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(HFA-305)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

21 CFR PART 341

50 FR 2220
1/15/85

[DOCKET NO. 76N-052N]

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

Comments 5/15/85

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.

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DATES: Written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by (insert date 120 days after date of publication in the FEDERAL REGISTER). New data by (insert date 12 months after date of publication in the FEDERAL REGISTER). Comments on the new data by (insert date 14 months after date of publication in the FEDERAL REGISTER). 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 (insert date 120 days after date of publication in the FEDERAL REGISTER).

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:

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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 Antiasthmatic 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 antiasthmatic 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 conclusions 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 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 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 a 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 or 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 physician. (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 should 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 throats 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 used 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, pharmacology, 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 l-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 l-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 l-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 l-desoxyephedrine and the combination of l-desoxyephedrine and aromatics, when compared to baseline measurements or placebo. Study 75-45 (Ref. 5) showed that l-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 l-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 l-desoxyephedrine. The data demonstrate that this ingredient does not cause rebound nasal congestion within a 7-day period. Therefore, the use of l-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 Rhinorheometer 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 recommended.

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 in 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 that 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 of 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 repeated 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 enlarged prostate should 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 Pharmacology 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 reponsibility 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 dosages 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), (v)(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 date 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 comments 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. CO112, Docket No. 76N-0052, Dockets Management Branch.

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

(3) Kuntzman, R. G., et al., "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 Management 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 Management 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, C., 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., et al., "A Bioavailability and Safety Study Comparing Actifed[R] 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, Burroughs-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 "difficulty 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)(1)(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 (Refs. 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 pnysician 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) in 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 in § 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 the 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 of 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 that camphor, thymol, menthol/peppermint oil, and eucalyptol/eucalyptus 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

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 0.1-percent concentration of xylometazoline, the agency concludes that, based on the Panel's recommended concentrations, which the agency has adopted in this tentative 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)(iv): "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 contended 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 autonomic nervous system enough during testing to 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 resistance 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 abstain 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 resistance. 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 recommended 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
Racephedrine 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	*
Phenylpropanolamine hydrochloride (oral)	I	*
Phenylpropanolamine maleate (oral)	I	*
Phenylpropanolamine hydrochloride (topical)	III	*
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

*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 l-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 addition to the required labeling for all topical nasal decongestants, specific labeling requirements for l-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 Cardiovascular System of the Cat," Archives Internationales de Pharmacodynamie 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 identified 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 l-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 l-desoxyephedrine and propylhexedrine when used in an inhaler become 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 type 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 § 341.80(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)(6) (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 no 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, 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 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 not 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.