comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

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

Dated: December 31, 1984.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

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Part VIII

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 341

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 341

[Docket No. 76N-052H]

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

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) antihistamine drug products (drug products used for the relief of the symptoms of hay fever and upper respiratory allergies (allergic rhinitis) and the symptoms of sneezing and runny nose associated with the common cold) 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 antihistamine drug products and is part of the ongoing review of OTC drug products conducted by FDA.

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

ADDRESS: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of September 9, 1976 (41 FR 38312) FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products, together with the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and 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 antiasthamtic 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 availaable 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 reopended have also been put on display in the Dockets Management Branch. In response to the advance notice of proposed rulemaking, 12 manufacturers, 2 manufacturers' associations, 16 health care professionals, and 6 health care professional societies submitted comments on antihistamine drug products. 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 antihistamine drug products is the fifth 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 productss, 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 fourth segment, on nasal decongestant 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), FDA states for the first time its position on the establishment of a monograph for OTC antihistamine 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 antihistamine 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 durg 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 paragraph (d); in Subpart B, by adding new § 341.12; and in Subpart C, by adding new § 341.72, and by adding in § 341.90, new paragraphs (b), (c), (d), (e), (f), (g), (h), (i), (j), and (k). This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC antihistamine 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 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 durg 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 show new labeling and have their products in compliance in the marketplace. However, if the agency detemines 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 doxylamine succinate be classified in Category I as an antihistamine at adult oral dosages of 7.5 to 12.5 milligrams (mg) every 4 to 6 hours, not to exceed 75 mg in 24 hours (see 41 FR 38419). However, since the Panel's report was published, controversy has arisen concerning whether or not there is an association of a prescription drug product containing doxylamine succinate with birth defects. This drug product is prescribed as an antinauseant for use during pregnancy. In 1982, Eskenazi and Bracken (Ref. 1) reported the results of a case control study of 1747 women, which suggests that a child born to a mother who used the doxylamine containing product was at an approximately four fold increased risk for developing pyloric stenosis. The Boston Collaborative Drug Surveillance Program recently reported to the agency preliminary results of a cohort study that also found an association between exposure to a product containing doxylamine succinate during pregnancy and the occurence of pyloric stenosis in infants. The reported increase in risk was 2.7 fold, a finding consistent with the Eskenazi and Bracken study. Preliminary results from this study suggest risk increasing with increasing numbers of prescriptions. These reports, however, do not establish that the association is causal. Other factors, in particular, the nausea and vomiting, may account for the observed association. Mitchell et al. (Ref. 2) recently presented the findings of a case-control study conducted by the Drug Epidemiology Unit of Boston University. This study, representing by far the largest available data base, compared the use of a product containing doxylamine succinate among the mothers of 325 infants with pyloric stenosis to its use in mothers of 3,153 infants with other malformations. No association between the use of a product containing doxylamine succinate during pregnancy and the development of pyloric stenosis was found. In addition, the agency has examined Medicaid data to determine whether in this data base there is an association between the use of a doxylamine succinate containing drug

product by women during pregnancy and the occurrence of pyloric stenosis in infants (Ref. 3). Based on an analysis of these data, the agency has concluded that the Medicaid data do not support such an association.

The agency is aware that at this time the scientific and medical communities are actively discussing and debating whether or not doxylamine succinate, in fact, plays a causal role in reported birth defects. This subject has been discussed and debated without resolution at several scientific meetings such as the Teratology Society meeting and the Society for Epidemiologic Research meeting that were held in June 1984. The possible association of doxylamine succinate with birth defects continues to be disputed.

The time necessary to complete a full review and evaluation of the new studies concerning the use of a product containing doxylamine succinate and birth defects could result in a considerable delay in the publication of the tentative final monograph for OTC antihistamine drug products. Accordingly, the agency has decided to remove all discussion of the safety and effectiveness of doxylamine succinate from this document.

The agency intends to review and evaluate the new data and information concerning the relationship between doxylamine succinate and birth defects that is currently being generated in as expeditious a manner as possible. Based on its review and evaluation of the data and information, the agency will publish a separate document in the **Federal Register** addressing the status of this ingredient.

At this time, drug products containing doxylamine succinate as an OTC antihistamine will remain in the marketplace with the warning required for all OTC drug products, as follows: "As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product."

References

(1) Eskenazi, B., and M. Bracken, "Bendectin (Debenox) as a Risk Factor for Pyloric Stenosis," *American Journal of Obstetrics and Gynecology*, 144:919–924, 1982.

(2) Mitchell, A. A., et al., "Birth Defects in Relation to Bendectin Use in Pregnancy II. Pyloric Stenosis," *American Journal of Obstetrics and Gynecology*, 147:737–742, 1983.

(3) Rosa, F.W., draft of unpublished study, OTC volume 04HTFM, Docket No. 76N–052H, Dockets Management Branch.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on Antihistamine Drug Products

1. One comment stated that the Panel gave certain antihistamines (i.e., diphenhydramine, methapyrilene, phenindamine, pheniramine, promethazine, pyrilamine, and thonzylamine) Category I status on the basis of low-quality evidence. The comment stated that the Panel recognized that there were no controlled clinical trials for these drugs, that chronic toxicity studies in animals had not been performed, and that there was no evidence that systematic literature searches were conducted or that FDA adverse reaction files were studied. The comment concluded that these drugs have been adjudged "safe" on the basis of superficial information. The comment contended that controlled clinical trials are required for general recognition of safety and effectiveness. The comment recommended that a complete new review of cough and cold ingredients be conducted by FDA and that FDA impose an immediate ban of all ingredients that are not proven safe and effective by scientific studies equivalent to those required for prescription drugs.

In determining that certain antihistamines should be generally recognized as safe and effective for OTC use, the Panel followed applicable regulations relating to the OTC drug review. The regulations, at 21 CFR 330.10(a)(4)(i), state: "Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data."

The Panel's conclusions as to the safety of the aforementioned antihistamine drugs were arrived at in accordance with the above regulation. For the determination of safety, the Panel reviewed published and unpublished studies, Poison Control Center statistics, FDA adverse reaction reports, and other data in the literature, and it used clinical and marketing experience to corroborate these data.

Subsequent to the Panel's determinations, new data were developed concerning some of these ingredients. On the basis of these data, the agency has taken appropriate regulatory action and in this tentative final monograph is making necessary changes to the Panel's recommendation. For example, the Panel recommended classification of methapyrilene hydrochloride and methapyrilene fumarate in Category I as antihistamines. Subsequent to this recommendation, a National Cancer Institute (NCI) study, not available to the Panel, provided data from which the agency concluded that methapyrilene is a potent carcinogen in animals and must be considered a potential carcinogen in man. These data are on file in the Dockets Management Branch (address above) under Docket No. 75N–0244 and have been published (Ref. 1).

In June 1979, the agency initiated a recall of all oral and topical products containing methapyrilene. Manufacturers have voluntarily recalled all methapyrilene-containing products from the market, and FDA has withdrawn all NDAs for products containing methapyrilene. Products containing methapyrilene are considered misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352) and "new drugs" under section 201(p) of the act (21 U.S.C. 321(p)). The agency has therefore placed methapyrilene fumarate and methapyrilene hydrochloride in Category II in this document.

The Panel recommended a Category I classification for promethazine hydrochloride. However, the agency has concerns regarding the safe use of promethazine hydrochloride as an OTC antihistamine and has determined that although promethazine hydrochloride has been widely used as a prescription drug product with a relatively low incidence of serious adverse reactions, at this time general recognition of the safety of this ingredient for long-term use as an OTC antihistamine has not been adequately established. (See comment 9 below.) Therefore, the agency is proposing that promethazine hydrochloride be Category III at this time as an OTC antihistamine.

For the determination of effectiveness, the agency agrees that the studies on which the Panel based its conclusions concerning diphenhydramine hydrochloride, phenindamine tartrate, pyrilamine maleate, and thonzylamine hydrochloride were not well-controlled. However, the Panel reviewed published studies, as cited in its report, and used clinical and marketing experience to corroborate these studies. The agency concludes that the evidence in these studies and the Panel's expertise in evaluating the clinical and marketing experience are sufficient to establish

general recognition of effectivenes of these ingredients as antihistamines.

The agency has reviewed the Panel's recommendations and all of the supporting data and concludes that there is a sufficient basis to determine that brompheniramine maleate, chlorpheniramine maleate, diphenhydramine hydrochloride, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, and thonzylamine hydrochloride are generally recognized as safe and effective when used as ingredients in antihistamine drug products intended for OTC use.

Reference

(1) Lijinsky, W., M. D. Reuber, and B. N. Blackwell, "Liver Tumors Induced in Rats by Chronic Oral Administration of the Common Antihistamine Methapyrilene Hydrochloride," *Science*, 209:817–819, 1980.

2. Several comments pointed out that the table of symptoms and pharmacological groups in part II. paragraph B. of the Panel's report (41 FR 38320) omitted antihistamines as a pharmacological group for treating runny nose. The comments stated that both the report and the Panel's recommended monograph contain "running nose" as a Category I claim for antihistamines. Several of the comments also criticized the Panel's omission from the table, the report, and the monograph of antihistamines as a pharmacological group for treating "sinus congestion." These comments argued that because "congestion" is a symptom of allergic rhinitis, and the Panel has placed antihistamines in Category I for the alleviation of the symptoms of allergic rhinitis, "sinus congestion" should be included as a symptom to be treated with antihistamines.

The agency agrees the antihistamines were inadvertently omitted from the table of symptoms and pharmacological groups as a treatment for runny nose. Runny nose as may occur in allergic rhinitis is listed as a Category I claim for antihistamines in the Panel's report and in § 341.72(a) (1), (2), and (6) of its recommended monograph. Therefore, the table of symptoms and pharmocological groups in part II. paragraph B. is amended by the publication of this document.

The agency does not agree that antihistamines should be included in the table, report, or recommended monograph for the treatment of "sinus congestion." The Panel recommended antihistamines only for the treatment of specific symptoms, i.e., runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes associated with allergic rhinitis, and did not recommended antihistamines for the alleviation of all symptoms associated with allergic rhinitis, as stated by the comment. Sinus congestion may result in impaired sinus drainage due to nasal obstruction caused by allergic rhinitis or the "common cold." The Panel reviewed studies that measured the effects of antihistamines or nasal obstructions (Refs. 1, 2, and 3). These studies demonstrated that antihistamines did not reduce nasal obstruction and therefore did not aid in sinus drainage. To the contrary, the studies indicated that antihistamines may sometimes further aggravate nasal obstruction (Refs. 2 and 3). For that reason, the Panel placed antihistamines in Category II for claims for the relief of symptoms such as nasal obstructions, nasal stuffiness, etc. The Comments did not provide any data that demonstrate that antihistamines are effective in the treatment of "sinus congestion." The agency concurs in the Panel's Category II classification.

References

(1) OTC Volume 040306.
(2) OTC Volume 040114.
(3) OTC Volume 040123.

3. One comment stated that two antihistamines 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 comment did not provide any information or examples. It is not clear whether there was concern about the simultaneous ingestion of two drug products each containing antihistamines ingredients that are specifically labeled as "antihistamines" or the simultaneous ingestion of two different drug products both containing antihistamines ingredients but for different use, e.g., one product labeled for "nighttime sleep-aid use" with no labeling as an antihistamine and another product labeled for "antihistamines use."

The agency recognizes that such products are currently available in the OTC drug marketplace but is unaware of any information that would raise health concerns. It is unlikely that a consumer would concurrently take two different OTC drug products both containing antihistamines. The proposed labeling for antihistamines in this tentative final monograph specifically requires that the product's principal intended use, i.e., "antihistamines," be stated in the labeling. By reading the labels, a consumer is made aware that different drug products contain antihistamine intended to treat the same symptoms. Therefore it is unlikely that two such products would be taken simultaneously.

The agency recognizes that at least one antihistamine ingredient, diphenhydramine hydrochloride, because of its numerous pharmacologic properties, is marketed as an "antihistamines," "antitussive," and "nighttime sleep-aid" drug product. A consumer could simultaneously ingest two such products to alleviate concurrent symptoms. However, the agency is unaware of any information that this does occur. In addition, the agency is unaware of any data demonstrating that the simultaneous ingestion of two antihistamines labled for different uses would result in a significant safety problem.

Therefore, the agency believes that the proposed labeling for antihistamines drug products in this tentative final monograph is adequate and that at this time there is no justification for expanding the labeling to include specific warnings regarding the simultaneous ingestion of two antihistamines. The agency invites specific comments on this issue.

4. Several comments requested that antihistamines, such as chlorpheniramine maleate, be allowed to make claims for the treatment of symptoms of the common cold. Symptoms for which Category I labeling claims were requested included the relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes when associated with the common cold. Two comments provided new data describing the results of clinical studies in which chlorpheniramine maleate was evaluated for treating symptoms of the common cold (Ref. 1). Another comment stated that there was little evidence to substantiate the usefulness of antihistamines for treating symptoms of the common cold and that, in fact, there are studies that demonstrate a lack of effectiveness for the use of antihistamines in treating symptoms of the common cold. The comment did not identify these studies.

The agency has reviewed the new data submitted in support of the use of chlorpheniramine maleate in treating the symptoms of the common cold enumerated above. The data submitted included independently conducted, multicenter, double-blind studies in which chlorpheniramine maleate was compared with a placebo in patients with the common cold over a 7-day period. In design and overall methodology, these studies follow the guidelines recommended by the Panel for studying antihistamines in the treatment of symptoms associated with

the common cold. An additional study conducted by a single investigator included 196 patients with the common cold who were followed for a 2-day period. This study was similar to the multicentered studies except for the length of time the patients were studied. The studies provide evidence that chlorpheniramine is significantly more effective than a placebo in alleviating the symptoms of runny nose and sneezing associated with the common cold. However, the data do not provide statistical evidence to show that chlorpheniramine is effective in relieving itching of the nose or throat, or itchy, watery eyes associated with the common cold. The agency has, therefore, concluded that chlorpheniramine is effective in treating runny nose and sneezing associated with the common cold. Because the pharmacologic actions of the various Category I antihistamines are similar, the agency believes that the data submitted for chlorpheniramine allow Category I status for these claims to be extended to all Category I antihistamine active ingredients. Accordingly, an indication for the temporary relief of runny nose and sneezing associated with the common cold has been added to proposed § 341.72(b) of this tentative final monograph.

Reference

(1) Comment Nos. SUP004 and SUP005, Docket No. 76N-0052, Dockets Management Branch.

5. One comment recommended that, in view of the reported toxicity of brompheniramine maleate and chlorpheniramine maleate, the quantity of these antihistamines contained in OTC packages should be limited. For example, the comment recommended limiting brompheniramine and chlorpheniramine products to 24 foil-wrapped tablets for the 4-mg strength tablets and to 12 tablets for the 8- and 12-mg strength tablets. The comment also recommended that containers of larger quantities of these antihistamines have child-resistant closures. The comment did not provide any data to support its recommendations.

FDA has established quantity limitations for certain OTC drugs in order to limit the possibility of accidental poisoning of children. See, for example, 21 CFR 201.308 (ipecac syrup) and 21 CFR 201.314 (children's aspirin). The Consumer Product Safety Commission (CPSC), however, has the authority to require child resistant closures for OTC drug containers. FDA is aware that CPSC has reviewed the available data on antihistamines to determine if child-resistant closures are warranted for OTC drug products containing these ingredients. CPSC has published a final rule that drug products containing more than 75 mg diphenhydramine hydrochloride in a single package and in a dosage form intended for oral administration be required to have child-resistant packaging. (See CPSC Requirements for Child-Resistant Packaging: Diphenhydramine Hydrochloride published in the Federal Register on February 15, 1984; 46 FR 5337.) CPSC found that serious toxic effects can be produced with doses of diphenhydramine hydrochloride as low as 100 mg.

CPSC reviewed the toxicity of antihistamines other than diphenhydramine. However, it did not propose that any antihistamine other than diphenhydramine be required to be packaged with child-resistant closures. Because of the lack of significant toxicity data for antihistamines other than diphenhydramine, CPSC concluded that child-resistant closures were not necessary for these drugs, regardless of the amount of drug contained in each package.

The comment did not submit any data demonstrating a need to limit the package size of non-diphenhydramine antihistamine drug products. Moreover, FDA does not have other data or information showing that limiting the package size for these antihistamines is necessary. In the case of diphenhydramine, CPSC is requiring that child-resistant closures be used for packages of drug products containing greater than 75 mg diphenhydramine. If the agency proposed limiting the package size of such drug products to 75 mg diphenhydramine or less, each package would contain only six children's doses of 12.5 mg or one and one-half adult doses of 50 mg. Limiting the package size to such low numbers of dosages would be impractical. The agency believes that CPSC's requirement for child-resistant closures for drug products containing diphenhydramine provides a sufficient safeguard against accidental overdose in children, and that package size limitations are therefore unnecessary for such drug products.

B. Comments on Switching Prescription Antihistamine Active Ingredients to OTC Status

6. Several comments agreed and others disagreed with the Panel's recommendation to allow the OTC marketing of certain antihistamines which were previously available only by prescription or at higher dosage levels than those currently permitted for OTC use. The comments which disagreed with the Panel unanimously recommended that those antihistamines which were previously available by prescription only, i.e., promethazine hydrochloride, diphenhydramine hydrochloride, brompheniramine maleate, chlorpheniramine maleate at a dosage of 4 mg, should remain prescription products. In general, the comments expressed opinions, without supporting data, that the benefits obtained from allowing these antihistamines to become available OTC would not outweigh the risks to which consumers would be exposed. Among the risks mentioned were (1) toxic effects from overdosage, (2) varying degrees of drowsiness and different adverse reactions in different patients, (3) a potential for becoming dependent on the sedative effect of antihistamines, (4) the development of a tolerance to antihistamines, and (5) confusion among consumers from too many antihistamines on the market. The comments also expressed concern that asthmatics with severe bronchitis would suffer from a thickening of secretions due to the anticholinergic effect of antihistamines.

In the preamble to the Panel's report at 41 FR 38313, the agency disagreed with the Panel's classification of diphenhydramine hydrochloride as a Category I antihistamine. The agency's objection to the Panel's recommendation to place these ingredients in Category I was based on the degree of drowsiness produced as a side effect. Subsequently, in a final decision concerning the OTC marketing of diphenhydramine hydrochloride as an OTC antitussive drug product, published in the Federal Register of August 31, 1979 (44 FR 51512), the Commissioner found that the risk of drowsiness in itself does not justify restricting a drug to prescription use if "the manufacturer provides essential information in the labeling and packages the drug in child-resistant containers." The requirement of child-resistant closures has been addressed in comment 5 above. The agency, therefore, is proposing in this tentative final monograph that diphenhydramine hydrochloride at an adult dosage of 25 to 50 mg and doxylamine succinate at an adult dosage of 7.5 to 12.5 mg every 4 to 6 hours be Category I as OTC antihistamine drug products. (See comments 8 and 15 below.)

The agency disagrees with a comment that contended that higher doses of chlorpheniramine maleate should not be allowed OTC. Chlorpheniramine maleate has been available by prescription at the 4-mg dosage level

and OTC at the 2-mg and the 4-mg dosage levels; however, data reviewed by the Panel shows that chlorpheniramine maleate at a dosage of 4 mg every 4 to 6 hours is the minimum effective dosage for adults. Therefore, the agency is proposing that chlorpheniramine maleate be available OTC at the 4-mg dosage. The warning statements proposed in § 341.72 of this tentative final monograph will advise consumers of the appropriate use of antihistamines and of the risks associated with them. (See comment 12 below.)

The agency agrees with the Panel's classification of brompheniramine maleate and is proposing that this ingredient be Category I.

Issues regarding the safety of promethazine hydrochloride have not yet been resolved. The agency is proposing a Category III classification of this ingredient at this time. (See comment 9 below.)

7. One comment contended that the antihistamine dexchlorpheniramine maleate should be made available OTC. The comment explained that chlorpheniramine maleate, which the Panel classified as a Category I antihistamine, is a mixture of dextro- and levo-optical forms in which most of the activity of the antihistamine results from the dextro-optical form. The comment pointed out that dexchlorpheniramine maleate is composed of the dextro-optical form. The comment argued that a small dose of the more active dexchlorpheniramine would give the same effectiveness as a larger dose of chlorpheniramine and would, therefore, be safer because patients would be exposed to a small amount of active ingredient. The comment cited "The United States Dispensatory" (Ref. 1) in support of its argument, as follows: "* * * it would appear that administration of the dextro isomer in half the dose of the racemic compound would provide practically the same antihistaminic activity as the latter (i.e., chlorpheniramine) and but half of its toxic effects; the expectation has been confirmed clinically." The comment recommended that the agency classify dexchlorpheniramine maleate as a Category I antihistamine in doses of 2, 4, and 6 mg.

Dexchlorpheniramine maleate is currently marketed under an approved abbreviated new drug application (ANDA) as a prescription drug at a dose of 2 mg every 4 to 6 hours for adults, a dose of 1 mg every 4 to 6 hours for children 6 to under 12 years of age, and a dose of 0.5 mg every 4 to 6 hours for children 2 to under 6 years of age (Refs. 2 and 3). Chlorpheniramine maleate is currently marketed as an OTC antihistamine drug, and the agency is proposing to place chlorpheniramine maleate in Category I at a dose of 4 mg every 4 to 6 hours for adults and a dose of 2 mg every 4 to 6 hours for children 6 to under 12 years of age. (See comment 12 below.)

An in vitro and an in vivo study of dexchlorpheniramine maleate, chlorpheniramine maleate (racemic mixture), and the levo-optical form of chlorpheniramine maleate in guinea pigs and dogs has demonstrated that the dextro-optical form (dexchlorpheniramine maleate) of chlorpheniramine maleate is the active moiety in the racemic mixture (Ref. 4). The data from this study demonstrate that dexchlorpheniramine maleate has approximately twice the antihistaminic activity of chlorpheniramine maleate (racemic mixture). Therefore, the appropriate OTC dosages for dexchlorpheniramine maleate are half the proposed dosages for chlorpheniramine maleate.

A review of FDA adverse reaction reports since 1976 (Ref. 5) indicates that only one adverse reaction (a patient fainting) has been reported in cases where dexchlorpheniramine maleate was the only drug given.

Based on the safe and effective use of dexchlorpheniramine maleate under an approved ANDA, the safe and effective use of chlorpheniramine maleate for many years as an OTC antihistamine, and a review of FDA adverse reaction reports, the agency believes that dexchlorpheniramine maleate can be generally recognized as safe and effective for OTC use. The agency is therefore proposing that dexchlorpheniramine maleate be classified as Category I as an OTC antihistamine at a dose of 2 mg every 4 to 6 hours, not to exceed 12 mg in 24 hours, for adults and a dose of 1 mg every 4 to 6 hours, not to exceed 6 mg in 24 hours, for children 6 to under 12 years of age. The agency also proposes a dose of 0.5 mg every 4 to 6 hours, not to exceed 3 mg in 24 hours, for children 2 to under 6 years of age under professional labeling in the tentative final monograph. The labeling warnings are identical to those being proposed for chlorpheniramine maleate.

Only timed-release dosage forms are currently approved for adult doses greater than 2 mg every 4 to 6 hours. An approved NDA is required for such products. (See comment 13 below.) Therefore, dosages of 4 to 6 mg will not be included in this tentative final monograph.

Although the agency is proposing in this tentative final monograph to switch dexchlorpheniramine maleate to OTC use from its present status as a prescription drug, OTC marketing may not begin at this time. In the **Federal Register** of June 3, 1983 (48 FR 24925), FDA explained the enforcement policy for drugs that were originally on prescription status but which were being proposed for OTC marketing under the OTC drug review. As noted there, 21 CFR 330.13 permits OTC marketing of a drug previously limited to prescription use prior to publication of a final monograph provided that certain conditions are met. To qualify for such treatment, the drug must, at a minimum, have been considered by an OTC drug advisory review panel and either recommended for OTC marketing by the panel or subsequently determined by FDA to be suitable for OTC marketing. Dexchlorpheniramine maleate was not considered by a panel and, therefore, does not qualify for early OTC marketing under the terms of the enforcement policy set out in § 330.13. Moreover, FDA believes that the drug is not appropriate for OTC marketing at this time. FDA believes that public comments submitted in response to the proposed switch in status should be evaluated before OTC marketing is begun. Accordingly, until such comments are reviewed, dexchlorpheniramine maleate remains a prescription drug subject to the terms and conditions specified in its approved ANDA.

References

(1) Osol, A., R. Pratt, and A.R. Gennaro, "The United States Dispensatory," 27th Ed., J.B. Lippincott Co., Philadelphia, p. 302, 1973.

(2) Letter from M. Seife, FDA, to Schering Corporation, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.

(3) Copy of FDA-approved labeling from ANDA 86-835, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.

(4) Roth, F. E., and W. M. Govier, "Comparative Pharmacology of Chlorpheniramine (Chlor-trimeton) and It's Optical Isomers," *Journal of Pharmacology and Experimental Therapeutics*, 124:347-349, 1958.

(5) Department of Health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listing," pertinent pages for the years 1976-1982, included in OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.

8. A number of comments discussed the Panel's recommendation to allow diphenhydramine hydrochloride to be marketed OTC for use as an antihistamine. The comments varied from complete disagreement with the Panel's recommendation to suggestions that the agency place limitations on the

strength of the tablets and/or the size of the packages and that child-resistant closures be required for all OTC products containing this ingredient. One comment suggested that diphenhydramine hydrochloride be available OTC only after consultation with a pharmacist or "prescriber." All of the comments were concerned about diphenhydramine hydrochloride's pronounced tendency for causing drowsiness.

In the preamble to the Panel's report at 41 FR 38313, the agency dissented from the Panel's Category I classification of diphenhydramine hydrochloride as an OTC antihistamine ingredient. It was pointed out that at that time no product containing diphenhydramine hydrochloride was marketed OTC as an antihistamine at any dosage level. In the preamble to the Panel's report, the agency also deferred a decision on the Panel's recommendation to place diphenhydramine hydrochloride in Category I as an antitussive ingredient until the agency made a decision concerning a pending supplemental NDA for OTC status of diphenhydramine hydrochloride as an antitussive. Subsequently, in a final decision concerning the OTC marketing of diphenhydramine hydrochloride as an antitussive drug product published in the **Federal Register** of August 31, 1979 (44 FR 51512), the Commissioner found that the risk of drowsiness in itself does not justify restricting a drug to prescription use if "the manufacturer provides essential information in the labeling and packages the drug in child-resistant containers." Diphenhydramine presently is marketed OTC as an antitussive under an approved supplemental NDA.

The agency believes that the proposed warning in this tentative final monograph that reads "May cause marked drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery" and the warning for products labeled for children under 12 years of age that reads "May cause marked drowsiness" are adequate to allow OTC marketing of diphenhydramine hydrochloride. These warnings are similar to those required under the approved supplemental NDA for the antitussive drug product containing diphenhydramine.

The agency, therefore, is proposing diphenhydramine hydrochloride as Category I in this tentative final monograph for use as an OTC antihistamine at an adult dosage of 25 to 50 mg every 4 to 6 hours, not to exceed 300 mg in 24 hours, and for children 6 to 12 years of age at a dosage of 12.5 to 25 mg every 4 to 6 hours, not to exceed 150 mg in 24 hours.

9. Many comments were opposed to the Panel's classification of promethazine hydrochloride as a Category I antihistamine for relieving the symptoms of allergic rhinitis. These comments agreed with the agency's decision (as stated in the preamble of the Panel's advance notice of proposed rulemaking) to limit promethazine hydrochloride to its present status as a prescription drug. The comments asserted that promethazine should not be available on an OTC basis because of (1) its adverse side effects (especially sedation and blood dyscrasias), (2) the potential for abuse and overdosage, (3) the risk in children, and (4) the possibility of increased development of promethazine-induced dyskineasias. The comments concluded that the risk of adverse effects from the OTC availability of promethazine hydrochloride is not justified in the absence of an offsetting benefit in the form of therapeutic superiority in comparison with antihistamine ingredients already marketed OTC.

Only one comment (a reply comment) agreed with the Panel's Category I classification, contending that promethazine has an outstanding safety record based on its long history of use, that there was no basis for implicating promethazine hydrochloride as the cause for blood dyscrasias, and that promethazine hydrochloride cannot be distinguished from other OTC antihistamines in terms of its sedative and other adverse effects on the central nervous system.

After reviewing these comments, the Center for Drugs and Biologics (CDB) expressed its concerns regarding the effect of promethazine hydrochloride on the central nervous system in a feedback letter to a manufacturer (Ref. 1). Based on an incidence of 1 in 2,468 (0.04 percent) of extrapyramidal syndrome associated with the use of promethazine hydrochloride that was cited by the Panel (41 FR 38390) and a report of four cases of choreoathetosis that were related to the use of promethazine at dosages comparable to those recommended by the Panel (Ref. 2), the CDB questioned whether a drug with the side effect of choreoathetosis and a known incidence of extrapyramidal side effects has an acceptable benefit-to-risk ratio for OTC use. The agency had previously stated in the preamble of the Panel's report (41 FR 38312) that children seem particularly liable to develop adverse central nervous system reactions, such as extrapyramidal disturbances from the use of promethazine, CDB added that it does not consider the rare drug-related cases of blood dyscrasias an issue that would preclude OTC use of this ingredient inasmuch as other OTC antihistamines also can be associated with such reactions, but because of its other concerns was proposing that promethazine hydrochloride be placed in Category III.

In response to this letter, the manufacturer petitioned the agency to reopen the administrative record for the OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products rulemaking to include new data and information regarding the safety of promethazine hydrochloride (Refs. 3 and 4). The new data and information submitted by the manufacturer clarify the data regarding the incidence of extrapyramidal effects associated with the use of promethazine in both adults and children and point out errors in the data cited by CDB regarding the association between the use of promethazine and the occurrence of choreoathetosis. The agency has included these data and information in the administrative record for this rulemaking in reaching its decision on the status of promethazine in this tentative final monograph (Ref. 5).

The manufacturer noted that the CDB's information on the 0.04 percent incidence rate of extrapyramidal syndrome was based on only one case in 2, 468 patients, as cited by the Panel at 41 FR 38390. The manufacturer stated that its review of the single case report disclosed that it involved the injectable dosage form of promethazine and not the oral dosage form. The agency has confirmed that this is correct. The 0.04 percent incidence rate was derived from the Panel's review of adverse reaction reports from the Boston Coillaborative Drug Surveillance Program (BCDSP) and the University of Florida Adverse Reaction Study. The manufacturer included in its petition a statement from Jick, a recognized epidemiologist of the BCDSP, that the one case cited by the Panel is the only United States case of extrapyramidal syndrome reported through the BCDSP program (Ref. 4). Jick added that the data in BCDSP were updated through the end of 1981, and four additional cases of extrapyramidal symptoms, all of which were from Western Europe, were identified. Of the four cases, three involved injectable promethazine in relatively high doses, and only one case involved a patient who received oral promethazine. Jick

stated that the patients were elderly, had chronic pulmonary problems and other serious disorders, and received other medications that are likely to have influenced what occurred. Jick concluded that the data do not indicate that promethazine at the suggested OTC oral dosages would present any important risk of the occurrence of extrapyramidal symptoms.

The manufacturer added that the only other reference cited in the agency's letter that describes cases of extrapyramidal effects associated with promethazine was the ADR Highlights (Ref. 2). Fourteen cases are described, of which four purportedly involved promethazine. The manufacturer stated that the ADR Highlights omitted information on the route of administration of the drug in addition to containing other errors on the drugs involved and the doses administered.

The agency acknowledges that inaccuracies existed in the data base and that correction of these errors leads FDA to conclude that the possibility of choreoathetosis occurring with OTC oral doses of promethazine is unlikely. This conclusion is supported by a review of FDA adverse reaction data for the period 1970–1981 and a review of the published literature. These sources reveal only a few cases of extrapyramidal effects possibly associated with dosages of promethazine that would be available OTC. Also, based on the above data, there is no evidence to indicate that these effects would be more likely to occur in children. Based upon the available data, the agency's concerns regarding the occurrence of extrapyramidal effects and choreoathetosis and the concern that children seem particularly liable to develop adverse central nervous system reactions to promethazine have been adequately addressed. Thus, these are no longer issues that would preclude use of this ingredient at proposed OTC oral dosages.

The agency has also reviewed additional information on promethazine obtained from the National Prescription Audit (NPA) and the National Disease and Therapeutic Index (NDTI) data systems (Ref. 6). The data show that promethazine hydrochloride has been widely used as a prescription drug product, primarily in combination with other active ingredients, with a relatively low incidence of serious adverse reactions. The agency has further concerns regarding the safe use of this ingredient solely as an OTC antihistamine drug product, particularly for extended periods of time as for allergy treatment. Promethazine hydrochloride is a phenothiazine, and long-term phenothiazine therapy has been associated with the occurrence of tardive dyskinesia (Ref. 7), a serious central nervous system syndrome that may persist indefinitely after discontinuation of the medication. Some of the comments also expressed concern about the possibility of increased development of promethazine-induced dyskinesias; however, specific cases of the occurrence of tardive dyskinesia with the use of promethazine hydrochloride have not been reported.

Based on data available to the agency (Ref. 6), FDA finds that promethazine hydrochloride has not been used extensively as an antihistamine on a long-term basis. A review of NPA and NDTI data for the period 1975 to 1981–1982 (Ref. 6) shows that the majcr use of the manufacturer's promethazine hyrochloride as a prescription drug is in combination products for acute cough/cold therapy. Single entity promethazine hydrochloride tablets are most frequently used for antiemetic actions and have the highest percentage of continued use. The data show that virtually all of the manufacturer's promethazine combination drug products are used for "cough/cold" indications while their use as an "antihistamine/anti-allergy" drug is virtually nil. The data also show that the single-ingredient promethazine drug products (i.e., tablets and syrup) are used as an antihistamine/antiallergy" drug to a limited degree (i.e., average of 12 percent of the NDTI mentions for the period 1975 to 1981–1982). In addition, the NDTI data indicate that these promethazine products are used mostly on a short-term rather than on a long-term basis, with the exception of single ingredient tablets (Ref. 6). The high ratios of new to refill prescriptions in the NPA data also demonstrate that these products are not used on a long-term basis with the exception of single ingredient tablets (Ref. 6). Long-term use of the single ingredient tablets most frequently represents its use as an antiemetic in chronic illnesses, such as cancer, and not as an antihistamine in patients with allergic rhinitis. The conclusion that promethazine hydrochloride has not been used extensively as an antihistamine on a long-term basis is further supported by the manufacturer's statement in its submission that "the average course of therapy under a prescription for an oral promethazine product is about 6–9 days" (Ref. 3).

The agency believes that many consumers who use OTC antihistamines to treat the symptoms of allergic rhinitis use these products on a long-term basis because the symptoms of allergic rhinitis usually occur for extended periods of time. However, promethazine hydrochloride has not been used extensively as an antihistamine on a long-term basis in the OTC target population, i.e., patients with allergic rhinitis. Therefore, there is no assurance that long-term use of promethaine hydrochloride as an OTC antihistamine will not cause the serious side effect tardive dyskinesia.

Accordingly, the agency remains unpersuaded that promethazine, as a phenothiazine, can be generally recognized as safe for OTC use. Many of the comments received in response to the Panel's Category I recommendation for promethazine hydrochloride were from health professionals who opposed OTC status for this drug. The CDB raised the concern in its May 7, 1982 letter that promethazine, as a phenothiazine, is distinct from other antihistamines in terms of its chemical structure and its adverse effects on the central nervous system (Ref. 1). In its petition (Ref. 4), the manufacturer acknowledged that promethazine is chemically related to phenothiazines, but that it is widely recognized that differences in chemical structures and pharmacology substantially lessen the possibility that promethazine could cause the range of side effects associated with other phenothiazines (Ref. 8). The manufacturer also stated that the Panel concluded, after analysis of published reference studies and adverse experience reports on promethazine, that this drug does not cause the wide range of serious or potentially toxic effects that characterize other members of the chemical class of phenothiazines (41 FR 38390). Despite the Panel's recommendation, at this time, FDA is not assured that general recognition of the safety of promethazine hydrochloride for OTC use has been adequately established. The agency is therefore proposing that promethazine hydrochloride as a single ingredient be Category III in this tentative final monograph. The agency specifically invites public comment on the issues discussed above and on the suitability of promethazine hydrochloride for OTC use as a single entity antihistamine drug. Combination drug products containing promethazine hydrochloride will be discussed in the combinations segment of the cough-cold tentative final monograph, in a future issue of the **Federal Register.**

References

(1) Letter from W.E. Gilbertson, FDA, to D.L. Shaw, Wyeth Laboratories, coded LET074, Docket No. 76N-052H, Dockets Management Branch.

(2) Mendelis, P.S., "Antipsychotic Drugs and Choreoathetosis," Adverse Drug Reaction Highlights, Division of Drug Experience, Center for Drugs and Biologics, FDA, Rockville, MD, January 25, 1982.

(3) Comment No. C00188, Docket No. 76N-052H, Dockets Management Branch.

(4) Comment No. CP0002, Docket No. 76N-052H, Dockets Management Branch.

(5) Letter from W.F. Randolph, FDA, to S.J. Land and W.W. Vodra, Arnold & Porter, coded PAV, Docket No. 76N-052H, Dockets Management Branch.

(6) Unpublished data obtained from the National Prescription Audit and the National Disease and Therapeutic Index data systems, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.

(7) Baldessarini, R.J., "Drugs and the Treatment of Psychiatric Disorders," *in* "The Pharmacologic Basis of Therapeutics," 6th Ed., edited by A.G. Gilman, L.S. Goodman, and A. Gilman, Macmillian Publishing Co., New York, pp. 391-447, 1980.

(8) Domino, E.F., "Antipsychotics: phenothiazines, Thioxamthines, Butyrophiones, and Rawolfia Alkaloids," *in* "Drill's Pharmacology in Medicine," 4th Ed., edited by J.R. DiPalma, McGraw-Hill Book Co., New York, p. 471, 1971.

C. Comments on Specific Antihistamine Active Ingredients

10. One comment submitted a study of the effectiveness of phenyltoloxamine citrate to support its reclassification from Category III to Category I as an OTC antihistamine active ingredient (Ref. 1).

The agency has reviewed the study and concludes that this study alone is inadequate to reclassify phenyltoloxamine citrate as a category I antihistamine active ingredient. After a statistical analysis of the data, the agency recognizes that the study demonstrates that there is a statistically significant difference between the pharmacologic action of the placebo and phenyltoloxamine in favor of the active ingredient at 1- and 2-hour intervals after a single dose has been given. However, the study does not demonstrate the effectiveness of phenyltoloxamine over a long enough period of time when given on a dosage schedule that would be representative of the actual conditions under which the drug would be used. The single-dose study can be characterized as a clinical pharmacology study and does not demonstrate that phenyltoloxamine citrate is clinically effective.

Additional data from multiple-dose clinical studies carried out over a period of at least 1 week, and including an adequate number of patients per dose level as well as placebo, demonstrating the effectiveness of phenyltoloxamine are necessary to reclassify this active ingredient in Category I. There may be a problem of carry-over effect in a crossover study in which each patient is on a drug for a week or more. Therefore, a sufficient washout period should be allowed if a crossover design is used. Phenyltoloxamine citrate will remain in Category III as an OTC antihistamine active ingredient until additional data are received, reviewed, and accepted by the agency.

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

References

(1) Comment Nos. C00168, LET003, and SUP007, Docket No. 76N-0052, Dockets Management Branch

(2) Letter from W.E. Gilbertson, FDA, to A.D. Flanagan, Warner/Chilcott, coded C00168/ANS, Docket No. 76N-052H, Dockets Management Branch.

D. Comments on Dosages for Antihistamine Active Ingredients

11. Several comments disagreed with the Panel's recommendation to increase the currently available OTC dosage of chlorpheniramine maleate from 2 mg every 4 to 6 hours to 4 mg every 4 to 6 hours with a maximum daily dose of 24 mg. The comments stated that chlorpheniramine maleate has been previously available only by prescription at the 4-mg dosage level and that the increase in dosage from 2 to 4 mg will lead to undersirable side effects, especially excessive drownsiness and overdosage. One comment recommended that chlorpheniramine maleate should continue to be sold OTC in its present dosage form. Another comment stated that the data on which the Panel based its decision to increase the maximum daily dose from 16 to 24 mg were inadequate. The comment explained that the majority of patients treated at the 24-mg daily dosage level were reported in a single uncontrolled study and were selected from a population of patients with a long history of allergy. Many patients had previously received antihistamine therapy. The comment questioned whether this group of patients is appropriate to assess the need for the higher OTC dose of chlorpheniramine maleate. The comment recommended that the maximum daily dose of chlorpheniramine maleate for OTC use the 16 mg since there are adequate data to support this dosage.

The agency has reviewed these comments and the data evaluated by the Panel and notes the Panel's conclusion that chlorpeniramine maleate has not been shown to be effective for adults at a dose less than 4 mg. In addition, chlorpheniramine maleate has been marketed first as a prescription drug product and then as an OTC drug product for many years at the Panel's recommended adult dose of 4 mg every 4 to 6 hours, not to exceed 24 mg in 24 hours. The safety and effectiveness of chlorpheniramine maleate at this dosage have been widely recognized. The agency concludes that chlorpheniramine maleate is safe and effective for OTC use at the Panel's recommended 4-mg dosage level. Therefore, it is unnecessary to change the Panel's recommended dosage in this tentative final monograph by restricting the dosage to 16 mg in 24 hours.

13. One comment expressed concern that certain time-release dosage forms containing chlorpheniramine maleate appear to release all of the ingredient in a short period of time. The comment argued that such dumping causes marked drowsiness in some patients. The comment, however, did not make any specific recommendation to the agency.

Timed-release formulations are considered new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)). Timed-release formulations are so complex that the state of the art does not permit standardization to the point of inclusion in an OTC drug monograph as a Category I condition. (See 42 FR 56736.) In order to market these drug products, an approved NDA, containing appropriate bioavailability data, is required under section 505 of the act (21 U.S.C. 355) and FDA regulations at Part 314 (21 CFR 314). This requirement is based on the agency's recognition that there is a possibility of overdosage if products that are designed to release the active ingredients over a prolonged period are improperly manufactured, and the active ingredients are released all at once or over too short a time interval.

Chlorpheniramine maleate is generally recognized as safe at an adult oral dosage of 4 mg every 4 to 6 hours, not to exceed 24 mg in 24 hours. An NDA is required for any timed-release product containing chlorpheniramine maleate.

E. Comments on Labeling of Antihistamine Drug Product

13. Several comments stressed the importance of making consumers aware through appropriate label warnings that drowsiness is a potential side effect of the use of antihistamines. One comment

specifically recommended that the warning state "Caution: May cause drowsiness. Alcohol may intensify this effect. Use care when operating a car or dangerous machinery."

The agency agrees with the comments that consumers should be warned that drowsiness is a potential side effect of antihistamine active ingredients. In fact, the Panel recommended the warnings "May cause drowsiness" or "May cause marked drowsiness" in § 341.72(b) (6) and (7) of its monograph. The degree and the frequency of the drowsiness produced by a specific antihistamine active ingredient determines which one of the above warnings is required.

The specific warning suggested by one comment would combine the drowsiness warning with related warnings concerning the use of alcohol or operating a motor vehicle or dangerous equipment when taking antihistamines. Combining these related warnings would be beneficial to consumers. However, the agency does not believe that all of the specific language suggested by the comment should be used in the warnings. The comment suggests that the warning "Alcohol may intensify this effect" be substituted for the Panel's recommended warning "Avoid alcoholic beverages while taking this product." The agency has determined that the consumer must be warned to avoid alcohol to ensure the safe use of antihistamines on an OTC basis. Moreover, adding the phrase "alcohol may increase the drowsiness effect" to the warning provides more information to the consumer as to why alcohol should be avoided while taking an antihistamine. The agency has, therefore, included this phrase in the warning.

In addition, the agency believes that revising the Panel's recommended wording "* * * operating heavy machinery" to the wording "* * * operating machinery" better conveys the intent of the Panel. Some equipment that requires mental alertness to operate safely is not "heavy." In addition, warning consumers to use care when operating "dangerous" machinery, as the comment suggests, may not be adequate. Consumers may not consider some machinery dangerous when operated by an alert individual. However, virtually all machinery is potentially dangerous if operated by a person who is drowsy and not alert.

The agency concludes that combining the specific laberling suggested by the comment with the warnings recommended by the Panel, with some modifications, will provide more informative labeling for the consumer. Therefore, the warnings concerning drowsiness, the use of alcohol, and driving a motor vehicle or operating machinery have been revised in this tentative final monograph. Section 341.72(c)(3) reads as follows: "May cause drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery." Section 341.72(c)(4) reads as follows: "May cause marked drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery."

14. One comment suggested that antihistamines should be labeled to inform consumers that these drugs are useful in treating allergic rhinitis and hives, but should not be labeled for treating the symptons of asthma.

The Panel recommended that antihistamines be lebeled for use in treating symptoms of allergic rhinitis. The agency agrees with the comment and the Panel's recommendations regarding this use.

The Panel recommended as part of § 341.72(b)(2), which has been redesignated § 341.72(c)(2) in the tentative final monograph, that antihistamines be labeled with a warning that persons with asthma should not take them except under the advice and supervision of a physician. The Panel pointed out in its report that many physicians consider the drying side effect of antihistamines to be undesirable in patients with bronchial asthma, and some doctors maintain that such drugs should be contraindicated in patients with this disease. The agency concurs with this recommendation and the warning proposed by the Panel.

Hives as a symptom of an allergic reaction was not included in the Panel's report. No data were submitted to the Panel concerning the use of antihistamines for hives, nor were any data reviewed by the Panel concerning this use of antihistamines. The comment also did not provide any data to substantiate its recommendation. Accordingly, an indication for the use of antihistamines in the treatment of hives as a symptom of an allergic reaction is not being proposed in this tentative final monograph.

15. Several comments pointed out that some OTC products containing antihistamines may be labeled and marketed for use only in pediatric populations. The comments argued that certain warnings and caution statements in the Panel's recommended monograph, i.e., "Do not take this product if you have glaucoma or difficulty in urination due to enlargement of the prostate gland, avoid driving a motor vehicle or operating heavy machinery, and avoid alcoholic beverages while taking this product," apply only to adults and should not be required on products labeled strictly for use in children. The comments recommended that an exemptiong 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 agrees that the warnings recommended by the Panel in § 341.72(b)(2), (3), and (4), which have been redesignated as § 341.72(c)(2), (3), and (4) in this tentative final monograph, concerning operating a motor vehicle or machinery, avoiding alcoholic beverages, and the part of the warning statements concerning "difficulty in urination due to enlargement of the prostate gland" are not necessary in the labeling of products intended only for pediatric use. These warnings are not applicable to children and their presence in the labeling would tend to distract parents from label warnings which are important. However, the agency does not agree that the part of the warning about glaucoma in § 341.72(b)(2) should be deleted from the labeling of pediatric products in this tentative final monograph because glaucoma does occur in children [Refs. 1 and 2]. In addition, the agency is proposing that the warnings be reworded to reflect the administration of the product by adults rather than self-administration. Accordingly, the tentative final monograph is amended by adding the following to new § 341.72(c):

(6) *For products labeled for children under 12 years of age.* The labeling of the product contains only the warnings identified in paragraphs (c) (1) and (5) of this section as well as the following:

(i) "Do not give this product to children who have asthma or glaucoma unless directed by a doctor."

(ii) *For products containing brompheniramine maleate, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in § 341.12(a), (b), (c), (d), (g), (h), (i), (j), and (k).* "May cause drowsiness."

(iii) *For products containing diphenhydramine hydrochloride and doxylamine succinate identified in*

§ 341.12(e) and (f). "May cause marked drowsiness."

References

(1) Scheie, H.G., and D.M. Albert, "Textbook of Ophthalmology," 9th Ed., W.B. Saunders Co., Philadelphia, pp. 542–547, 1977.

(2) Ellis, P.P., and D.L. Smith, "Handbook of Ocular Therapeutics and Pharmacology," 4th Ed., the C.V. Mosby Co., St. Louis, p. 108, 1973.

16. One comment disagreed with the Panel's recommended label warning for pheniramine maleate that states "May cause marked drowsiness." The comment pointed out that pheniramine maleate is in the same chemical class of antihistamines as chlorpheniramine and brompheniramine, i.e., the alkylamines, that this class of antihistamines causes the least amount of drowsiness, and that the Panel recommended the less severe warning "May cause drowsiness" for chlorpheniramine and brompheniramine maleate. The comment urged the agency to require the same label warning, "May cause drowsiness", for pheniramine maleate as allowed for chlorpheniramine and brompheniramine maleate.

The agency has reviewed the data cited in the Panel's report concerning the sedative effects of pheniramine maleate as compared with brompheniramine maleate and chlorpheniramine maleate. In one study reviewed by the Panel, 20, percent of 171 patients receiving a 25-mg dose of pheniramine maleate experienced sedation as a side effect (Ref. 1). In comparison, the Panel states at 41 FR 38382 that brompheniramine maleate produced sedation in 20 percent of less of the individuals taking the ingredient and at 41 FR 38383 that chlorpheniramine maleate produced sedation in 10 to 20 percent of the individuals taking the ingredient. In another study reviewed by the Panel, the frequency of side effects, chiefly drowsiness, seen in 184 subjects receiving 10 mg pheniramine did not exceed the number of side effects in an equal number of subjects receiving a placebo (Ref. 2). Roth and Tabachnick (Ref. 3) have classified the sedative effect of pheniramine maleate as "moderate," compared to a classification of "slight sedation" for brompheniramine maleate and chlorpheniramine maleate. However, Roth and Tabachnick (Ref. 3) did not classify the sedative effect of pheniramine as "marked sedation." The agency agrees with the comment that the warning regarding drowsiness for pheniramine should be the same as that required for chlorpheniramine and brompheniranine. The agency concludes that the data reviewed by the Panel do not support the need for a stronger warning regarding drowsiness for drug products containing pheniramine maleate. Therefore, the agency proposes to change the warning statement for pheniramine maleate to "May cause drowsiness."

References

(1) Loveless, M.H., and M. Dworin, "Allergy and Antihistamine Therapy: A Review," *The Bulletin of the New York Academy of Medicine*, 25:473–487, 1949.

(2) Lowell, F.C., et al., "The Antihistamine Drugs in the Treatment of the Common Cold," *New England Journal of Medicine*, 244:132, 1951.

(3) Roth, F.E., and I.I.A. Tabachnick, "Histamine and Antihistamine," *in* "Drill's Pharmacology in Medicine," 4th Ed., edited by J.R. DiPalma, McGraw-Hill Book Co., New York, p. 1009, 1971.

17. One comment stated that the Panel's recommended warning in § 341.72(b)(8), "*Caution*: May cause nervousness and insomnia in some individuals," is unnecessary for phenindamine tartrate. The comment cited OTC Volume 040126 (Ref. 1) for review with respect to the necessity for the above warning.

The agency has reviewed six references contained in OTC Volume 040126 that were reviewed and cited by the Panel in its report and finds that insomnia and nervousness are dominant side effects which may occur with the use of phenindamine tartrate. Paul et al. (Ref. 2) evaluated phenindamine tartrate in 280 patients. Sleeplessness occurred in 6.4 percent and nervousness in 5.4 percent. In this study, the total daily dosage ranged from 25 to 150 mg, with most adults taking 25 mg three times a day. McGavack et al. (Ref. 3) found that dryness of the mouth, insomnia, and constipation were the major symptoms in patients receiving a total daily dose of 75 to 600 mg of phenindamine tartrate. Boyd, Weissberg, and McGavack (Ref. 4) found that 24 percent of patients who received a total daily dose of 150 mg experienced insomnia and dryness of the mouth. Criep and Aaron (Ref. 5) evaluated 389 patients who received a dosage of 25 mg of phenindamine tartrate every 4 hours and found that 89 (23 percent) experienced side reactions. Of the 89 patients who had side reactions, 22 percent experienced nervousness and palpitations, 22 percent had nausea, and 10 percent had insomnia.

Pennypacker and Sharpless (Ref. 6) gave patients 25 to 50 mg of phenindamine tartrate daily and found that of 40 patients, 35 percent (14) experienced insomnia and 22.5 percent (9) tenseness. Cohen, Davis, and Mowry (Ref. 7) studied 292 patients who received a total daily dose of 50 to 200 mg of phenindamine tartrate; 54 of the patients (18 percent) experienced side effects. Of these 54 patients, 33 experienced nervous side reactions.

In other unpublished studies contained in OTC Volume 040126, the recommended effective adult oral dosage of 25 mg of phenindamine tartrate was not used. The evaluations were done with tablets which contained only 10 mg of phenindamine tartrate. For this reason, the data on side effects reported in these studies cannot be used to support the comment's request to eliminate the warning.

Because the data reviewed by the Panel (Refs. 1 through 7) show that phenindamine tartrate may cause insomnia and nervousness, the agency agrees with the Panel's recommendation that the warning, "May cause nervousness and insomnia in some individuals," be required for phenindamine tartrate.

References

(1) OTC Volume 040126.

(2) Paul, A.B., et al., Clinical Evaluation of a New Antihistaminic Compound," *The Laryngoscope*, 58:1044–1054, 1948.

(3) McGavack, T.H., et al., "Clinical Evaluation of Phenindamine (2-Methyl-9-phenyl-2, 3, 4, 9-Tetra-hydro-1-Pyridindene Hydrogen Tartrate) as an Antihistamine Agent," *American Journal of the Medical Sciences*, 216:437–475, 1948.

(4) Boyd, L.J., J. Weissberg, and T.H. McGavack, "Tolerance Studies of the Antihistamine Drug Thephorin," *New York State Journal of Medicine*, 48:1596–1598, 1948.

(5) Criep, L.H., and T.H. Aaron, "Thephorin: An Experimental and Clinical Evaluation in Allergic States," *Journal of Allergy*, 19:304–312, 1948.

(6) Pennypacker, C.S., and I. Sharpless, "Clinical Study of a New Antihistaminic Drug—Thephorin," *Pennsylvania Medical Journal*, 51:1407–1411, 1948.

(7) Cohen, E.B., H.P. Davis, and W.A. Mowry, "Thephorin in Allergy," *American Journal of Medicine*, 5:44–47, 1948.

18. One comment stated that the Panel used an inappropriate standard in categorizing some Category II claims and that the claims "fast" and "prompt" were rejected by the Panel for antihistamine labeling because the time is indeterminate. The comment stated that if the drug provides fast or prompt relief, as these terms are understood by consumers, then these claims are not misleading and should be permitted.

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 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: products 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.

As with all OTC drug products, antihistamines are expected to achieve their intended results within a reasonable period of time. However, the specific period of time within which antihistamines 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 "prompt" 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

The agency emphasize that even though terms such as "fast" or "prompt" are outside the scope of the OTC drug review for this class of products, 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 the are not false or misleading.

F. Comments on Testing Guidelines

19. Two comments disagreed with the Panel's recommended Category III testing criteria for the evaluation of antihistamines in treating the symptoms of the common cold. (See part VII. paragraph C.2.d. of the Panel's report—Methods of study (41 FR 38396).) The comments argued that it was unreasonable to give the antihistamine throughout the entire course of the cold if the specific symptom being treated, e.g., runny nose, is no longer in evidence. The comments recommended that the testing criteria be changed so that the study need only be of sufficient length to distinguish clearly between the effect of the drug and the placebo. One of the comments argued that requiring three positive studies from three different investigators, as the Panel recommended, was unnecessary and contended that because two studies were considered adequate in other Category III testing recommended by the Panel, the same requirement should apply in this case.

The other comment argued that the criteria for stratifying patients according to age, sex, and severity of symptoms were unnecessary. The comment contended that stratifying by sex and age would be insignificant as a factor in patients' response to medication and that in view of other strict criteria, which would eliminate potential patients, stratifying by sex and age would result in an additional loss of qualified patients for investigation. The comment believe that stratifying by symptom severity would be too prone to subject interpretation because one could not specify when peak severity would occur in the course of the illness. Both comments recommended that the agency reject the specified panel testing criteria.

The agency has reviewed data in studies designed to demonstrate the effectiveness of the antihistamine chlorpheniramine maleate in treating the symptoms of the common cold that were submitted in response to the advance notice of proposed rulemaking (Ref. 1). Although they do not meet all of the criteria of the Panel's testing guidelines, they have been accepted by the agency as demonstrating the effectiveness of chlorpheniramine for use in treating the symptoms of runny nose and sneezing when associated with the common cold. (See comment 4 above.) One of the acceptable studies did not follow the patients for the entire course of the illness. The study covered the time period over which the symptoms studied were in evidence. Therefore, studies which are of sufficient length to distinguish between the effectiveness of the drug and the placebo in treating a particular symptom are acceptable. In addition, because the pharmacologic actions of the various Category I antihistamines are similar, the agency believes that the data submitted for chlorpheniramine maleate allow Category I status for treating the symptoms of runny nose and sneezing when associated with the common cold to be extended to all Category I antihistamine active ingredients. (See comment 4 above.)

In summary, the agency concludes that adequate data demonstrating the safety and/or effectiveness of a Category III condition are necessary to reclassify that condition to Category I status but that this does not necessarily require that the guidelines recommended by the Panel be followed. The Panel's testing criteria are considered to be recommendations to the agency. Although the submitted chlorpheniramine studies did not stratify patients according to age, sex, severity, and duration of illness, they have been accepted by the agency. Stratification of patients by the above criteria is not a necessary requirement for studies designed to demonstrate the effectiveness of antihistamines in treating symptoms associated with the common cold. Studies submitted in support of the effectiveness and safety of a Category III condition are evaluated on the basis of their own merits rather than on how well they meet the Panel's requirements. However, the agency emphasizes that each study submitted to support a request for the reclassification of a Category III condition to Category I status must substantiate the reclassification whether or not the Panel's recommended guidelines are followed.

Reference

(1) Comment Nos. SUP004 and SUP005, Docket No. 76N-0052, Dockets Management Branch.

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 has made some changes in the categorization of antihistamine active ingredients recommended by the Panel. As a convenience to the reader, the following list is included as a summary of the categorization of antihistamine active ingredients recommended by the Panel and the proposed categorization by the agency.

Antihistamine active ingredients	Panel	Agency
Brompheniramine maleate	I	I
Chlorpheniramine maleate	I	I
Dexbrompheniramine maleate	(*)	I
Dexchlorpheniramine maleate	(*)	I
Diphenhydramine hydrochloride	I	I
Methapyrilene fumarate	I	II
Methapyrilene hydrochloride	I	II
Phenindamine tartrate	I	I
Phenindamine tartrate	I	I

Antihistamine active ingredients	Panel	Agency
Phenyltoloxamine citrate	III	III
Pyrrobutamine hydrochloride	I	III
Pyrilamine maleate	I	I
Thenyldiamine hydrochloride	III	III
Thonzylamine hydrochloride	I	I
Triprolidine hydrochloride	(*)	I

*Not reviewed.

The agency points out that any of the antihistamines proposed as Category I in this tentative final monograph, except dexchlorpheniramine (see comment 7 above), may be marketed OTC in a combination drug product in accord with the Panel's permitted combinations of Category I active ingredients in the analgesic, antitussive, and decongestant categories recommend in § 341.40 of the advance notice of proposed rulemaking (41 FR 38420). The tentative final monograph on cough-cold combination drug products will be published in a future issue of the Federal Register and will discuss the combinations proposed by the agency. Any interim marketing that is permitted is subject to the agency's conclusions in the final monograph.

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for antihistamine drug products (41 FR 38329 and 38394). The agency's position regarding the Panel's testing guidelines is discussed in comment 23 above. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any antihistamine 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 in the Panel's Recommendations

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the antihistamine 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 has modified § 341.3(d) and § 341.72(a) (redesignated § 341.72(b) in the tentative final monograph) to include the use of antihistamines for the temporary relief of runny nose and sneezing associated with the common cold. The agency has reviewed and accepted data which demonstrate the effectiveness of chlorpheniramine maleate in treating these symptoms when associated with the common cold. In addition, because the pharmacologic actions of the various Category I antihistamines are similar, the agency believes that the data submitted on chlorpheniramine allow an indication for treating the symptoms of runny nose and sneezing when associated with the common cold to be extended to all Category I antihistamine active ingredients. The agency proposes to substitute the term "runny" for the term "running" which was used by the Panel. The agency recognizes that the term "runny" is grammatically correct, particulary when it is used in reference to a condition of the nose. The agency believes the term "runny" is more commonly used than the term "running" and is, therefore, better understood by consumers. (See comment 4 above.)

2. Dexbrompheniramine maleate has been marketed as a single ingredient prescription drug product under an approved NDA for 23 years (Ref. 1). It has also been marketed in combination with pseudoephedrine sulfate under an approved NDA for 19 years as a prescription drug product that delivers an adult dose of 2 mg of dexbrompheniramine every 4 hours using a sustained release delivery from a 6-mg tablet taken every 12 hours (Ref. 2). This product has been approved for OTC marketing under an NDA (Ref. 3). The agency has reviewed the literature concerning the safety and effectiveness of dexbrompheniramine maleate as an antihistamine. Based on this literature, and the review by the Drug Efficacy Study Group (DESI) published in the Federal Register of March 19, 1973 (38 FR 7265), the agency believes that the drug can be generally recognized as safe and effective for OTC use.

Dexbrompheniramine maleate is the dextrorotatory isomer (d-isomer) of brompheniramine maleate, which is a racemic histamine antagonist composed of d- and l-isomers. Pharmacological studies have shown that the antihistaminic activity resides almost exclusively in the d-isomer, and that there is very little difference in the toxicities of the d-isomer and the d,l mixture in experimental animals (Ref. 4). Because dexbrompheniramine maleate is about twice as potent as brompheniramine maleate, it is used in clinical practice at one-half the does of brompheniramine maleate.

The agency has reviewed studies by Frank (Ref. 5), Olansky and Olansky (Ref. 6), and Romanoff and Guidatti (Ref. 7) concerning the safety and effectiveness of dexbrompheniramine maleate alone. The studies showed the drug to be an effective antihistamine, at a dosage of 2 mg, with a low incidence of side effects (drowsiness, slight dizziness). One of the studies, using a double-blind design, showed a significant response to dexbrompheniramine, compared to a placebo, among ptients with respiratory symptoms due to allergic rhinitis and pollinosis. Symptoms such as itching, sneezing, and watery eyes were relieved in the patients receiving the drug (Ref. 7).

In addition, the agency has reviewed studies by Mayer and Savitt (Ref. 8), Kapstad and Warland (Ref. 9) Lofkvist and Svenson (Ref. 10), and Fierburg (Ref. 11) concerning the safety and effectiveness of dexbrompheniramine meleate in combination with pseudoephedrine sulfate. All of these studies were double-blinded and evaluated combination drug products that are marketed under the approved NDA (Refs. 8 through 11). The studies were performed in patients with perennial allergic rhinitis or vasomotor rhinitis. A crossover design was used in three of the studies (Refs. 8, 10 and 11). All of these studies demonstrated that dexbrompheniramine maleate in combination with pseudoephedrine sulfate is effective in relieving symptons when compared to several different reference drugs or placebos. Patients receiving the dexbrompheniramine-pseudoephedrine combination experienced a lessening of sinus congestion and of runny nose. Three other studies, which were not double-blind but controlled clinical comparisons, showed similar results (Refs. 12, 13, and 14).

Side effects reported in these studies were similar to those reported for other antihistamine-nasal decongestant drugs and included drowsiness, dry mouth and dry throat, dizziness, nausea, swelling in the face, headache, restlessness, tachycardia, and constipation. There were relatively few side-effects reported in all, and in only one case did a patient reduce the medication to one tablet a day because of drowsiness and dry mouth (Ref. 5).

A review of FDA adverse reaction reports since 1970 indicates that conditions such as rash, hypertension, transient myopia, nervousness, and insomnia have been reported in cases where the combination drug dexbrompheniramine-pseudophedrine

was taken (Ref. 15). In these cases, overdose was not indicated, nor was enough information available to indicate a possible cause-and-effect relationship between the use of dexbrompheniramine maleate and the reaction.

Based on the above data and information, the agency believes that dexbrompheniramine maleate can be generally recognized as safe and effective for OTC use. The agency is therefore proposing that dexbrompheniramine maleate be classified as Category I as an OTC antihistamine at a dose of 2 mg every 4 to 6 hours, not to exceed 12 mg in 24 hours, for adults and a dose of 1 mg every 4 to 6 hours, not to exceed 6 mg in 24 hours, for children 6 to under 12 years of age. The agency also proposes a dose of 0.5 mg every 4 to 6 hours, not to exceed 3 mg in 24 hours, for children 2 to under 6 years of age under professional labeling in the tentative final monograph. The labeling warnings are identical to those being proposed for brompheniramine maleate.

Dexbrompheniramine maleate was not considered by an OTC advisory review panel and, therefore, does not meet the terms of the enforcement policy in § 330.13. The agency has approved an NDA that currently allows the OTC marketing of products containing dexbrompheniramine. Thus, FDA does not believe it is necessary to prohibit OTC marketing of dexbrompheniramine under this proposal while public comments to its proposed monograph status are being evaluated. OTC marketing may be initiated subject to the terms and conditions specified in this tentative final monograph and subject to the risk that FDA may adopt a different position in the final monograph that may require relabeling, recall, or other regulatory action.

References

(1) Letter from I. Siegel, FDA, to White Laboratories, Inc., OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.

(2) Letter from J.W. Winkler, FDA, to White Laboratories, Inc., OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.

(3) Letter from J.P. Mann, FDA, to Schering Corporation, OTC Volume 04HTFM, Docket No. 76N-052H, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.

(4) Roth, F.E., "Antihistimine Activity of the Optical Isomers of Pheniramine and its Chlor- and Brom-Substituted Derivatives," *Chemotherapia*, 3:120–127, 1961.

(5) Frank, D.I., "Clinical Evaluation of Dexbrompheniramine Maleate (Disomer) in Ear, Nose and Throat Allergies," *Current Therapeutic Research*, 1:115–121, 1959.

(6) Olansky, M., and S. Olansky, "Antihistaminic Activity of Dexbrompheniramine (Disomer). Appraisal in Pediatric Allergies," *Annals of Allergy*, 18:415–419, 1960.

(7) Romanoff, A., and F.P. Guidotti, "Evaluation of Dexbrompheniramine Maleate in Allergy by Double-Blind Procedure. Preliminary Report," *New York State Journal of Medicine*, 60:3800–3803, 1960.

(8) Mayer, P.S., and A.E. Savitt, "Allergic Rhinitis and Air Pollution: A Double-Blind Crossover Analysis," *The Eye, Ear, Nose and Throat Monthly*, 51:9–12, 1972.

(9) Kapstad, B., and A. Warland, "Therapeutic Effectiveness of an Oral Anti-Histamine Combination (Dexbrompheniramine Maleate/D-Isoephedrine Sulfate) in the Treatment of Patients with Allergic Rhinitis," *Acta Allergologica*, 31:233–226, 1976.

(10) Lofkvist, T., and G. Svensson, "A Comparative Evaluation of Oral Decongestants in the Treatment of Vasomotor Rhinitis," *The Journal of International Medical Research*, 6:56–60, 1978.

(11) Fierberg, A.A., "Allergic Nasal Congestion, Effects of Oral Treatment with a Combination of Dexbrompheniramine and D-Isoephedrine," *Annals of Allergy*, 22:324–328, 1964.

(12) Frank, D.I., "Evaluation of Two Sustained-Action Oral Decongestants: A Controlled Study," *Current Therapeutic Research*, 6:158–161, 1964.

(13) Pullen, F.W., and W.W. Montgomery, "Comparative Evaluation of Oral Decongestants," *Archives of Otolaryngology*, 77:10–12, 1963.

(14) Jungert, S., "A Comparison of the Efficacy and Safety of Two Preparations in the Treatment of Allergic and Vasomotor Rhinitis, Disophrol Chronosule Capsules and Tavegyl Tablets," *Current Therapeutic Research*, 24:269–273, 1978.

(15) Department of Health and Human Services, Food and Drug Administration, Adverse Reaction Summary Listings, pertinent pages for 1970–82, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.

3. The agency has proposed placing dexchlorpheniramine maleate in Category I based on the safe and effective use of this drug product as a prescription drug under an approved ANDA, a review of FDA adverse reaction reports, and the safe and effective use of the racemic mixture, chlorpheniramine maleate, as an OTC drug product for many years. However, it may not be marketed OTC at this time. (See comment 7 above.)

4. The agency has deleted the reference to methapyrilene in § 341.12(e), the reference to § 341.12(e) in § 341.72(b)(7), and the reference to methapyrilene in § 341.90(f) of the Panel's recommended monograph. These sections provided dosages, a warning, and professional labeling for methapyrilene preparations, which are no longer marketed because of the NCI study showing that these drugs are associated with the development of tumors in laboratory animals. The agency has reclassified methapyrilene preparations in Category II. (See comments 1 and 6 above.)

5. The agency has deleted the reference to promethazine hydrochloride in § 341.12(h), the reference to § 341.12(h) in § 341.72(b)(7), and the reference to promethazine hydrochloride in § 341.90(i) of the Panel's recommended monograph. These sections provided dosages, a warning, and professional labeling for promethazine hydrochloride. In the agency's preamble to the Panel's report and recommended monograph (41 FR 38312), the agency disagreed with the Panel's Category I classification of promethazine hydrochloride. The agency concludes that general recognition of the safety of this ingredient for OTC use has not been adequately established. Consequently, the agency has reclassified promethazine hydrochloride in Category III. (See comment 9 above.)

6. Triprolidine hydrochloride has been marketed under an approved NDA for 24 years as a prescription drug product at a dose of 2.5 mg every 6 to 8 hours for adults, a dose of 1.25 mg every 6 to 8 hours for children 6 to 12 years of age, a dose of 0.938 mg every 6 to 8 hours for children 4 to under 6 years of age, a dose of 0.625 mg every 6 to 8 hours for children 2 to under 4 years of age, and a dose of 0.313 mg every 6 to 8 hours for infants 4 months to under 2 years of age (Refs. 1 and 2). In addition, drug products containing triprolidine hydrochloride as a single ingredient and in combination with pseudoephedrine hydrochloride have been approved for OTC marketing under NDAs (Ref. 3). In a 1973 Drug Efficacy Study Implementation (DESI) notice (38 FR 9339), the agency concluded that this drug is effective. FDA has reviewed the literature and marketing history of triprolidine hydrochloride as an antihistamine and believes that this drug can be generally recognized as safe and effective for OTC use.

Studies by Fruchard and Fruchard (Ref. 4); Britton et al. (Ref. 5); Wolfromm and Liacopoulos (Ref. 6); Bye et al. (Ref. 7); Nicholson (Ref. 8); Bye et al. (Ref. 9); and Peck, Fowle, and Bye (Ref. 10) were reviewed for the safety and effectiveness of triprolidine hydrochloride. Most of the studies were double-blind (Refs. 5, 7, 8, and 9). In 27 out of 36 vasomotor rhinitis cases, triprolidine hydrochloride promptly relieved the symptoms (within 15

minutes), had a long duration of action (about 5 to 6 hours), and was well tolerated (Ref. 6). In another study (Ref. 4), good results were reported in all patients with symptoms of spasmodic rhinitis. These authors also reported that triprolidine hydrochloride acts rapidly and is well tolerated. Both studies (Refs. 4 and 6) indicated that triprolidine is a powerful antihistamine and antianaphylactic agent with mild side effects and rapid action. Studies by Nicholson (Ref. 8) and Peck, Fowle, and Bye (Ref. 10) showed that the effect of triprolidine hydrochloride was immediate and lasts for about 7 hours wiht a maximum effect at the third hour. The double-blind studies of this drug indicated that, after repeated doses of the drug in a 24-hour period, the degree of drowsiness tended to decrease (Refs. 5, 7, and 9). No evidence of an increased drug effect due to accumulation was reported (Ref. 9). The reported side effects were drowsiness (Refs. 4, 5, 6, 7, and 9) and digestive disturbance (Refs. 4 and 6). FDA adverse reaction reports for triprolidine hydrochloride since 1969 show only two reports of rash (Ref. 11).

Based on the above data and information, the agency is proposing that triprolidine hydrochloride be classified as Category I as an OTC antihistamine at a dose of 2.5 mg every 6 to 8 hours, not to exceed 10 mg in 24 hours, for adults, and a dose of 1.25 mg every 6 to 8 hours, not to exceed 5 mg in 24 hours, for children 6 to under 12 years of age. The agency also proposes to place in professional labeling a dose of 0.938 mg every 6 to 8 hours, not to exceed 3.75 mg in 24 hours, for children 4 to under 6 years of age; a dose of 0.625 mg every 6 to 8 hours, not to exceed 2.5 mg in 24 hours, for children 2 to under 4 years of age; and a dose of 0.313 mg every 6 to 8 hours, not to exceed 1.25 mg in 24 hours, for infants 4 months to under 2 years of age. The agency is proposing that the general labeling recommended by the Panel for OTC antihistamine drugs be used for triprolidine hydrochloride.

Triprolidine was not considered by an OTC advisory review panel and, therefore, does not meet the terms of the enforcement policy in § 330.13. The agency has approved several NDAs that currently allow the OTC marketing of products containing triprolidine. Thus, FDA does not believe it is necessary to prohibit OTC marketing of triprolidine under this proposal while public comments to its proposed monograph status are being evaluated. OTC marketing may be initiated subject to the terms and conditions specified in this tentative final monograph and subject to the risk that FDA may adopt a different position in the final monograph that may require relabeling, recall, or other regulatory action.

References

(1) Letters from P. DeFelice, FDA, to Burroughs-Wellcome Co., Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.

(2) Copies of FDA-approved labeling from NDA 11-110 and NDA 11-496, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.

(3) Letters from J.P. Mann, FDA, to Burroughs-Wellcome Co., OTC Volume 04HTFM, Docket No. 76N-052H, Docket Management Branch.

(4) Fruchard, J., and J. Fruchard, "Un Nouval Antihistaminique: Actidil," *Journal de Medecine de Bordeaux et du Sud-Quest, 134:1356-1358, 1957.*

(5) Britton, M.G., et al., "Two Doses of Triprolidine for Treatment of Allergic Rhinitis," *Annals of Allergy*, 4(5):330-332, 1979.

(6) Wolfromm, R., and P. Liacopoulos, "Clinical Trial of a New Synthetic Antihistamine-Trans-1 (4 methylephenyl)-1-(2-pyridyl)-3-pyrrolidinoprop-ene Hydrochloride," Extract from *La Semaine des Hopitaux de Paris (La Semaine Medicale Professionelle et Medico-Sociale)* 13, 1957.

(7) Bye, C., et al., "The Effects of Repeated Doses of Triprolidine on Subjective Drownsiness and Peformance Tests in Man," *British Journal of Clinical Pharmacology*, 2(4):379p-380p, 1975.

(8) Nicholson, A.N., "Effect of the Antihistamines Brompheniramine Maleate and Triprolidine Hydrochloride on Performance in Man," *British Journal of Clinical Pharmacology*, 8:321-324, 1979.

(9) Bye, C.E., et al., "Evidence for Tolerance to the Central Nervous Effects of the Histamine Antagonist, Triprolidine, in Man," *European Journal of Clinical Pharocology*, 12:181-186, 1977.

(10) Peck W., A. S. E. Fowle, and C. Bye, "A comparison of triprolidine and Clemastine on Histamine Antagonism and Performance Tests in Man: Implications for the Mechanism of Drug Induced Drowsiness," *European Journal of Clinical Pharmacology*, 8:455-463, 1975.

(11) Department of health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listing," pertinent pages for the years 1969-1982, OTC Volume 04HTFM, Docket No. 76N-052H, Dockets Management Branch.

7. The agency has added to § 341.72 a "Statement of identity" paragraph (designated as § 341.72(a)) and a "Directions" paragraph (designated as § 341.72(d)) to conform with the format of other recently published advance notices of proposed rulemaking and tentative final monographs. Inclusion of the "Statement of identity" paragraph has necessitated a redesignation of § 341.72(a) to § 341.72(b), and § 341.72(b) to § 341.72(c). The agency is also redesignating Subpart D as Subpart C and placing the labeling sections of the monograph in Subpart C.

8. The agency has proposed a new indication for the use of antihistamines for the temporary relief of runny nose and sneezing associated with the common cold in paragraph (2) of new § 341.72(b). (See comment 4 and part II, paragraph B. 1. above.) The agency has also combined serveral required indications under new § 341.72(b)(1). The agency has replaced the Panel's wording "Alleviates, decreases, or temporarily relieves" with the option to select the word "relieves," "alleviates, "decreases," "reduces," or "dries" for the symptom "runny nose" and the option to select the word "relieves," "alleviates," "decreases," or "reduces" for the Symptoms "Sneezing, itching of the nose or throat, and itchy, watery eyes" in the combined indications for antihistamines. These options provide manufacturers the flexiblity to select different terms for labeling. Manfacturers are encouraged to submit additional words for possible inclusion as selection options in the "Indications" section of the final monograph for antihistamines drug products. Therefore, indications in § 341.72(a), which has been redesignated § 341.72(b) have been revised as follows: Paragraphs (2), (3), (4), (5), and (6), of § 341.72(a) have been revised and combined in paragraph (1) of new § 341.72(b). The new indication for the use of antihistamines for symptoms associated with the common cold has been added in paragraph (2) of new § 341.72(b). New § 341.72(b) (1) and (2) reflect the combining of indications for the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to allergic rhinitis and for the temporary relief of runny nose and sneezing associated with the common cold.

9. The agency has deleted § 341.72(b)(5) of the Panel's recommended monograph. This section provided the warning "Do not give this product to children under 6 years except under advise and supervision of a physician," for all antihistamine drug products. The directions provided under new § 341.72(d) state clearly that a doctor should be consulted for the use of anthistamine drug products in children under 6 years of age. The agency believes that the warning is therefore repetitious and unnecessary.

10. In § 341.72(b) (3), (4), and (8) the Panel recommended the use of the signal word "Caution" in a section of the labeling where the heading *"Warnings"* is also recommended. The agency notes that historically there has not been a consistent usage for the signal words "warning" and "caution" in OTC drug labeling. For example, in §§ 369.20 and

369.21 (21 CFR 396.20 and 396.21), which list "warning" and "caution" statements for drugs, the signal words "warning" and "caution" are both used. In some instances either of these signal words is used to convey the same or smiliar precautionary information.

FDA has considered which of these signal words would be most likely to attract consumers' attention to that information describing conditions under which the drug product should not be used or its use should be discontinued. The agency concludes that the signal word "warning" is more likely to flag potential danges so that consumers will read the information being conveyed. Therefore, FDA has determined that the signal word "warning," rather than the word "caution," will be used routinely in OTC drug labeling that is intended to alert consumers to potential safety problems. Accordingly, the signal word "Caution" has deleted from this tentative final monograph.

11. The agency has added to § 341.72(b) (redesignated as § 341.72(c)) a paragraph on warnings that are appropriate for products that are labeled for children under 12 years of age. The agency acknowledges that some warnings which the Panel recommended for all antihistamine drug products are inappropriate for products which are labeled for children under 12 years of age. In addition, the warnings for products labeled for children under 12 years of age have been worded to reflect the administration of the product by adults rather than self-administration. (See comment 15 above.)

12. The agency has combined several warnings under new § 341.72(c) and believes that combining the drowsiness warning with related warnings concerning the use of alcohol or operating a motor vehicle or machinery while taking antihistamines will provide more informative labeling for the consumer. Therefore, the warnings (in § 341.72(b), which has been redesignated § 341.72(c)), have been revised as follows: Paragraphs (6), (7), and (8) have been redesignated as (3), (4), and (5). Paragraphs (3) and (4) of § 341.72(b) have been revised, combined, and added to paragraphs (3) and (4) of new § 341.72(c). New § 341.72(c) (3) and (4) reflect a combining of warnings concerning drowsiness and the use of alcohol or operating a motor vehicle or machinery while taking antihistamines. (See comment 13 above.)

13. Because antihistamines have an anticholinergic effect which can reduce the volume of bronchial secretions and cause thickening of these secretions, the Panel recommended that antihistamines bear a warning that people with asthma not take these drugs unless directed by a doctor, and the agency is proposing such a warning in this tentative final monograph. The agency believes that in addition to this warning, the labeling of antihistamine drug products should inlcude a warning against use of antihistamines in patients with any obstructive pulmonary disease in which clearance of secretions is a problem. The Panel stated that it is important to avoid anticholinergics in the presence of bronchial asthma or chronic obstructive pulmonary disease because of the possibility that anticholinergics may cause secretions to become less fluid and difficult to remove, and thus cause obstruction of the respiratory passages (41 FR 38377). The Panel's recommended warning in § 341.72(b)(2) of the advance notice of proposed rulemaking included asthma, but did not include chronic obstructive pulmonary disease as a contraindication for the use of antihistamines. The agency believes that this warning should be expanded to include all types of chronic obstructive pulmonary disease. This term applies to patients with clinically significant, irreversible, generalized airways obstruction associated with varying degrees of chronic bronchitis, abnormalities in small airways, and/or emphysema (Ref. 1). Because respiratory distress symptoms such as difficulty in beathing and shortness of breath are characteristic of chronic obstructive pulmonary disease, the agency believes that such descriptive terms should also be included in the warning in order to provide more information to the consumer. Therefore, the agency is proposing to amend the Panel's recommended warning to read, "Do not take this product if you have asthma, glaucoma, emphysema, chronic pulmonary disease, shortness of breath, difficulty in breathing, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." The agency is proposing the term chronic pulmonary disease rather than chronic obstructive pulmonary disease in this warning because it believes that the shorter term will be more understandable to consumers.

Reference

(1) Berkow, R., editor, "The Merck Manual," 14th Ed., Merck Sharp & Dohme Research Laboratories, Rahway, NJ, pp. 628–635, 1982.

14. 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 and 369.21, and exemptions for certain drugs limited by NDAs to prescription sale in § 310.201(a)(13), for oral antihistamine drug products at the time that this monograph becomes effective. The agency proposes to revoke § 310.201(a)(4) and to delete phenyltoloxamine citrate from bearing the warning and caution statements required by § 369.21 at the time that this monograph becomes effective if this ingredient is reclassified in Category I as an OTC antihistamine in the final monograph.

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** on 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 antihistamine 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 antihistamine 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 antihistamine 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 antihistamine drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific coment on the economic impact of the OTC drug review on antihistamine drug products, a period of 120 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has carefully consídered the potential environmental effects of this proposal and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement therefore will not be prepared. The agency's finding of no significant impact, and the evidence supporting this finding, contained in an environmental assessment (under 21 CFR 25.31, proposed in the **Federal Register** of December 11, 1979; 44 FR 71742), which may be seen in the Dockets Management Branch, Food and Drug Administration.

List of Subjects in 21 CFR Part 341

OTC drugs: Anticholinergics, Expectorants, Bronchodilators, Antitussives, Nasal decongestants, Antihistamines.

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

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11, it is proposed to make the following amendments:

PART 341—[AMENDED]

1. In proposed Subpart A, § 341.3 is amended by adding new paragraph (d) to read as folows:

§ 341.3 Definitions.

* * * * *

(d) *Antihistamine drug.* A drug used for the relief of the symptoms of hay fever and upper respiratory allergies (allergic rhinitis) and the symptoms of sneezing and runny nose associated with the common cold.

2. In proposed Subpart B, new § 341.12 is added to read as follows:

§ 341.12 Antihistamine active ingredients.

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

(a) Brompheniramine maleate.
(b) Chlorpheniramine maleate.
(c) Dexbrompheniramine maleate.
(d) Dexchlorpheniramine maleate.
(e) Diphenhydramine hydrochloride.
(f) Phenindamine tartrate.
(g) Pheniramine maleate.
(h) Pyrilamine maleate.
(i) Thonzylamine hydrochloride.
(j) Triprolidine hydrochloride.

3. In proposed Subpart C, new § 341.72 is added and § 341.90 is amended by adding new paragraphs (b), (c), (d), (e), (f), (g), (h), (i), (j), and (k) to read as follows:

§ 341.72 Labeling of antihistamine drug products.

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

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to both of the following phrases: (1) "Temporarily" (select one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (select one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" (which may be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)")."

(2) "Temporarily" (select one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (select one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing associated with the common cold."

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

(1) "May cause excitability especially in children."

(2) "Do not take this product if you have asthma, glaucoma, emphysema, chronic pulmonary disease, shortness of breath, difficulty in breathing, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(3) *For products containing brompheniramine maleate, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride identified in § 341.12 (a), (b), (c), (d), (f), (g), (h), (i), and (j).* "May cause drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery."

(4) *For products containing diphenhydramine hydrochloride identified in § 341.12(e).* "May cause marked drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Use caution when driving a motor vehicle or operating machinery."

(5) *For products containing phenindamine tartrate identified in § 341.12(f).* "May cause nervousness and insomnia in some individuals."

(6) *For products that are labeled only for use by children under 12 years of age.* The labeling of the product contains only the warnings identified in paragraphs (c) (1) and (5) of this section as well as the following:

(i) "Do not give this product to children who have asthma or glaucoma unless directed by a doctor."

(ii) *For products containing brompheniramine maleate, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hyrochloride identified in § 341.12(a), (b), (c), (d), (f), (g), (h), (i), and (j).* "May cause drowsiness."

(iii) *For products containing diphenhydramine hydrochloride identified in § 341.12(e).* "May cause marked drowsiness."

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

(1) *For products containing brompheniramine maleate identified in § 341.12(a).* Adults: oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 24 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as

directed by a doctor. Children under 6 years of age: consult a doctor.

(2) *For products containing chlorpheniramine maleate identified in § 341.12(b).* Adults: oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 24 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(3) *For products containing dexbrompheniramine maleate identified in § 341.12(c).* Adults: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(4) *For products containing dexchlorpheniramine maleate identified in § 341.12(c).* Adults: oral dosage is 2 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(5) *For products containing diphenhydramine hydrochloride identified in § 341.12(e).* Adults: oral dosage is 25 to 50 milligrams every 4 to 6 hours, not to exceed 300 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(6) *For products containing phenindamine tartrate identified in § 341.12(f).* Adults: oral Dosage is 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(7) *For products containing pheniramine maleate identified in § 341.12(g).* Adults: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 6.25 to 12.5 milligrams every 4 to 6 hours, not to exceed 75 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(8) *For products containing pyrilamine maleate identified in § 341.12(h).* Adults: oral dosage is 25 to 50 milligrams every 6 to 8 hours, not to exceed 200 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 to 25 milligrams every 6 to 8 hours, not to exceed 100 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(9) *For products containing thonzylamine hydrochloride identified in § 341.12(i).* Adults: oral dosage is 50 to 100 milligrams every 4 to 6 hours, not to exceed 600 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 25 to 50 milligrams every 4 to 6 hours, not to exceed 300 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(10) *For products containing tripolidine hydrochloride identified in § 341.12(j).* Adults: oral dosage is 2.5 to 6 milligrams every 8 to 8 hours, not to exceed 10 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 1.25 milligrams every 6 to 8 hours, not to exceed 5 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor. (e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

§ 341.90 Professional labeling.

* * * * *

(b) *For products containing brompheniramine maleate identified in § 341.12(a).* Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours.

(c) *For products containing chlorpheniramine maleate identified in § 341.12(b).* Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours.

(d) *For products containing dexbrompheniramine maleate identified in § 341.12(c).* Children 2 to under 6 years of age: oral dosage is 0.5 milligram every 4 to 6 hours, not to exceed 3 milligrams in 24 hours.

(e) *For products containing dexchlorpheniramine maleate identified in § 341.12(d).* Children 2 to under 6 years: oral dosage is 0.5 milligram every 4 to 6 hours, not to exceed 3 milligrams in 24 hours.

(f) *For products containing diphenhydramine hydrochloride identified in § 341.12(e).* Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 mg in 24 hours.

(g) *For products containing phenindamine tartrate identified in § 341.12(f).* Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours.

(h) *For products containing pheniramine maleate identified in § 341.12(g).* Children 2 to under 6 years of age: oral dose is 3.125 to 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours.

(i) *For products containing pyrilamine maleate identified in § 341.12(h).* Children 2 to under 6 years of age: oral dosage is 6.25 to 12.5 milligrams every 4 to 6 hours, not to exceed 50 milligrams in 24 hours.

(j) *For products containing thonzylamine hydrochloride identified in § 341.12(i).* Children 2 to under 6 years of age: oral dosage is 12.5 to 25 milligrams every 4 to 6 hours, not to exceed 150 milligrams in 24 hours.

(k) *For products containing triprolidine hydrochloride identified in § 341.12(j).* Children 2 to under 6 years of age: oral dosage is 0.938 milligram every 4 to 6 hours, not to exceed 3.744 milligrams in 24 hours. Children 2 to under 4 years of age: oral dosage is 0.625 milligram every 6 to 8 hours, not to exceed 2.5 milligrams in 24 hours. Infants 4 months to under 2 years of age: oral dosage is 0.313 milligram every 6 to 8 hours, not to exceed 1.252 milligrams in 24 hours.

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

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

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

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

Dated: December 31, 1984.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

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January 15, 1985

Part IX

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 341

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 76N-052N]

21 CFR Part 341

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

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

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

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

ADDRESS: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

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

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

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

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

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

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

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

29, 1981; 46 FR 47730.) The Court in *Cutler* held that the OTC drug review regulations were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision has been deleted from the regulations, which now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

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

In the advance notice of proposed rulemaking for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products (published in the **Federal Register** of September 9, 1976 (41 FR 38312)), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

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

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

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

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

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

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on Nasal Decongestant Drug Products

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

References

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

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

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

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

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

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

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

C. Comments on Specific OTC Nasal Decongestant Active Ingredients

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

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

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

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

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

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

References

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

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

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

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

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

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

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

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

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

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

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

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

References

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

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

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

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

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

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

References

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

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

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

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

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

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

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

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

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

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

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

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

Reference

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

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

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

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

References

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

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

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

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

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

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

References

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

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

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

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

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

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

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

References

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

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

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

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

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

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

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

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

References

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

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

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

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

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

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

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

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

D. Comments on Dosages for OTC Nasal Decongestants

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

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

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

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

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

References

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

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

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

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

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

Reference

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

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

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

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

Reference

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

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

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

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

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

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

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

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

References

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Reference

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

E. Comments on OTC Nasal Decongestant Labeling and Warnings

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

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

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

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

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

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

References

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

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

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

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

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

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

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

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

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

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

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

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

References

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

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

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

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

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

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

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

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

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

References

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

References

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

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

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

F. Comments on Testing Guidelines

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

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

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

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

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

References

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

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

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

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

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

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

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

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

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

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

B. Summary of the Agency's Changes

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

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

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

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

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

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

Reference

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

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

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

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

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

Reference

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

List of Subjects in 21 CFR Part 341

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

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

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 it is proposed to make the following amendments:

PART 341—[AMENDED]

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

§ 341.3 Definitions.

* * * * *

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

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

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

§ 341.20 Nasal decongestant active ingredients.

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

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

(2) Pseudoephedrine hydrochloride.

(3) Pseudoephedrine sulfate.

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

(2) Ephedrine.

(3) Ephedrine hydrochloride.

(4) Ephedrine sulfate.

(5) Racephedrine hydrochloride.

(6) Naphazoline hydrochloride.

(7) Oxymetazoline hydrochloride.

(8) Phenylephrine hydrochloride.

(9) Propylhexedrine.

(10) Xylometazoline hydrochloride.

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

§ 341.80 Labeling of nasal decongestant drug products.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

§ 341.90 Professional labeling.

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

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

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

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

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

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

Dated: December 31, 1984.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

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