently needed in the Panel's recommended monograph.

27. One comment suggested that the Panel's recommended warning statement in § 341.80(b)(1)(iii) "The use of this dispenser by more than one person may spread infection" be required only for products administered by inhalers and not for nasal decongestants administered by other routes of administration.

The Panel pointed out that the use of a dispenser by more than one person may spread infection. The comment did not specify the other routes of administration of nasal decongestants. A nasal decongestant drug may also be administered by direct application into the nostrils in the form of a drop, spray, or nasal jelly. The use of a dropper, nasal spray, or nasal jelly applicator by more than one person may also result in the spread of infection. Therefore, the agency disagrees with the comment's recommendation that the warning should be required for inhalant nasal decongestants only and concludes that this warning statement should be required in the labeling for all topical nasal decongestant products which are directly applied to the nasal mucosa or directly inhaled through the nostrils. The agency has slightly revised the Panel's warning to make it more readily understood by consumers. The warning in § 341.80(c)(2)(i)(*b*) in this tentative final monograph reads as follows: "The use of this container by more than one person may spread infection."

28. One comment stated that the Panel's recommended labeling for xylometazoline hydrochloride contains special warnings related to the use of adult and pediatric concentrations of the drug, while no special warnings are suggested for the different concentrations of oxymetazoline hydrochloride. The comment argued that the labeling requirements for similar ingredients should be standard and requested that the additional warning statements be removed from the labeling for xylometazoline hydrochloride.

The comment refers to the warning recommended by the Panel in § 341.80(b)(10) for 0.05 percent zylometazoline hydrochloride which states, "Do not give this product to children under 2 years except under the advice and supervision of a physician," and the warning in § 341.80(b)(11) for 0.1 percent xylometazoline hydrochloride which states, "For adult use only. Do not give this product to children under 12 years except under the advice and supervision of a physician." The comment argued that similar warnings were not recommended by the Panel for oxymetazoline hydrochloride.

The agency has reviewed the literature for oxymetazoline hydrochloride and xylometazoline hydrochloride used as topical nasal decongestants. Oxymetazoline hydrochloride and xylometazoline hydrochloride are vasoconstrictors which may cause side effects. They also have a longer duration of action than the other Category I topical nasal decongestants. In a small child it is difficult to measure a correct dose and the child may inadvertently receive an excessive dose by swallowing the administered medication. Because these drugs are potent, long-acting, and the possibility of systemic effects exists, the agency believes that, in the interest of safety, oxymetazoline hydrochloride and xylometazoline hydrochloride should not be used in children under 6 years of age unless directed by a doctor. Therefore, the agency is restricting the use of both xylometazoline and oxymetazoline in children under 6 years of age. The agency is proposing that labeling for the use of oxymetazoline hydrochloride and xylometazoline hydrochloride in children under 6 years of age be provided to health professionals, but not to the general public. Thus, the Panel's recommended dosage instructions for oxymetazoline

hydrochloride and xylometazoline hydrochloride for children under 6 years of age in § 341.20 (c) and (h) have been deleted and moved to professional labeling in § 341.90 (m) and (n). The Panel's recommended warnings in § 341.80 (b) (3)(ii), (4), (5), first part of (6), and (7) through (11), have been revised in order to conform to the format of recently published tentative final monographs. These warnings have been moved from § 341.80(b) and included as directions in new § 341.80(d). Therefore, although the agency is deleting the warning regarding children's dosages for 0.05 percent xylometazoline from general OTC labeling, the directions for 0.05 percent oxymetazoline and 0.05 percent xylometazoline will state that the product is for use by adults and children 6 to under 12 years of age and that for use in children under 6 years of age a doctor should be consulted.

Regarding the comment's request for deletion of the Panel's recommended warning in § 341.80(b)(11) dealing with the 0.01-percent concentration of xylometazoline, the agency concludes that, based on the Panel's recommended concentrations, which the agency has adopted in this tenative final monograph, there is a need for a statement on products containing 0.1 percent xylometazoline against use by children under 12 years of age (because the 0.05 percent concentration is to be used in this age group). Thus, although the warning in § 341.80(b)(11) has been removed from the warnings section, as noted above, the content of the warning has been retained and restated as directions in new § 341.80(d)(2)(vii) (*a*)(*1*) and (*b*)(*1*). There is, however, no need for such a statement on products containing oxymetazoline because the same strength solution (0.05 percent) is used for both adults and children 6 to under 12 years of age; there is no 0.1 percent concentration of oxymetazoline proposed for inclusion in the monograph.

29. One comment was opposed to the Panel's recommended warning for inhalant nasal decongestant products in § 341.80(b)(3)(v): "*Caution:* Not for use by mouth." The comment stated that use by mouth is not a normal or expected use of this dosage form and that the directions for use clearly indicate that the product is to be used intranasally. The comment further stated that the company's records show no evidence of inadvertent misuse in this way due to lack of understanding. The comment believed that this warning, rather than providing needed instruction, actually has a potential for inciting possible abuse by stimulating the imagination. The comment recommended that this warning not be required for inhalers.

The agency agrees with the comment's recommendation that the warning in § 341.80(b)(3)(iv), "*Caution:* Not for use by mouth" is not needed for inhalant nasal decongestants. The dosage and directions for propylhexedrine in § 341.80(d)(2)(vi) and the dosage and directions for l-desoxyephedrine in § 341.80(d)(2)(i) of this tentative final monograph clearly indicate that these inhalants are to be used intranasally. Therefore, the warning recommended by the Panel in § 341.80(b)(3)(iv) for inhalant nasal decongestants will not be included in this tentative final monograph.

30. One comment recommended that the "warning" proposed by the Panel in § 341.80(b)(3)(i) concerning warming nasal decongestant inhalers before use should be deleted or moved to the "Directions" section. The comment expressed the opinion that, based on its extensive consumer experience with inhaler products, this instruction is unnecessary.

The agency agrees that the Panel's recommended warning in § 341.80(b)(3)(i), "This inhaler should be warmed in the hand before use to increase effectiveness," should be deleted. Inhalers are designed to release a safe and effective dose of active drug through vaporization at room temperature. The agency has reviewed the Panel's report, and additional material (Refs. 1, 2, and 3), and can find no scientific or medical data to support the inclusion of this instruction in the monograph. Therefore, the agency has deleted this instruction from § 341.80(b)(3) of the Panel's recommendations.

References

(1) Harvey, S.C., "Sympathomimetic Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 820, 1975.

(2) Kennon, L., and J.J. Gulesich, "Some Aspects of Inhaler Technology," *Journal of Pharmaceutical Sciences*, 51:278–286, 1972.

(3) Ziment, I., "Respiratory Pharmacology and Therapeutics," W.B. Saunders Co., Philadelphia, p. 327, 1978.

F. Comments on Testing Guidelines

31. Two comments disagreed with the Panel's recommendation that smoking by test subjects should be prohibited 24 hours prior to and during the testing of nasal decongestant drugs. They argued that coryza and hay fever studies have shown that smokers constitute the majority of the target population and that it is therefore practical to attempt to determine the response of smokers to nasal decongestants. The comments also contented that this recommendation would make it more difficult to find suitable test subjects and that studies might become prohibitive in both cost and time. Another potential problem cited in the comments was the possibility that both the psychological effects of smoking withdrawal, e.g., tension and anxiety, as well as the decongestant effect of nasal decongestant drugs might modify the automatic nervous system enough during testing to result in result in studies with biased conclusions. Clinical data and a statistical analysis, which alleged that smoking has no discernible consistent effect on results obtained from testing nasal decongestants, were submitted as part of one of the comments (Ref. 1).

The agency has reviewed the results of these studies. They showed that the effect of the various drugs on the nasal flow rate as well as the clinical symptoms of both hay fever and acute coryza on smokers were frequently quite different from those observed in nonsmokers. The values sometimes differed tenfold, and the direction of the differences was unpredictable. These studies and the statistical analysis indicated that it would be advisable to use both smokers and nonsmokers in clinical trials for nasal decongestants.

The agency reviewed another study on the response of over 500 subjects to nasal decongestants (Ref. 2). The test population included 43 percent smokers. No discernible difference in nasal airway resistence or in subjective assessment of congestion existed when the subjects entered the study. The results of the study showed that the smokers' response to every one of the topical nasal decongestants tested tended to be less than that of the nonsmokers; however, that difference was great enough to be significant in only one group (phenylephrine). The results of this study support the proposal that there should be no curtailment of smoking by subjects participating in nasal decongestant studies. Considering that a significant portion of the target population is made up of smokers, it seems advisable to use both smokers and nonsmokers in clinical trials. Based on the data reviewed, the agency disagrees with the Panel's recommendation that smokers be required to obstain from smoking 24 hours prior to and during participation in the testing of nasal decongestants. An important problem in studying smokers who have abstained from cigarettes for 24 hours is the introduction of anxiety, restlessness, and autonomic responses, which may influence their nasal resistence. As an alternative to the Panel's recommendation, the agency concludes that the results of testing in smokers and nonsmokers should be tabulated separately, analyzed separately, and submitted in this form

by the manufacturer. This procedure would permit analysis of the data to establish if smokers are indeed different from nonsmokers in their response to nasal decongestants.

(Note.—In revising the OTC drug review procedures relating to Category III, published in the **Federal Register** of September 29, 1981 (46 FR 47730), the agency advised that tentative final and final monographs will not include recomended testing guidelines for conditions that industry wishes to upgrade to monograph status. Instead, the agency will meet with industry representatives at their request to discuss testing protocols. The revised procedures also state the time in which test data must be submitted for consideration in developing the final monograph. (See also part II, paragraph A.2 below—Testing of Category II and Category III conditions.))

References

(1) Comment No. C0097, Docket No. 76N–0052, Dockets Management Branch.

(2) Hamilton, L.H., "Report on Response to Nasal Decongestants by Smokers and Nonsmokers," draft of unpublished paper in OTC Volume 040298.

32. One comment contended that the method of substantiating the claim "reduction of sinus pressure" for nasal decongestants, as described in the Panel's report at 41 FR 38414 and 38415, was a pilot approach, not widely used or recognized as a clinical research tool applicable to the documentation of sinus pressure changes, and could not be properly or reproducibly executed. This method involves the insertion of a trocar or needle into the maxillary sinus under topical anesthesia. The comment pointed out that the very act of repeatedly inserting the trocar or needle causes changes in the sinus pressure which makes this method impractical as a tool to substantiate pressure changes due to the nasal decongestant. In addition, the comment opposed the use of this method on moral and ethical grounds because it involved the use of "invasive surgical techniques" in volunteer subjects to obtain clinical research data on OTC drugs and therefore would not receive approval from institutional peer review committees.

The agency agrees with the comment. Further, the agency has determined that the claim "relieves sinus pressure" will be reclassified from Category III to Category I. (See comment 24 above.) Therefore, a discussion of methods to substantiate this claim is unnecessary.

II. The Agency's Tentative Adoption of the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and is proposing to reclassify one nasal decongestant active ingredient from Category III to Category I. For the convenience of the reader, the following table is included as a summary of the categorization of nasal decongestant active ingredients by the Panel and the proposed classification by the agency.

Nasal decongestant active ingredients	Panel	Agency
Beechwood creosote (oral)	III	III
Bornyl acetate (topical)	III	III
Camphor (topical/inhalant)	III	III
Cedar leaf oil (topical)	III	III
1-Desoxyephedrine (inhalant)	III	I
Ephedrine (oral)	III	III
Ephedrine hydrochloride (oral)	III	III
Ephedrine sulfate (oral)	III	III
Racephodrine hydrochloride (oral)	III	III
Ephedrine (topical)	I	I
Ephedrine hydrochloride (topical)	I	I
Ephedrine sulfate (topical)	I	I
Racephedrine hydrochloride (topical)	I	I
Eucalyptol/eucalyptus oil (topical/inhalant).	III	III
Menthol/peppermint oil (topical/inhalant)	III	III
Mustard oil (allylisothiocyanate) (topical/inhalant).	II	II
Naphazoline hydrochloride (topical)	I	I
Oxymetazoline hydrochloride (topical)	I	I
Phenylephrine hydrochloride (oral)	I	I
Phenylephrine hydrochloride (topical)	I	I
Phenylpropanolamine bitartrate (oral)	I	(1)
Phenylpropanolamins hydrochloride (oral)	I	(1)
Phenylpropanolamine maleate (oral)	I	(1)
Phenylpropanolamine hydrochloride (topical).	III	(1)
Propylhexedrine (inhalant)	I	I
Pseudoephedrine hydrochloride (oral)	I	I
Pseudoephedrine sulfate (oral)	I	I
Thenyldiamine hydrochloride (topical)	III	III
Thymol (inhalant)	III	III
Turpentine oil (spirits of turpentine) (oral)	II	II
Turpentine oil (spirits of turpentine) (topical/inhalant).	III	III
Xylometazoline hydrochloride (topical)	I	I

[1] To be addressed in a future FEDERAL REGISTER document.

2. *Testing of Category II and Category III Conditions.* The Panel recommended testing guidelines for nasal decongestant drug products (41 FR 38376 and 38437). The agency is offering these guidelines as the Panel's recomendations without adopting them or making any formal comment on them. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any nasal decongestant ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the nasal decongestant section of the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency follows.

1. The agency is amending the definitions proposed by the Panel in § 341.3 to include a definition of an "oral nasal decongestant drug" and a "topical nasal decongestant drug."

2. The agency is reclassifying 1-desoxyephedrine as a topical nasal decongestant (administered by a nasal inhaler) from Category III to Category I. Accordingly, this ingredient is included in the tentative final monograph in § 341.20(b)(1). In additon to the required labeling for all topical nasal decongestants, specific labeling requirements for 1-desoxyephedrine is being added in § 341.80(c)(2)(ii), and § 341.80(d)(2) (i) and (viii). (See comment 8 above.)

3. The agency is deleting the dosage instructions for the use of oxymetazoline hydrochloride and xylometazoline hydrochloride in children under 6 years of age that were recommended by the Panel in § 341.20 (c) and (h) and moving these dosage instructions to professional labeling in § 341.90 (m) and (n). The agency concluded that oxymetazoline hydrochloride and xylometazoline hydrochloride should not be used in children under 6 years of age unless directed by a doctor. (See comment 28 above.)

4. The agency is amending the dosage instruction for oxymetazoline hydrochloride that was recommended by the Panel in § 341.20(c) (redesignated as § 341.80(d)(2)(iv) so that the dosage interval of use will be stated in terms of "hours" as follows: "Adults and children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 10 to 12 hours. Do not exceed 2 applications in any 24-hour period. Children under 6 years of age: consult a doctor." The Panel had recommended a topical dosage of oxymetazoline hydrochloride of "2 to 3 drops or sprays of a 0.05-percent aqueous solution in each nostril 2 times daily (in the morning and evening)." The recommended dosages for all of the other topical nasal decongestants in the Panel's monograph were stated in terms of "hours." The agency has evaluated data on the use of this drug and concludes that a dosage interval of

every 10 to 12 hours is an appropriate interval for this drug (Ref. 1).

Reference

(1) Mujik, M., and J.M. Van Rossum, "Comparative Pharmacodynamics of Sympathomimetic Imidazolines: Studies on Intestinal Smooth Muscle of the Rabbit and the Cardivascular System of the Cat," *Archives Internationales de Pharamacodynamie et de Therapie*, 155:432-449, 1965.

5. The agency is classifying 1 percent phenylephrine hydrochloride as a Category I topical nasal decongestant. Because the data suggest that the 1-percent concentration is more likely to induce rebound congestion, the agency is proposing the following warning in § 341.80(c)(v) for the 1-percent concentration of phenylephrine hydrochloride: "Frequent use of this product may cause nasal congestion to recur or worsen." (See comment 17 above.)

6. The agency is deleting from the Panel's recommendation in § 341.20(d)(2) the provision that topical nasal decongestant drug products containing phenylephrine hydrochloride when administered to children 2 to under 6 years of age should be used only in the form of nose drops and not in the form of nasal sprays. The dosage instruction for phenylephrine hydrochloride in a 0.125-percent aqueous solution idendified in § 341.80(d)(2)(v)(*a*)(*4*) in the tentative final monograph will now permit the use of drops or sprays for children 2 to under 6 years of age. (See comment 19 above.)

7. Phenylpropanolamine preparations for use as nasal decongestants are not classified in this tentative final monograph. Instead, issues related to the use of phenylpropanolamine in OTC nasal decongestant drug products, as well as in OTC weight control drug products, will be discussed in detail in a separate document to be published in the **Federal Register** in the near future.

8. The agency is deleting the statement regarding propylhexedrine proposed by the Panel in § 341.20(f): "This inhaler should retain effectiveness for a minimum of 2 to 3 months." A modification of that statement and a related statement are now included in new § 341.80(d)(2)(viii), "Other required statements," and are applicable to inhalers containing either 1-desoxyephedrine or propylhexedrine. The new statements are: "This inhaler is effective for a minimum of 3 months after first use," and "Keep inhaler tightly closed." The agency concluded that these statements are important for consumers' information because volatile substances such as 1-desoxyephedrine and propylhexedrine when used in an inhaler becomes less potent upon continued exposure to air. Manufacturers of these products recognize this fact and include such statements on their product labels (Ref. 1).

Reference

(1) Baker, C.E., et al., "Physicians' Desk Reference for Nonprescription Drugs," 3rd Ed., Medical Economics Co., Oradell, NJ, pp. 582, 583, and 659, 1982.

9. The agency is modifying the Panel's recommendations in § 341.20(g) (redesignated as § 341.80(d)(1)(ii)) by providing for a more flexible dosage interval and by reducing the adult oral dosage of pseudoephedrine preparations from 60 mg every 4 hours, not to exceed 360 mg in 24 hours, to 60 mg every 4 to 6 hours not to exceed 240 mg in 24 hours. For children 6 to under 12 years of age, the oral dosage has been reduced from 30 mg every 4 hours, not to exceed 180 mg in 24 hours, to 30 mg every 4 to 6 hours, not to exceed 120 mg in 24 hours. For children 2 to under 6 years of age, the oral dosage has been reduced from 15 mg every 4 hours, not to exceed 90 mg in 24 hours, to 15 mg every 4 to 6 hours, not to exceed 60 mg in 24 hours. (See comment 18 above.)

10. The agency is adding to § 341.80 a "Statement of identity" paragraph (designated as § 341.80(a)) to conform with the format of other recently published advance notices of proposed rulemaking or tentative final monographs. Inclusion of the new paragraph has necessitated a redesignation of § 341.80(a) to § 341.80(b), and § 341.80(b) to § 341.80(c). The agency is also redesignating Subpart D as Subpart C and placing the labeling sections of the monograph in Subpart C.

11. The agency is combining several indications that were required under § 341.80(a) (redesignated as § 341.80(b)). The agency believes that combining these indications presents them to the consumer in a clearer and more concise manner. Therefore, the indications recommended by the Panel in § 341.80(a) (1), (2), and (3) have been revised, combined, and redesignated as § 341.80(b)(1). The Panel's recommended indications in § 341.80(a) (5), (6), and (8) are also being combined, revised, and redesignated as new § 341.80(b)(2) ("Other allowable indications") which provides manufacturers the option to use additional indications in labeling.

12. The agency is reclassifying the claim "relieves sinus pressure" from Category III to Category I. Accordingly, the Category I indications for nasal decongestants recommended by the Panel in § 341.80(a) (9) and (10) (redesignated as § 341.80(b)(2) (iv) and (v)) are being expanded to include this claim in the tentative final monograph as follows:

"(iv) 'Helps decongest sinus openings and passages; relieves sinus pressure.'"

"(v) 'Promotes nasal and/or sinus drainage; relieves sinus pressure.'" (See comment 23 above.)

13. The agency is deleting the Panel's recommendation in § 341.80(a)(11) that claims relating to duration of effect for nasal decongestant products must be substantiated and accompanied by a specific time period. The agency points out that duration of effect has been included in the established dosages and directions for these products by stating the frequency of use (in terms of hours), which indirectly tells the consumer the duration of the products' effects.

14. The agency is deleting the Panel's recommendation for topical nasal decongestants in § 341.80(a)(12) regarding statements related to time to onset of action, such as fast or quick. As with all OTC drug products, nasal decongestants are expected to achieve their intended results within a reasonable period of time. However, the specific period of time within which nasal decongestants achieve these results is not related in a significant way to the safe and effective use of the products. Therefore, terms such as "fast" or "quick" are outside the scope of the OTC drug review. For other classes of products in the OTC drug review, however, statements relating to time of action may properly fall within the list of terms covered by the monograph. (See comment 2 above.)

15. The agency is deleting the Panel's recommendation in § 341.80(a)(13) which refers to claims describing a "cooling sensation" demonstrated by certain topical nasal decongestants. The agency has concluded that it has no objection to the use of terms which describe certain physical and chemical qualities of a drug, as long as these terms do not imply that any therapeutic effect might occur, are true and not misleading, and are distinctly separated from labeling indications. Terms describing product characteristics, e.g., color, odor, flavor, and feel, appear in the labeling for consumers' information and will not be specifically addressed in the monograph.

16. The agency is revising the warnings section proposed by the Panel in § 341.80(b) (redesignated as § 341.80(c)) for clarity by listing the warnings according to ingredient and dosage form (i.e., oral or topical nasal decongestants).

17. The agency is revising the warning recommended by the Panel in § 341.80(b)(1)(i) (redesignated as § 341.80(c)(2)(i)(*a*)) to read as follows: "Do not exceed recommended dosage

because burning, stinging, sneezing, or increase of nasal discharge may occur." (See comment 25 above.)

18. The agency is slightly revising the warning recommended by the Panel in § 341.80(b)(1)(iii) (redesignated as § 341.80(c)(2)(i)(*b*)) to read as follows: "The use of this container by more than one person may spread infection." (See comment 27 above.)

19. The agency is deleting the word "high" (in reference to fever) from the warning for oral nasal decongestants recommended by the Panel in § 341.80(b)(2)(ii) (redesignated as § 341.80(c)(1)(i)(*b*)). Fever can be defined as a body temperature above the normal temperature of 98.6 °F (37 °C). In the same or different disease states, however, fevers may vary significantly. Fever may be low grade, moderate, high, intermittent, or sustained. The particular characteristics of a fever depend on the disease state, and, in many cases, on the stage of development of the disease. The word "high" has been deleted from the warning because the agency believes that it is important for the consumer to recognize the presence of fever, regardless of whether the fever is high or low. Additionally, the Panel's warning in § 341.80(6)(2)(ii) (redesignated as § 341.80(c)(1)(i)(*b*)) is being revised to conform with the format of similar warnings in the tentative final monograph.

20. The agency is amending the warning for oral nasal decongestants recommended by the Panel in § 341.80(b)(2)(iii) (redesignated as § 341.80(c)(1)(i)(*c*)), to include "difficulty in urination." The amended warning will read as follows: "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." (See comment 13 above.) In addition, the agency has concluded that the warning in new § 341.80(c)(1)(i)(*c*)) for oral nasal decongestants should also apply to all topical nasal decongestants, except topical inhalants. Accordingly, the warning is also being added to this tentative final monograph as § 341.80(c)(2)(iii)(*b*). (See comment 4 above.) (NOTE: For oral and topical nasal decongestant warnings in the monograph, the agency is proposing to use the word "use" to denote topical use, and the word "take" to denote oral use.)

21. The agency is simplifying the warning recommended by the Panel in § 341.80(b)(2)(iv) (redesignated as § 341.80(c)(1)(i)(*d*)) to read as follows: "*Drug interaction precaution.* Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor." (See comment 22 above.)

22. The agency is deleting the warning recommended by the Panel in § 341.80(b)(3)(i) which states: "This inhaler should be warmed in the hand before use to increase effectiveness." The agency found this warning unnecessary because inhalers are designed to release a safe and effective dose of active drug through vaporization at room temperature. (See comment 30 above.)

23. The agency is moving and revising the Panel's recommended warnings in § 341.80(b) (3)(ii), (4), (5), first part of (6), (7), (8), (9) (10), and (11) and including them as part of the directions in the appropriate sections in new § 341.80(d).

24. The agency is moving the warning recommended by the Panel in § 341.80(b)(3)(iii) and is including it as part of the directions. The warning previously stated: "Children should not have unsupervised access to this inhaler." The agency believes that a statement of this should apply not only to inhalers, but also to any topical nasal decongestant product labeled for use in children because of the possibility of adverse reactions occurring from misuse or overuse of these products. Therefore, the phrase "with adult supervision" is being added to the directions for topical nasal decongestants which are labeled for use in children.

25. The agency is deleting the Panel's recommended warning in § 341.80(b)(3)(iv) for inhalant nasal decongestants which states: "*Caution:* Not for use by mouth." The agency has concluded that the directions for use of inhalant nasal decongestants as stated in § 342.80(d)(2) (i) and (vi) in the tentative final monograph clearly indicate that these products are to be used intranasally and not by mouth. (See comment 29 above.)

26. The agency is revising for clarity the warning for 0.05 percent naphazoline hydrochloride recommended by the Panel in § 341.80(b)(8) (redesignated as § 341.80(c)(2)(iv)) to read as follows: "Do not use this product in children under 12 years of age because it may cause sedation if swallowed." (See comment 14 above.)

27. The agency is adding to § 341.80 a "*Directions*" paragraph (designated as § 341.80(d)), to conform with the format of other recently published advance notices of proposed rulemaking and tentative final monographs. To simplify and clarify the labeling, FDA is also slightly modifying the Panel's directions for use.

28. The Panel did not address topical nasal decongestants in a jelly dosage form, although these products are presently marketed. The agency has concluded that a nasal jelly should not be used in children under 6 years of age and therefore this restriction is being added to the appropriate "Directions" sections. (See comment 19 above.)

29. The warning concerning enlargement of the prostate gland in § 341.80(c)(1)(i)(*c*) and § 341.80(c)(2)(iii)(*b*) proposed by the agency in this document for oral and topical nasal decongestants is being modified for products labeled for use only in children. The reference to "enlargement of the prostate gland "is not needed for products labeled for use only in children. The new warning "Do not give this product to children who have heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor," is being added to the tentative final monograph in § 341.80(c)(1)(ii)(*c*) and § 341.80(c)(2)(ix)(*b*). (See comments 13 and 21 above.) Additionally, all warnings for products which are labeled for use only in children 2 to under 12 years of age are being designated in the monograph and reworded to reflect the administration of the products by adults rather than self administration. Warnings for products which are labeled for both adults and children are also being proposed in the tentative final monograph.

30. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option.

The agency proposes to revoke the existing warning and caution statements in § 369.20 for "nasal preparations; oil base," "nasal preparations in plastic spray containers," "nasal preparations; vasoconstrictors," and "phenylephrine hydrochloride preparations, oral" at the time that this monograph becomes effective.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the

Federal Register of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that not one of these rules, including this proposed rule for OTC nasal decongestant drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96-354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC nasal decongestant drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC nasal decongestant drug products. Types of impact may include, but are limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC nasal decongestant drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on nasal decongestant drug products, a period of 120 days from the date of publication of this proposed rulemaking in the Federal Register will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has carefully considered the potential environmental effects of this proposal and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement therefore will not be prepared. The agency's finding of no significant impact, and the evidence supporting this finding, is contained in an environmental assessment (under 21 CFR 25.31, proposed in the Federal Register of December 11, 1979; 44 FR 71741), which may be seen in the Dockets Management Branch, Food and Drug Administration.

List of Subjects in 21 CFR Part 341

OTC drugs: Anticholinergics; Expectorants; Bronchodilators; Antitussives; Nasal decongestants.

On July 9, 1982 at 47 FR 40002, FDA proposed to amend 21 CFR Subchapter B by adding a new Part 341. Proposed Part 341, as amended on October 26, 1982 (47 FR 47520) and October 19, 1983 (48 FR 48576), would be further amended as follows:

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), 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 it is proposed to make the following amendments:

PART 341—[AMENDED]

1. In proposed Subpart A, § 341.3 is amended by adding new paragraphs (h) and (i) to read as follows:

§ 341.3 Definitions.

* * * * *

(h) *Oral nasal decongestant drug.* A drug which is taken by mouth and acts systemically to reduce nasal congestion caused by acute or chronic rhinitis.

(i) *Topical nasal decongestant drug.* A drug which when applied topically inside the nose, in the form of drops, jellies, or sprays, or when inhaled intranasally reduces nasal congestion caused by acute or chronic rhinitis.

2. In Subpart B, new § 341.20 is added, to read as follows:

§ 341.20 Nasal decongestant active ingredients.

The active ingredients of the product consist of any of the following when used within the dosage limits and in the dosage forms established for each ingredient in § 341.80(d):

(a) *Oral nasal decongestants.* (1) Phenylephrine hydrochloride.

(2) Pseudoephedrine hydrochloride.

(3) Pseudoephedrine sulfate.

(b) *Topical nasal decongestants.* (1) 1-Desoxyephedrine.

(2) Ephedrine.

(3) Ephedrine hydrochloride.

(4) Ephedrine sulfate.

(5) Racephedrine hydrochloride.

(6) Naphazoline hydrochloride.

(7) Oxymetazoline hydrochloride.

(8) Phenylephrine hydrochloride.

(9) Propylhexedrine.

(10) Xylometazoline hydrochloride.

3. In proposed Subpart C, new § 341.80 is added and § 341.90 is amended by adding new paragraphs (m) and (n) to read as follows:

§ 341.80 Labeling of nasal decongestant drug products.

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

(b) *Indications.* (1) The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following phrase: "For the temporary relief of nasal congestion due to the common cold (cold), hay fever" (which may be followed by any of the following: "(allergic rhinitis)," "or other upper respiratory allergies," or "or other upper respiratory allergies (allergic rhinitis,") "or associated with sinusitus."

(2) *Other allowable indications.* In addition to the required information identified in paragraph (b)(1) of this section, the labeling of the product may contain any of the following statements provided such statements are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicousness than the required information.

(i) "For the temporary relief of" (select one of the following: "stuffy nose," "stopped up nose," "nasal stuffiness," or "clogged up nose.")

(ii) (Selected one of the following: "Reduces swelling of," "Decongests," or "Helps clear") "nasal passages; shrinks swollen membranes."

(iii) "Temporarily restores freer breathing through the nose."

(iv) "Helps decongest sinus openings and passages; relieves sinus pressure."

(v) "Promotes nasal and/or sinus drainage; relieves sinus pressure."

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

(1) *Oral nasal decongestants*—(i) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, or pseudoephedrine sulfate identified in § 341.20(a) (1), (2), and (3) when labeled for adults.* (*a*) "Do not exceed recommended dosage because at higher doses nervousness, dizziness, or sleeplessness may occur."

(*b*) "Do not take this product for more than 7 days. If symptoms do not improve or are accompained by fever, consult a doctor."

(c) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(d) "*Drug Interaction Precaution.* Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor."

(ii) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, or pseudoephedrine sulfate identified in § 341.20(a) (1), (2), and (3) when labeled for children under 12 years of age.* (a) "Do not exceed recommended dosage because at higher doses nervousness, dizziness, or sleeplessness may occur."

(b) "Do not give this product to children for more than 7 days. If symptoms do not improve or are accompained by fever, consult a doctor."

(c) "Do not give this product to children who have heart disease, high blood pressure, thyroid disease, or diabetes, unless directed by a doctor."

(d) "*Drug Interaction Precaution.* Do not give this product to a child who is taking a prescription drug for high blood pressure or depression, without first consulting the child's doctor."

(iii) *For oral nasal decongestant products labeled for both adults and children under 12 years of age.* The labeling of the product contains the warnings identified in paragraph (c)(1)(i) of this section.

(2) *Topical nasal decongestants*—(i) *For products containing any topical nasal decongestant identified in § 341.20(b) when labeled for adults.* (a) "Do not exceed recommended dosage because burning, stinging, sneezing, or increase of nasal discharge may occur."

(b) "The use of this container by more than one person may spread infection."

(ii) *For products containing 1-desoxyephedrine identified in § 341.20(b)(1) when used in an inhalant dosage form and when labeled for adults.* "Do not use this product for more than 7 days. If symptoms persist, consult a doctor."

(iii) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, or xylometazoline hydrochloride identified in § 341.20(b) (2), (3), (4), (5), (6), (7), (8), and (10) when used as nasal sprays, drops, or jellies and when labeled for adults.* (a) "Do not use this product for more than 3 days. If symptoms persist, consult a doctor."

(b) "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(iv) *For products containing naphazoline hydrochloride identified in § 341.20(b)(8) at a concentration of 0.05 percent.* "Do not use this product in children under 12 years of age because it may cause sedation if swallowed."

(v) *For products containing phenylephrine hydrochloride identified in § 341.20(b)(8) at a concentration of 1 percent.* "Frequent use of this product may cause nasal congestion to recur or worsen."

(vi) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form and when labeled for adults.* "Do not use this product for more than 3 days. If symptoms persist, consult a doctor."

(vii) *For products containing any topical nasal decongestant identified in § 341.20(b) when labeled for children under 12 years of age.* The labeling of the product contains the warnings identified in paragraph (c)(2)(i) of this section.

(viii) *For products containing 1-desoxyephedrine identified in § 341.20(b)(1) when used in an inhalant dosage form and when labeled for children under 12 years of age.* "Do not use this product for more than 7 days. If symptoms persist, consult a doctor."

(ix) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, or xylometazoline hydrochloride identified in § 341.20(b) (2), (3), (4), (5), (6), (7), (8), and (10) when used as nasal sprays, drops, or jellies, and when labeled for children under 12 years of age.* (a) "Do not use this product for more than 3 days. If symptoms persist, consult a doctor."

(b) "Do not use this product in children who have heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor."

(x) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form and when labeled for children under 12 years of age.* "Do not use this product for more than 3 days. If symptoms persist, consult a doctor."

(xi) *For topical nasal decongestant products labeled for both adults and for children under 12 years of age.* The labeling of the product contains the applicable warnings identified in paragraphs (c)(2)(i), (ii), (iii), and (vi) of this section.

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

(1) *Oral nasal decongestants*—(i) *For products containing phenylephrine hydrochloride identified in § 341.20(a)(1).* Adults: 10 milligrams every 4 hours not to exceed 60 milligrams in 24 hours. Children 6 to under 12 years of age: 5 milligrams every 4 hours not to exceed 30 milligram in 24 hours. Children 2 to under 6 years of age: 2.5 milligrams every 4 hours not to exceed 15 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

(ii) *For products containing pseudoephedrine hydrochloride or pseudoephedrine sulfate identified in § 341.20(a) (2) and (3).* Adults: 60 milligrams every 4 to 6 hours not to exceed 240 milligrams in 24 hours. Children 6 to under 12 years of age: 30 milligrams every 4 to 6 hours not to exceed 120 milligrams in 24 hours. Children 2 to under 6 years of age: 15 milligrams every 4 to 6 hours not to exceed 60 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

(2) *Topical nasal decongestants*—(i) *For products containing 1-desoxyephedrine identified in § 341.20(b)(1) when used in an inhalant dosage form.* The product delivers in each 800 milliliters of air 0.04 to 0.150 milligrams of 1-desoxyephedrine. Adults: 2 inhalations in each nostril not more often than every 2 hours. Children 6 to under 12 yearas of age (with adult supervision): 1 inhalation in each nostril not more often than every 2 hours. Children under 6 years of age: consult a doctor.

(ii) For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, or racephedrine hydrochloride identified in § 341.20(b) (2), (3), (4), and (5)—(a) *Nasal drops or sprays—For a 0.5-percent aqueous solution.* Adults: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Children 6 to under 12 years of age (with adult supervision): 1 or 2 drops or sprays in each nostril not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(b) *Nasal jelly—For a 0.5-percent water-based jelly.* Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(iii) *For products containing naphazoline hydrochloride identified in § 341.20(b)(6)*—(*a*) *Nasal drops or sprays*—(*1*) *For a 0.05-percent aqueous solution.* Adults: 1 or 2 drops or sprays in each nostril not more often than every 6 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*2*) *For a 0.025-percent aqueous solution.* Children 6 to under 12 years of age (with adult supervision): 1 or 2 drops or sprays in each nostril not more often than every 6 hours. Children under 6 years of age: consult a doctor.

(*b*) *Nasal jelly*—(*1*) *For a 0.05 percent water-based jelly.* Adults: place a small amount in each nostril and inhale well back into the nasal passages not more often than every 6 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*2*) *For a 0.025-percent water-based jelly.* Children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages not more often than every 6 hours. Children under 6 years of age: consult a doctor.

(iv) *For products containing oxymetazoline hydrochloride identified in § 341.20(b)(7)*—(*a*) *Nasal drops or sprays—For a 0.05-percent aqueous solution.* Adults and children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 10 to 12 hours. Do not exceed 2 applications in any 24-hour period. Children under 6 years of age: consult a doctor.

(*b*) *Nasal jelly—For a 0.05-percent water-based jelly.* Adults and children 6 to under 12 years of age (with adult supervision): place a small amoun' in each nostril and inhale well back into the nasal passages not more often than every 10 to 12 hours. Do not exceed 2 applications in any 24-hour period. Children under 6 years of age: consult a doctor.

(v) *For products containing phenylephrine hydrochloride identified in § 341.20(b)(8)*—(*a*) *Nasal drops or sprays—(1) For a 1-percent aqueous solution.* Adults: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*2*) *For a 0.5-percent aqueous solution.* Adults: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*3*) *For a 0.25-percent aqueous solution.* Adults and children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(*4*) *For a 0.125-percent aqueous solution.* Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Children under 2 years of age: consult a doctor.

(*b*) *Nasal jelly*—(*1*) *For a 1-percent water-based jelly.* Adults: place a small amount in each nostril and inhale well back into the nasal passages not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*2*) *For a 0.5-percent water-based jelly.* Adults: place a small amount in each nostril and inhale well back into the nasal passages not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*3*) *For a 0.25-percent water-based jelly.* Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(vi) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form.* The product delivers in each 800 milliliters of air 0.04 to 0.50 milligrams of propylhexedrine. Adults and children 6 to under 12 years of age (with adult supervision): 2 inhalations in each nostril not more often than every 2 hours. Children under 6 years of age: consult a doctor.

(vii) *For products containing xylometazoline hydrochloride identified in § 341.20(b(10)*—(*a*) Nasal drops or sprays—(*1*) *For a 0.1-percent aqueous solution.* Adults: 2 or 3 drops or sprays in each nostril not more often than evey 8 to 10 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*2*) *For a 0.05-percent aqueous solution.* Children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than evey 8 to 10 hours. Children under 6 years of age: consult a doctor.

(*b*) *Nasal jelly*—(*1*) *For a 0.1-percent water-based jelly.* Adults: placed a small amount in each nostril and inhale well back into the nasal passages not more often than every 8 to 10 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*2*) *For a 0.05-percent water-based jelly.* Children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages not more oftern than evey 8 to 10 hours. Children under 6 years of age: consult a doctor.

(viii) *Other required statements—For products containing 1-desoxyephedrine or propylhexedrine identified in § 341.20(b)(1) or (9) when used in an inhalamt dosage form.*

(*a*) "This inhaler is effective for a minimum of 3 months after first use."

(*b*) "Keep inhaler tightly closed."

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements above.

§ 341.90 Professional labeling.

* * * * *

(m) *For products containing oxymetazoline hydrochloride identified in § 341.20(b)(7).* Children 2 to under 6 years of age: 2 or 3 drops of sprays in each nostril of a 0.025-percent aqueous solution not more often than every 10 to 12 hours. Do not exceed 2 applications in any 24-hour period.

(n) *For products containing xylometazoline hydrochloride identified in § 341.20(b)(10).* Children 2 to under 6 years of age: 2 or 3 drops or sprays in each nostril of a 0.05-percent aqueous solution not more often than every 8 to 10 hours.

Interested persons, may, or or before May 15, 1985, submit to the Docket Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. The agency has provided this 120 day period (instead of the normal 60 days) because of the number of OTC drug review documents being published concurrently. Written comments on the agency's economic impact determination may be submitted on or before May 15, 1985. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the hearing of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

Interested persons, on or before January 15, 1986, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before March 17, 1986. These dates are consistent with

the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the Federal Register of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addresed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on March 17, 1986. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the Federal Register unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: December 31, 1984.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

[FR Doc. 85-681 Filed 1-14-85; 8:45 am]

BILLING CODE 4160-01-M

federal register

Tuesday
January 15, 1985

Part X

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 357

Poison Treatment Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 357

[Docket No. 81N-0050]

Poison Treatment Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) poison treatment drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the reports and recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products and the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, public comments to the advance notices of proposed rulemaking on OTC emetic drug products and OTC drug products for the treatment of acute toxic ingestion that were based on the respective Panels' recommendations, and public comments on the agency's proposed regulation on OTC emetic drug products, which was issued in the form of a tentative final monograph. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by May 15, 1985. Written comments on the agency's economic impact determination by May 15, 1985.

ADDRESS: Written comments, objections, new data, or requests for oral hearing 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, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of March 21, 1975 (40 FR 12902) FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC laxative, antidiarrheal, emetic,and antiemetic drug products, together with the recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. Interested persons were invited to submit comments by June 19, 1975. Reply comments in response to comments filed in the initial comment period could be submitted by July 19, 1975.

In the **Federal Register** of September 5, 1978 (43 FR 39544), the agency published a proposed rule, in the form of a tentative final monograph, for OTC emetic drug products. Interested persons were invited to file by October 5, 1978 written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation.

In response to the emetic tentative final monograph 16 poison control centers, 18 hospitals, 8 medical schools, 6 state health departments, 5 state pharmaceutical associations, 1 trade association, and 6 individuals submitted comments.

In a notice published in the **Federal Register** of March 21, 1980 (45 FR 18398), the agency advised that it had reopended the administrative record for OTC emetic drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch after the date the administrative record previously had officially closed. The agency concluded that any new data and information filed prior to March 21, 1980 should be available to the agency in developing a proposed regulation in the form of a tentative final monograph.

In the **Federal Register** of January 5, 1982 (47 FR 444.), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC drug products for the treatment of acute toxic ingestion, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, which was the advisory review panel responsible for evaluating data on active ingredients in this drug class. Interested persons were invited to submit comments by April 5, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by May 5, 1982. In response to this advance notice of proposed rulemaking, 3 poison control centers and 3 pharmaceutical companies submitted comments.

In accordance with § 303.10(a)(10), the data and information considered by the Panels and the agency are on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above) after deletion of a small amount of trade secret information. Copies of the comments received are also on public display in the Dockets Management Branch.

There is considerable overlap between in the rulemaking on OTC emetic drug products and the rulemaking on OTC drug products for the treatment of acute toxic ingestion. The intent of both rulemakings is to identify those ingredients that are generally recognized as safe and effective in the treatment of poisonings. Ipecac syrup, the one ingredient included in the rulemaking on emetic drug products, was also included in the rulemaking on OTC drug products for the treatment of acute toxic ingestion. Because of the overlap between the two rulemakings and because of the large number of comments submitted to the emetic tentative final monograph, the agency has decided to combine the two rulemakings and to publish a single tentative final monograph (proposed rule) to establish Subpart A of Part 357 entitled "Poison Treatment Drug Products." Part 337, previously designated for Emetic Drug Products for Over-The-Counter Human Use, will be reserved.

In this tentative final monograph (proposed rule) to establish Subpart A of Part 357 (21 CFR Part 357, Subpart A), FDA states for the first time its position on the establishment of monograph for OTC poison treatment drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC poison treatment drug products.

This proposal constitute FDA's tentative adoption of the Miscellaneous Internal Panel's conclusions and recommendations on OTC drug products for acute toxic ingestion as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report, and the agency's re-evaluation of the previously published proposed rule on OTC emetic drug products. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them. Based on the comments received, the agency has proposed in this tentative final monograph a number of changes in the content and format of the labeling of posion treatment drug products. FDA recognizes that it is

important for the labeling of these products to be very easily and rapidly comprehensible, because the products would almost always be used in an emergency situation. Therefore, the agency invites specific comment on the revised labeling proposed in this tentative final monograph.

The OTC procedural regulations (21 CFR 330.10) have been revised to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). (See the **Federal Register** of September 29, 1981; 46 FR 47730.) The court in *Cutler* held that the OTC drug review regulations were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision has been deleted from the regulations, which 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 OCT 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" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead 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 at the tentative final monograph stage.

The regulations in § 330.10(a)(7)(iii) provide for a 12-month period to submit data and information to support a condition excluded from the monograph in the tentative final order. The only ingredients reviewed and considered for poison treatment, ipecac syrup and activated charcoal, have been placed in Category I and are included in this tentative final monograph. The agency is unaware of any other ingredients that have potential for OTC use in poison treatment drug products. Therefore, the agency believes the usual 12-month period for submission of new data or information is unnecessary in developing a final monograph for OTC poison treatment drug products. Because there is no need for this 12-month period, the time for filing written comments or objections or requesting an oral hearing before the Commissioner following publication of a tentative final monograph (§ 330.10(a)(7)(i)) is 60 days. However, because of the number of OTC drug review documents being published concurrently, the agency is providing 120 days for comments or objections rather than the usual 60 days.

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 that 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 unless they are the subject of an approved new drug application (NDA). Further, any OTC drug products subject to this monograph that 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 the proposed rulemaking for OTC emetic drug products (published in the **Federal Register** of September 5, 1978 (43 FR 39544)) and in the advance notice of proposed rulemaking for OTC drug products for the treatment of acute toxic ingestion (published in the **Federal Register** of January 5, 1982 (47 FR 444), the agency suggested different effective dates for the final monographs. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products may have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

I. The Agency's Tentative Conclusions on the Comments and Objections

A. General Comments

1. One comment urged the agency to recognize explicitly the legal status of the monographs issued under the OTC drug review as being interpretive, as distinguished from substantive, regulations.

The agency addressed this issue in paragraphs 85 through 91 of the preamble of the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464) and in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated there. Subsequent court decisions have confirmed the agency'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. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D. N.Y. 1980), *aff'd*, 637 F. 2d 887 (2d Cir. 1981).

2. One comment argued that the indications for OTC drug products should not be limited to the precise words as set forth in quotation marks in proposed monographs. The comment

argued that since there are other ways and other words that can be used to convey the same meaning as the phrases set forth in the proposed monographs, it is unduly restrictive, unlawful, and unconstitutional to prevent the use of such alternatives. The comment further charged that this restriction is arbitrary and capricious because the agency's arguments, which support this policy (OTC Nighttime Sleep-aid and Stimulant Products Tentative Final Monographs, June 13, 1978, paragraph 5 (43 FR 25545)) as necessary to prevent consumer deception and unsafe use, are unsupported by any objective evidence that such negative effects might occur.

During the course of the OTC drug review, the agency has maintained that the terms that may be used in an OTC drug product's labeling are limited to those terms included in a final OTC drug monograph. (This policy has become known as the "exclusivity rule.") The agency's position has been that it is necessary to limit the acceptable labeling language to that developed and approved through the OTC drug review process in order to ensure the proper and safe use of OTC drugs. The agency has never contended, however, that any list of terms developed during the course of the review exhausts all the possibilities of terms that appropriately can be used in OTC drug labeling. Suggestions for additional terms or for other labeling changes may be submitted as comments to proposed or tentative final monographs within the specified time periods or through petitions to amend monographs under § 330.10(a)(12).

During the course of the review, FDA's position on the "exclusivity rule" has been questioned many times in comments and objections filed in response to particular proceedings and in correspondence with the agency. The agency has also been asked by The Proprietary Association to reconsider its position. In a notice published in the **Federal Register** of July 2, 1982 (47 FR 29002), FDA announced that a hearing would be held to assist the agency in resolving this issue. On September 29, 1982, FDA conducted an open public forum at which interested parties presented their views. The forum was a legislative type administrative hearing under 21 CFR Part 15 that was held in response to a request for a hearing on the tentative final monographs for nighttime sleep-aids and stimulants (published in the **Federal Register** of June 13, 1978; 43 FR 25544). The agency's decision on this matter will be announced in the **Federal Register** following conclusion of its review of the material presented at the hearing.

3. One comment suggested that FDA should sponsor a study on developing labeling which can be easily understood by individuals with limited education.

FDA has sponsored several labeling studies over the past few years. The first phase of the contract entitled "Consumer Comprehension of OTC Drug Labeling Language" (contract no. 223–80–3023) was completed in 1981. Unfortunately, budgeting restrictions forced the agency to cancel plans for the second phase of this study, which was designed to provide guidance in drafting labeling that can be easily understood by the public.

4. One comment objected to the current wording of the statement "In case of accidental overdose, seek professional assistance or contact a poison control center immediately," which is required for all orally administered OTC drugs. The comment argued that such a statement seems to imply that Poison Control Center personnel are not professionals. The comment suggested rewording this warning to read "In case of accidental overdose, contact a Poison Control Center or seek other professional assistance immediately."

FDA is proposing to exempt OTC poison treatment drug products from that portion of the warning in § 330.1(g) (21 CFR 330.1(g)) that is referred to by the comment. The comment is, therefore, not applicable to the labeling of these drugs. However, the agency recognizes that some change in the wording of this general warning may be necessary because the Advisory Review Panel on OTC Miscellaneous Internal Drug Products also has suggested a change in this warning (47 FR 55681). However, this issue will not be addressed in this document but will be addressed at a later date in another **Federal Register** document.

B. General Comments on Poison Treatment Drug Products

5. One comment disagreed with the Miscellaneous Internal Panel's statement that large volumes of water or milk should be ingested to dilute acidic or alkaline corrosive substances (47 FR 447). The comment pointed out that although the role of dilution with large volumes of fluid for poisoning in general is presently controversial, some evidence suggests that excessive dilution may have detrimental effects, especially in the case of caustics where large volumes of fluid may induce emesis and expose the esophagus again to the caustic. The comment suggested that it would be more prudent to suggest dilution of caustics with one glassful or less or water or milk.

Although the comment raises a valid point regarding the proper amount of fluid to be used in diluting caustics, the Panel's statement was made as part of a general discussion of poisoning and was not a specific recommendation to be included in the labeling of products covered by the monograph.

Labeling proposed in this tentative final monograph is limited to that necessary to insure the proper use of ipecac syrup and activated charcoal in treating poisoning. The labeling for both activated charcoal and ipecac syrup clearly states that these drugs are not to be administered in a poisoning that involves corrosives. Thus, there is no labeling proposed in this tentative final monograph regarding the amount of fluid to be used in diluting corrosive poisons because ipecac syrup and activated charcoal are only to be used in conjunction with noncorrosive poisons.

6. Four comments urged that the labeling be amended to include the word "pharmacist" in all phrases that include the word "physician." The comments argued that because pharmacists are readily available and extremely well informed regarding drugs, they should be named in the labeling as a contract for information regarding treatment on poisonings. Several of the comments reported the results of a recent survey as showing a good pharmacist-patient communication relationship because although 87 percent of the people surveyed were seen by more than one doctor, 86 percent will have their prescriptions filled at only one pharmacy. These comments further pointed out that former FDA Commissioner Kennedy, in a 1978 address to the American Pharmacists Association meeting in Canada, stated that "the pharmacist's knowledge of drugs, including adverse reactions, usually exceeds that of the physician."

Although physicians or pharmacists would be likely health professionals to be consulted because of their availability and recognized expertise, the agency does not believe that the labeling of OTC drug products should specify one or both of these health professionals. Many professional groups, such as nurses, nurse practitioners, and physician's assistants, are also sources of sound information on poison treatment. Consumers who are looking for poison treatment information are in the best position to choose the health professional to help them, and the warning should not limit their source of information. Therefore, the agency is revising the labeling in this tentative

final monograph for poison treatment drug products to advise consumers to contact a "health professional" for advise rather than any particular health professional.

7. A number of comments urged that the sentence "Call a physician, poison control center, or emergency room . . . ." in proposed § 337.50(c)(1) be revised to list "poison control center" first because poison control centers possess greater expertise in treating poisoning cases and are more easily reached by phone on a 24-hour basis than the other listed sources. The comments also pointed out that this change in wording would be consistent with national public education efforts to make the public aware that contacting a poison control center is the first action to take when a poisoning occurs or is suspected. Other comments suggested, in addition, that emergency room be listed second and physician last to assure that the most experienced sources are listed first.

FDA recognizes that poison control centers are the first source of information in treating poisonings and occurs with the suggested change in the labeling. The agency also believes that emergency personnel may be more readily available than other health professionals and should be listed second. (See also comment 8 below.)

8. Two comments requested that the term "emergency room" be replaced in labeling by the term "emergency medical facility" or "emergency medical center" because many emergency treatment centers are not situated within a hospital as the term "emergency room" implies. A third comment objected to the phrase "emergency medical facility" as being meaningless because the word "hospital" is the listing most often found in telephone books. The comment suggested revising the warning to read, "If you can, before using, call a poison control center, hospital, or doctor for advice."

FDA acknowledges that "emergency medical facility" or "emergency medical center" is a more descriptive term than "emergency room" because, as the comments pointed out, many emergency treatment centers are not located in hospitals. The agency does not agree that the term "emergency medical facility" is meaningless. In many parts of the United States, treatment or advise for poisoning can be obtained from hospitals, small clinics, poison control centers, medical centers, fire and emergency rescue services, etc. The term "emergency medical facility" encompasses all of these sources of information. Therefore, the agency is proposing that this term be used throughout the tentative final monograph.

9. Several comments expressed concern over the amount and complexity of labeling proposed for poison treatment drug products arguing that such labeling might be difficult to read because of the small print size and difficult to understand under rushed emergency conditions. Some of the comments urged the use of simple and brief labeling similar to the following:

> Before Use: Call your Poison Center, Physician, or Emergency Room. Do Not Use in a patient who is Comatose, Convulsing, or who has taken a Caustic. Dose: 30 mL (1 oz)—adult, 15 mL (½ oz)—child over 1 yr.

Another comment suggested the use of a package insert or an oversize bottle to allow adequate room for the labeling.

The comments raise a valid concern with respect to all poison treatment drug products. A simple, brief label is more likely to be read and understood under emergency conditions. However, it is equally important that adequate directions and warnings regarding the use of poison treatment drug products be available to the consumer when professional emergency help cannot be reached quickly.

In an effect to accomplish both objectives, FDA is proposing to divide the labeling for poison treatment drug products into two distinct segments. First, the agency proposes that the principal display panel contain the following brief emergency instructions in a conspicuously boxed area: "If possible call a poison control center, emergency medical facility, or health professional for help before using this product. If help cannot be reached quickly follow the directions (manufacturer to indicate location of directions, e.g., on the back of the bottle). Read the warnings and directions as soon as you buy this product. Insert emergency phone number(s) in space provided on the label." A space should also be provided, on the principal display panel, for writing in the phone number(s) of the appropriate poison control center or other emergency medical facility.

Second, the agency proposes that full warnings and directions be placed on a separate portion of the label. Wrap around or fold-over labels may be used to provide more label space with room for larger and more legible print. A package insert would not be acceptable because of the risk that it might become separated from the product. An oversize bottle might create confusion in the case of ipecac syrup because the quantity that may be sold OTC is limited to 30 milliliters (mL) per container, and determining a children's dose of ½ bottle as provided for in § 357.56(d)(2) of this tentative final monograph could be difficult under emergency conditions.

10. Three comments agreed with the proposed labeling for ipecac syrup (proposed § 337.50(c)(1)), which advises consumers to seek professional help before administering ipecac syrup. One of the comments stated that if consumers did not contact a professional before using ipecac syrup, it may be given many times when it is contraindicated, e.g., in instances of petroleum distillate or corrosive poisonings. Two other comments expressed the opposite opinion that attempting to contact professional help before using the product could result in a critical delay in an emergency situation. Another comment objected to a similar warning recommended for activated charcoal and poison treatment kits (recommended § 357.50(c)(1) and § 357.54(a)(1), respectively) because a written warning could be interpreted as prohibiting the administration of the product if a health professional could not be reached.

The agency believes that is any poisoning situation it would be best to seek professional help before using poison treatment drug products. However, there are times when such contact may not be possible. In those cases, the consumer should not be discouraged from using poison treatment drug products.

The agency is proposing that the principal display panel contain statements advising consumers to contact professional help if possible, but if help cannot be reached, to follow the directions provided elsewhere on the label. These statements will replace the warnings previously recommended in §§ 337.50(c)(1), 375.50(c)(1), and 357.54(c)(1). In those cases where professional help cannot be reached, the warnings contained on the labels of poison treatment drug products will list those poisoning situations in which the products should not be used.

11. One comment urged that labeling for ipecac syrup be printed in languages other than English in view of the extensive non-English speaking populations in many large cities.

The agency agrees that it would be valuable to have both emetics and adsorbents available with foreign language labeling. The regulations at 21 CFR 201.15(c) provide for labeling in other languages in addition to English. The foreign language version of the labeling statements must be a complete

and accurate translation of the required English labeling.

12. One comment pointed out that many poisoning reference sources, such as the Poisindex, recommend the administration of a saline cathartic when activated charcoal is administered in the management of poisoning. The comment questioned whether the Panel has considered the use of cathartics in poisoning.

The agency has reviewed the Miscellaneous Internal Panel's report and summary minutes of meetings and determined that the Panel did not consider the use of cathartics in acute poison treatment. A number of sources suggest the use of cathartics in poison treatment to remove unabsorbed poisons from the intestinal tract or to speed the passage of activated charcoal through the intestinal tract (Ref. 1, 2, and 3). According to Levy (Ref. 1), it has been customary to administer a saline laxative together with an adsorbent to prevent constipation or impaction. However, Levy noted that it would be advisable to use a conservative dose of a laxative to prevent excessive fluid loss and electrolyte disturbances. Dreisbach (Ref. 2) noted that catharsis or intestinal lavage can be used to remove unabsorbed poisons or poisons that have passed into the intestinal tract, but pointed out that catharsis should not be used in patients showing distrubed electrolyte balance. Cashman and Shirkey (Ref. 3) agree that laxatives may hasten transit through the bowel, thus decreasing the absorption of poisons that cannot be recovered by emesis or absorbed by activated charcoal, but believe judgment must be exercised by comparing the risk of poisoning to the theoretical value of the laxative. In view of these opinions, the agency believes that professional judgment is necessary to assess the appropriateness of using laxatives in poisoning situations. Thus, the agency does not believe that the labeling of OTC poison treatment drug products should mention the use of laxatives.

References

(1) Levy, G., "Gastrointestinal Clearance of Drugs with Activated Charcoal," *New England Journal of Medicine*, 307:676–678, 1982.

(2) Dreisbach, R.H., "Handbook of Poisoning," Lange Medical Publication, Los Altos, CA, p. 23, 1980.

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

13. One comment stated that the Miscellaneous Internal Panel appeared to mandate the use of ipecac syrup at all times before the use of activated charcoal. The comment stated that ipecac-induced emesis is not suitable in certain cases, such as ingestion of caustic substances or petroleum distillates, because it takes an average of 19 minutes to induce emisis, and sometimes a second dose is needed to induce emesis. The comment added that these delays could permot absorption of toxins that could be prevented by prompt administration of activated charcoal (Ref. 1). The comment stated that in at least one study an average of only 28 percent (range 0 to 78 percent) of stomach contents were recovered by ipecac-induced emesis (Ref. 2). The comment added that "the consensus now emerging among clincial physicians is that the best way of handling overdoses consists of the immediate administration of large amounts (100 grams (g) or more) of powdered charcoal" (Ref. 3). The comment requested that the labeling be modified to permit the use of activated charcoal without first ingesting ipecac syrup and having vomiting occur, because activated charcoal is safe under virtually all conditions.

As the Panel discussed in its report (47 FR 448), the efficiency of activated charcoal varies considerably according to the chemical ingested. A number of substances, including inorganic acids, certain alkalies (sodium and potassium hydroxide), sodium metasilicate, cupric copper, ferrous iron, boric acid, drugs that are solids and insoluble in acidic aqueous solutions, and certain insecticides, are not very well absorbed. In addition, in those situations in which ipecac syrup is contraindicated (corrosives and petroleum distillates), activated charcoal is not very effective (see comment 51 below). Although the agency acknowledges the one report that showed an average of only 28 percent recovery of stomach contents, there are numerous reports in the literature (Refs. 4 through 8), plus vast experience reported in poison control centers and emergency medical facilities, attesting to ipecac syrup's effectiveness in treating poisonings. The agency agrees with the Panel that in the majority of poisoning cases it is best to remove as much of the ingested substance as possible from the stomach by inducing vomiting before administering activated charcoal. However, the agency recognizes that in certain specific poisoning cases, a physician or other health professional may choose to administer activated charcoal rather than ipecac syrup. Therefore, the agency is proposing that the labeling for activated charcoal be modified to include this provision. (See comment 43 below.)

References

(1) Robertson, W.O., "Syrup of Ipecac: A Fast or Slow Emetic," *American Journal of Diseases in Children*, 103:136–139, 1962.

(2) Corby, D.G., et al., "Clinical Comparison of Pharmacologic Emetics in Children," *Pediatrics*, 42:361–364, 1968.

(3) Cooney, D.O., "Activated Charcoal, Antidotal and Other Medicinal Uses," Marcel Dikker, Inc., New York, p. 3, 1980.

(4) King, W.D., "Syrup of Ipecac: A Drug Review," *Clinical Toxicology*, 17:353–358, 1980.

(5) Krenzelok, E.P., "How to Manage Poisoning Emergencies," *Pharmacy Times*, 45:71–82, 1979.

(6) Rauber, A., "The Cardiac Safety of Ipecac Used as a Therapeutic Emetic," *Veterinary and Human Toxicology*, 20:166–168, 1978.

(7) Veltri, J.C., and A.R. Temple, "Telephone Management of Poisonings Using Syrup of Ipecac," *Clinical Toxicology*, 9:407–417, 1976.

(8) Ilett, K.F., S.M. Gibb, and R.W. Unsworth, "Syrup of Ipecacunha as an Emetic in Adults," *The Medical Journal of Australia*, 2:91–93, 1977.

14. Two comments suggested that the phase "or as directed by a physician" be deleted from the directions statement because advice on doses of ipecac syrup or activated charcoal may not be given by a physician, but may be given by a pharmacist, nurse, or other health professional working in a poison control center or emergency medical facility.

The agency agrees with the comment. The assistance from a poison control center or emergency medical facility may be provided by specially trained professional personnel other than physicians. Therefore, the agency is proposing that the phrase "or as directed by a physician" read "or as directed by a health professional" in the directions of poison treatment drug products.

15. One comment urged that the indication statement for emetics be revised to state clearly that ipecac syrup is to be used for the treatment of poisoning. A second comment suggested that the indications statement "for the treatment of acute poisoning" recommended for adsorbents and poison treatment kits be revised by deleting the word "acute" because it has no meaning to the general public in describing the type of poisoning. This comment further suggested that the indications statement for poison treatment drug products permit alternative language that is more understandable to the public, such as "emergency first aid treatment for poisoning," "emergency treatment for poisoning," "emergency treatment for accidental poisoning," "for the treatment of accidental poisoning," "emergency

first aid treatment for accidential poisoning," "emergency poison treatment," or "first aid poison treatment."

The agency believes that the labeling of any OTC drug product should clearly reflect the intended action of the product. In the case of ipecac syrup the agency believes it is important for consumers to be advised that vomiting is expected. Therefore, the agency is proposing the following statement as the indication for ipecac syrup: "For emergency use to cause vomiting of swallowed poisons." In the case of activated charcoal the agency believes that consumers should be informed that it is intended to absorb poisons and the indication proposed in this tentative final monograph reads "For emergency use to absorb swallowed poisons." The agency agrees with the one comment that the word "acute" is meaningless to the general public and has not included it in the proposed indications. The other statements suggested by the comments are acceptable as additional statements for inclusion on poison treatment drug products, but the agency does not believe that these statements should appear in conjunction with the required information.

C. Comments of Emetics

16. One comment contended that zinc sulfate, rather than ipecac syrup, is the emetic of choice in the treatment of accidental poisoning. The comment submitted an article stating that zinc sulfate, which produces vomiting by a purely local action in its action on the gastrointestinal tract, is both faster and more certain in its action then ipecac syrup (Ref. 1). The comment also emphasized that zinc sulfate lacks the central nervous system depressant action of ipecac syrup.

The agency recognizes that zinc sulfate is often effective as an emetic; however, its potential toxicity is too great to recommend its use as an OTC emetic drug product (Refs. 2, 3, and 4). The emetic dose of zinc sulfate is 2 g dissolved in 200 mL of water, repeated in 15 minutes if necessary. If emesis does not occur after the second dose, the zinc sulfate must be removed by stomach tube. If it is not removed, its absorption into the bloodstream can cause hemolytic effects and renal toxicity or even death (Refs. 2, 3, and 4). The lethal dose is estimated in the literature to be anywhere from 3 to 15 g (Refs. 2, 5, 6, and 7). The article submitted by the comment discussed a 1950 animal study conducted to develop a method for prevention of suicidal deaths caused by barbiturates. This study does not, however, support the general use of zinc sulfate as an OTC emetic.

In view of the reported toxicity of zinc sulfate and the narrow margin of safety between its effective dose (2 g) and its lowest reported lethal dose (3 g), the agency concludes that zinc sulfate is not suitable for use as an OTC emetic drug product.

References

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(2) "The United States Dispensatory," 27th Ed., J.P. Lippincott Co., Philadelphia, p. 1256, 1973.

(3) "AMA Drug Evaluations," 4th Ed., American Medical Association, New York, pp. 1435–1440, 1980.

(4) Arena, J.M., "Poisoning—Treatment and Prevention. Part I," *Journal of the American Medical Association*, 232:1272–1275, 1975.

(5) Moeschlin, S., "Poisoning. Diagnosis and Treatment," 1st Ed., Grune and Stratton, New York, pp. 121–123, 1965.

(6) Dreisback, R.H., "Handbook of Poisoning," 9th Ed., Lange Medical Publications, Los Altos, CA, pp. 406–407, 1977.

(7) Arena, J.M., "Poisoning. Toxicology—Symptoms—Treatments," 3rd Ed., Charles C. Thomas, Springfield, IL, pp. 37–40 and 241, 1974.

17. Four comments took exception to the agency's statement at 43 FR 39545 in the preamble to the prvious emetic tentative final monograph that "ipecac acts directly on the vomiting reflex center in the brain to produce vomiting." The comments were concerned that this statement implied that this is the only mechanism by which ipecac syrup produces emesis. Two of comments submitted documentation showing that ipecac syrup induces emesis via two mechanisms (Refs. 1, 2, and 3). The first mechanism is direct irritation of the upper gastrointestinal tract by ipecac, i.e., the "gas reflex." When this mechanism is operative, vomiting usually occurs within a relatively short period of time after the ipecac syrup is ingested. The second mechanism is the action of ipecac alkaloids on the vomiting reflex center of the brain. Because absorption from the gastrointestinal tract and distribution to the brain are required before ipecac syrup can induce emesis via this second mechanism, there is usually a delay between the ingestion of the ipecac syrup and the onset of vomiting.

The agency did not intend to imply that ipecac syrup induces emesis solely by acting on the vomiting reflex center of the brain. As the comments correctly point out, ipecac may act either by direct irritation of the upper gastrointestinal tract, i.e., "gas reflex," or by central action on the vomiting center of the brain.

References

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(2) Oderda, G.M., and S. West, "Emetic and Antiemetic Products," *in* "Handbook of Nonprescription Drugs," 5th Ed., American Pharmaceutical Association, Washington, pp. 57–58, 1977.

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18. Two comments were concerned about possible confusion between tincture of ipecac, fluidextract of ipecac, and the more dilute syrup of ipecac and the toxicity that could result if confusion occurred. One comment pointed out that vitually all published reports which discuss the toxicity of ipecac refer to toxicity resulting from the administration of fluidextract of ipecac rather than ipecac syrup. The fluidextract of ipecac contains over 10 times the concentration of the alkaloids, emetine and cephaline, found in ipecac syrup. The second comment urged that a sentence be added to the labeling of ipecac syrup advising individuals that syrup of ipecac and not the more concentrated and extremely dangerous tincture of ipecac is to be used in poisoning situations.

The first comment correctly identifies a misconception regarding the toxicity of ipecac syrup. As the comment indicated, most of the articles and reports discussing ipecac toxicity or ipecac overdose deal with situations in which the fluidextract of ipecac was administered rather than the more dilute ipecac syrup. In the past the fluidextract was frequently mistaken for the syrup. The tincture of ipecac and the fluidextract of ipecac are no longer recognized in the official compendia and are no longer commercially available. Further, such products are proposed as Category II because of their potential toxicity if incorrectly used. Therefore, the possibility of confusing the fluidextract or tincture of ipecac for the syrup of ipecac has been eliminated and the need for a label warning as suggested by the second comment is not necessary.

19. One comment urged that ipecac syrup be restricted to sale by pharmacists only because the public might consider ipecac syrup to be a specific poison antidote rather than an emetic, and may use it erroneously for

certain types of poisonings for which vomiting is contraindicated.

The issue of restricting the sale of OTC drugs to pharmacists only was discussed previously by the agency in the **Federal Register** of June 4, 1974 (39 FR 19880). There, the agency concluded that there was no public health concern that would justify the creation of a third class of drugs to be dispensed only by a pharmacist or in a pharmacy. Although the agency recognizes that the pharmacist is a health professional who can offer sound advice concerning poisoning situations, the agency believes that the proposed labeling of ipecac syrup provides adequate safeguards against its erroneous use.

20. A number of comments disagreed with the statement that ipecac syrup should be recovered by gastric lavage if a second dose does not induce vomiting (43 FR 39545). Some of the comments pointed out that the amount of ipecac syrup consumed in two doses (30 mL) is lower than the dosage (90 to 120 mL) that would have to be consumed without emesis before any cardiac arrhythmias might be induced. One comment added that a study on adults to see if syrup of ipecac in therapeutic doses would affect stress electrocardiograms (EKG's) indicated that syrup of ipecac produced no effect on the stress EKG (Ref. 1). The comments opposed any use of gastric lavage unless it was necessary to remove the poison or toxic substance that the patient had originally ingested. The comments stressed that it was not necessary to remove the ipecac syrup. One comment stated that any mention of gastric lavage in labeling is not appropriate as people of all educational levels would be using these products. An opposing comment urged that the labeling for ipecac syrup emphasize the necessity for gastric lavage if a second dose of ipecac syrup does not produce vomiting within 30 minutes. This comment was not accompanied by any supporting documentation.

The agency concluded in paragraph 9 of the emetic tentative final monograph, published on September 5, 1978 (43 FR 39545), that "gastric lavage" was inappropriate terminology for use on a label designed to be read and entirely understood by consumers in emergency situations. FDA thus deleted any mention of gastric lavage from the labeling provisions proposed in that tentative final monograph. The agency has not been presented with any data or reasoning that persuades it to change that conclusion. FDA further agrees that gastric lavage need not necessarily be performed if emesis fails to occur within 30 minutes of giving a second dose of ipecac syrup (a total of 60 mL in adults or 30 mL in children age 1 to 12), because data show that a therapeutic dose (up to 60 mL) of ipecac syrup is not cardiotoxic and produces only a mild drowsiness and diarrhea (Refs. 1 through 4). In fact as much as 105 mL of ipecac syrup have been retained by a child with only minor electrocardiograph changes occurring (Ref. 2).

References

(1) Comment No. OB0018, Docket No. 81N-0050, Dockets Management Branch.

(2) King, W.D., "Syrup of Ipecac: A Drug Review," *Clinical Toxicology*, 17:353-358, 1980.

(3) Meester, W.D., "Emesis and Lavage," *Veterinary and Human Toxicology*, 22:225-234, 1980.

(4) Rauber, A., "The Cardiac Safety of Ipecac Used as a Therapeutic Emetic," *Veterinary and Human Toxicology*, 20:166-168, 1978.

D. Comments on Emetic Labeling

21. One comment suggested that it may be more appropriate to use metric units in addition to English units when indicating the volume of water to be given along with ipecac syrup in the directions in § 357.50(e).

The agency is aware of the trend towards using metric units. However, the volume of water or other clear liquid to be given after the ipecac syrup is large (120 to 480 mL). The agency believes that American consumers would be more familiar with the English volume measures (ounces) when the volume is large and that the English measures should be used in the labeling in addition to "glassful" measures. The agency would have no objection to using the metric units in addition to the English units. However, the use of metric units will not be required in this tentative final monograph.

22. Two comments suggested that the recommended doses of ipecac syrup be expressed in terms of container size, i.e., 1 tablespoonful (15 mL or ½ bottle), in addition to the presently proposed units of teaspoonful and tablespoonful, and their metric equivalents. The comments argued that this would be more meaningful to the consumer because teaspoons and tablespoons found in the home vary in size, and many people are not yet familiar with the metric system.

While there may be some variation in teaspoons and tablespoons from home to home, they represent a common form of measurement with which most people are readily familiar. The agency has no objection to manufacturers expressing the 30 mL or 15 mL dose in terms of bottle size equivalent in addition to the tablespoon measures and is proposing this option in the monograph. However, the dose for children from 6 months to 1 year of age of 1 teaspoon (5 mL) should not be expressed in terms of bottle size equivalent, i.e., ⅙ bottle, because of the obvious difficulty in accurately measuring such a dose in that manner.

23. A number of comments urged that the warning, "Do not use in semiconscious or unconscious persons," in § 337.50(c)(2) of the emetic tentative final monograph, be amended because it does not include all of the conditions which might contraindicate the use of ipecac syrup. Five comments urged that the warning be written to include persons suffering seizures or convulsions because such people might choke while vomiting. Two comments suggested that the warning be expanded to include people who are drowsy or comatose or who might be expected to lose consciousness within 20 minutes after administering ipecac syrup. Two other comments suggested that the warning could be conveyed more simply and succinctly if it was changed to read: "Do not use in persons who are not fully conscious."

FDA agrees that reference to "semi-conscious or unconscious persons" may not be correctly interpreted as including all of the conditions under which ipecac syrup should be used. Because the average consumer does not have the experience to diagnose the onset of a seizure or convulsion or that a person may lose consciousness within 20 minutes, this information should not be included in the warning. The warning "Do not use in persons who are not fully conscious," suggested by two of the comments, would more accurately and simply convey the various states of consciousness in which ipecac syrup is contraindicated. Therefore, FDA is proposing this wording in the warning included in this tentative final monograph.

24. Four comments disagreed with the statement proposed in § 337.50(c)(3) that ipecac syrup should not be used if petroleum distillates such as kerosene, gasoline, paint thinner, or cleaning fluid have been ingested. The comments argued that the ingestion of petroleum distillates or hydrocarbons is not an absolute contraindication to the use of ipecac syrup. The comments asserted that emesis can be safely induced with ipecac syrup in the alert patient who has swallowed a large quantity of a petroleum distillate (i.e., two ounces or more) or when the petroleum distillate contains a substance in a quantity that is toxic to the patient. One comment cited FDA's "Handbook of Common Poisonings in Children" (Ref. 1), an

editorial (Ref. 2), and an unpublished study (Ref. 3) as examples that current thinking among toxicologists is that emesis can be induced safely in petroleum distillate poisonings.

Four other comments urged a revision or expansion of § 337.50(c)(3). Two of these comments suggested that furniture polish be included in the warning. One of the comments states that, although the generic term "paint thinner" includes "turpentine," turpentine should be specifically mentioned in the labeling. However, the other comment countered this view stating that turpentine is not a petroleum distillate and, therefore, should not be included under the generic term "paint thinner." The comment argued that turpentine has a minimal potential for pulmonary toxicity and a high potential for central nervous system toxicity if systemically absorbed, a fact which would warrant inducing vomiting.

The agency recognizes that induction of emesis may be indicated in certain cases of hydrocarbon ingestion. However, the agency is also aware that controversy exists whether or not emesis should be induced in these cases. Some sources recommend induction of emesis when certain hydrocarbons are ingested (Ref. 2) or when the amount of hydrocarbon ingested exceeds a certain volume (Refs. 1, 2, 4, and 5). Other sources state that emetics are definitely contraindicated (Ref. 6). The major argument against inducing emesis in the pulmonary complications that occur from aspiration of the ingested substance into the lung when vomiting is induced. Some investigators have shown that vomiting is associated with a higher incidence of pulmonary complications and central nervous system involvement (Refs. 7 through 10). Others (Ref. 4) have shown that patients treated with ipecac syrup had a lower incidence of pneumonia and that the pneumonia was less severe than in those treated with gastric lavage.

In view of the controversy regarding the treatment of ingestions of hydrocarbons, the agency believes that emesis should be induced in such cases only under the guidance of a health professional. Therefore, the agency is proposing to retain in this tentative final monograph the warning that ipecac syrup should not be given in petroleum distillate poisonings unless directed by a health professional.

Because "furniture polish" is a petroleum distillate commonly found in the home, the agency agrees with the comments that it should be added to the warning as an additional example of petroleum distillates. As one comment pointed out, turpentine in not a petroleum distillate, but is a hydrocarbon commonly found in the household. Therefore, the agency proposes to add it to the warning proposed in § 337.54(c)(2). Because other paint thinners may consist of petroleum distillates, this example will be retained in the warning. The agency is proposing that the warning in § 337.54(c)(2) read, "Do not use this product, unless directed by a health professional, if turpentine, corrosives, such as alkalies (lye) and strong acids, or petroleum distillates, such as kerosene, gasoline, paint thinner, cleaning fluid, or furniture polish, have been ingested."

References

(1) American Academy of Pediatrics, "Handbook of Common Poisonings in Children," Food and Drug Administrative, pp. 1, 52, 53, and 76, 1976.

(2) Rumack, B.H., "Hydrocarbon Ingestions in Perspective," *Annals Of Emergency Medicine*, 6:172, 1977.

(3) Rumack, B.H., "Hydrocarbons-Poisoning Emesis or Not," draft of unpublished paper, in Comment No. OB0001, Docket No. 78N-0036E, Dockets Management Branch.

(4) NG, R.C., et al., "Emergency Treatment of Petroleum Distillate and Turpentine Ingestion," *Canadian Medical Association Journal*, 3:537–538, 1974.

(5) Dreisbach, R.H., "Handbook of Poisoning," Lange Medical Publications, Los Altos, CA, pp. 19 and 181–182, 1960.

(6) Gosselin, R.E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., The Williams and Wilkins Co., Baltimore, pp. 188–192, 1976.

(7) Press, E., et al., "Cooperative Kerosene Poisoning Study: Evaluation of Gastric Lavage and Other Factors In the Treatment of Accidental Ingestions of Petroleum Distillate Products," *Pediatrics*, 29:648–674, 1962.

(8) Wolfsdorf, J., and H. Kundig, "Kerosene Poisoning In Primates," *South African Medical Journal*, 46:619–621, 1972.

(9) Sperling, E., "In Vivo and In Vitro Toxicology of Turpentine," *Clinical Toxicology*, 2:21–35, 1969.

(10) Beamon, R.F., et al., "Hydrocarbon Ingestion in Children: A Six-Year Retrospective Study," *Annals of Emergency Medicine*, 5:771–775, 1976.

25. Two comments asked for revision of the warning proposed in § 337.50(c)(3) for ipecac syrup which reads, "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." One comment suggested that, although strychnine is the most rapidly acting convulsant, other convulsants such as camphor should be mentioned. The other comment argued that ingestions of strychnine are extremely rare in the United States, and the presence of strychnine in the warning may distract the consumer from the more important contradictions to ipecac-induced emesis. The comment added that the experiences of both medical and poison control centers indicate that the risks associated with inducing emesis after ingestion of convulsant drugs (e.g., camphor, amphetamines, tricyclic antidepressants, isoniazid) is small compared to the risk of allowing these extremely toxic compounds to be absorbed into the bloodstream. The comment urged that specific references to convulsant drugs be avoided.

The agency believes that in cases of overdoses of convulsants (e.g., camphor, amphetamines, tricyclic antidepressants, isoniazid), an emetic such as ipecac syrup should be given unless the patient is comatose, convulsing, has no gag reflex, or is rapidly declining in levels of consciousness (Ref. 1 through 4). The agency agrees with the latter comment that the risk of administering ipecac to a person who has ingested a toxic dose of a rapidly acting convulsant is considerably less than the risk of allowing these toxic compounds to be absorbed into the bloodstream. Therefore, the agency is proposing not to include strychnine or any other convulsant, such as camphor, in the warning. As discussed in comment 23 above, the agency is proposing the warning "do not use in persons who are not fully conscious" to include the various stages of consciousness in which ipecac syrup is contraindicated.

References

(1) Polson, C.J., "Clinical Toxicology," J.B. Lippincott Co., Philadelphia, pp. 17–20, 1959.

(2) Callahan, M., "Tricyclic Antidepressant Overdose," *Emergency Medicine*, 8:413–425, 1979.

(3) Arena, J.M., "Poisoning, Toxicology—Symptoms—Treatments," 3d Ed., Charles C. Thomas, Springfield, pp. 368–369 and 399–400, 1974.

(4) Czajka, P.A., and J.P. Duffy, "Poisoning Emergencies. A Guide for Emergency Medical Personnel," The C.V. Mosby Co., St. Louis, pp. 39, 40, and 47–50, 1980.

26. Two comments urged that ipecac syrup labeling indicates the need for prompt administration or the need for caution when a delay occurs in administering the product after ingestion of toxic doses of phenothiazines, central nervous system depressants (i.e., alcohol, barbiturates, sedative hypnotics, narcotics), or convulsants that have a slow-to-moderate onset of action. One comment cited a study which showed that, despite the antemetic action of the phenothiazines, the induction of emesis with syrup of ipecac was successful (Ref. 1). The comment also cited one case in which

emesis failed to occur and fatal ipecac cardiotoxicity resulted (Ref. 2). The comment stated that the risk of emesis failing to occur increases with the delay between the ingestion of the toxic dose and the administration of ipecac syrup because of the amount of the drug absorbed. Both comments pointed out that this delay, along with the 15 to 30 minute or longer latency period for emesis to be induced by ipecac syrup, increases the chance that the patient may lose consciousness or experience convulsions before the onset of emesis.

The comments raise a valid concern which the agency shares. However, it is usually impossible for the average consumer to determine whether a particular substance ingested is a central nervous system depressant or convulsant, let alone decide whether it possesses a slow-to-moderate onset of action. The agency is proposing a warning on the principal display panel of the ipecac syrup label instructing the consumer to "If possible call a poison control center, emergency medical facility, or health professional for help before using this product." These sources are qualified to identify the nature of the toxic substance ingested and provide guidance in the correct emergency treatment. The labeling also instructs consumers to read and follow the directions for use elsewhere on the bottle in an emergency situation when help cannot be reached quickly. The purpose of this statement is to advise consumers not to delay administering ipecac syrup in those cases when professional help cannot be contacted immediately.

The agency believes that in the case of overdoses of phenothiazines, central nervous system depressants, or convulsants, the risk of giving ipecac syrup when professional help cannot be contacted is considerably less than the risk of allowing the patient to absorb a toxic dose of these compounds. However, for the reasons stated above, a specific labeling statement mentioning these drugs in particular is not being proposed.

References

(1) Thoman, M.E., and H.L. Verhulst, "Ipecac Syrup in Antiemetic Ingestion," *Journal of the American Medical Association*, 196:147–148, 1966.

(2) MacLeod, J., "Hazards to Health. Ipecac Intoxication—Use of a Cardiac Pacemaker in Management," *The New England Journal of Medicine*, 268:146–147, 1963.

27. One comment questioned whether ipecac syrup would be effective in patients who had ingested an antiemetic drug and whether it should be contraindicated in such cases. A second comment referred to several studies that demonstrated the effectiveness of ipecac syrup in inducing vomiting in patients who had ingested a variety of antiemetic drugs including phenothiazines, tricyclic antidepressants, antihistamines, and anticholinergics (Refs. 1 and 2). The comment attributed the effectiveness of ipecac syrup in these cases to local gastrointestinal irritation rather than to an action on the vomiting center of the brain.

As discussed in comment 17 above, ipecac syrup induces vomiting either by local gastrointestinal irritation or, following systemic absorption, by the effect of its alkoloids on the vomiting reflex center of the brain. In the case of ingestion of antiemetic drugs, which may depress the vomiting center in the brain, ipecac syrup may still induce emesis by virtue of its local gastrointestinal irritation. Manoguerra and Krenzelok (Ref. 1) reported that of 63 patients who ingested drugs with antiemetic properties, 51 (81 percent) vomited following the first dose of ipecac, 9 (14 percent) vomited after a second dose, and only 3 (5 Percent) failed to vomit. These results are consistent with the studies of Ilett et al. (Ref. 2) and Thoman and Verhulst (Ref. 3) who reported that the emetic efficiency (percentage of patients vomiting) was not decreased when either phenothiozines or antihistamines were identified as the ingested substance. Ilett et al. (Ref. 2) reported 100 percent emetic efficacy in seven persons who had ingested drugs with antiemetic properties. Thoman and Verhulst (Ref. 3) reported that the administration of ipecac syrup induced vomiting in 94.5 percent of a group of 291 patients who had ingested antiemetic drugs. Based on these data, the agency concludes that there is no need to contraindicate the use of ipecac syrup in cases where antiemetic drugs have been ingested.

References

(1) Manoguerra, A.S., and E.P. Krenzelok, "Rapid Emesis from High-Dose Ipecac Syrup in Adults and Children Intoxicated with Antiemetics or Other Drugs," *American Journal of Hospital Pharmacy*, 35:1360–1362, 1978.

(2) Ilett, K.F., S.M. Gibb, and R.W. Unsworth, "Syrup of Ipecacuanha as an Emetic in Adults," *The Medical Journal of Australia*, 2:91–93, 1977.

(3) Thoman, M.E., and H.L. Verhulst, "Ipecac Syrup in Antiemetic Ingestion," *Journal of the American Medical Association*, 196:433–434, 1966.

28. A number of comments discussed the warning in proposed § 337.50(c)(4), which reads "Do not administer milk or carbonated beverages with this product [ipecac syrup]." Two comments strongly supported the reference to milk in this warning because milk reduces the effectiveness of ipecac syrup; one of these comments also supported the contraindication to the use of carbonated beverages as a diluent. Another comment suggested that the warning in § 337.50(c)(4) be revised to make it less dogmatic, i.e., *"It is preferable* not to administer milk or carbonated beverages with this product," rather than, "do not." The comment argued that the administration of fluid followed by ambulation is important to the successful induction of emesis when syrup of ipecac is used.

Several comments suggested deleting the reference to "carbonated beverages" from the proposed warning. The comments asserted that there are no reports in the published literature that contraindicate the administration of carbonated beverages, instead of water, as a diluent after giving ipecac syrup. One comment stated that the administration of carbonated beverages after giving syrup of ipecac could have been confused with the administration of carbonated beverages where caustics have been ingested and the resulting gastric distention might lead to perforation. Ipecac syrup is already contraindicated in such cases.

Two comments stated that the administration of fluid is important to successful induction of emesis; however, it is sometimes difficult to get children, who are most likely to need ipecac syrup, to drink water, and clear juices or carbonated beverages may be more acceptable. These comments cited a study showing that the use of carbonated beverages caused no adverse affects or alteration of the effectiveness of ipecac syrup in inducing emesis, leading the authors of the study to conclude that carbonated beverages do not appear to affect the patient adversely or alter the effectiveness of ipecac syrup (Ref. 1). A final comment argued that the entire warning in § 337.50(c)(4) is not warranted, is likely to be in error, and should be deleted.

After reviewing the data, the agency concludes that carbonated beverages can be safely administered after ingesting ipecac syrup. The agency agrees that administration of fluids is important to assure successful induction of emesis. The agency also recognizes the difficulty in getting children to drink water. Therefore, the agency is proposing that the directons be revised to state that water or other clear liquids are to be given with ipecac syrup. Because studies have shown that milk interfers with the ability of ipecac syrup

to induce emesis, the agency disagrees that the entire warning should be deleted (Ref. 2).

References

(1) Uden, D.L., G.J. Davison, and D.P. Kohen, "The Effect of Carbonated Beverages on Ipecac-Induced Emesis," *Annals of Emergency Medicine*, 10:79–81, 1981.

(2) Varipapa, R.J., and G.M. Oderda, "Effect of Milk on Ipecac-Induced Emesis," *Journal of the American Pharmaceutical Association*, 17:510, 1977.

29. Two comments strongly supported the need for a drug interaction precaution to guard against the use of activated charcoal in conjunction with ipecac syrup.

As discussed in the tentative final monograph for emetic drug products (43 FR 39545), the agency agrees that a drug interaction precaution is necessary on ipecac syrup to warn against the simultaneous use of activated charcoal and ipecac syrup. The agency is modifying this statement in this tentiative final monograph and proposing is as follows: "*Drug Interaction Precaution:* Activated charcoal will adsorb ipecac syrup. Do not give activated charcoal until after patient has vomited, unless directed by a health professional." This modification is being proposed in order to be consistent with the wording of a warning proposed for activated charcoal. (See comment 43 below.)

30. Two comments pointed out that the first sentence of § 337.50(d) "Drug interaction precautions" incorrectly states that "Activated charcoal will *absorb* ipecac syrup" instead of stating that "Activated charcoal will *adsorb* ipecac syrup." One comment contended that the basis of this drug interaction is the adsorption of ipecac alkaloids to the surface of activated charcoal particles.

This error was corrected in a notice published in the **Federal Register** of November 28, 1978 (43 FR 55417).

31. One comment suggested that the labeling of ipecac syrup include a statement warning that an overdose of ipecac syrup could be toxic in a child who fails to vomit. The comment stated that there is no statement in the labeling that would make the consumer aware that an overdose of ipecac syrup itself can be toxic.

FDA has reduced the likelihood of an overdose by placing a 30-mL container size limit on ipecac sprup that is sold OTC. Thirty mL of ipecac syrup is not a toxic dose, even for children. (See comment 20 above.) In addition, the labeling of ipecac syrup has been revised to instruct consumers to call a Poison Control Center, emergency medical facility, or health professional for help before using the product and to call again if the patient fails to vomit within 30 minutes. For these reasons, the agency concludes that the warning suggested in the comment is unnecessary.

32. Two comments supported the recommended dose of 15 mL (1 tablespoonful) of ipecac syrup. One comment expressed the opinion that although 15 mL of ipecac syrup is the usual dose in children less than 5 years of age, and 30 mL is the usual dose for adults and children over 5 years of age, standardizing the dose at 15 mL for everyone as proposed is a suitable alternative and would alleviate any possible confusion. However, five comments by poison control centers disagreed with the recommended 15-mL dose of ipecac syrup for persons over 1 year of age. These comments urged that this dosage be increased to 30 mL for adults. One comment submitted supporting data showing that 30 mL of ipecac produced an 81-percent incidenced of vomiting in adults. The incidence of vomiting was increased to 96-percent when a second 30-mL dose was administered to those patients who failed to vomit initially (Ref. 1). Another study (Ref. 2) demonstrated that the incidence of vomiting was only 55 to 68 percent when a 15-mL dose of ipecac was administered. The comments stated further that, in the experience of poison control centers and according to current articles (Ref. 3), the appropriate adult dose of ipecac syrup is recognized as 30 mL followed by 1 to 2 glasses of water.

FDA agrees with the position and supporting data submitted by the poison control centers. The agency is proposing that the recommended dose of ipecac syrup for adults, i.e., individuals over 12 years of age, in § 337.54(d)(1) be an initial dose of 2 tablespoonsful (30 mL) rather than the previously proposed 1 tablespoonful (15 mL) dose, with a second dose of 2 tablespoonsful to given if vomiting does not occur within 30 minutes.

References

(1) Comment OB0003, Docket No. 81N–0033, Dockets Management Branch.

(2) Ilett, K.F., S.M. Gibb, and R.W. Unsworth, "Syrup of Ipecacuahna as an Emetic in Adults," *Medical Journal of Australia*, 2:91–93, 1977.

(3) Velri, J.C., and A.R. Temple, "Telephone Management of Poisonings using Syrup of Ipecac," *Clinical Toxicology*, 9:407–417, 1976.

33. Several comments objected to the proposed directions for use, which recommend the administration of ipecac syrup in infants under 1 year of age without medical supervision. The comments argued that infants under 1 year of age need to be carefully attended when vomiting occurs in order to help the child become properly positioned to prevent aspiration of vomitus. Some comments further argued that because many people believe incorrectly that ipecac is an "antidote" rather than an emetic and because ipecac takes approximately 30 minutes to be effective, a large number of children may not be properly attended during this critical period, thereby needlessly exposing them to accidents involving aspiration of vomitus and possible death by suffocation or aspiration pneumonitis. Two other comments urged that the use of ipecac syrup for infants under 6 months of age be restricted to a physician's office or emergency room. One of the comments cited a statement in a recently published text supporting this proposed restriction (Ref. 1).

Although the agency shares the comments' concern that it is best to use ipecac syrup in infants under 1 year of age only under professional advice and guidance because of the risk that infants might aspirate their vomitus, the comments have not provided adequate or convincing justification for deletion of the dosage statement for infants under 1 year of age. The labeling contains directions to seek professional assistance before administering ipecac syrup to any age group. The agency recognizes there may be situations when professional assistance cannot be obtained and believes that the risk of aspiration may be less in such situations than the risk of allowing a toxic substance to be absorbed. The agency also recognizes that infants between the ages of 6 months and 1 year are quite mobile and thus susceptible to accidental poisoning and believes that a dosage for this age group should be provided in this tentative final monograph. Because the chance of accidental poisoning in infants under 6 months would be extremely rare, a dose for this age group is not being proposed in the monograph. A statement has been added advising that ipecac syrup should not be given to children under 6 months of age unless directed by a health professional.

Reference

(1) Goldfrank, L.R., "Managing of the Overdosed or Poisoned Patient who is Alert," *in* "Toxicological Emergencies," Appleton, Century, Crofts, New York, p. 12, 1982.

34. Three comments recommended against administering a second dose of ipecac syrup. Two of the comments stated that a second dose of ipecac syrup at home would delay treatment at

a hospital or other medical facility. The third comment stated that the only time that a second dose of ipecac syrup would be needed is for overdoses in adults who fail to vomit following the first dose. The comment stated that overdoses in adults are usually intentional and involve ingestion of large amounts of drugs and multiple combinations. According to the comment, these patients should be treated in emergency facilities and should receive psychiatric evaluation. The comment stated that, because home treatment would involve no more than administration of the first dose of ipecac syrup and then transportation of the patient to the hospital, only one dose of ipecac syrup is necessary.

The agency does not agree that directions to give a second dose of ipecac should be deleted from the monograph. One of the basic reasons for having ipecac syrup in the home is so that consumers can treat cases of poisoning even if professional help cannot be obtained. The agency fully supports the idea that professional help should be sought before ipecac syrup is used but realizes that some cases may exist where help cannot be obtained quickly. In those cases, consumers should have directions for the proper use of ipecac syrup, including directions to administer a second dose. In further support of giving a second dose Veltri and Temple (Ref. 1) report that the ability to induce emesis at home is a significant advantage because the average delay between ingestion and arrival at an emergency room has been reported to be in excess of 60 minutes, and delays longer than 60 minutes are associated with a decrease in the efficiency of emesis. The need for psychiatric evaluation is unrelated to the safe and effective use of OTC poison treatment drug products. Therefore, this subject is not covered in the monograph for OTC poison treatment drug products.

Reference

(1) Veltri, J.C., and A.R. Temple, "Telephone Management of Poisoning Using Syrup of Ipecac," *Clinical Toxicology*, 9:407–417, 1976.

35. Three comments opposed the recommendations, proposed in §§337.50 (c)(1), (e)(i), and (e)(ii), to repeat the dose of ipecac syrup if vomiting does not occur within 20 minutes. The comments noted that Rauber (Ref. 1) has reported that after administering ipecac syrup the time to emesis was as high as 26 minutes in the 24 patients studied, and, in the author's personal experience, 25 to 30 minutes is more often the time to emesis. One comment stated that in a recent series of experiments in normal healthy male volunteers, the average time to induce emesis was 22 minutes (Ref. 2). The comments, therefore, urged that the recommended time limit before repeating the dose of ipecac syrup be raised to 30 minutes. Three other comments recommended deletion of the recommendation that a second dose of ipecac syrup be given if the first dose does not induce vomiting within 20 minutes because waiting for a second dose to take effect could cause excessive delay and loss of valuable time before transporting the patient to a medical facility. One of these comments recommended that the patient be advised to call a physician immediately if vomiting does not occur within 20 minutes.

The agency has reviewed the data cited by the comments and is persuaded that the directions for ipecac syrup should be revised to indicate that a second dose of ipecac syrup should be administered if vomiting has not occurred within 30 minutes. Veltri and Temple (Ref. 2) reported that of 776 cases, 419 subjects (54 percent) vomited within 15 minutes of ipecac administration. The number increased to 689 cases (88.9 percent) within 30 minutes. This finding is supported by Rauber (Ref. 1) who found a mean time to vomiting of 26 minutes. Similar results were obtained in a study by Manoguerra and Krenzelok (Ref. 3) on 232 patients and in a study by Robertson (Ref. 4) on 214 patients. Analysis of the data from the Manoguerra and Krenzelok study shows that 144 of 232 patients (62.1 percent) vomited in the 0-to-20-minute interval, while 44 patients (18.9 percent) vomited in the 20-to-30-minute interval. Similarly, the Robertson data showed that 33 of 214 patients (15.4 percent) vomited in the 20-to-30-minute interval, while successful emesis occurred in 156 of 214 patients (72.9 percent) within the 0-to-20-minute interval. The agency believes that the increases in successful emesis shown by the above studies for the 20-to-30-minute time interval represent a significant increase in successful emesis. The agency does not agree that directions to give a second dose of ipecac should be deleted from the monograph. As discussed in response to comment 34 above, a principal reason for having ipecac in the home is to permit treatment of poisoning when professional help cannot be reached. Ideally, professional help should be sought before ipecac syrup is used; however, in some cases it may not be possible to obtain help promptly. In those cases, consumers should have directions for the proper use of ipecac syrup. If vomiting does not occur within 30 minutes, a second dose should be given to take advantage of any cumulative effect of the second dose of ipecac. In further support of giving a second dose, Veltri and Temple (Ref. 2) report that the ability to induce emesis at home is a significant advantage because the average delay between ingestion and arrival at an emergency room has been reported in excess of 60 minutes, and delays longer than 60 minutes are associated with a decrease in efficiency of emesis.

References

(1) Rauber, A., "The Cardiac Safety of Ipecac Used as a Therapeutic Emetic," *Veterinary and Human Toxicology*, 20:166–168, 1978.

(2) Veltri, J.C., and A.R. Temple, "Telephone Management of Poisoning Using Syrup of Ipeca," *Clinical Toxicology*, 9:407–417, 1976.

(3) Manoguerra, A.S., and E.P. Krenzelok, "Rapid Emesis from High-Dose Ipecac Syrup in Adults and Children Intoxicated with Antiemetics or Other Drugs," *American Journal of Hospital Pharmacy*, 35:1360–1362, 1978.

(4) Robertson, W.O., "Syrup of Ipecac—A Slow or Fast Emetic?," *American Journal of Diseases of Children*, 103:58–61, 1962.

36. Several comments supported the second portion of the warning proposed in § 337.50(c)(1), "Call a physician, Poison Control Center, or emergency room . . . immediately if vomiting does not occur within 20 minutes after a second dose has been given." However, one comment believed this information should also appear as a direction because most people would look in the directions for further advice if vomiting does not occur.

The directions being proposed in this tentative final monograph for ipecac syrup include the dosages to be given and instructions to repeat the dose if vomiting has not occurred within 30 minutes. The principal display panel of an ipecac syrup container will contain advice to call a poison control center, emergency medical facility, or health professional for help before using the product. The agency agrees that the directions should reinforce the importance of continued attempts to obtain professional help when using any poison treatment product and, therefore, proposes the following statement for inclusion in the directions of all poison treatment drug products: "If previous attempts to contact a poison control center, emergency medical facility, or health professional were unsuccessful, continue trying."

37. One comment urged that ipecac syrup labeling contain a recommendation to check the label of

the ingested substance for pertinent first aid instructions because many commercial chemical products containing caustic substances or organic solvents now carry warnings against inducing emesis in case of ingestion. The comment added that the Consumer Product Safety Commission is currently considering a requirement that labeling on all chemical products under its jurisdiction carry first aid instructions, including instructions on whether or not to induce vomiting.

The agency recognizes that the Federal Hazardous Substances Act (15 U.S.C. 1261.2(p)(1)(G)) and related regulations (16 CFR 1500.3(b)(14)(i) and 21 CFR 1230.14) contain requirements for labeling hazardous or caustic substances with instructions for first aid treatment. However, many household products are labeled with inadequate, incorrect, and potentially misleading first aid instructions. Alderman, et al. (Ref. 1) surveyed 1,019 household product labels and found that 85 percent had inadequate first aid information. In view of this information, the agency believes that it would be inappropriate and potentially harmful to include such a statement in the ipecac syrup labeling. At some future time, if product first aid labeling becomes more reliable, the agency will reevaluate its position.

Reference

(1) Alderman, D., et al., "How Adequate are Warnings and First Aid Instructions on Consumer Product Labels?: An Investigation," *Veterinary and Human Toxicology*, 24:1:8–11, 1982.

38. Three comments stressed the importance of keeping the patient ambulatory after the administration of ipecac syrup. One of these comments, from a poison control center, stated that its experience had shown that emesis is greatly delayed if the patient is kept inactive following the administration of ipecac syrup. The comment urged that labeling be modified to mention this concern. Another comment submitted a study showing no significant difference in the time it took to induce emesis in patients kept in motion versus those assigned bedrest (Ref. 1).

Keeping the person who has been given ipecac syrup active may or may not speed up emesis; however, regardless of the poison treatment used, activity may prevent loss of consciousness, which is a particular problem with people who have ingested an overdose of a central nervous system depressant. Therefore, the agency is proposing that the statement, "Keeping patient active and moving," be added to the directions for use of all poison treatment drug products.

Reference

(1) Meester, W.D., "Emesis and Lavage," *Veterinary and Human Toxicology*, 22:225–234, 1980.

39. Referring to the Miscellaneous Internal Panel's statement that, "when retching and vomiting begin, the patient should be placed face down with head lower than hips" (47 FR 447), one comment suggested that children be seated or held on an adult's lap near a basin or sink while vomiting so that the mouth can be cleared of any vomitus. The comment stated that it is difficult to expect a child or adult to be placed face down with head lower than hips, when vomiting begins.

The agency agrees with the Panel that when vomiting begins the head-lower-than-hip position helps prevent aspiration of the vomitus into the lungs. However, as the comment pointed out, this position would be difficult for a patient to maintain under some circumstances. Although the Panel included the statement in its report, it was not included in the labeling recommended in its monograph. In view of the potentially conflicting results, the agency does not believe a statement regarding positioning of the patient should be included in the monograph.

Reference

(1) Goldfrank, L.R., "Managing of the Overdosed or Poisoned Patient who is Alert," *in* "Toxicological Emergencies," Appleton, Century, Crofts, New York, p. 12, 1982.

40. Four comments urged that ipecac syrup should be packaged and marketed only in 30-mL containers, arguing that this container size provides two 15-mL doses, which would be convenient, safe, and effective; any larger amount could lead to overdoses in children and any less might be ineffective. Two other comments supported the 30-mL size, but suggested that two 15-mL containers should also be permitted. Three comments favored the 15-mL size only, arguing that 15 mL is the unit dose for a child. One of these comments suggested that the 15-mL containers should be marketed in packages of four to permit simultaneous treatment of several patients.

Current FDA regulations (21 CFR 201.308(c)) require that the OTC marketing of ipecac syrup be limited to 30 mL containers. This package size is convenient in that it provides one adult dose or two 15 mL doses for children age 1 to 12. The comments did not present any convincing arguments to warrant a change in the container size. Therefore, the 30 mL container size requirement is proposed in this tentative final monograph.

41. One comment urged that safety caps not be used on bottles of ipecac syrup.

The Poison Prevention Packaging Act (15 U.S.C. 1471–1476), which requires safety packaging for certain drug products, is administered by the Consumer Product Safety Commission (CPSC). Where necessary, FDA can request CPSC to require safety closures on OTC drugs. However, because ipecac syrup is packaged only in 30 mL containers, each of which contains a less-than-toxic dose for a small child, and the presence of safety closures could result in unwarranted delay and confusion in the administration of ipecac syrup to treat poisoning victims in emergency situations, the agency agrees that safety closures should not be used on bottles of ipecac syrup sold OTC.

42. One comment suggested that, to prevent misunderstanding by dispensing pharmacists, every bottle of ipecac syrup larger than 30 mL should bear the following statement on the label: "Remember, 30 mL may be dispensed without a prescription."

This monograph establishes conditions of marketing of OTC drugs only. It does not address prescription labeling. Thus the statement suggested by the comment is not included in the monograph. The agency has no objection to a statement similar to that suggested by the comment appearing in the labeling of prescription size bottles of ipecac syrup and is aware that such labeling is currently used (Ref. 1). However, the agency suggests that when such labeling is used it should also include a statement that complete labeling information as specified in the poison treatment drug products monograph (21 CFR Part 357 Subpart A) must be provided to consumers to whom the product is sold. The agency suggests that manufacturers of prescription size bottles of ipecac syrup provide pharmacists complete auxillary labeling to provide to consumer when smaller quantities are sold from prescription size bottles.

Reference

(1) Physician's Desk Reference, 37th Edition, Medical Economics Company, Orandell, NJ, p. 1141, 1983.

E. Comments on Adsorbents

43. Two comments objected to the OTC availability of activated charcoal as a poison adsorbent. The comments contended that poisoning cases serious enough to require the use of activated charcoal should be treated in an emergency room or other health care

facility. A comment from a poison control center stated that its experience indicates that only about 10 percent of toxic ingestion exposures are serious enough to require both the induction of emesis and the additional decontamination provided by activated charcoal. The other comment expressed that use of activated charcoal in the home may create a false sense of security and delay consultation with a poison control center.

Although syrup of ipecac has long been recognized as the first line of defense in the home treatment of poisoning, a number of studies have shown that vomiting induced by ipecac is often not complete, with recovery of stomach contents varying from 0 to 78 percent (Ref. 1). Activated charcoal has been demonstrated to be safe and effective in adsorbing poison that may remain in the gastrointestinal tract after vomiting has occurred. The Miscellaneous Internal Panel recognized (47 FR 448) and the agency concurs that, generally, the use of activated charcoal should be restricted to administration following the induction of vomiting. The agency is therefore proposing the following statement for inclusion on activated charcoal products as a drug interaction precaution: "Do not give activated charcoal until after patient has vomited unless directed by a health professional." There are situations in which activated charcoal can be administered without inducing vomiting. However, the agency believes that this decision should be made by a health professional on an individual case basis. This warning will replace the warning recommended by the panel in § 357.20(c)(3).

Reference

(1) Meester, W.D., "Emesis and Lavage," *Veterinary and Human Toxicology*, 22:225–234, 1980

44. Three comments commended the Panel for both anticipating and encouraging the development of new and more palatable dosage forms of activated charcoal, but expressed concern over the Panel's recommended criteria for comparison of the adsorptive capacity of new dosage forms with the existing dosage form. One comment urged development of a methodology for an in vivo comparison of dosage forms. Another comment asserted that the testing criteria recommended by the Panel are unnecessary because there are adequate compendial standards for measuring the adsorptive capacity of activated charcoal in the United States Pharmacopeia (U.S.P.) (Ref. 1). The comment stated that any product containing activated charcoal U.S.P. as its active ingredient would have to meet these standards for adsorptivity, and that these standards, which can be applied to final formulations, make in vivo testing scientifically and legally unnecessary.

The agency agrees that additional testing criteria for activated charcoal beyond final formulation conformity to U.S.P. adsorptivity standards (Ref. 1) should not be necessary for any activated charcoal product. The agency is proposing that the monograph specify that final formulations, in amounts equivalent to one gram (g) of activated charcoal, must meet or exceed the standards for adsorptivity for activated charcoal, U.S.P. However, the U.S.P. adsorptivity standard is specific to a dry powdered dosage form and may not be readily applicable to the testing of other dosage forms. The agency invites specific comment on suitable testing standards and methods, including modifications of the U.S.P. adsorptivity standard, for dosage forms other than the traditional dry powdered activated charcoal.

Reference

(1) "United States Pharmacopeia XX—National Formulary XV," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 128–129, 1980.

45. One comment questioned the possibility of aspiration of activated charcoal in powdered form.

Athough activated charcoal is normally packaged in powdered form, the likelihood of aspiration is minimal because the directions for use instruct the consumer to mix the activated charcoal in water before it is administered.

46. One comment supported the Miscellaneous Internal Panel's 30 g minimum dosage recommendation for activated charcoal and urged the agency to restrict the OTC marketing of activated charcoal products to a unit dose form containing a minimum of 30 g. The comment expressed concern that the dosage of activated charcoal may not be adequate if the Panel's volume measure recommendation (6 level tablespoonsful) was used because of the varying densities of charcoal powder and because 1 tablespoonful could supply from 3.5 to 6 g of activated charcoal (Refs. 1 and 2).

Another comment disagreed with the Panel's 30-g recommendations and requested that the dose be changed to 25 g. The comment supplied information indicating that a much wider effective dosage range (from 5 to 60 g) exists in actual practice and that a product containing 25 g activated charcoal is in widespread use with general acceptance by emergency medical facilities (Ref. 3).

The agency recognizes that the density of activated charcoal may vary considerably. As pointed out by one comment, a tablespoonful of activated charcoal can contain anywhere from 3.5 to 6 g (Refs. 1 and 2); thus, 6 tablespoonsful could contain from 21 to 36 g. The dose of activated charcoal generally recommended is 8 to 10 times the amount of the toxic substance ingested (Refs. 1 and 2) with the maximum limit determined only by the feasibility of administration (47 FR 449). For these reasons, the agency does not believe the dose of activated charcoal needs to be limited to a specific weight amount. Instead, the agency is proposing a range of 20 to 30 g as a dose of activated charcoal. Taking into consideration the varying densities of activated charcoal, this dosage approximates the Panel's recommendation of 6 tablespoonsful. It will also include the 25 g product that is recommended by one comment. As the comment and the Panel pointed out, there is a wide effective dosage range for activated charcoal, and the agency is proposing that a second dose be given if possible. (See comment 50 below.)

References

(1) Greensher, J., et al., "Activated Charcoal Updated," *Annals of Emergency Medicine*, 8:261–263, 1979.

(2) Dipalma, J.R., "Activated Charcoal—A Neglected Antidote," *Clinical Pharmacology*, 20:155–156, 1979.

(3) Comment No. C00005, Docket No. 81N-0050, Dockets Management Branch.

F. Comments on Adsorbent Labeling

47. One comment suggested that the statement of identity recommended in § 357.50(a) for poison treatment drug products containing activated charcoal be changed from the term "adsorbent" to a more easily understood term such as "poison antidote," "emergency poison antidote," or "first aid poison antidote."

Webster defines antidote as a remedy to counteract the effect of a poison (Ref. 1). Activated charcoal acts by means of adsorbing poisons, not by counteracting their effects. Thus, it would be false and misleading to replace the term "adsorbent" with any term implying that activated charcoal is a poison antidote. However, acceptable statements of identity are provided by replacing the word "antidote" with the word "adsorbent" in the phrases suggested by the comment, i.e., "poison adsorbent," "emergency poison adsorbent" or "first aid poison adsorbent." Therefore, the agency is proposing that any one of

these phrases may be used as the statement of identity in place of the word "adsorbent" for poison treatment drug products containing activated charcoal.

Reference

(1) "Webster's New Collegiate Dictionary," G. and C. Merriam Co., Springfield, MA, 1979, s.v. "antidote."

48. One comment believed that the Miscellaneous Internal Panel's recommended directions of mixing 4 ozs (120 mL) of water with 30 g of activated charcoal would result in too thick a slurry with increased chances of complications if aspiration of the charcoal mixture occurs. The comment cited a case in which a mixture of 9 g of charcoal in 35 mL of water was administered to a patient who regurgitated and aspirated the mixture, resulting in the immediate development of airway obstruction (Ref. 1). The comment pointed out that the water to charcoal ratio in this case (3.89:1) is very close to the ratio (4:1) recommended by the Panel. The comment recommended that the charcoal be mixed with 8 oz (240 mL) of water, adding that such a mixture allows for a better dispersion of the charcoal in water and has the advantage of making the charcoal more palatable.

Upon evaluation of the report of the case of airway obstruction resulting from the aspiration of a thick charcoal-water slurry, the agency agrees with the comment that increasing the amount of water mixed with activated charcoal will reduce this danger, aid in the dispersion of the charcoal in water, and make the mixture more palatable and thus more likely to be ingested. Therefore, the agency is proposing that the directions for activated charcoal provide that the dose is to be administrated in a minimum of 8 oz of liquid.

Reference

(1) Pollack, M.H., et al., "Aspiration of Activated Charcoal and Gastric Contents," *Annals of Emergency Medicine*, 10:528–529, 1981.

49. Several comments stated that the directions for activated charcoal recommened by the Panel in § 357.50(d) are too specific and restrictive in that they do not allow the mention of dosage forms other than aqueous solutions. The comments requested that the directions be modified to allow these alternative dosage forms to be mentioned.

The agency agrees. As pointed out in comment 44 above, the agency has no objection to alternative dosage forms as long as suitable testing methods can be developed to insure that the final product meets USP XX standards for adsorbency. Accordingly, the agency has revised the directions in this tentative final monograph to allow for alternative dosage forms.

50. Two comments suggested that the labeling of activated charcoal include a statement that the dose of activated charcoal should be repeated if possible. One comment stated that the upper limits of charcoal administration are governed only the feasibility of administration.

The agency agrees. Doses of activated charcoal up to 120 g have been administered with no reported side effects (Refs. 1 and 2) and, in general, the larger the does of activated charcoal the greater the adsorption of the ingested poison. Therefore, the agency is proposing the following statement in the directions for activated charcoal: "Repeat dose immediately, if possible."

References

(1) Greensher, J., et al., "Activated Charcoal Updated," *Annals of Emergency Medicine*, 8:261–263, 1979.

(2) Dipalma, J.R., "Activated Charcoal—A Neglected Antidote," *Clinical Pharmacology*, 20:155–156, 1979.

51. One comment suggested that the warning "Do not give activated charcoal to people who have swallowed petroleum distillate or corrosive products" be added to the warnings for products containing activated charcoal because the administration of activated charcoal is not infrequently followed by vomiting and the induction of emesis for corrosive products is contraindicated. The comment added that an additional complication to the use of activated charcoal with corrosives is that it may obscure visual observation of gastroesophageal lesions by endoscopy. The comment concluded that there is a lack of evidence documenting the beneficial effects of activated charcoal in humans who have ingested corrosives or petroleum distillates, and, therefore, activated charcoal should not be used following ingestion of these substances.

The agency agrees with the comment. Decker, Combs, and Corby (Ref. 1) found that corrosives such as inorganic acids, sodium and potassium hydroxides, and sodium metasilicate are not adsorbed to any measurable extent by activated charcoal. Picchioni, Chin, and Laird (Ref. 2) reported that, in rats, kerosene is adsorbed by activated charcoal, but that there is a lack of data on the ability of activated charcoal to adsorb other petroleum distillates. Some authors report that activated charcoal is ineffective in petroleum distillate ingestions (Ref. 3). For these reasons, the agency believes that the labeling of activated charcoal should include the same corrosive, petroleum distillate warning as that required for ipecac syrup.

References

(1) 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.

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

(3) Czajka, P.A., and J.P. Duffy, "Drugs for the Management of Acute Poisonings," *in* "Poisoning Emergencies. A Guide for Emergency Medical Personnel," The C.V. Mosby Co., St. Louis, p. 15, 1980.

G. Comments on Poison Treatment Kits

52. Nine comments supported the concept of poison treatment kits containing both activated charcoal and ipecac syrup and encouraged their availability. Eight other comments, While supporting the OTC availability of ipecac syrup, opposed the OTC marketing of kits containing activated charcoal as well as ipecac syrup. The comments pointed out that the kits would be more expensive than ipecac syrup alone, that activated charcoal could be administered at the wrong time and interfere with the functioning of the ipecac syrup, and that ingestion serious enough to warrant the use of activated charcoal should properly be treated in an emergency room.

The agency appreciates the concerns and objections raised by the comments opposing the marketing of activated charcoal with ipecac syrup in poison treatment kits. The kits will undoubtedly be more expensive than ipecac syrup alone, but they are not intended to replace or prevent the sale of ipecac syrup packaged alone. Although activated charcoal can adsorb ipecac syrup and prevent its functioning if administered before the ipecac syrup has had time to induce vomiting, the agency believes that the direction and warnings for both activated charcoal and ipecac syrup being proposed in this tentative final monograph adequately caution against such use. In addition, the labeling for a poison treatment kit clearly instructs the user to ". . . call a poison control center, emergency medical facility, or health professional for help before using this product." While most cases of poisoning may call for the use of ipecac syrup only, the presence of both ipecac syrup and activated charcoal in the kit would provide the poison control center personnel or other health professional flexibility in responding to the needs of

any individual case of poisoning. In addition, when professional advice cannot be obtained, the administration of activated charcoal after vomiting had occurred provides an added margin of protection because the activated charcoal can adsorb residual poison.

The agency therefore concludes that poison treatment kits containing both activated charcoal and ipecac should be available OTC.

53. One comment urged that the poison treatment monograph contain a statement expressing a preference for ipecac syrup alone rather than the more costly dual ingredient kit containing both ipecac syrup and activated charcoal.

The agency agrees that ipecac syrup is the first line of defense in poison treatment and is less costly than the dual ingredient poison treatment kit. It would, however, be inappropriate to attempt to influence purchasing practices by requiring a label statement expressing an opinion as to the agency's preference between two products, both of which have been determined to be safe and effective.

54. Numerous comments objected to the ingredient and dosage specifications recommended by the Panel in proposed § 357.14 for a poison treatment kit. Two comments did not believe that there was any potential safety problems with the amount of ipecac syrup present in the kit. Most of the comments objected to the requirement that the kit contain 60 mL of ipecac syrup because of the potential for ipecac overdose, especially in small children. Two of these comments stated that 60 mL of ipecac syrup would not pose a safety problem if "child resistant" tops were used on the bottles, and another comment stated that a warning against overdosing could adequately handle this risk. The majority of the comments urged that the kit be limited to some smaller quantity of ipecac syrup; three suggested a limit of 15 mL of ipecac syrup, and one suggested a 45 mL limit. Thirty mL was, however, the most commonly suggested limit.

In addition, two comments objected to the requirement that the kit contain exactly four (30 g) containers of activated charcoal, with one comment suggesting that the requirement be changed from 30 g containers to 25 g containers. One of these comments also questioned the agency's authority to establish exact numerical limits on the size and type of dosage forms in such a kit.

The agency has authority under sections 502(f) and 701(a) of the Act (21 U.S.C. 352(f) and 371(a)) to establish limits on size and types of dosage forms and limits on package contents, e.g., the 36-tablet limitation per container of 1¼ grain (pediatric) aspirin tablets specified in § 201.314(c)(2). The agency has, however, reviewed both the Panel's report and the comments and agrees that the Panel's action in establishing exact ingredient and dosage specifications for a poison treatment kit, including the exact size and number of containers, is overly restrictive. The agency is proposing that the tentative final monograph establish that poison treatment kits contain one adult dose of ipecac syrup, 30 mL, and a minimum of one dose of activitated charcoal, 20 g. This requirement will provide a minimum of one dose each of both an emetic and an adsorbent. As discussed in comment 30 above, containers of ipecac syrup are limited to 30 mL due to the potential toxicity of this ingredient. The kit can therefore contain only one 30-mL container of ipecac syrup. There is no reason, however, for any restriction on the size or number of containers of activitated charcoal beyond the minimum dosage requirement of 20 g. As discussed in comment 44 above, new dosage forms of activated charcoal are also acceptable. The agency has also considered the suggestion that 60 mL of ipecac syrup could be safely packaged in a kit if placed in separate containers equipped with "child resistant" caps. The safety advantage of using such caps to permit inclusion of more ipecac syrup in the kit would, however, be offset by the risk that such caps could delay administration of the initial dose of ipecac syrup. There is, of course, no restriction on the number of kits that an individual can purchase.

55. One comment pointed out that the description of the acute toxic ingestion kit recommended by the Panel in § 357.14, which specifies charcoal containers that facilitate mixing the contents, is in contradiction to the directions in § 357.50(d) which state "Mix 6 level tablespoonfuls in ½ glassful of water."

The agency agrees that there was a discrepancy. The revisions that have been made in this tentative final monograph have resolved this discrepancy. (See comments 48 and 49 above.)

56. Three comments suggested revising the direction statements recommended by the Panel in § 357.54(d). One comment suggested deleting the direction in § 357.54(d)(1) "When professional advice is not available, first give ipecac * * * " because professional advice in the form of a poison control center, an emergency facility, or a health professional is always available by telephone. The comment contended that this direction on the outside of a poison treatment kit could cause parents not to review the additional labeling in the kit and to give activated charcoal or ipecac syrup unnecessarily.

A second comment suggested rewording the directions statements by reversing the order of § 357.54(d)(1) and § 357.54(d)(3) to give greater prominence to the statement "Save the container of poison" and to require that the statement recommended in § 357.54(d)(2) "Read instruction at time of purchase and insert phone numbers" be placed on the principal or front display panel rather than just the outside of the kit. The third comment suggested that the directions be expanded to allow inclusion of a booklet containing more detailed first aid instruction in the kit.

The agency disagrees that professional help can always be reached by telephone. There are circumstances such as in isolated locations or during severe weather when such advice will not be available. As discussed in comment 9 above, the agency has revised the labeling of poison treatment drug products to require the following statements on the principal display panel: "If possible call a poison control center, emergency medical facility, or health professional for help before using this product." "If help cannot be reached quickly, follow the directions on * * * (manufacturers to indicate location of directions, e.g., on the back of the bottle)" and "Read the warnings and directions as soon as you buy this product. Insert emergency phone number(s) in space provided on the label."

The remainder of the warnings and directions are to be placed on a separate portion of the label. The agency disagrees that the statement "Save the container of poison" should be given any special prominence as compared with other labeling. However, the agency believes that this statement is applicable to all poison treatment drug products and thus is proposing that the monograph include the statement on ipecac syrup as well as activated charcoal products. The agency has no objection to the inclusion of labeling, folders, booklets, or leaflets containing more detailed first aid or poison treatment information as long as such information does not distract from required labeling.

II. The Agency's Tentative Adoption of the Panels' Reports

A. Summary of Ingredient Categories

The agency has reviewed the only active emetic ingredient submitted to the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products, ipecac syrup, and the single claimed active adsorbent ingredient submitted to the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, activated charcoal, as well as other data and information available at this time, and concurs with the Panels' Category I classification of these ingredients as OTC poison treatment drugs.

For the convenience of the reader, the following table is included as a summary of the agency's categorization of OTC poison treatment active ingredients.

	Category
Emetics:	
Ipecac fluidextract	II.
Ipecac syrup	I.
Ipecac tincture	II.
Zinc sulfate	II.
Poison Adsorbents:	
Charcoal, activated	I.

B. Summary of the Agency's Changes in the Panels' Recommendations

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panels' reports and recommended monographs and will combine them into a single monograph for OTC poison treatment drug products with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made in the Panels' conclusions and recommendations and to the previous tentative final monograph for OTC emetic drug products follows:

1. The process of combining the emetic rulemaking (proposed 21 CFR Part 337) and the acute toxic ingestion rulemaking (proposed 21 CFR Part 357, Subpart A) into the present tentative final monograph under 21 CFR Part 357 (entitled Poison Treatment Drug Products for OTC Human Use,) has required the redesignation of many section and paragraph numbers.

2. The term "health professional" is being proposed in labeling in place of the term "physician," "doctor," or "pharmacist." (See comments 6 and 14 above.)

3. The term "emergency medical facility" is being proposed in labeling in place of the term "emergency room." (See comment 8 above.)

4. Labeling for all poison treatment drug products has been revised to change the order of listing of sources of help and information for poison treatment from "physician, poison control center or emergency room" to "poison control center, emergency medical facility, or health professional." (See comment 7 above.)

5. Labeling is being divided into two distinct sections: First, the principal display panel would contain the following instruction in a conspicuously boxed area: "If possible, call a poison control center, emergency medical facility, or health professional for help before using this product. If help cannot be reached quickly, follow the directions (manufacturer to indicate location of directions, e.g., on the back of the bottle)." The statements, "Read the warnings and directions as soon as you buy this product." "Insert emergency phone number(s) in space provided on the label," must also appear prominently on the principal display panel. Second, full warnings and directions are to be placed on a separate portion of the label. (See comment 9 above.)

6. A space for writing in the phone number(s) of the appropriate poison control center or other emergency medical facility must be provided on the principal display panel. (See comment 9 above.)

7. The terms "for the treatment of poisoning," "emergency first aid treatment for poisoning," "emergency treatment for poisoning," "emergency treatment for accidental poisoning," "for the treatment of accidental poisoning," "emergency first aid treatment for accidental poisoning," "emergency poison treatment," and "first aid poison treatment" have been proposed as other allowable statements for all poison treatment drug products. (See comment 15 above.)

8. The indication statement for ipecac syrup has been revised to read "for emergency use to cause vomiting of swallowed poisons." The indication statement for activated charcoal has been revised to read "for emergency use to adsorb swallowed poisons." (See comment 15 above.)

9. The dosage of ipecac syrup for individuals 1 year of age and over has been revised to allow manufacturers to express the dosage in terms of container size i.e., 1 or ½ bottle. (See comment 22 above.)

10. The warning "Do not use in semiconscious or unconscious persons" previously proposed for ipecac syrup has been revised to read "Do not use in persons who are not fully conscious." (See comment 23 above.)

11. The corrosive-petroleum distillate warning for ipecac syrup has been revised to read "Do not use this product, unless directed by a health professional, if turpentine, corrosives, such as alkalies (lye) and strong acids, or petroleum distillates, such as kerosene, gasoline, paint thinner, cleaning fluid, or furniture polish, have been ingested." (See comment 24 above.) This same warning is being proposed for activated charcoal products. (See comment 51 above.)

12. The warning "Do not administer milk or carbonated beverages with this product" previously proposed for ipecac syrup has been revised to read "Do not administer milk with this product." (See comment 28 above.)

13. The directions for ipecac syrup have been revised to provide for water or other clear liquids to be administered following ipecac syrup. (See comment 28 above.)

14. The drug interaction precaution for emetics has been revised to read "*Drug Interaction Precaution*: Activated charcoal will adsorb ipecac syrup. Do not give activated charcoal until after patient has vomited unless directed by a health professional." (See comment 29 above.)

15. The adult dose of ipecac syrup has been increased from 15 mL to 30 mL. (See comment 32 above.)

16. A dosage of ipecac syrup for children under 6 months of age is no longer provided in the monograph. A statement advising that ipecac syrup should not be given to children under 6 months of age unless directed by a health professional has been added to the monograph. (See comment 33 above.)

17. The time interval between the first and second doses of ipecac syrup has been increased from 20 to 30 minutes. (See comment 35 above.)

18. The directions for all poison treatment drug products have been revised to include the statement "If previous attempts to contact a poison control center, emergency medical facility, or health professional were unsuccessful, continue trying." (See comment 36 above.)

19. The directions for poison treatment drug products have been revised to include the statement "Keep patient active and moving." (See comment 38 above.)

20. The warning against use of activated charcoal before vomiting has occurred has been revised to read "Do not give activated charcoal until after patient has vomited unless directed by a health professional." (See comments 29, 43, and 51 above.)

21. Formulations for activated charcoal now provide for dosage forms other than a powder. (See comment 44 above.)

22. The dosage for activated charcoal has been revised to provide a range of 20 to 30 g. (See comment 46 above.)

23. The statement of identity for activated charcoal, "adsorbent," has been revised to "poison adsorbent" or optionally "emergency poison adsorbent" or "first aid poison adsorbent." (See comment 47 above.)

24. The directions for use of activated charcoal have been revised to require that the dose be administered in a minimum of 8 oz of liquid. (See comment 48 above.)

25. The statement "Repeat dose immediately, if possible" has been added to the directions for activated charcoal. (See comment 50 above.)

26. The contents of the poison treatment kit have been revised to provide for a content of one 30-mL container of ipecac syrup and a minimum of 1 adult dose of activated charcoal (20 g). Although kit contents are limited to 30 mL of ipecac syrup, there is no restriction on the size or number of containers of activated charcoal in the kit. (See comment 54 above.)

27. The direction "Save the container of poison" has been proposed for all poison treatment drug products. (See comment 56 above.)

28. The agency advises that those portions of § 201.308 and § 369.21 applicable to ipecac syrup will be revoked at the time that the final monograph becomes effective.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that not one of these rules, including this proposed rule for OTC poison treatment drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Public Law 96-354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC poison treatment drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC poison treatment drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC poison treatment drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on poison treatment drug products, a period of 120 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined that under 21 CFR 25.24(d)(9) (proposed in the **Federal Register** of December 11, 1979, 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 357

OTC drugs, Poison treatment drug products, Anthelmintic drug products, and Cholecystokinetic drug products.

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, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Part 357, Subpart A, to read as follows:

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

Subpart A—Poison Treatment Drug Products

Sec.

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

Subpart A—Poison Treatment Drug Products

§ 357.1 Scope.

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

(b) References in this subpart of 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) *Adsorbent.* An agent that causes another substance to adhere to its surface.

(b) *Emesis.* Vomiting.

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

§ 357.10 Active ingredients for poison treatment.

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.* The active ingredient is in a formulation such that the equivalent of one gram activated charcoal mets or exceeds the standards of adsorption for activated charcoal, U.S.P.

(b) *Ipecac syrup.* The active ingredient of the product is powdered ipecac. It is marketed as ipecac syrup, U.S.P. in the

quantity of 1 fluid ounce (30 milliliters) only.

§ 357.14 Poison treatment kit.

The kit is a single outer package labeled according to §§ 357.50 and 357.58 that consists of one 30 milliliter container of ipecac syrup identified in § 357.10(b) and a minimum of one dose 20 gram of activated charcoal identified in § 357.10(a).

§ 357.50 Principal display panel of all poison treatment drug products.

In addition to the statements of identity required in §§ 357.52, 357.54, or 357.56, the principal display panel contains the following information:

(a) The following statements should appear in a conspicuously boxed area.

(1) "If possible call a Poison Control Center, emergency medical facility, or health professional for help before using this product."

(2) "If help cannot be reached quickly, follow the directions" (manufacturer to indicate location of directions, e.g., on the back of the bottle).

(3) "Read the warnings and directions as soon as you buy this product. Insert emergency phone number(s) in space provided on the label."

(b) A space must also be provided for writing in phone number(s) of the appropriate Poison Control Center, emergency mecical facility, or health professional.

§ 357.52 Labeling of activated charcoal drug products.

In addition to the labeling identified in § 357.50, the labeling of the product containing the ingredient identified in § 357.10(a) contains the following:

(a) *Statement of identity.* The labeling of the product includes the established name of the drug, if any, and identifies the product as a "poison adsorbent" "emergency poison adsorbent," or "first aid poison adsorbent."

(b) *Indication.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "For emergency use to adsorb swallowed poisons."

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

(1) "Do not give activated charcoal until after the patient has vomited unless directed by a health professional."

(2) "Do not use in persons who are not fully conscious."

(3) "Do not use this product, unless directed by a health professional, if turpentine, corrosives, such as alkalies (lye) and strong acids, or petroleum distillates, such as kerosene, gasoline, paint thinner, cleaning fluid or furniture polish, have been ingested."

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

(1) Oral dosage: 20 to 30 grams of activated charcoal in a minimum of 8 ounces of liquid or as directed by a health professional.

(2) "Repeat dose immediately, if possible."

(3) "If previous attempts to contact a poison control center, emergency medical facility, or health professional were unsuccessful, continue trying."

(4) "Keep patient active and moving."

(5) "Save the container of poison."

§ 357.54 Labeling of ipecac syrup drug products.

In addition to the labeling identified in § 357.50 the labeling of the product containing the ingredient identified in § 357.10(b) contains the following:

(a) *Statement of identity.* The labeling of the product includes 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 "For emergency use to cause vomiting of swallowed poisons."

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

(1) "Do not use in persons who are not fully conscious."

(2) "Do not use this product, unless directed by a health professional, if turpentine, corrosives, such as alkalies (lye) and strong acids, or petroleum distillates, such as kerosene, gasoline, paint thinner, cleaning fluid, or furniture polish, have been ingested."

(3) "Do not administer milk with this product."

(4) "*Drug Interaction Precaution:* Activated charcoal will adsorb ipecac syrup. Do not give activated charcoal until after the patient has vomited, unless directed by a health professional."

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

(1) Adults and children 12 years of age and over: oral dosage is 2 tablespoonsful (30 milliliters of 1 bottle) followed by 1 to 2 glasses (8 to 16 ounces) of water or other clear liquid or as directed by a health professional.

(2) Children 1 to under 12 years of age: oral dosage is 1 tablespoonful (15 milliliters or ½ bottle) followed by 1 to 2 glasses (8 to 16 ounces) of water or other clear liquid or as directed by a health professional.

(3) Children 6 months to under 1 year of age: oral dosage is 1 teaspoonful (5 milliliters) followed by ½ to 1 glass (4 to 8 ounces) of water or other clear liquid or as directed by a health professional.

(4) Children under 6 months of age: Do no administer unless directed by a health professional."

(5) "If vomiting does not occur within 30 minutes, repeat the dose."

(6) "If previous attempts to contact a poison control center, emergency medical facility, or health professional were unsuccessful, continue trying."

(7) "Keep patient active and moving."

(8) "Save the container or poison."

§ 357.56 Labeling of poison treatment kits.

The individual components of the kit must contain the labeling identified in §§ 357.52 and 357.54. The outer label of the kit must contain the information identified in § 357.50 and, in addition, the following:

(a) *Statement of identity.* The labeling of the product includes the established name of the drugs, if any, and identifies the product as a "Poison treatment kit," "Emergency poison treatment kit," or "Emergency first aid poison treatment kit."

(b) *Directions.* The labeling contains the following information under the heading "Directions": "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."

§ 357.58 Other allowable statements for poison treatment drug products.

The following additional statements may be included in the labeling of poison treatment drug products, but should not be included in conjunction with the required labeling identified in §§ 357.50, 357.52, 357.54, and 357.56:

(a) "For the treatment of poisoning."

(b) "Emergency first aid treatment for poisoning."

(c) "Emergency treatment for poisoning."

(d) "Emergency treatment for accidental poisoning."

(e) "For the treatment of accidental poisoning."

(f) "Emergency first aid treatment for accidental poisoning.

(g) "Emergency poison treatment."

(h) "First aid poison treatment."

§ 357.60 Nonapplicability of § 330.1(g) to poison treatment drug products.

The second portion of the warning required by § 330.1(g) concerning

accidental overdose is not required on poison treatment drug products.

Interested persons may, on or before May 15, 1985 submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. The agency has provided this 120 day period (instead of the normal 60 days) because of the number of OTC drug review documents being published concurrently. Written comments on the agency's economic impact determination may be submitted on or before May 15, 1985. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on May 15, 1985. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: December 31, 1984.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

[FR Doc. 85-682 Filed 1-14-85; 8:45 am]

BILLING CODE 4160-01-M

Federal Register

Tuesday
January 15, 1985

Part XI

Department of the Interior

Minerals Management Service to Delineate Areas of Interest for Further Evaluation for Potential Leasing of Strategic and Nonenergy Minerals Found in the Exclusive Economic Zone and Outer Continental Shelf

Call for Information

DEPARTMENT OF THE INTERIOR

Minerals Management Service

Call for Information to Delineate Areas of Interest for Further Evaluation for Potential Leasing of Strategic and Nonenergy Minerals Found in the Exclusive Economic Zone and Outer Continental Shelf

AGENCY: Minerals Management Service, Interior.

ACTION: Call for Information.

SUMMARY: The Minerals Management Service is requesting comments and information from interested parties to assist in the delineation of areas to be included in more detailed resource, environmental and economic reviews for possible leasing of minerals other than oil, gas, and sulphur in the Exclusive Economic Zone (EEZ) and Outer Continental Shelf (OCS). Responses to this Call will be used to establish priority areas for such reviews for the possible leasing of construction materials, placer deposits, phosphorites, polymetallic sulfides, cobalt-manganese minerals, or other nonenergy minerals within the EEZ and OCS on a case-by-case basis.

DATES: Comments and information in response to this request should postmarked or hand delivered no later than May 15, 1985.

ADDRESSES: Comments and information may be mailed or delivered to the Minerals Managment Service, Office of Strategic and International Minerals, Attention: Program Director, 11 Golden Shore, Suite 260, Long Beach, California 90802.

Proprietary Information

If information of a privileged nature is submitted, it should be enclosed in a separate sealed envelope and market PROPRIETARY. This information will be exempt from disclosure pursuant to the Freedom of Information Act (5 U.S.C. 552). Indications of interest are considered to be privileged information; however, the names of persons or entities indicating interest or submitting comments will be of public record.

FOR FURTHER INFORMATION CONTACT

Mr. Reid T. Stone, Office of Strategic and International Minerals, 11 Golden Shore, Suite 260, Long Beach, California 90802, telephone (213) 548–2901. FTS 796–2901.

SUPPLEMENTARY INFORMATION:

Background

Recent task force studies, workshops, and symposia included (1) a program feasibility study on nonenergy minerals leasing (with 23 appendices) of August 1979; (2) a workshop on OCS hard minerals at OCEANS '83, San Francisco, California, in September 1980; (3) a study entitled "National Ocean Goals and Objectives for the 1980's, MARINE MINERALS: An Alternative Mineral Supply," by the National Advisory Committee on Oceans and Atmosphere, July 1983; and (4) a symposium on a National Program for the Assessment and Development of the Mineral Resources of the United States Exclusive Economic Zone by the U.S. Geological Survey, Minerals Management Service, and Bureau of Mines at Reston, Virginia, in November 1983. These have each indicated substantial potential resources of strategic and other nonenergy minerals off our shores.

The resources may be classified basically in five groups: Construction materials, including sands, gravels, shells, and other high-bulk, low unit-value materials, placer deposits of metals or minerals containing gold, platinum, tin, titanium, thorium, or rare earths; phosphorites used primarily for the production of phosphatic fertilizers and found as shallow bedded deposits or as deposits formed as nodules, sands, or encrustations on the seabed; metalliferous oxides occurring as nodules or crusts in water depths from several hundred to several thousands of meters and containing significant amounts of the metals manganese, copper, nickel, and cobalt; and metalliferous sulfides found in a variety of possible forms at the surface of the seabed and beneath the surface in water depths, generally, of several thousand meters containing significant amounts of such as copper, zinc, cadmium, molybdenum, chromium, barium, strontium, silver, or gold.

The possibility of offering leases for the exploration and possible development of both metalliferous oxides and metalliferous sulfides is being evaluated for the area of Hawaiian Islands and the Gorda Ridge off Oregon and northern California, respectively. The initial step in each case will be to prepare an impact statement on the economic, engineering, and environmental impact of exploration and development in these areas, including any unavoidable adverse effects, appropriate alternatives, and other factors. No decision has been made to offer yet in either area. In the case of the other three commodity groups, no such specific proposals are under consideration.

In keeping with the mandates of the Mining and Minerals Policy Act of 1970 and the National Materials and Minerals Policy Research and Development Act of 1980 in which the Secretary of the Interior is required among other things to promote and encourage private enterprise in the development of economically sound and stable domestic materials industries, the advisability of developing a program for leasing of nonenergy minerals on the OCS on a case-by-case basis is being considered.

Purpose of Call

The purpose of the Call is to assist the Secretary of the Interior in carrying out his responsibilities under the OCS Lands Act (43–U.S.C. 1331–1343), as amended (92 Stat. 629), and to assist various Federal/State Task Forces and Regional Technical Working Groups in delineating areas of interest for strategic and other nonenergy minerals. Interested parties are requested to outline on a map areas within the EEZ and OCS that they believe have potential for development of construction materials, placer deposits, phosphorites, polymetallic sulfides, cobalt-rich manganese crust, and/or other nonenergy minerals that may occur and for which they may have an interest in leasing. Interested parties are also requested to identify areas that they believe should be excluded from consideration for leasing and the reasons therefore.

Use of Information for Call

Information submitted in response to this Call will be considered in the advisability of examining and possibly formulating a case-by-case leasing program for strategic and other nonenergy minerals. Comments received on possible environmental effects and use conflicts may be used in the analysis of specific environmental conditions within the Call area so that the potential effects of exploration, development, and mining, other than the benefits accruing to the Nation as a result of inventorying and producing minerals, can be assessed.

Description of the Areas

Construction Materials: The potential resources of construction materials on the U.S. continental shelves are considered excellent. In 1979, the OCS Mining Policy Task Force estimated sand and gravel resources of 830, 269, 29, and 19 billion cubic meters on the Atlantic, Gulf of Mexico, Pacific, and Hawaiian offshore areas, respectively. There is a large potential for sand and gravel offshore of Alaska.

A study of the northeastern continental margin to approximately 2,000 meters of water depth showed that

much of the shelf is mantled with sand of up to 3 meters thick and of considerable lateral continuity and that gravel is also present in a more discontinuous patchy distribution. These sand deposits were estimated at 400 billion tons. The inner continental shelf areas of the Atlantic, Gulf of Mexico, and southern California have been surveyed from the shore to 20 km seaward to assess marine sand and gravel resources. The results indicate nearly 17 billion cubic meters of sand and gravel within the upper 6 m of the seafloor. Seismic data suggest that in some regions the thicknesses and volumes are considerably greater. Sand is abundant in many regions; however, it varies considerably in textural properties and in some places is admixed with or covered by mud. Gravel is most common on glaciated shelf regions of the northeast and northwest, but south of about 40°N, gravel appears limited to a carbonate shall fraction or residual coarse sediment overlying outcrops of relict fluvial channel deposits or coastal plain strata. The most promising sand and gravel deposits ar associated with glacial moraines and drift, outwash-sand plains, and glaciofluvial deltas. Also promising are ancestral river channels that crossed the shelf in the Quaternary period prior to the Holocene transgression, as well as the various classes of shoals (e.g. linear, cape-associated, and tidal-inlet-associated) that are present from the shoreface to the shelf edge.

On the Pacific coast, deposits of sand and gravel occur near Grays Harbor off central Washington within shipping distance of the Portland and Seattle metropolitan areas. Deposits offshore of California are relatively small and fine-grained, consisting of relict beach and fluvial materials. One of the most promising deposits, because of its proximity to Los Angeles and San Diego, lies off Imperial Beach and consists of reworked gravel on the submerged former delta of the Tijuana River.

In Hawaii, a potential white-sand supply is located 35 km from Honolulu on Penguin Bank in water depths of 50–60 m. This area is believed to be part of a deposit containing 350 million cubic yards. This calcareous sand is located on drowned Pleistocene sea level terraces.

Placer deposits: Placer deposits show most potential for their heavy mineral content. Heavy-mineral sands of variable composition and grade on the Atlantic shelf have been estimated to be about 1.3 billion cubic meters or more. Surficial relict sand bodies, often occurring as ridges (submarine highs), are present over most of the Atlantic shelf. They range in thickness from about 20 m to 80–140 m near the shelf edge. Some of these relict features are interpreted as ancient shore deposits that formed as the ocean transgressed the shelf at the end of the most recent glaciation. Supporting evidence for this interpretation is the presence of submerged terraces and beach ridges which are the types of features associated with interim stages of change in sea level. It has been inferred that concentrations of heavy minerals are associated with these former shoreline features.

Heavy minerals have been identified in sediments within the inner New York Bight area. Marine sediments offshore of Virginia may have greater heavy mineral concentration than offshore areas to the south and are almost as rich as an onshore control area in South Carolina. Heavy-mineral placers have been mined onshore from ancient beach sands along the coasts of New Jersey, Georgia and Florida and from coastal plain deposits in New Jersey. Kyanite, sillimanite, ilmenite, zircon, and other heavy minerals occur in beach and nearshore sediments around the Apalachicola River and in various locations along the coasts of Florida, Alabama, Louisiana, and Texas.

No quantitative estimates of heavy-mineral sand on the Gulf of Mexico continental shelf are available. Identified or indicated heavy minerals of economic interest include many of the species found on the Atlantic shelf, but very little mineralogic information is available.

In northern California, gold occurrences have been reported in offshore sediments near Crescent City and offshore of rivers in southern California. Other heavy-minerals occurrences, especially zircon and chromite, have been reported in offshore sediments near Crescent City. Platinum has been reported in beach sediments near Crescent City, north of Orick, and at Monterey Bay. Heavy-minerals occurrences have been reported offshore of Oregon, seaward of rivers including Neholem, Rogue, Siltcoas, and Umpqua to water depths of 185 meters. Heavy-minerals occurrences also have been reported seaward of Cape Blanco and near the shelf break adjacent to the Rogue Submarine Canyon.

Discontinuous placer deposits have been identified along the coast of Washington from Cape Flattery to the Columbia River. Favorable locations for placer deposits are relict sand bodies paralleling the coast, submerged beaches, and offshore of the Columbia River. On the Pacific continental shelf, heavy-mineral sand of various composition and grade is estimated to be about 2.06 billion cubic meters. Gold and heavy-mineral sand deposits occur rather extensively in relict beaches, buried river channels, and in reworked Pleistocene gravels. High-grade titanium and zircon sands have been inferred to be widespread.

Submerged shorelines and stream channels offshore Alaska near Nome and Goodnews Bay are prime localities for gold placers. A shoal north-northeast of Cape Prince of Wales may contain heavy-mineral placers including gold. Other areas where onshore lode deposits of gold are near enough to the continental shelf to merit serious investigations included Captains Bay located within the western part of Alaska; the Aleutian Islands; west of Kodiak Island; lower Cook Inlet in Kamishak Bay extending around the lower end of Kenai Peninsula; and possibly Resurrection Bay near Seaward Peninsula.

Other offshore areas possessing potential for placers include offshore of the western part of St. Lawrence Island, Shelikof Straits, offshore of the Copper River Delta, and most of southeast Alaska.

No definite estimates are available for these resources in Alaskan waters, although there are some indications that heavy-mineral deposits may far exceed those of all the remaining EEZ.

Phosphorite deposits: Phosphorite deposits are known to occur off both the east and west coasts of the United States. Phosphorite has been dredged, cored, and/or photographed at the surface of the continental shelf from the sourthern part of Florida to the shelf off North Carolina. Drilling has shown that these deposits also occur at depth beneath the shelf in Middle Tertiary rocks.

Although the size of these deposits can be only roughly estimated, they represent an enormous resource of phosphorite. Approximately 2 billion metric tons of phosphorite are present on the Blake Plateau alone. About half this much is also present as a pavement in which the phosphorite is associated with ferromanganese oxides. An equal amount of phosphorite may exist off the coast of North Carolina in the form of bedded deposits below the seabed.

Phosphorites off the coast of California have been widely recovered from the tops of submarine banks and ridges in the continental borderland and have been dredged from rather steep slopes at depths as great as 3,000 meters

and from the shelf to the north near Monterey Bay. This deposit represents a resource of approximately 115 million metric tons.

Phosphorite has been recovered from several seamounts in the Pacific Ocean, where it is usually associated with cobalt-rich ferromanganese oxides. The size of these deposits is only superficially delineated at present.

Surficial phosphorite deposits off both coasts are considered to be lag deposits that have been eroded from rocks of Middle Tertiary age. The phosphorite ranges in size from pellets to pavements but most often occurs as irregular-shaped nodules. The phosphate mineral is francolite and is associated with caronate sands. The source beds crop out on land, and in Florida they are dominantly limestones. In California, they include dolomite and highly siliceous rocks, many with high concentrations of organic carbon.

In Onslow Bay, about 100 kilometers offshore of North Carolina, preliminary evaluations have indicated a vast phosphate resource potential occurring in the Miocene Pungo River formation. This formation is a major sedimentary phosphorite unit under the coastal plain and outcrops offshore as a northeast-southwest belt about 150 kilometers long by 40 kilometers wide and dips into the subsurface to the southeast. The economically valuable beds within this formation have been estimated to contain 1.36 billion metric tons of phosphate concentrated grading between 28 to 30 percent phosphate.

Polymetallic sulfide deposits: Polymetallic sulfides have been found along several seafloor spreading centers in the Pacific Ocean. The active zone of spreading can be hundreds of kilometers long but is usually less than 2 km wide. Deeply circulating hot seawater leaches heavy metals (zinc, silver, copper, manganese, cadmium, iron, etc.) and sulphur at high temperatures from the surrounding rocks. The upward movement of these hot mineral-rich waters is confined to narrow channels. Upon reaching the seafloor, the water discharges upward in a plume called a smoker. The sudden mixing with the cold seawater causes metallic sulfide minerals to be precipitated in mounds and chimneys around the vents. Subsurface concentrations of massive metallic sulfide minerals may also be formed in the vicinity of active vents and in areas of active spreading which are covered by thick sediment. Such deposits may be preserved and carried with the spreading plate—far from the spreading centers.

More than six smokers have been found on the Juan de Fuca Ridge. A sample recovered near a smoker just outside the EEZ was almost pure zinc sulfide (55 percent zinc) and contained 300 parts per million silver.

Microscopic amounts of metallic sulfides have been identified in rock samples recently collected from the Gorda Ridge suggesting the presence of hydrothermal activity in the area.

Polymetallic sulfides may also be deposited on the flanks of active volcanoes in back arc basins such as that of the Northern Marianas and around volcanoes formed over hot spots in the crust like the Hawaiian Islands.

Cobalt-rich manganese oxide crusts: These crusts occur on flank areas of islands and seamounts in the Pacific region including the Hawaiian archipelago. Measured cobalt content ranges from 0.4 percent in the crusts in deeper water to 1.2 percent in the crusts on seamount tops in waters less than 2,500 meters. The mean crust thickness is more than 2 centimeters (cm) in upper slope areas and may be as thich as 6–8 cm. Accessible concentrations could yield 16 kg per square meter of crustal surface. The monetary value per unit area of cobalt, nickel, manganese, copper, and molybdenum in these crusts is significantly greater than in known deepwater nodules.

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Instructions on Call

Indications of interest should be limited to the OCS, as defined in the OCS Lands Act, which extends a minimum of 200 miles from the coasts of the states of the Union. Respondents are requested to rank areas according to priority of interest (e.g. priority 1, 2, and 3).

Dated: January 9, 1985.

William D. Bettenberg,

Director, Minerals Management Service.

[FR Doc. 85–1099 Filed 1–14–85; 8:45 am]

BILLING CODE 4310-MR-M