

**Wednesday
December 9 1992**

Food and Drug Administration

Part IV

**Department of
Health and Human
Services**

Food and Drug Administration

**21 CFR Parts 201, 310, 341, and 369
Cold, Cough, Allergy, Bronchodilator, and
Antiasthmatic Drug Products for Over-
the-Counter Human Use; Final Monograph
for OTC Antihistamine Drug Products;
Final Rule**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 310, 341, and 369

[Docket No. 76N-052H]

RIN 0905-AA06

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing 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)) are generally recognized as safe and effective and not misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on antihistamine drug products that have come to the agency's attention. Also, this final rule amends the regulation that lists nonmonograph active ingredients by adding those OTC antihistamine ingredients that have been found to be not generally recognized as safe and effective or are misbranded and were not previously listed in the regulation. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: December 9, 1993.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

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 (Cough-Cold Panel), 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 accordance with § 330.10(a)(10), the data and information considered by the Panel were put on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of tentative final monographs for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products, was issued in the following segments: anticholinergics and expectorants, bronchodilators, antitussives, nasal decongestants, antihistamines, and combinations. The fifth segment, the tentative final monograph for OTC antihistamine drug products, was published in the Federal Register of January 15, 1985 (50 FR 2200). Interested persons were invited to file by May 15, 1985, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by May 15, 1985. New data could have been submitted until January 15, 1986, and comments on the new data until March 17, 1986.

In this tentative final monograph, the agency acknowledged a need to evaluate new data and information concerning doxylamine succinate and birth defects (50 FR 2200 at 2202). This information arose after the Cough-Cold Panel recommended that doxylamine succinate be generally recognized as safe and effective as an OTC antihistamine (41 FR 38312 at 38419). In the Federal Register of August 24, 1987 (52 FR 31892), FDA published a notice of proposed rulemaking on OTC antihistamine drug products that amended the tentative final monograph that was published on January 15, 1985 to include chlorcyclizine hydrochloride and doxylamine succinate as Category I OTC antihistamine active ingredients and to revise the proposed dosage for triprolidine hydrochloride. Interested persons were invited to file by October 23, 1987, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by December 22, 1987

New data could have been submitted until August 24, 1988, and comments on the new data until October 25, 1988. No comments were received concerning chlorcyclizine hydrochloride or triprolidine hydrochloride. Therefore, final agency action on chlorcyclizine hydrochloride and triprolidine hydrochloride occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC antihistamine drug products.

With regard to doxylamine succinate, the agency received a technical report concerning a 2-year carcinogenicity and chronic toxicity study of doxylamine succinate in Fischer 344 rats and B6C3F1 mice that was conducted by the National Center for Toxicological Research (NCTR) under the auspices of the National Toxicology Program (NTP) (Ref. 1). The study was prompted by the National Cancer Institute's finding that methapyrilene, a similar antihistamine, is a potent liver carcinogen in the rat. The data on methapyrilene are on file in the Dockets Management Branch (address above) under Docket No. 75N-0244 and have been published (Ref. 2).

In the NCTR study (Ref. 1), doxylamine succinate was administered, ad libitum, as an admixture in the feed to male and female rats at dose levels of 0, 500, 1,000, or 2,000 parts per million (ppm) for 2 years. Mice of both sexes received food containing dose levels of 0, 190, 375, or 750 ppm. Each group contained 48 weanling animals per sex; the animals were scheduled for sacrifice at the end of 104 weeks. An additional group of animals (9 rats and 12 mice per sex) in each dose group was sacrificed at the end of 65 weeks. There were no significant treatment-related differences in survival in either rats or mice. In rats, the highest doxylamine succinate dose group had final body weights that were 22.8 percent (females) and 8.4 percent (males) lower than controls. A number of nonneoplastic lesions was observed in rats, including fatty change, degeneration, and hyperplasia of the liver and increased cytoplasmic alteration in the salivary glands. In mice, there was evidence of hepatotoxicity including hypertrophy, clear and mixed cell foci, and, in females, fatty change. There also was a treatment-related increase in "atypical" hepatocytes in male mice. Both male and female mice had a dose-related increase in thyroid follicular cell hyperplasia. There was a significant positive trend for increased incidence with increasing dose for both hepatocellular adenomas and carcinomas in male rats. When the

incidence of adenomas and carcinomas were combined, the trend test was positive ($p < 0.01$) and the incidence in the highest dose group was significantly ($p < 0.05$) increased over that of controls. No treatment-related increase in neoplasms was found in female rats. Although not statistically significant, one rat in each of the high dose groups of male and female rats was found to have a pineal gland tumor. Given the extreme rarity of this neoplasm in rats, these tumors may be reason for concern despite the lack of a statistically significant increase. In mice, doxylamine succinate administration produced an increased incidence of hepatocellular adenoma in both males and females. Also, both male and female mice had a treatment-related increase in follicular cell adenoma of the thyroid gland.

On June 13 and 14, 1991, the agency's Pulmonary-Allergy Drugs Advisory Committee met to discuss the results of the NCTR study. By a vote of five to one, the Committee concluded that the human carcinogenic potential of doxylamine is not likely. The Committee also recommended (again by a vote of five to one) that doxylamine remain OTC but that there be some warning to the consumer that these data exist (Ref. 3). The agency is currently evaluating the relevance of the study findings to humans and the advisory committee's recommendations. The agency will publish its final decision on doxylamine in OTC antihistamine drug products in a future issue of the *Federal Register*. At this time, drug products containing doxylamine succinate as an OTC antihistamine can remain in the marketplace with the labeling proposed for this ingredient in the tentative final monograph (52 FR 31892 at 31913 and 31914).

The agency's final rule, in the form of a final monograph, for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products is also being published in segments. Because the agency has completed its evaluation of all OTC antihistamine active ingredients other than doxylamine succinate, it is proceeding at this time with its final rule for products containing these ingredients. Final agency action on all OTC antihistamine drug products, except those containing doxylamine, occurs with the publication of this final monograph, which establishes §§ 341.3(g), 341.12, 341.72, and 341.90(e) through (q) for OTC antihistamine drug products in 21 CFR part 341. Combination drug products containing antihistamine ingredients are addressed in the tentative final monograph on OTC cough-cold

combination drug products, which was published in the *Federal Register* of August 12, 1988 (53 FR 30522). A final rule on combination drug products containing antihistamine ingredients will be published in a future issue of the *Federal Register*.

In the tentative final monograph published in the *Federal Register* of January 15, 1985, the agency discussed data submitted in support of the use of chlorpheniramine maleate in treating the symptoms of the common cold and, based on those data, proposed an indication for the temporary relief of runny nose and sneezing associated with the common cold in § 341.72(b) of the tentative final monograph (50 FR 2200 at 2203, 2204, and 2216). Recently, the agency has been evaluating applications requesting prescription-to-OTC switch for drug products containing antihistamines. Some have included labeling for use in the common cold without direct support from clinical studies. The requested claim is based on similarity of pharmacologic action to the other antihistamines included in the tentative final monograph for OTC antihistamine drug products, in which the agency proposed common cold claims based on clinical studies for chlorpheniramine maleate and the similarity of pharmacologic action of all the other monograph antihistamines (50 FR 2216). However, the agency has concerns whether the pharmacologic effects of older Category I ingredients that it considered previously as providing relief of common cold symptoms are characteristic of newer antihistamine drugs. The agency is presently evaluating whether data on chlorpheniramine maleate for this use should be extrapolated to other antihistamines included in this final monograph or any other antihistamines that may be switched from prescription to OTC status. Also, the agency is aware that there is controversy within the scientific community as to whether antihistamines are effective in treating symptoms of the common cold. Before completing this aspect of the rulemaking, the agency wishes to evaluate more recent clinical studies as well as the older data concerning the effectiveness of antihistamines in treating symptoms of the common cold. The agency will discuss these matters in a future issue of the *Federal Register*. Thus, the agency is deferring, at this time, a final conclusion concerning the use of antihistamines for the relief of sneezing and runny nose associated with the common cold, but is publishing its conclusions concerning

the use of antihistamines for allergic rhinitis.

The OTC drug procedural regulation: (§ 330.10) 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. Accordingly, FDA is no longer using 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 is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

As discussed in the proposed regulation for OTC antihistamine drug products (50 FR 2200), the agency advised that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the *Federal Register*. Therefore, on or after December 9, 1993, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application or abbreviated application (hereinafter called application). Further, any OTC drug product subject to this monograph that is 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 response to the proposed rule and amended proposed rule on OTC antihistamine drug products, 10 drug manufacturers, 1 drug manufacturers' association, 1 health care professional, 1 consumer group, and 8 consumers submitted comments. Copies of the comments are on public display in the Dockets Management Branch (address above). Additional information that has come to the agency's attention since

publication of the proposed rule and amended proposed rule is also on display in the Dockets Management Branch.

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 notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

REFERENCES

(1) Department of Health and Human Services, NCTR, "Technical Report for Experiments 406 and 407; Chronic Study of Doxylamine in Fischer 344 Rats and B6C3F1 Mice," 1991, included in OTC Vol. No. 04HFM, Docket No. 76N-052H, Dockets Management Branch.

(2) 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.

(3) Transcript of the June 13-14, 1991 meeting of the FDA Pulmonary-Allergy Drugs Advisory Committee, Vol. II, pp. 172-182, in OTC Vol. No. 04HFM, Docket No. 76N-052H, Dockets Management Branch.

I. THE AGENCY'S CONCLUSIONS ON THE COMMENTS

A. General Comments on OTC Antihistamine Drug Products

1. One comment contended that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comment referred to statements on this issue submitted earlier to other OTC drug rulemaking proceedings.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the *Federal Register* of May 11, 1972 (37 FR 9464 at 9471 to 9472); in paragraph 3 of the preamble to the tentative final monograph for OTC antacid drug products, published in the *Federal Register* of November 12, 1973 (38 FR 31260); and in paragraph 2 of the preamble to the tentative final monograph for OTC cough-cold combination drug products, published in the *Federal Register* of August 12, 1988 (53 FR 30522 at 30524). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by informal rulemaking. (See, e.g., *National Nutritional Foods Association v. Weinberger*, 512 F.2d 688, 696-98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers v. FDA*,

487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).)

2. One comment contended that antihistamines are not effective in alleviating the symptoms of runny nose or sneezing associated with the common cold and thus objected to the agency's decision that chlorpheniramine is effective for this use and that the data from the chlorpheniramine studies allow Category I status for this claim to be extended to all antihistamines. The comment contended that the studies upon which the agency based its decision (Refs. 1 and 2) are inadequate "to prove chlorpheniramine effective for treating colds" because the studies do not meet the standards of the Panel.

The comment described what it considered to be several major design flaws in the two studies. The comment maintained that neither study carefully excludes subjects with hay fever or other allergies from its study group and that the criteria (i.e., "cold symptoms for at least 24 hours, but not longer than 48 hours") for diagnosis of colds are weak. The comment stated that because the symptoms of hay fever mimic those of a cold and because antihistamines are effective in treating hay fever, careful exclusion of subjects with hay fever is essential in a study testing the effectiveness of antihistamines in treating colds. The comment asserted that the only effort made to exclude subjects with allergies was to ask whether they had known allergies. The comment stated that although the studies were conducted in the winter, in several cases they began as early as November or ended as late as May. The comment argued that both November and May are within the hay fever and allergy seasons. The comment suggested that the studies should have included only victims of known cold outbreaks or subjects with colds produced by virus challenge, or that, at the minimum, nasal eosinophil smears should have been done to exclude active allergies. The comment asserted that even a small number of subjects with hay fever could have skewed the study to benefit chlorpheniramine, "especially in view of the minimal effect that chlorpheniramine had."

The comment also alleged that one of the submissions to the agency (Ref. 1) excluded from its tables the results of one of its three investigators because these results were "inconsistent with the results of the other two studies." The comment maintained that if these studies are included, subjects taking chlorpheniramine are not significantly better off in most categories (e.g., patients' overall evaluation, total objective score, and physicians' global

evaluation) than subjects who took the placebo.

The comment added that the other study submitted to the agency (Ref. 2) only demonstrates minimal improvement in subjects taking chlorpheniramine because for each symptom (i.e., sneezing, runny nose, or nose blowing) the drug-treated subjects felt significantly better than those taking placebo at only one or two of the six measurement times.

Additionally, the comment asserted that one could not know how well subjects were randomized in these studies and that the bitter taste of chlorpheniramine could have confounded the results by foiling the double-blind design.

The comment cited two published reports that purported to demonstrate the ineffectiveness of antihistamines in "treating the common cold." One report reviewed 35 published studies of antihistamine use in colds and found that only 2 of the studies were well designed (Ref. 3). The comment noted that neither of these two well-designed studies supported the use of antihistamines to treat colds. The other published report cited by the comment involved a study of the effectiveness of two antihistamines in preventing or improving colds induced by inoculating volunteers with a cold virus. The comment concluded that the drugs were not beneficial because the severity of the colds and the duration of the symptoms were the same in both the drug-treated and the placebo-treated subjects (Ref. 4).

Noting that the overwhelming majority of cold preparations containing an antihistamine also contain a nasal decongestant, the comment suggested that the major flaw in both studies (Refs. 1 and 2) is that neither study demonstrates that the antihistamine adds to the effectiveness of the decongestant in treating colds. The comment maintained that although antihistamines alone may or may not have a small effect in decreasing sneezing and runny nose, this effect is likely to be overshadowed, if not lost, when an antihistamine is combined with a nasal decongestant. The comment added that because the two studies do not address the question of whether or not antihistamines add any benefit when they are used in combination "cold" drugs, the studies do not support the use of antihistamines as they are currently used in cold preparations on the United States OTC drug market. The comment also pointed out that under FDA's prescription drug review one antihistamine-nasal decongestant combination containing triprolidine hydrochloride and

pseudoephedrine hydrochloride was unable to be proven effective for the treatment of colds as a prescription drug, but that it is currently being promoted OTC almost exclusively for use in colds.

As discussed previously, the agency is deferring final action on this issue at this time.

References

- (1) Comment No. SUP004, Docket No. 76N-0052, Dockets Management Branch.
- (2) Comment No. SUP005, Docket No. 76N-0052, Dockets Management Branch.
- (3) West, S., et al., "A Review of Antihistamines and the Common Cold," *Pediatrics*, 56:100-107, 1975.
- (4) Feller, A. E., et al., "The Failure of Antihistaminic Drugs to Prevent or Cure the Common Cold and Undifferentiated Respiratory Diseases," *The New England Journal of Medicine*, 242:737-744, 1950.

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

3. One comment commended the agency for its initiative in proposing additional antihistamine active ingredients (dexchlorpheniramine maleate, dexbrompheniramine maleate, diphenhydramine hydrochloride, and triprolidine hydrochloride) for OTC status. The comment pointed out that dexchlorpheniramine maleate and dexbrompheniramine maleate are the dextrorotary isomers of drugs that have long been generally recognized as safe and effective. Adding that both ingredients have a long history of safe and effective use as prescription antihistamines, the comment noted that dexbrompheniramine maleate recently was switched to OTC use through the new drug application (NDA) process. The comment also stated that diphenhydramine hydrochloride and triprolidine hydrochloride have been safely and effectively used for years both as prescription and OTC drugs. The comment concluded that the inclusion of these four ingredients in proposed § 341.12 is a logical, correct, and justifiable action. On the other hand, another comment maintained that "more and stronger antihistamines" should not be available without requiring a physician's prescription.

In its report (41 FR 38312 at 38379 to 38396), the Panel concluded that several antihistamines, including diphenhydramine hydrochloride, that had previously been available only by prescription could be safely marketed OTC with appropriate labeling. Although the agency originally dissented from the Panel's Category I classification of diphenhydramine hydrochloride (41 FR 38313), in the

tentative final monograph for OTC antihistamine drug products, the agency concluded that diphenhydramine hydrochloride could be safely marketed OTC (50 FR 2200 at 2205). The agency also proposed that the antihistamines dexbrompheniramine hydrochloride, dexchlorpheniramine hydrochloride, and triprolidine hydrochloride, which had previously been available by prescription or for OTC marketing under NDA's, be generally recognized as safe and effective (50 FR 2205 and 2212 to 2214).

When considering whether or not a certain ingredient should be available OTC, the agency's primary concern is an assessment of the overall margin of safety. Factors included in the agency's determination of the margin of safety include toxicity, potential for harmful effects and collateral measures necessary for safe use, abuse and misuse potential, and the benefit-to-risk ratio. The agency has carefully evaluated the risk inherent in the OTC availability of antihistamines, including some ingredients that had been marketed OTC under approved NDA's for many years, and others that had been available only as prescription drugs. The agency concludes that, with appropriate labeling, the ingredients listed in § 341.12 of this final monograph are safe for OTC use within the dosage limits established in the monograph. The second comment did not submit any data demonstrating that these ingredients are not safe for OTC use, or that a physician's prescription is needed for their proper use. Based on adequate evidence establishing that these ingredients are generally recognized as safe and effective for OTC use as antihistamines, the agency is including dexchlorpheniramine maleate, dexbrompheniramine maleate, diphenhydramine hydrochloride, and triprolidine hydrochloride in § 341.12 of this final monograph.

4. One comment noted that the tentative final monograph for OTC antihistamine drug products lists diphenhydramine hydrochloride as Category I and suggested that the same status be accorded diphenhydramine monocitrate (now named diphenhydramine citrate). The comment pointed out that the agency concluded that the citrate salt could be considered identical to the hydrochloride salt in a notice of enforcement policy relating to diphenhydramine as a nighttime sleep-aid, which was published in the *Federal Register* on April 23, 1982 (47 FR 17740). Hence, the comment concluded that the diphenhydramine citrate dose equivalent to the diphenhydramine

hydrochloride dose should be classified Category I as an antihistamine.

A second comment (which was submitted to the agency prior to the publication of the tentative final monograph for OTC antihistamine drug products, but after the administrative record had closed), in the form of a citizen petition, also recommended that diphenhydramine be included in the antihistamine monograph as a Category I OTC antihistamine drug as both the hydrochloride and the citrate salts. In support of this recommendation, the petition stated that the Cough-Cold Panel had recommended that diphenhydramine hydrochloride be classified in Category I for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis at adult dosages of 25 to 50 mg every 4 to 6 hours, not to exceed 300 mg daily, and at children's (6 years and over) dosages of 12.5 to 25 mg every 4 to 6 hours, not to exceed 150 mg daily (41 FR 38312 at 38419). The petition presented a number of reasons why diphenhydramine could be considered safe and effective, as the hydrochloride salt and as the citrate salt, for use as an OTC antihistamine. These included: (1) The Panel's Category I recommendation for diphenhydramine hydrochloride; (2) diphenhydramine is a member of the ethanolamine class of antihistamines with clinical use dating to 1946; (3) the ingredient does not pose a serious safety question beyond its sedation qualities; and (4) proper labeling will minimize problems. A second citizen petition also requested that diphenhydramine citrate be included in the OTC antihistamine final monograph. The petition referenced agency statements in the rulemaking for OTC nighttime sleep-aid drug products (47 FR 17740 at 17741 and 54 FR 6814 at 6824) that the citrate salt could be considered identical to the hydrochloride salt.

The agency agrees with the first comment and the citizen petitions that diphenhydramine, in both the hydrochloride and the citrate salt forms, be included in the final monograph for OTC antihistamine drug products. The agency proposed in the antihistamine tentative final monograph (50 FR 2200 at 2204) that diphenhydramine hydrochloride is safe and effective for OTC use as an antihistamine and proposed that diphenhydramine hydrochloride be Category I at an adult dosage of 25 to 50 mg every 4 to 6 hours for use in OTC antihistamine drug products (50 FR 2204). The agency confirms that proposal in this final monograph.

With respect to diphenhydramine citrate for use as an OTC nighttime

sleep-aid ingredient, the agency stated in the final rule for OTC nighttime sleep-aid drug products (February 14, 1989; 54 FR 6814 at 6823 and 6824) that diphenhydramine hydrochloride and diphenhydramine citrate are safe and effective. The agency concluded that the citrate salt could be considered identical to the hydrochloride salt, because the citrate salt is rapidly converted in the stomach to the hydrochloride salt. The agency also concluded that a dose of 76 mg diphenhydramine citrate is necessary to supply a diphenhydramine content equivalent to 50 mg diphenhydramine hydrochloride.

Therefore, the agency is including diphenhydramine citrate as an active ingredient in the antihistamine final monograph with the following directions: Adults and children 12 years of age and over: oral dosage is 38 to 76 milligrams every 4 to 6 hours, not to exceed 456 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 19 to 38 milligrams every 4 to 6 hours, not to exceed 228 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

The agency will also include directions for diphenhydramine citrate in the antihistamine final monograph under professional labeling as follows: Children 2 to under 6 years of age: oral dosage is 9.5 milligrams every 4 to 6 hours, not to exceed 57 milligrams in 24 hours.

5. A health care professional had no real reservations about diphenhydramine hydrochloride being marketed OTC for treating allergic symptoms, but reported that an adult patient had committed suicide with an overdose of a drug product containing diphenhydramine hydrochloride.

The Panel, in its evaluation of whether a drug product is safe and effective for OTC use, considered the potential for misuse and abuse (41 FR 38312 at 38385) and did not find any data on diphenhydramine hydrochloride to warrant such concerns. Likewise, the agency at this time is not aware of any data to demonstrate that the misuse of diphenhydramine is a widespread problem. 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 drugs in the marketplace (both OTC and prescription) can be and are knowingly misused by some individuals. However, the agency does not find that potential misuse by certain individuals should deprive the majority of the population from having OTC access to drugs that can be used safely and effectively when

labeled directions and warnings are followed. The agency has determined that the labeling and warnings required by this final monograph for OTC antihistamine drug products should provide for the safe and effective use of diphenhydramine hydrochloride when used at the monograph dosages. The agency concludes that diphenhydramine hydrochloride should be available as an OTC antihistamine because it is safe and effective when used as instructed in the labeling.

6. One comment contended that the agency's reasons for placing promethazine hydrochloride in Category III as a single ingredient in the tentative final monograph for OTC antihistamine drug products were in error. The comment stated that the agency's objections against OTC use of this ingredient are exclusively limited to the separate indication of temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever or other upper respiratory allergies or allergic rhinitis. The comment urged the agency to recognize promethazine hydrochloride as a single entity as safe and effective for OTC use, at least for the indication pertaining to the temporary relief of runny nose and sneezing associated with the common cold. The comment argued that promethazine has been generally recognized as effective for a long time. The comment also alleged that the agency's rejection of general recognition of promethazine is based solely on the theoretical safety concern that use of this drug over an extended period of time to relieve symptoms of allergic rhinitis might result in tardive dyskinesia, a serious central nervous system syndrome that may persist indefinitely after discontinuation of the drug. The comment asserted that this safety concern does not exist because no case of tardive dyskinesia has ever been associated with promethazine use, and there has been a total lack of any adverse reports through the 34 years of continuous marketing of this drug in the United States. Further, although promethazine is structurally related to the other phenothiazine drugs which have been linked to causing tardive dyskinesia, the differences in chemical structures and pharmacological effects between promethazine and other phenothiazine drugs substantially lessen the possibility that promethazine could cause the range of side effects associated with other phenothiazine drugs. The comment concluded that the self-limiting use of promethazine to relieve symptoms of the common cold (7 to 14 days) negates the agency's safety

concern that extended use may cause tardive dyskinesia.

The Cough-Cold Panel classified promethazine hydrochloride in Category I as an OTC antihistamine (42 FR 38312 at 38390 to 38391). The agency dissented from the Panel's Category I classification of promethazine hydrochloride in the preamble to the Panel's report (41 FR 38313) based on the degree of drowsiness produced by promethazine hydrochloride and the possible adverse effects in children, such as extrapyramidal disturbances.

In the tentative final monograph for OTC antihistamine drug products (50 FR 2200 at 2206 to 2208), the agency stated that the possibility of choreoathetosis (a condition marked by jerky, involuntary movements) occurring with OTC oral doses of promethazine is unlikely and that there was no evidence to indicate that extrapyramidal side effects were more likely to occur with children. However, the agency placed promethazine hydrochloride in Category III as a single ingredient because of concerns that the rare, but serious adverse reaction of the central nervous system known as tardive dyskinesia might occur if promethazine is used on a long-term basis (50 FR 2200 at 2206 to 2208). The agency also stated that promethazine hydrochloride has not been used extensively as a single ingredient for antihistamine/allergic rhinitis/antiallergy use on a long-term basis. Data submitted to the agency were not sufficient to alleviate these concerns, and promethazine hydrochloride as a single ingredient was placed in Category III in the OTC antihistamine tentative final monograph.

In the tentative final monograph for OTC cough-cold combination drug products published in the Federal Register of August 12, 1988 (53 FR 30522 at 30558 to 30559 and 30563), the agency noted that promethazine has been widely used as a prescription drug, primarily in combination with other active ingredients for acute cough-cold symptoms on a short-term basis. At that time, the data and information indicated that such short-term use of promethazine hydrochloride in these products was safe and that under conditions of short-term use for the relief of cold symptoms, the possibility of tardive dyskinesia occurring was no longer a concern. Therefore, the agency proposed that promethazine hydrochloride in combination with other cough-cold and/or analgesic-antipyretic ingredients be Category I as an OTC antihistamine ingredient in combination drug products for short-term (7-day) use in relieving the

symptoms of runny nose and sneezing due to the common cold (53 FR 30563).

In response to the agency's decision to allow the OTC marketing of promethazine hydrochloride-containing cough-cold combination drug products for short-term (7-day) use for relief of the symptoms of the common cold, the Public Citizen Health Research Group (HRG) and the University of Maryland SIDS Institute (Ref. 1) submitted a citizen petition objecting to the OTC marketing of promethazine-containing cough-cold combination drug products. A number of physicians (Refs. 2 through 9) also objected to OTC status. The major concern that the petition and the physicians raised was that there is a possibility that the use of promethazine-containing drug products in children under 2 years of age may be associated with the occurrence of sudden infant death syndrome (SIDS) and that OTC availability of these drug products could "dramatically increase" "overuse" of these drug products in children in this age group. The petition also raised concerns about possible adverse neurological reactions associated with these drug products and about the use of prescription promethazine-containing drug products in children under age 2, in pregnant or nursing women, and in the elderly.

One manufacturer of promethazine-containing combination drug products submitted data and information to the OTC cough-cold combination drug products rulemaking in response to the concerns raised in the citizen petition, and has objected to the request of the petition (Ref. 10). In addition, the agency has received other information concerning OTC use of drug products containing promethazine hydrochloride in Canada (Ref. 11).

In response to the citizen petition and the manufacturer's submission, the agency scheduled a meeting of the Pulmonary-Allergy Drugs Advisory Committee on July 31, 1989, to discuss the advisability of switching the marketing of cough-cold combination drug products containing promethazine hydrochloride from prescription status to OTC status. Presentations were made by FDA staff and consultants, by representatives of Public Citizen Health Research Group, representatives of a major manufacturer of promethazine hydrochloride drug products, and by other interested persons. The agency has placed the transcripts of that meeting in the docket for the rulemaking for OTC cough-cold combination drug products (Ref. 12). Minutes of that meeting also will be included in that docket when available.

Presentations by FDA staff (Ref. 12) noted that adverse reaction reports from FDA's Annual Adverse Reaction Summaries since 1969 may not be adequate to establish incidence rates because of under reporting of reactions and the lack of a known number of patients receiving the product. It was also noted that because promethazine has been in use since 1951 and the agency did not begin computerizing its data base until 1969, that reporting of adverse reactions for this drug by that time would be at a minimal level because much was already known in the medical community about this drug's adverse reactions, which may cause a loss of interest in reporting reactions.

One case discussed involved a 27-year-old pregnant woman who was prescribed promethazine hydrochloride 25-mg suppositories, initially every 24 hours for 2 days and subsequently twice a day as needed, for persistent morning nausea and vomiting during her 12th week of pregnancy. After 3 days of use, she developed acute dystonic reactions that caused involuntary abnormal posturing of the neck, trunk, and left arm which lasted for about a year and a half. This case was considered unusual because promethazine was used for a very short time, i.e., 3 days, rather than on a long-term basis. Further, it was noted that although the treating physician initially diagnosed the condition as an acute dystonic reaction to promethazine, the long-term persistence of the condition (one and one-half years) qualified the diagnosis of the condition to be defined as both tardive dystonia and acute dystonia.

Manufacturer representatives in their presentations concluded that there was no real evidence of tardive dyskinesia (a condition primarily characterized by involuntary movement of the facial, buccal, oral, and cervical (neck) musculature (Ref. 13)) associated with promethazine use and that the case of the pregnant woman who developed dystonia (a condition that involves involuntary muscle clonic contortions characterized by abnormal sustained posturing of the neck, trunk, and extremities (Ref. 13)) after 3 days of therapy could have been idiosyncratic, and the condition may have been a movement disorder of pregnancy. The representatives stated further that the only reports of tardive dyskinesia with the use of promethazine occurred with patients using multiple neuroleptic drugs and occurred only after long-term use of phenothiazines. Therefore, short-term use would eliminate any risk of the occurrence of tardive dyskinesia.

After hearing the presentations, the Advisory Committee members voted on

a number of the issues presented. In response to the issue concerning the relationship between the use of promethazine-containing drug products and SIDS and/or sleep apnea, one committee member voted that no relationship exists, while the other seven members voted that there is a possible relationship. In response to the issue of whether there is a reason for concern about the use in the elderly of the proposed adult oral dosage of promethazine hydrochloride (6.25 mg every 4 to 6 hours, not to exceed 37.5 mg in 24 hours) on a short-term (7-day) basis, four committee members voted yes, and four members voted no. With respect to the potential neurologic toxicities at the proposed OTC dosage, none of the committee members felt there was a definite concern, but all voted that there are possible concerns. In response to the question (based on the data presented) concerning whether promethazine hydrochloride at proposed OTC doses with specific labeling requirements for short-term (7-day) use should be marketed OTC for relief of the symptoms of the common cold, the Committee recommended to FDA by a vote of seven to one that these drug products not be marketed OTC at this time.

In a notice in the Federal Register of September 5, 1989 (54 FR 36762), FDA concluded that it should accept the Advisory Committee's recommendations and announced that promethazine-containing combination drug products for use in treating the symptoms of the common cold may not be marketed OTC at this time. In that policy statement, the agency stated that before making a final decision concerning OTC status for these products and before responding to the citizen petition, that it intended to fully and thoroughly evaluate data and information submitted to date, data presented at the July 31, 1989 advisory committee meeting, and other data and information that may be pertinent. Additional comments and safety data have been submitted by a manufacturer of promethazine-containing drug products (Ref. 14). The submissions respond to issues raised at the July 31, 1989 advisory committee meeting and requests that combination cough-cold drug products containing promethazine hydrochloride be allowed to be marketed OTC.

Therefore, at the present time, the marketing status of promethazine-containing cough-cold drug products remains prescription only. After all the data and information have been reviewed and evaluated, the agency will publish its decision regarding the OTC

marketing status of combination drug products containing promethazine hydrochloride in a future issue of the Federal Register.

Irrespective of that evaluation, the agency continues to believe that promethazine as a single ingredient has not been used extensively either to treat the symptoms of allergic rhinitis or the common cold and that unresolved questions remain concerning a causal role in tardive dyskinesia. In addition, presentations at the July 1989 advisory committee meeting regarding promethazine association with both acute and tardive dystonia and tardive dyskinesia reinforce the agency's concern that these conditions may occur with long-term use of promethazine hydrochloride at OTC dosages. Therefore, promethazine hydrochloride as a single ingredient is not being included in this final monograph. If, at a later date, promethazine is considered a monograph condition for use in OTC cough-cold combination drug products, the agency will reconsider its potential OTC use as a single ingredient antihistamine for the temporary relief of runny nose and sneezing associated with the common cold. This will be done in a future Federal Register notice in which the agency discusses the use of antihistamines for relief of the symptoms of the common cold or discusses the use of cough-cold combination drug products.

References

- (1) Comment No. CP, Docket No. 76N-052G, Dockets Management Branch.
- (2) Comment No. C00205, Docket No. 76N-052G, Dockets Management Branch.
- (3) Comment No. C00206, Docket No. 76N-052G, Dockets Management Branch.
- (4) Comment No. C00207, Docket No. 76N-052G, Dockets Management Branch.
- (5) Comment No. C00208, Docket No. 76N-052G, Dockets Management Branch.
- (6) Comment No. C00209, Docket No. 76N-052G, Dockets Management Branch.
- (7) Comment No. C00212, Docket No. 76N-052G, Dockets Management Branch.
- (8) Comment No. C00214, Docket No. 76N-052G, Dockets Management Branch.
- (9) Comment No. C00220, Docket No. 76N-052G, Dockets Management Branch.
- (10) Comments No. RC0001 and RC0002, Docket No. 76N-052G, Dockets Management Branch.
- (11) Comments No. LET 088 and LET089, Docket No. 76N-052G, Dockets Management Branch.
- (12) Transcripts of the July 31, 1989 meeting of the FDA Pulmonary-Allergy Drugs Advisory Committee, coded TR1, Docket No. 76N-052G, Dockets Management Branch.
- (13) "Dorland's Illustrated Medical Dictionary," 27th Ed., W. B. Saunders Company, Philadelphia, 1988, s.v. "dystonia" and "dyskinesia."

(14) Comments No. C00223, C00224, and C00225, Docket No. 76N-052G, Dockets Management Branch.

7. One comment requested that tripeleminamine hydrochloride be switched from prescription to OTC status, contending that this drug is nonaddictive and has no more harmful side effects than other "deregulated" (OTC) drugs. Noting that a number of antihistamines, including tripeleminamine hydrochloride, have a mild sedative effect, the comment stated that the side effects from some OTC drugs (such as alcohol, aspirin, acetaminophen, and dimenhydrinate hydrochloride) cause more harm to the abuser than tripeleminamine hydrochloride. The comment added that the benefits from the use of tripeleminamine hydrochloride outweigh any potential misuse or abuse of the drug. The comment mentioned that a number of common household substances from alcohol to household cleaners can be abused or misused, but this potential for abuse and misuse does not curtail the public's beneficial uses of these items. The comment added that tripeleminamine hydrochloride is marketed as an OTC drug product in Canada and there do not appear to be any unfavorable reports in the current literature. The comment pointed out that because antihistamines are often used for allergies for extensive periods of time, the cost factor to the consumer would be greatly reduced if tripeleminamine hydrochloride was marketed OTC.

Because no data concerning tripeleminamine hydrochloride were submitted to the Panel, it did not review this ingredient or make any recommendations on the safety or effectiveness of this drug for use as an OTC antihistamine. Although the comment presented some good reasons to support OTC status for this drug, unfortunately it did not provide any data concerning the safety and effectiveness of tripeleminamine hydrochloride for OTC use as an antihistamine. Therefore, the agency is not including tripeleminamine hydrochloride in this final monograph. However, if appropriate safety and effectiveness data are submitted in accordance with the requirements of 21 CFR 330.10(a)(4), the agency will consider OTC status for this drug and a possible future amendment of this final monograph.

C. Comments on Specific OTC Antihistamine Active Ingredients

8. One comment requested that brompheniramine maleate be removed from OTC use based on information in

the "Handbook for Prescribing Medication During Pregnancy" (Ref. 1) that cited this ingredient as the only antihistamine associated with increased incidence of birth defects.

The agency believes that the statement that the comment refers to was cited in the above reference as "A large-scale study of drugs that could possibly have a teratogenic effect * * * included chlorpheniramine, pheniramine, and brompheniramine. Of these, only with brompheniramine was there a statistically significant increased risk of teratogenicity." Based on a review of the references cited in the "Handbook for Prescribing Medication During Pregnancy," the agency believes that the large-scale study referenced was a study by Heinonen, Slone, and Shapiro (Ref. 2). The agency has reviewed this study and concludes that a causal association between the use of brompheniramine maleate during pregnancy and the occurrence of birth defects has not been established.

The Heinonen, Slone, and Shapiro study (Ref. 2) is a retrospective study of 50,282 mother-child pairs that included 3,248 malformed children and that considered the relationships between the occurrence of birth defects during the first 4 months of pregnancy and the exposure to antinauseant, antihistamine, and phenothiazine drug products. The agency notes that some of the exposure times reported in this study may not be precise. In this study, the relative risks for occurrence of malformations are presented as crude values, values standardized for hospital variability, and values standardized for the mother's ethnic group and for survival of the child.

In one analysis, the investigators considered all 3,248 malformed children in relation to exposure to the entire group of antinauseants, antihistamines, and phenothiazines in the first 4 lunar months of pregnancy. Out of 65 mother-child pairs with exposure to brompheniramine, they found 10 children with malformations. Based on these data, the investigators stated that brompheniramine was the only drug that had an estimated relative risk that was statistically significant at the 0.05 level. The investigators added that this was the only drug for which the relative risk was greater than 1.5. However, when the investigators analyzed the data confined to the 2,277 children who had malformations which were uniformly distributed across the hospitals studied, they found a hospital-standardized relative risk of 1.98 (6 malformed infants in 65 exposed mother-child pairs) for brompheniramine. The agency believes

that, if the small sample size is taken into consideration and an adjustment were made to account for the large number of associations tested (i.e., analysis of multiple drug categories and multiple types of birth defects) involved in the study, these standardized relative-risk findings would not be considered statistically significant based on the increased probability that the findings in this study may have occurred by chance.

The data presented by Heinonen, Slone, and Shapiro are from the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke. The agency obtained a printout of the Collaborative Perinatal Project pertaining to brompheniramine exposure in the first 3 lunar months of pregnancy (Ref. 3). This printout shows that during the first 3 lunar months of pregnancy, birth defects occurred in 4 children out of 22 mother-child pairs exposed to brompheniramine. The structural birth defects were syndactyly (two cases), polydactyly, and pectus excavatum. Because it is generally accepted that the development of these structural malformations occurs in the first 3 lunar months of pregnancy and exposure to the drug during the fourth lunar month would not cause a structural birth defect (Refs. 4 and 5), the agency concludes that the two structural malformations mentioned by Heinonen, Slone, and Shapiro (Ref. 2) as occurring in mother-child pairs in the fourth lunar month are probably related to environmental factors or genetic factors or may be due to chance. In addition, the agency notes that all mothers of the four malformed children who were exposed to brompheniramine during the first 3 lunar months of pregnancy were also exposed to one or more other medications (Ref. 3).

The Heinonen, Slone, and Shapiro study was an exploratory investigation of several drugs and several possible adverse events. An exploratory study may identify possible associations and suggest areas for further study. However, without advance credibility of specific associations, an exploratory study is not the proper mechanism for confirming such associations. The agency concludes that an association cannot be confirmed from the same data set that suggested the association in the first place.

For the above reasons, this study does not establish a definite association between brompheniramine exposure and birth defects. The agency recognizes that this does not rule out the possibility that this association exists, but concludes that such an association is

not supported by the study. In addition, Heinonen, Slone, and Shapiro do not make any statement specifically about brompheniramine teratogenicity and conclude that there was essentially no association between uniform malformations and the large categories of drug groups studied and that "there was no evidence to suggest that exposure to antihistamines * * * was related to malformations overall, or to large categories of major or minor malformations."

Based on the above information, the agency concludes that this study does not demonstrate that brompheniramine maleate is a teratogen. Further, the agency is not aware of any other studies that would establish a causal association between the use of brompheniramine maleate and birth defects. Thus, the agency believes that brompheniramine maleate when labeled with the pregnancy/nursing warning required in 21 CFR 201.63 is safe for OTC use and is including this ingredient in this final monograph.

References

- (1) Berkowitz, R. L., D. R. Coustan, and T. K. Mochizuki, "Antihistamines (over-the-counter): Brompheniramine, Chlorpheniramine, Cyclizine, Doxylamine, Meclizine, Phenindamine, Pheniramine, Pyrilamine," in "Handbook for Prescribing Medications During Pregnancy," 1st Ed., Little, Brown and Co., Boston, pp. 24 and 26, 1986.
- (2) Heinonen, O. P., D. Slone, and S. Shapiro, "Antinauseants, Antihistamines, and Phenothiazines," in "Birth Defects and Drugs in Pregnancy," Publishing Sciences Group, Inc., Littleton, MA, pp. 322-334 and 475, 1977.
- (3) Excerpts of data from the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke and Boston University, 1981, OTC Vol. 04HFM, Docket No. 76N-052H, Dockets Management Branch.
- (4) Shepard, T. H., "Catalog of Teratogenic Agents," 5th Ed., The Johns Hopkins University Press, Baltimore, p. xvii, 1986.
- (5) Tuchmann-Duplessis, H., and P. Haegel, "Volume 2 Organogenesis," Springer-Verlag, New York, pp. 2-11, 1974.

9. One comment submitted data (Ref. 1) to support reclassification of phenyltoloxamine citrate from Category III to Category I at an adult dose of 30 to 60 mg every 4 to 6 hours, not to exceed 360 mg in 24 hours, and at a children's (ages 6 to 12 years) dosage equal to one-half the adult dose. The submitted data consisted of two clinical studies (Ref. 1) and a published pharmacology study (Ref. 2).

The agency has reviewed the submitted data and other information and determined that the data are not sufficient to establish the effectiveness

of phenyltoloxamine citrate as an OTC antihistamine. The agency finds that the study design of the two clinical studies (CRD 85-17 and 85-18) is flawed, and the studies were not adequately controlled.

Study CRD 85-17 was a double-blind parallel, placebo-controlled study involving 108 subjects ranging in age from 18 to 59 years with a confirmed diagnosis of seasonal allergic rhinitis. The study was designed to assess the antihistaminic effectiveness of phenyltoloxamine citrate in the treatment of seasonal allergic rhinitis. Subjects were randomized into one of three treatment categories: those taking the 30-mg test product, those taking the 60-mg test product, and those taking the placebo, for a 1-week period at a dosage of one capsule four times a day at 8:30 a.m., 12:30, 5:00, and 10:00 p.m. Measurement of the relief of symptoms was done in two ways: on days 1, 2 and 8, the symptoms were evaluated hourly from 8:30 a.m. to 4:30 p.m. at the study site by an investigator and the subject; on days 3 to 7, the effect of the test product on symptoms was evaluated by the subjects at home on four occasions (morning, noon, evening, and bedtime) and recorded in a diary.

The study results divide subjects into two groups: those who missed a dose of study medication and those who had to take rescue medication. These differences in the study subjects were subsequently ignored, and the two groups were combined (and included in the analysis of the results of this study) and considered as being similar. Even though the total number of each test group of subjects who missed a dose or took rescue medication was similar, there were differences in the number of subjects who had missed a dose versus those who took rescue medication in each group as follows: in the 30-mg dose group, three subjects took rescue medication and two subjects missed doses; in the 60-mg dose group, three subjects took rescue medication and three subjects missed doses; while in the placebo group, five subjects took rescue medication and one subject missed doses. In addition, there was a variance in the total number of days and dosage interval doses that were missed as well as when the rescue medication was taken. The agency believes that these differences should have been noted and considered in the analysis of the data rather than combined and ignored.

In analyzing this study, the agency noted considerable variation in the test results of the effect of the 30-mg drug product on symptom relief, which may be due to operative variables such as

variations in pollen counts and humidity that were not considered in the methodology of the study. For example, for the relief of nasal congestion, the data indicated that the active drug ingredient was more effective than the placebo on day 1 (at three observation points), on day 2 (at six points), and on day 8 (at five points). While these differences were between the lower 30-mg dose of the active drug and the placebo, the data show that at several of these same observation points this lower dose was more effective than the higher 60-mg dose of the drug. On days 4, 6, and 7, the difference between regimens (also in favor of the lower dose of active drug) was only apparent at one observation point. On days 3 and 5, no differences were noted. On days 2 and 8, there were 12 observation points, while on the other days, there were only 4 observation points. On days 2 and 8, the subjects remained indoors for 8 hours, while on days 3 through 7, the subjects were not confined and their whereabouts were not stated. Although statistical methods were not mentioned in detail, observation points were compared with baseline mean values and days were compared to days. Irrespective of the results, even if differences were demonstrated, it would be difficult to determine whether they were attributable to drug effect, a variation in the pollen count, humidity, or the effect of a controlled versus an uncontrolled environment. The agency believes that a comparison of effects for site days and a separate comparison of nonsite days would have reduced the uncontrolled operative variables.

The agency also found that differences between the three treatment groups with respect to relief of the symptoms of allergic rhinitis were not consistently demonstrated and were erratic. Further, on those days when differences were noted, it was difficult to determine whether the results were due to drug effect or the inadequacies of the study design and analysis. Phenyltoloxamine citrate was shown to be more effective than the placebo (i.e., with a statistically significant p value of 0.05 or less) on only one day (day 2) for relieving both wet and itchy symptoms. Further, on only a few occasions was the higher 60-mg dose of active drug more effective than the placebo. In addition, the lower 30-mg dose of active drug was found to be superior to both the higher 60-mg active drug dose and to the placebo. When the effects of the drug on wet and itchy symptoms were combined, the agency finds that statistically significant differences were recorded for only 3 out of the 59

observation points (on day 2 at 2:30 p.m., on day 6 at bedtime, and on day 7 in the morning). The data for nasal flow measurements demonstrated that on only one day was the 30-mg dose more effective than the 60-mg dose. In addition, the placebo appeared to be more effective than the 60-mg dose. Thus, the nasal flow measurements were not very helpful.

The protocol for study CRD 85-18 was essentially identical to study CRD 85-17 with the exception that there were 74 subjects who participated in the study. Other minor variations between the two studies included the following: (1) analysis of the data was done by comparing the effect of the active drugs and placebo on relieving the symptoms by days at study site, days at home, and by combining study site days and home site days, whereas study CRD 85-17 compared observation points on each day and overall days, and (2) a different grading system was used to record symptoms of a stuffy nose and the methodology of performing or recording nasal airway resistance. The second evaluation day was staggered over a 4-day period (either day 2, 3, 4, or 5), while in study 85-17, day 2 was always the second 8-hour evaluation day. The agency believes that these differences would tend to bias the results in favor of the active drug because there are less points of comparison in this study and the additional 3-day period would create a steady state condition. Even the comment concluded that the data were not supportive of any demonstrable efficacy for the active drug. The reported results of the study confirm this conclusion.

The agency disagrees with the comment's explanation of study CRD 85-18 and its contention that this study is incomplete and therefore inconclusive. The number of subjects recruited (74) for the study was adequate to demonstrate efficacy. In addition, carrying out the study over two allergy seasons (spring and fall) is not a reason to reject the study because symptoms of allergic rhinitis were required for entrance into the study. Also, the complexity of the case report forms for study CRD 85-18 was not greater than the complexity of the case report forms for study CRD 85-17, and thus is not a reason to reject the study. In fact, the design of study CRD 85-18 may have introduced bias into this study in favor of the active ingredient rather than the control, because steady state would more likely have been achieved on the staggered second evaluation day schedule that was used in this study.

The published study by Falliers et al. (Ref. 2) and the pharmacology study (Ref. 3) reviewed by the agency in the tentative final monograph for OTC antihistamine drug products (50 FR 2200 at 2208) are the same study. The agency stated in the tentative final monograph that this study demonstrated that there is a statistically significant difference between the pharmacologic action of a placebo and phenyltoloxamine citrate in favor of the active ingredient at 1- and 2-hour intervals after a single dose has been given. However, the study did not demonstrate the effectiveness of phenyltoloxamine over a long enough period of time that would be representative of the actual conditions under which the drug would be used. The agency stated that 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 of test ingredient and placebo, demonstrating the effectiveness of phenyltoloxamine would be necessary to reclassify this active ingredient in Category I. The agency's conclusions regarding that study remain the same. Further, the results of studies CRD 85-17 and 85-18 do not alter the agency's clinical opinion that these studies do not adequately support the effectiveness of phenyltoloxamine citrate as an OTC antihistamine.

Based on a lack of adequate clinical efficacy data, the agency concludes that phenyltoloxamine citrate should not be upgraded to monograph status. Therefore, this ingredient is not being included in this final monograph.

The agency's detailed comments and evaluations of the data are on file in the Dockets Management Branch (Ref. 4).

References

- (1) Comments No. RPT003 and RPT004, Docket No. 76N-052H, Dockets Management Branch.
 - (2) Falliers, et al., "Inhibition of Cutaneous and Mucosal Allergy with Phenyltoloxamine," *Annals of Allergy*, 41:140-144, 1978.
 - (3) Comments No. C00168, LET003, and SUP007, Docket No. 76N-0052, Dockets Management Branch.
 - (4) Letter from W. E. Gilbertson, FDA, to E. H. Hanus, Richardson-Vicks, coded LET085, Docket No. 76N-052H, Dockets Management Branch.
10. One comment described personal experience in using several different antihistamines, including methapyrilene hydrochloride and pyrilamine maleate, for self-treatment of hay fever. The comment stated that these drugs worked well but noted that methapyrilene hydrochloride had been

removed from the market because it was a potent carcinogen in animal tests. The comment stated that it did not find pyrilamine maleate listed in the tentative final monograph and questioned whether pyrilamine maleate is similar to methapyrilene and whether it has been tested as cancer-causing.

The agency concluded in the tentative final monograph, based on data provided in a National Cancer Institute study, that methapyrilene is a potent carcinogen in animals and must be considered a potential carcinogen in man (50 FR 2200 at 2202). The agency initiated a recall of all oral and topical products containing methapyrilene and placed methapyrilene fumarate and methapyrilene hydrochloride in Category II (50 FR 2202). Thus, methapyrilene was not included in the tentative final monograph. However, pyrilamine maleate was proposed as a Category I antihistamine in the tentative final monograph (50 FR 2216).

Because of the similarity in chemical structure between pyrilamine and methapyrilene and because of the extensive use of pyrilamine maleate in both prescription and OTC drug products, it was nominated for testing by NCTR, under the auspices of the NTP (Ref. 1). Studies, in which pyrilamine was tested in rats and mice in chronic (104 weeks) bioassays, were completed in February and March 1987 and preliminary findings indicated no cancer-causing potential (Ref. 2). The final report was published in June 1991 with the conclusion that there was no evidence for a carcinogenic response to pyrilamine maleate by either F344 rats or B6C3F1 mice (Ref. 3). Based on the above information, the agency concludes that pyrilamine maleate is safe for OTC use and is including this ingredient in this final monograph.

References

- (1) "Final Report—90 Day Subchronic Study Report on Pyrilamine in Fischer Rats," paragraph 1.0, Introduction, NCTR, Jefferson, AR, page 5, OTC Vol. 04HFM, Docket No. 76N-052H, Dockets Management Branch.
- (2) Memorandum of telephone conversation between G. Kerner, FDA, and W. Allaben, NCTR, January 27, 1989, OTC Vol. 04HFM, Docket No. 76N-052H, Dockets Management Branch.
- (3) Department of Health and Human Services, NTP, "Technical Report for, Experiment No. 408 and 409 (NTP Experiments 05013-03 and 05013-04); Pyrilamine: 104 Week Chronic Dose Study in Rats, and Pyrilamine: 104 Week Chronic Dose Study in Mice," June 1991.

D. Comments on Dosages for OTC Antihistamine Active Ingredients

11. Two consumers questioned the safety of a higher dosage of

chlorpheniramine maleate than previously permitted for OTC use. One consumer stated that a higher dosage of chlorpheniramine maleate may cause reactions and any antihistamine should be tested properly before the public is allowed to self-administer the product. Another consumer stated that the agency should warn against the overuse of OTC antihistamines. The consumer did not further elaborate on what was meant by the term "overuse."

The Panel reviewed extensive test data on antihistamine active ingredients, including chlorpheniramine maleate. The Panel recommended that a number of antihistamines could be generally recognized as safe and effective for OTC use in specified dosages and with specific labeling. In general, the agency has concurred with the Panel's recommendations.

Based on its review of clinical data on chlorpheniramine maleate, the Panel recommended that this ingredient be available OTC at a dosage that was twice that previously permitted for OTC use (41 FR 38312 at 38383). The Panel made this dosage recommendation because it found that chlorpheniramine maleate had not been shown to be effective for adults at a dose less than 4 mg. (The Panel recommended that the dose for children 6 to under 12 years of age be one-half the adult dose.) The Panel's proposed OTC dosage was as follows: adults, 4 mg every 4 to 6 hours, not to exceed 24 mg in 24 hours; children 6 to under 12 years of age, 2 mg every 4 to 6 hours, not to exceed 12 mg in 24 hours. The Panel noted that the chief side effect of chlorpheniramine maleate is sedation and recommended an appropriate warning, "May cause drowsiness." The Panel also recommended warnings that would inform the consumer to avoid driving a motor vehicle or operating heavy machinery and to avoid alcoholic beverages while taking a product containing this drug.

In the tentative final monograph for OTC antihistamine drug products (50 FR 2200), the agency concurred with the Panel's determination that an adult dose of less than 4 mg chlorpheniramine maleate is not effective (50 FR 2205) and that extensive data support the safety and effectiveness of the higher dosages for chlorpheniramine for OTC use (50 FR 2208). Further, the agency proposed a revised warning concerning the drowsiness effect of antihistamines to include sedatives and tranquilizers in addition to alcohol as drugs that may intensify the drowsiness effect of antihistamines (52 FR 31913).

With regard to warnings concerning the overuse of OTC antihistamine drug products, the agency believes that the required labeling set forth in this final monograph is adequate to provide for the safe and effective use of these products. Antihistamines have been used OTC for many years for the relief of the symptoms of hay fever and upper respiratory allergies (allergic rhinitis), which may be seasonal as well as perennial. It is generally recognized that these drugs are safe for their intended use under monograph conditions, even when used over extended periods of time and that the warnings required by this monograph would adequately address any concerns regarding any significant side effects that could occur.

A concern about two antihistamines being taken simultaneously was addressed in the tentative final monograph (50 FR 2203). The agency stated that it recognized that many products containing antihistamines for relieving symptoms of hay fever and the common cold are available in the OTC drug marketplace, but is unaware of any specific information that would raise health concerns about these products being marketed OTC under the conditions stated in the monograph. Because each product is required to be prominently labeled with the product's statement of identity, i.e., "antihistamine" (21 CFR 201.61), consumers are provided adequate information that these products contain an antihistamine drug. By reading the labels, consumers are informed that different drug products contain an antihistamine intended to treat the same symptoms. Thus, the agency believes that the likelihood that such products would be taken simultaneously is very low.

The agency therefore concludes that the warnings and directions set forth in this final monograph should provide for the safe and effective OTC use of antihistamine drug products and at this time there is no need to expand the monograph to include additional warnings against overuse of these products.

E. Comments on Labeling of OTC Antihistamine Drug Products

12. Two comments stated that FDA lacks statutory authority to prescribe exclusive lists of terms from which indications for use for OTC drug products must be drawn and to prohibit alternative labeling terminology which is truthful, accurate, not misleading, and intelligible to the consumer. One comment recommended that instead of prohibiting the use of alternative truthful terminology, FDA should

permit manufacturers to choose consumer oriented language to communicate the desired label indications, so long as such language is not false or misleading. Both comments noted that FDA proposed certain revisions to the "Exclusivity Policy" on April 22, 1985 (50 FR 15810) and stated that they would submit further comments on that proposal.

In the *Federal Register* of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g). The final rule in this document is subject to the labeling provisions in § 330.1(c)(2).

13. One comment stated that the numerous pharmacological properties of diphenhydramine should permit a sleep-aid claim for this ingredient when it is used as an antihistamine. The comment noted that diphenhydramine has previously been classified Category I as a nighttime sleep-aid and requested that this type of claim be permitted in addition to the allowable antihistamine claims.

After this comment was submitted, the agency addressed the issue of "multi-use" labeling, i.e., labeling a drug product with some or all of the proven pharmacologic activities of the drug whether or not the conditions to be treated are related, in another segment (tentative final monograph) of the rulemaking for OTC cough-cold combination drug products (53 FR 30522 at 30551 to 30552). In that

segment of the rulemaking for these drug products, the agency stated that there is no legal restriction that prevents multi-use labeling. For products that contain an ingredient with multi-use labeling, the labeling for each "different" use of the ingredient would have to be distinct and not confusing and would have to meet the requirements of the applicable OTC drug monographs in part 330 and the labeling requirements for OTC drugs in subpart C of 21 CFR part 201.

Thus, the manufacturer would need to provide labeling for all Category I intended uses in such a manner that the labeling for each approved indication that the manufacturer chooses to promote is distinct and not confusing. Labeling should be written so that consumers may readily understand the indications, directions for use, and warnings for each intended use. Further, the labeling must provide adequate information to prevent the possibility of overdosing and misuse when multiple and/or overlapping symptoms are self-treated.

As stated in the cough-cold combination drug products tentative final monograph, because of the labeling requirements and the need to provide information that is not confusing to consumers, the agency invites manufacturers to consult with it before labeling their OTC drug products with multi-use labeling.

14. One comment requested that the phrases "temporarily relieves" (proposed in the antihistamine tentative final monograph) and "for the temporary relief of" (proposed in the nasal decongestant tentative final monograph) be interchangeable.

The agency agrees with the comment. Because the phrases "for the temporary relief of" and "temporarily relieves" are interchangeable, the agency is including the option of using either phrase in the indications included in § 341.72(b) of this final monograph.

15. Three comments requested that manufacturers be allowed to use either of the indications proposed in § 341.72(b)(1) and (2) rather than be required to use both indications in the labeling of antihistamine drug products. The comments contended that an antihistamine product promoted primarily for a specific indication, i.e., for the common cold or for hay fever, should be allowed to use only the corresponding indication in its labeling. Two of the comments stated that the consumer market to whom allergy products are directed is different than the consumer market using cold products and that having both indications on the same product would

confuse consumers looking for a product for only one of the specified indications. One comment added that, in its view, it is inappropriate to include allergy and hay fever indications in the labeling of an OTC combination drug product intended to be used for relieving symptoms of the common cold. The comments concluded that the wording of proposed § 341.72(b) should be changed from "limited to both" to "limited to one or both" (of the indications).

The agency agrees with the comments' arguments that for some OTC antihistamine-containing drug products it would be inappropriate to include both the allergy and common cold indications in the labeling. Where an antihistamine drug product is marketed generally as an antihistamine, it is beneficial to consumers to have all of the indications stated in the product's labeling, and manufacturers are encouraged to do so. However, when an antihistamine drug product is marketed for a specific target population (e.g., allergy sufferers) or when the antihistamine is present in a combination drug product marketed for a different specific target population (e.g., cold sufferers), the agency does not find that it is necessary for the products to be labeled with both the allergy and the common cold indications. The agency is addressing "allergy" indications only in this final rule and will respond to the comments' requests in a future issue of the *Federal Register* when a final decision is made on the use of antihistamines for symptoms of the common cold.

16. One comment submitted two consumer surveys to demonstrate that substantial numbers of consumers recognize that relief of "post-nasal drip" is a desirable end benefit and consequence of the use of OTC drug products containing antihistamines which, through their drying (anti-secretory) actions, relieve symptoms of sinus congestion and allergic rhinitis (hay fever) and, furthermore, that consumers clearly understand the term "post-nasal drip." The comment requested that indications pertaining to "post-nasal drip," i.e., "Helps (relieve, alleviate, decrease, reduce or dry up) post-nasal drip" be included in the final monograph for OTC antihistamine drug products and for OTC cough-cold combinations containing antihistamines.

The agency has reviewed the comment and other information and determined that the consumer surveys do not demonstrate the effectiveness of OTC antihistamine drug products in relieving "post-nasal drip." The two

consumer mail panel studies were designed to investigate consumer attitudes towards, and usage of, sinus and hay fever remedies. The agency notes that the comment stated that of the 263 responding sinus sufferers, 49 percent (129) considered relief of post-nasal drip important when choosing a sinus remedy. Similarly, 48 percent (119) of the 248 hay fever respondents indicated that relief of post-nasal drip was important when consumers choose a hay fever product.

The Panel referred to "checking post-nasal drip" as an unsubstantiated labeling claim unless studies specifically designed to assess this activity were presented (41 FR 38312 at 38415). The Panel did not assess this claim for antihistamines, but placed the claim in Category III for nasal decongestants. The Panel stated that studies of nasal decongestants have assessed the effect on nasal airway resistance or the ease of breathing but not the effect on rhinorrhea.

The submitted consumer surveys were not designed to demonstrate the effectiveness of OTC antihistamine drug products in relieving the symptom "post-nasal drip." In addition, the surveys do not define the term "post-nasal drip" or the ability of consumers to recognize specific symptoms that would allow them to determine whether they were experiencing "post-nasal drip." The consumer surveys do not demonstrate understanding of the term "post-nasal drip" or provide a basis for a "post-nasal drip" indication.

The agency has not approved a "post-nasal drip" claim in any new drug application for an antihistamine drug product. Clinical studies specifically designed to demonstrate the effectiveness of antihistamines in relieving "post-nasal drip" would be necessary before this claim could be used in the labeling of any antihistamine drug product. Such studies should be designed to evaluate the symptoms of "post-nasal drip" in terms of specific symptoms that can be recognized by consumers as "post-nasal drip." The agency suggests that any party interested in studying the use of an antihistamine for this claim meet with the agency to discuss an appropriate protocol before beginning the study. For the above reasons, indications pertaining to "post-nasal drip" are not being included in this final monograph for OTC antihistamine drug products.

17. Noting that, in the tentative final monograph (50 FR 2200 at 2203), the agency proposed to exclude "sinus congestion" as an approved indication for single-ingredient antihistamine drug

products, one comment requested that "sinus congestion" be an approved indication for combination drug products containing an oral nasal decongestant and an antihistamine. The comment noted the Panel's recommendation that "any single [Category I] antihistamine * * * may be combined with any [Category I] single oral nasal decongestant active ingredient * * *" (41 FR 38312 at 38420) and urged FDA to adopt this recommendation and to include "sinus congestion" as an approved indication for such combination drug products.

The agency reaffirms its conclusion as stated in the tentative final monograph that data have not demonstrated that antihistamines are effective in the treatment of "sinus congestion." Therefore, such claims for single-ingredient OTC antihistamine drug products are not included in this final monograph.

In § 341.80(b)(2) of the tentative final monograph for OTC nasal decongestant drug products (50 FR 2220 at 2238), the agency proposed the following indications that refer to sinus congestion for nasal decongestant drug products:

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

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

In the tentative final monograph for OTC cough-cold combination drug products, the agency proposed that combination drug products containing an oral nasal decongestant and an antihistamine be Category I (53 FR 30522 at 30561). Such combination drug products can be labeled with the indications that are applicable to each pharmacologic group included in the combination. Therefore, under the tentative final monograph for OTC nasal decongestant drug products (50 FR 2238) and the tentative final monograph for OTC cough-cold combination drug products (53 FR 30561 to 30562), combination products containing a Category I oral nasal decongestant and a Category I antihistamine can be labeled with indications relating to "sinus congestion."

18. One comment objected to the proposed elimination of the term "Caution(s)" in the labeling of OTC drug products. The comment contended that "Warnings" are harsher (stronger) and more serious than "Cautions" and even preclude use of a product under certain conditions. The comment stated that a "Caution," on the other hand, does not preclude use unless something occurs during use; but it often alerts the consumer to a potential problem. The comment added that a caution may also

address a monitoring function to be performed while the product is in use. The comment felt that it is important for the consumer to be able to distinguish between precautionary statements and more serious warnings. Also, because the same phrases may be warnings with regard to one class of products and merely cautions with regard to another, the comment stated that flexibility to use both terms is essential in order to prepare accurate and comprehensible labeling.

Another comment suggested that the agency differentiate between "Warnings," "Cautions," and "Precautions" in OTC drug product labeling. The comment stated that the term "Warning" is the strongest of the terms and should be taken the most seriously. The comment contended that the term "Caution" should be used to convey important information related to the safe and effective use of the product but which allows for judgment on the part of the user, e.g., "This product may cause drowsiness." The comment felt that it undermines the importance of a "Warning" section if it contains too much information or if it includes less than serious language. The comment provided examples of the types of information that it considered appropriate as warnings and cautions for products containing the maleate salt of brompheniramine, chlorpheniramine dextrobrompheniramine, and dexchlorpheniramine.

Section 502(f)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(f)(2)) states, in part, that any drug marketed OTC must bear in labeling " * * * such adequate warnings * * * as are necessary for the protection of users * * * ." Section 330.10(a)(4)(v) of the OTC drug regulations (21 CFR 330.10(a)(4)(v)) provides that labeling of OTC drug products should include " * * * warnings against unsafe use, side effects, and adverse reactions * * * ."

The agency notes that historically there has not been consistent usage of the signal words "warning" and "caution" in OTC drug labeling. For example, in §§ 369.20 and 369.21 (21 CFR 369.20 and 369.21), 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 similar precautionary information. In addition, the term "precaution(s)," as in "Drug Interaction Precaution(s)" is often used in OTC drug monographs, but is listed under "Warnings" as, for example, in the rulemakings for OTC nasal decongestant drug products and OTC

bronchodilator drug products. (See the Federal Register of January 15, 1985 (50 FR 2220 at 2239) and October 2, 1986 (51 FR 35326 at 35339), respectively.)

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 dangers so that consumers will read the information being conveyed. The agency is not convinced that consumers will make the distinctions between "warnings" and "cautions" that the comments have made. Further, the agency does not believe that the importance of the "Warnings" section will be undermined if all of the information about unsafe use, side effects, and adverse reactions is presented under a single heading. 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. However, except in instances where the agency has stated that a particular warning statement must appear as the first warning after the "Warnings" heading, the agency has no objections if manufacturers list the various warnings statements in their order of preference, e.g., listing first those they consider more serious followed by those they consider to be less serious statements. Drug interaction precaution information will continue to be listed under the heading "Drug Interaction Precautions" as part of the warnings information.

19. One comment stated that the Panel made a factual error in the number of subjects in a study (Ref. 1) mentioned in its discussion of phenindamine tartrate (41 FR 38312 at 38388). The Panel's report stated that 250 subjects were in the study, whereas the article (Ref. 1) indicated that 1,589 subjects were observed. The comment contended that this large discrepancy in the number of subjects in the study is significant with respect to the validity of the study data on the frequency of stimulation or drowsiness and thus phenindamine tartrate should be exempt from the Panel's proposed warning regarding the occurrence of drowsiness as a side effect. [Note: This comment was submitted after the administrative record following publication of the advance notice of proposed rulemaking closed and thus is not discussed in the tentative final monograph.]

The agency has reviewed the discrepancy described by the comment and agrees that the correct number of subjects in the study is 1,589, not 250 as mentioned in the Panel's report. Although the agency is unable to ascertain how the number 250 appeared in the Panel's report, it appears that the Panel based its conclusions on the study's actual findings that 3 percent (51) of the 1,589 subjects experienced drowsiness and 12 percent (196) of the 1,589 subjects experienced stimulation. (See Table II at page 478 of Ref. 1.) Based on these percentages and the number of subjects, the agency agrees with the Panel's conclusion that "data that would establish the frequency of stimulation or drowsiness among those taking the drug in recommended dosages are inadequate and cannot be used for making phenindamine an exception with respect to a warning regarding the occurrence of drowsiness as a side effect" (41 FR 38388). The comment did not submit additional data to support an exemption from this warning for phenindamine tartrate. Therefore, the warning "May cause drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery," in § 341.72(c)(3) of the final monograph is required for OTC antihistamine drug products containing phenindamine tartrate.

Reference

(1) Loveless, M. H., and M. Dworin, "Allergy and Antihistamine Therapy. A Review," *Bulletin of the New York Academy of Medicine*, 25:473-487, 1947.

20. Several comments stated that it is difficult to read labels of antihistamine drug products because the print on the labels is small. The comments were particularly concerned that the required warnings would not be legible and thus could lead to adverse use of the product. The comments requested larger print size and greater prominence of warnings on antihistamine drug products. One comment added that most OTC antihistamine products are very repetitious in their warning labeling and recommended bold lettering or a colored label to enhance warning statements.

The agency believes that the labeling proposed in this final monograph includes only essential information that is necessary to assure proper and safe use of OTC antihistamine drug products by consumers. Moreover, the labeling of

drugs must comply with section 502(c) of the act (21 U.S.C. 352(c)) which states that a drug shall be deemed to be misbranded "If any word, statement, or other information required by or under authority of this Act to appear on the label or labeling is not prominently placed thereon with such conspicuousness (as compared with other words, statements, designs, or devices, in the labeling) and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use."

When an OTC drug product is packaged in a container that is too small to contain all the required labeling, the agency recommends that the product be enclosed in a carton or be accompanied by a package insert or booklet that contains the information complying with the monograph. Manufacturers are also encouraged to print a statement on the product container label, carton, or package insert suggesting that the consumer retain the carton or package insert for complete information about the use of the product when all the required labeling does not appear on the product container label. Manufacturers who use this supplemental labeling should be able to readily provide all labeling information in a larger print size than if all of the labeling is presented on the immediate container. Further, the agency is aware that many manufacturers use bold lettering and a colored label to emphasize certain labeling information, including warnings, on the immediate container and in package inserts. All manufacturers are encouraged to use these as appropriate to highlight and emphasize certain labeling information for consumers. The agency recently published a request for public comment (56 FR 9363 to 9365, March 6, 1991) on the issue of print size and style of labeling for OTC drug products, and will evaluate comments received before making a final decision on the feasibility of establishing a Federal regulation pertaining to print size and style of OTC labeling. In addition, the Nonprescription Drug Manufacturers Association (NDMA) has recently promulgated guidelines for industry to consider when examining product labels for readability and legibility (Ref. 1). These guidelines are designed to assist manufacturers in making the labels of OTC drug products as legible as possible. The agency commends this voluntary effort and urges all OTC drug manufacturers to examine their product labels for legibility.

Reference

(1) "Label Readability Guidelines," NDMA, Washington, copy included in OTC Vol. 04HFM, Docket No. 76N-052H, Dockets Management Branch.

21. One comment recommended removal of the phrase "difficulty in breathing" from the proposed warning in § 341.72(c)(2), which states "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 comment contended that the phrase "difficulty in breathing" is redundant because the terms asthma, emphysema, chronic pulmonary disease, and shortness of breath specifically describe those breathing problems which may contraindicate antihistamine use. The comment added that the phrase "difficulty in breathing" is too broadly worded and could be interpreted by consumers to mean "difficulty in nasal breathing." The comment argued that such an interpretation could lead to consumer confusion in reading the labeling of an OTC cough-cold combination drug product containing an antihistamine and a nasal decongestant. Such a product would be indicated for relieving nasal congestion but would also state not to use the product if you have difficulty in [nasal] breathing. The comment concluded that removal of the phrase "difficulty in breathing" from the warning would lessen consumer confusion caused by the labeling of some combination products without changing the substance of the warning information provided to consumers.

The agency proposed the warning in § 341.72(c)(2) in the tentative final monograph for OTC antihistamine drug products based on the medical rationale that antihistamines should not be used by patients with any obstructive pulmonary disease in which clearance of secretions is a problem (50 FR 2200 at 2215). In making this proposal, the agency stated that respiratory distress symptoms such as difficulty in breathing and shortness of breath are characteristic of chronic obstructive pulmonary disease. The agency concluded that such descriptive terms should also be included in the warning in addition to the names of the diseases in order to provide more information to the consumer.

The agency disagrees with the comment that the phrase "difficulty in breathing" will be confusing to consumers using single ingredient antihistamine drug products because

such products are not indicated for the relief of nasal congestion. However, the agency does believe that using the broader phrase "breathing problems" to describe such symptoms (e.g., "shortness of breath" and "difficulty in breathing") related to obstructive pulmonary disease would allow the consumer to more readily recognize any respiratory distress symptoms that he/she may experience. Therefore, the agency is deleting the phrases "shortness of breath" and "difficulty in breathing" and replacing them with the phrase "breathing problem" in the warning in § 341.72(c)(2) of this final monograph.

At a meeting on June 11 and 12, 1990, the agency's Pulmonary-Allergy Drugs Advisory Committee discussed the need to continue labeling prescription and OTC antihistamine drug products with a warning against the use of antihistamines by people with asthma (Ref. 1). Participants at the meeting expressed the belief that the warning is no longer accurate, and questioned the continued validity of the reasoning for the warning. It was noted that early first-generation antihistamines, which are no longer on the market, had anticholinergic activity that could be a problem in asthma, but that the newer compounds have been shown to be mildly effective as well as safe in people with asthma. An agency consultant stated that the problem is that many asthmatic patients are also afflicted with upper-airway disorders, and the prescribing physician is on the horns of a dilemma because there is a labeled contraindication about the use of antihistamines by people with asthma, but there is also evidence to show that antihistamines are safe for use by asthmatics. This anomaly places physicians in the awkward position of telling patients to ignore a labeled warning.

The consultant presented a survey of published medical reports and literature to support the position that antihistamines should not be contraindicated in people with asthma unless an individual has previously experienced an adverse reaction (Refs. 2 through 24). Positive effects of antihistamines on asthma have been reported. Investigators have shown that antihistamines may inhibit exercise-induced asthma (Refs. 4, 5, 9 through 12, and 23), and that they may prevent histamine-induced and allergen-induced bronchospasm (Refs. 2, 4, 6, 7, 8, 10, 13, 19, 20, and 23). Further, antihistamines have been demonstrated to be mild bronchodilators that improve pulmonary function (Refs. 4, 5, 10, 19, 23, and 24). A reduction of pulmonary

function has been observed following diphenhydramine, hydroxyzine, and brompheniramine challenges in asthmatic children, but premedication with bronchodilators prevented the decrease (Refs. 14 and 15). Some suggest the beneficial effects of antihistamines are dose related (Refs. 5, 9, 12, and 23), while one investigator observed that low concentrations inhibit histamine release, but high concentrations may stimulate histamine release, in vitro, in the absence of antigen challenge (Ref. 12). It is generally believed that histamine released from airway mast cells is a major mediator of bronchospasm, although other mediators may be involved (Refs. 3, 4, 6, 7, 8, 10, 19, 21, 23, and 24). Therefore, as far as treatment of asthma is concerned, an antihistamine is not the drug of first choice (Refs. 17 and 23), but it need be withheld from asthmatics who are also afflicted with upper-airway disorders. There does not seem to be any direct evidence that anticholinergic effects of some antihistamines will cause drying of bronchial secretions and exacerbate asthma (Refs. 17 and 23).

The advisory committee was asked to vote on the question of whether current evidence supports continued use of the warning statement about possible adverse effects of antihistamines on asthma. The advisory committee recommended to FDA by a vote of seven to zero, with one abstention, that current evidence does not support continuation of the warning regarding possible adverse effects of antihistamines when used by asthmatic patients and the warning should be rescinded (Ref. 1).

The agency has evaluated the references cited by the consultant (Refs. 2 through 24) and concludes that it concurs with the advisory committee's recommendation. Accordingly, in this final rule, the agency is removing the descriptive term "asthma" from the warning included in § 341.72(c)(2).

In the tentative final monograph for OTC antihistamine drug products (50 FR 2200 at 2215), the agency proposed the descriptive term "chronic pulmonary diseases" to cover all types of chronic obstructive pulmonary diseases such as emphysema and chronic bronchitis. However, because consumers may associate the term "chronic pulmonary disease" with asthma, the agency now believes that this term is no longer appropriate and that clarifying the term would be more helpful to consumers. The agency believes that consumers will recognize and understand the terms chronic bronchitis and emphysema and is

containing alcohol with an alcoholic beverage and thus construe these warnings to mean that the drug product should not be used. Additionally, the comment did not provide any data supporting its contention that the proposed warning is confusing. Finally, the agency does not believe that products formulated with alcohol and labeled for nighttime use should have a different warning. The agency is aware that such products often are also labeled for use during the day and are, in fact, used by consumers during the day whether or not they contain labeling for this use. The agency believes that products containing an antihistamine should contain the same warnings, with the only exception being that the word "marked" is required for several of the antihistamines to describe the degree of the drowsiness that may occur. Therefore, the agency is not including the comment's suggested alternative in § 341.72(c)(3) and (4) of this final monograph, but is including the warning that was proposed in the amendment to the tentative final monograph for OTC antihistamine drug products, as stated above.

23. One comment suggested that labeling for drug products containing diphenhydramine, chlorpheniramine, and related substances should contain warnings of possible effects on the heart, particularly heart problems requiring treatment with beta blocker drugs. The comment based its suggestion on a personal experience while using a prescription drug product containing diphenhydramine "for a bad case of allergy" and, subsequently, using an OTC drug product containing chlorpheniramine. The comment contended that these drugs "began to cause trouble, a stepped-up heart beat, and a very disabling weak feeling in the chest."

The agency has reviewed the Panel's report with respect to side effects of the antihistamines. The Panel stated that the most common side effects are drowsiness and dryness of the mouth (41 FR 38312 at 38380). The Panel also stated that other side effects which are not as common have been reported in scientific texts but are poorly documented and often cannot be definitely ascribed to antihistamines. These include gastrointestinal effects

safety discussions of diphenhydramine (41 FR 38340, 38341, 38384, and 38385), chlorpheniramine (41 FR 38383 and 38384), or any other Category I antihistamine, the Panel did not cite any cardiovascular problems associated with the use of these ingredients as mentioned specifically by the comment. The comment did not submit any data to support its suggestion to add warnings concerning cardiovascular effects to the labeling of OTC antihistamine drug products beyond reporting one personal experience.

Based on the Panel's determination that cardiovascular symptoms rarely occur with the use of OTC antihistamines, and the lack of other information, the agency concludes that there is not an adequate basis for OTC antihistamine drug products to bear label warnings regarding possible adverse cardiovascular effects. Accordingly, the agency is not including such warnings in this final monograph.

24. One comment suggested that all antihistamine drug products contain warnings to the elderly that these products may produce congestion in the lungs, particularly in case of bronchitis, flu, pneumonia, or even a bad cold.

The comment did not provide any data demonstrating that lung congestion results from taking an OTC antihistamine drug product. The agency is not aware of any studies or published literature that would support the comment's statement. If lung congestion occurs when a person has bronchitis, flu, pneumonia, or a bad cold, it would appear that the congestion is likely the result of the underlying condition. The agency does not believe that a warning expanded beyond that discussed in comment 21, "Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland," is warranted at this time.

25. Two comments requested that the agency include the symptomatic treatment of allergic itching as a monograph condition in the final monograph for OTC antihistamine drug products. One comment requested this indication specifically for oral diphenhydramine, while the other comment requested the indication for

inhaled allergens (dust, mold, spores), poison ivy, oak, or sumac, soaps, detergents, cosmetics, and jewelry." The comment contended that the proposed indication involves only symptoms which consumers can recognize and treat, and that the indication is currently approved for prescription dispensing of diphenhydramine hydrochloride at the dose already accepted for OTC marketing. This comment was subsequently withdrawn, but no reasons were given (Ref. 1).

The second comment cited statements from three references to support the effectiveness of orally administered antihistamines for the relief of pruritus, angioedema, and other manifestations of skin allergies: (1) prior administration of chlorpheniramine raised the itch thresholds to both 2-methyl histamine and histamine itself (Ref. 2), (2) traditional antihistamines of the H1 type are the mainstay in the management of urticaria (Ref. 3), and (3) certain of the allergic dermatoses respond favorably to H1 blockers; H1 blockers also have a place in the treatment of itching pruritus; and some relief may be obtained in many patients suffering atopic dermatitis and contact dermatitis, although topical corticosteroids seem to be more valuable in such diverse conditions as insect bites and ivy poisonings (Ref. 4). The comment requested that the indications in § 341.72(b) be expanded to permit the following claim: " * * * or the itching skin caused by allergy to local irritants such as poison ivy, oak, or sumac, or caused by hives."

The agency has reviewed the information provided by the comment and determined that it is insufficient to support general recognition of the symptomatic treatment of allergic itching as an appropriate OTC indication for oral antihistamine drug products. Hives and pruritic rashes secondary to foods, animal allergies, and insect stings and bites can be one component of a systemic anaphylactic reaction, and the use of an OTC antihistamine could potentially delay more appropriate treatment that may be needed. The agency is unaware of any data demonstrating that the average person can distinguish between a mild allergic reaction and a life-threatening reaction that may begin with itching

phenyltoloxamine hydrochloride, and tripeleonnamine hydrochloride. The agency has established 21 CFR 310.545 in which it lists certain active ingredients that are not generally recognized as safe and effective for certain OTC drug uses. Methapyrilene hydrochloride, methapyrilene fumarate, and thenyldiamine hydrochloride are presently listed in § 310.545(a)(6)(i) for antihistamine drug products. In this final rule, the agency is amending § 310.545(a)(6)(i) by adding phenyltoloxamine dihydrogen citrate. Promethazine hydrochloride (as a single ingredient) and tripeleonnamine hydrochloride are not included in § 310.545 because these ingredients have not been marketed OTC and were considered in this rulemaking only as possible prescription-to-OTC switch drugs. Promethazine hydrochloride in cough-cold combination drug products will be discussed in the final rule for OTC cough-cold combination drug products in a future issue of the Federal Register. The use of antihistamines to relieve symptoms of a cold will be discussed in a future issue of the Federal Register.

Any drug product marketed for use as an OTC antihistamine drug product that is not in conformance with the monograph (21 CFR part 341, subparts A, B, and C) (except the labeling of an antihistamine included in the monograph to relieve symptoms of a cold) is considered misbranded under section 502 of the act (21 U.S.C. 352) and a new drug under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved application or abbreviated application under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations (21 CFR part 314) is required for marketing. In appropriate circumstances, a citizen petition to amend the monograph may be submitted under 21 CFR 10.30 in lieu of an application. Any OTC antihistamine drug product initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule that is not in compliance with the regulations is subject to regulatory action. The effective date of this final monograph does not apply to antihistamines marketed for relief of symptoms of a cold. Such products may remain in the

Manufacturers of products containing an antihistamine labeled only to relieve symptoms of a cold are encouraged to voluntarily label the product with all of the information required by this final monograph. However, such products may not bear the FDA "APPROVED USES" language provided for in § 330.1(c)(2)(i).

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (50 FR 2200 at 2215 through 2216 and 52 FR 31892 at 31911). The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the Federal Register of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this final 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 (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 antihistamine drug products is not expected to pose such an impact on small businesses. This final rule will require some relabeling for products containing monograph ingredients. Manufacturers will have one year to implement this relabeling. This final rule does not affect antihistamine products labeled to relieve symptoms of a cold. This final rule will also require reformulation of a few products containing phenyltoloxamine dihydrogen citrate. For all other nonmonograph active ingredients listed above, the effective date was May 7, 1991. Therefore, the

same in § 310.201(a)(25) (applicable to chlorcyclizine hydrochloride preparations) because most portions of those regulations are superseded by the requirements of the antiemetic final monograph (21 CFR part 336) and the antihistamine final monograph (21 CFR part 341) (for chlorcyclizine hydrochloride). Section 201.307 also addresses the marketing of parenteral drugs containing chlorcyclizine, cyclizine, or meclizine. These products are all marketed as prescription drugs and, as such, must comply with the pregnancy labeling requirements of § 201.57 (21 CFR 201.57). Accordingly, § 201.307 is no longer required. The agency is also adding and reserving paragraph (b) in § 310.201, and amending an entry in §§ 369.20 and 369.21. The items being removed include: (1) all of § 201.307; (2) § 310.201(a)(25); and (3) the references to § 201.307 and § 310.201(a)(25) in the introductory text of the entry for "ANTIHISTAMINICS, ORAL" in § 369.20. The agency is also removing the reference to paragraph (a)(6) of § 310.201 in this same entry because that paragraph was removed on April 30, 1987 and reserved for future use. (See 52 FR 15886 at 15892.) In this final rule, the agency is amending § 310.545 by adding phenyltoloxamine dihydrogen citrate in paragraph (a)(6)(i), and by adding new paragraph (d)(6). The agency is also revising the entry for "ANTIHISTAMINICS, ORAL (PHENYLTOLOXAMINE DIHYDROGEN CITRATE, DOXYLAMINE SUCCINATE, CHLOROTHEN CITRATE, AND CHLORCYCLIZINE HYDROCHLORIDE PREPARATIONS)" in § 369.21 by revising the introductory text and by removing those portions of the entry pertaining specifically to chlorcyclizine hydrochloride, including the references to § 201.307 and paragraphs (a)(6) and (a)(25) of § 310.201 in this entry.

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical

of the labeling statements in this section.

10. Section 341.90 is amended by adding paragraphs (e) through (q) to read as follows:

§ 341.90 Professional labeling.

* * * * *

(e) 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.

(f) For products containing chlorcyclizine hydrochloride identified in § 341.12(b). Children 6 to under 12 years of age: oral dosage is 12.5 milligrams every 6 to 8 hours, not to exceed 37.5 milligrams in 24 hours. Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 6 to 8 hours, not to exceed 18.75 milligrams in 24 hours.

(g) For products containing chlorpheniramine maleate identified in § 341.12(c). 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.

(h) For products containing dexbrompheniramine maleate identified in § 341.12(d). 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.

(i) For products containing dexchlorpheniramine maleate identified in § 341.12(e). 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.

(j) For products containing diphenhydramine citrate identified in § 341.12(f). Children 2 to under 6 years of age: oral dosage is 9.5 milligrams every 4 to 6 hours, not to exceed 57 milligrams in 24 hours.

(k) For products containing diphenhydramine hydrochloride identified in § 341.12(g). 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.

(l) [Reserved]

(m) For products containing phenindamine tartrate identified in § 341.12(i). 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.

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

(o) For products containing pyrrolamine maleate identified in § 341.12(k). Children 2 to under 6 years of age: oral dosage is 6.25 to 12.5 milligrams every 6 to 8 hours, not to exceed 50 milligrams in 24 hours.

(p) For products containing thonzylamine hydrochloride identified in § 341.12(l). 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.

(q) For products containing triprolidine hydrochloride identified in § 341.12(m). Children 4 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 4 to 6 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 4 to 6 hours, not to exceed 1.252 milligrams in 24 hours.

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

11. The authority citation for 21 CFR part 369 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371).

§ 369.20 [Amended]

13. Section 369.20 *Drugs; recommended warning and caution*

statements is amended by revising the introductory text of the entry for "ANTIHISTAMINICS, ORAL" to read: ANTIHISTAMINICS, ORAL. (See also § 310.201(a)(4) and (a)(24) of this chapter.)

* * * * *

§ 369.21 [Amended]

13. Section 369.21 *Drugs; warning and caution statements required by regulations* is amended by revising the introductory text of the entry for "ANTIHISTAMINICS, ORAL (PHENYLTOLOXAMINE DIHYDROGEN CITRATE, DOXYLAMINE SUCCINATE, CHLOROTHEN CITRATE, AND CHLORCYCLIZINE HYDROCHLORIDE PREPARATIONS)" to read: "ANTIHISTAMINICS, ORAL (PHENYLTOLOXAMINE DIHYDROGEN CITRATE, DOXYLAMINE SUCCINATE, AND CHLOROTHEN CITRATE PREPARATIONS). (See § 310.201(a)(4), (a)(13), and (a)(24) of this chapter.)" and by removing the warning statement for chlorcyclizine-containing preparations.

Dated: August 5, 1992.

Michael R. Taylor,

Deputy Commissioner for Policy.

{FR Doc. 92-29718 Filed 12-8-92, 8:45 am}

BILLING CODE 4160-01-F