DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 341

[Docket No. 76N-052G]

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

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products (drug products that contain more than one active ingredient and are used for the relief of symptoms such as nasal congestion, runny nose, coughing, watery eyes, sore throat, headache, and fever) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal deals with cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products, general comments on the advance notice of proposed rulemaking, and comments on miscellaneous ingredients, as well as the conclusions and recommendations of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products on the use of internal analgesic ingredients in cough-cold combination drug products, and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by December 12, 1988. Because of the length and complexity of this proposed regulation, the agency is allowing a period of 120 days for comments and objections instead of the normal 60 days. New data by August 14, 1989. Comments on the new data by October 12, 1989. Written comments on the agency's economic impact determination by December 12, 1988.

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

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), 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, which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. Interested persons were invited to submit comments by December 8, 1976. Reply comments in response to comments filed in the initial comment period could be submitted by January 7, 1977.

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

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration, (address above), after deletion of a small amount of trade secret information. Data and information received after the administrative record was reopened have also been put on display in the Dockets Management Branch.

In response to the advance notice of proposed rulemaking, 13 manufacturers, 2 manufacturers' associations, 41 consumers, 14 health care professionals, and 14 health care professional societies submitted general comments on cold, cough, allergy, bronchodilator, and antiasthmatic drugs. One manufacturer, 2 consumers, and 1 consumer group submitted comments on miscellaneous ingredients. Fifteen manufacturers, 2 manufacturers' associations, 4 consumers, 3 health care professionals, and 3 health care professional societies submitted comments on cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products. Copies of the comments received are on public display in the Dockets Management Branch.

FDA has issued the tentative final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products in segments. This document on combination drug products, general issues, and miscellaneous ingredients is the sixth and final segment. The first segment, on anticholinergic drug products and expectorant drug products, was published in the **Federal Register** of July 9, 1982 (47 FR 30002). The second segment, on bronchodilator drug products, was published in the **Federal Register** of October 26, 1982 (47 FR 47520). The third segment, on antitussive drug products, was published in the **Federal Register** of October 19, 1983 (48 FR 48576). The fourth segment, on nasal decongestant drug products, was published in the **Federal Register** of January 15, 1985 (50 FR 2220), and the fifth segment, on antihistamine drug products, was published in the **Federal Register** of January 15, 1985 (50 FR 2200). Additionally, an amendment to the tentative final monograph for OTC antihistamine drug products was published in the **Federal Register** of August 24, 1987 (52 FR 31892).

The advance notice of proposed rulemaking, which was published in the **Federal Register** on September 9, 1976 (41 FR 38312), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. This tentative final monograph would amend Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations in Part 341 (as set forth in the tentative final monograph on OTC anticholinergic drug products and expectorant drug products that was published in the **Federal Register** of July 9, 1982 (47 FR 30002)) in Subpart B, by adding new § 341.40; and in Subpart C, by adding new § 341.85. In this tentative final monograph (proposed rule) the FDA states for the first time its position on the establishment of a monograph for OTC cold, cough, allergy,

bronchodilator, and antiasthmatic combination drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products, as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them. When the tentative final monograph for OTC anticholinergic drug products and expectorant drug products was published on July 9, 1982, no ingredients were classified in Category I; thus no ingredients were included in the active ingredient section under Part 341 of that monograph. Subsequently, data were submitted which support the effectiveness of guaifenesin as an expectorant. Because guaifenesin will be included as a monograph condition in § 341.18 of the final monograph for OTC expectorant drug products, to be published in a future issue of the **Federal Register**, combinations in this proposal containing an expectorant refer to § 341.18.

The OTC drug procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register**. On or after that date, no OTC drug 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. 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 the advance notice of proposed rulemaking for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products (published in the **Federal Register** of September 9, 1976 (41 FR 38312)), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

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

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace.

If the agency determines that any labeling for a condition included in the final monograph should be implemented sooner than the 12-month effective date, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products. All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of August 9, 1972 (37 FR 16029) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch (address above).

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products

1. One comment expressed concern about the impact of the OTC drug review. The comment felt that the review would remove certain cough-cold products from the OTC market and force consumers to see a physician just to obtain a prescription for cough-cold products, causing a financial drain on persons dependent on social security.

The purpose of the OTC drug review is to assure consumers that OTC drug products are safe and effective. The review will result in the removal of unsafe or ineffective drug products from the OTC market. Also, some products may be reformulated to contain ingredients that are found to be

generally recognized as safe and effective. Products already on the market which contain ingredients that are generally recognized as safe and effective will remain available to consumers. In addition, a number of drug products that have been available only by prescription are being changed to OTC status and will be more readily available to consumers. Thus, the OTC drug review will not result in a financial drain on persons dependent on a fixed income but will ensure that safe and effective OTC drug products are available for self-treatment of colds, coughs, allergy, and asthma.

2. Several comments questioned the legality of the procedures used to establish OTC drug monographs and contended that FDA does not have the authority to establish substantive rules. The comments requested that monographs be clearly identified as interpretive rather than substantive regulations.

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), and in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F.2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).

3. One comment objected to the Panel's classification of "official drugs" in Category III. The comment contended that Congress has recognized the United States Pharmacopeia (USP) and the National Formulary (NF) as legal standards under the Federal Food, Drug, and Cosmetic Act (the act) and that the Committees on Scope of the Compendia have stated that their policy is "to select from among substances which possess medicinal power, those, the utility of which is most fully established and best understood. The value of the Compendia depends upon the fidelity with which they conform to the best medicinal knowledge of the day."

Formerly, articles judged to have medical merit were selected for inclusion in the USP and NF. USP XIX (1975) and NF XIV (1975) were the last editions of the compendia in which the articles were selected for inclusion on this basis. The USP and NF have now been combined (USP XX–NF XV, 1980) with the stated goal of setting standards relating to measurements of strength, quality and purity, packaging, etc. for "all" drugs that are in the marketplace (Ref. 1). This goal is also stated in the current edition of the USP XXI–NF XVI (Ref. 2). Thus, the current basis for inclusion of a drug in the combined compendia is whether it is marketed. The OTC Panel's review of drug ingredients is different from the USP and NF standards in that ingredients used in OTC drug products are evaluated for general recognition of safety and effectiveness in accordance with statutory authority set out in the act. A drug in the marketplace that has been labeled as meeting the USP or NF standards does not necessarily meet the FDA requirements relating to general recognition of safety and effectiveness, and to misbranding. Hence, a drug may meet USP or NF standards but still be classified as a Category II or Category III OTC drug.

References

(1) "The United States Pharmacopeia XX—National Formulary XV," United States Pharmacopeial Convention, Rockville, MD pp. xxxiv–xlii, 1980.

(2) "The United States Pharmacopeia XXI—National Formulary XVI," United States Pharmacopeial Convention, Rockville, MD, pp. xliv–xlv, 1985.

4. One comment stated that the agency's objections to various decisions made by the Panel should be based on more than just the referenced "AMA Drug Evaluations." The comment expressed the hope that the agency consulted the same source material that the Panel used, and recommended that the agency mention all of its sources when publishing decisions.

The comment's statements were in reference to the preamble to the Panel's report (41 FR 38312 to 38313), where the agency disagreed with the Panel's recommendations that three drugs (doxylamine succinate, promethazine hydrochloride, and diphenhydramine hydrochloride) that were previously available only by prescription be made available for OTC use.

The three ingredients mentioned above are discussed in the tentative final monograph for OTC antihistamine drug products. (See the **Federal Register** of January 15, 1985 (50 FR 2200) and August 24, 1987 (52 FR 31892).) In these documents, the agency has proposed a Category I classification for diphenhydramine hydrochloride and doxylamine succinate as an OTC antihistamine, and a Category III classification for promethazine hydrochloride. In the tentative final monograph for OTC antitussive drug products, the agency placed diphenhydramine hydrochloride in Category III as an antitussive (see the **Federal Register** of October 19, 1983; 48 FR 48581) and classified it as a nonmonograph ingredient in the final monograph for OTC antitussive drug products (see the **Federal Register** of August 12, 1987; 52 FR 30054). In those documents, references that were used to support decisions have been cited.

Many sources of information are available to and used by the agency in making decisions related to the OTC drug review. Such sources include data submitted to the panels, data submitted as comments to the agency, data in the literature, and data obtained from various computerized information retrieval systems which provide information on published literature, adverse drug reactions, poison control statistics, etc. The agency also uses the medical expertise of its staff in reaching decisions. This expertise includes the review of adverse drug reaction data that are incorporated into agency computerized information retrieval systems. This is especially done when prescription-to-OTC switches are involved, as in the situation discussed by the comment. Such information reviewed is regularly incorporated in the public administrative file for the applicable rulemaking.

5. Three comments stated that inactive chemicals, dyes (coloring), perfumes, flavorings, alcohol, and preservatives should not be in OTC drug products. One of the comments added that many adults and children are allergic to flavorings and colorings and contended that these additives serve no useful function and are added only for cosmetic purposes.

FDA does not agree that the inactive ingredients the comments describe should not be in OTC drug products. The agency recognizes that the use of such ingredients in OTC drug products is often important in securing consumer acceptance. Although they offer no particular therapeutic advantage, the use of these agents can be of considerable importance psychologically (Ref. 1). An OTC drug product that is rejected by consumers because of objectionable taste or appearance may be made acceptable by use of carefully selected coloring, flavoring, and diluting agents. If a safety problem with one of these agents is found to exist, the agency will take appropriate action, as, for example, in the case of the regulations adopted concerning sensitivity to the color

additive FD&C Yellow No. 5. In § 201.20 (21 CFR 201.20), the agency requires that all OTC and prescription drug products containing this agent declare its presence in labeling, using the names FD&C Yellow No. 5 and tartrazine. While not requiring that all inactive ingredients be listed in labeling, the agency urges manufacturers to list these ingredients voluntarily to assist consumers who may have allergies to some of these substances. (See also comment 20 below.)

Reference

(1) Gennaro, A.R., editor, "Remington's Pharmaceutical Sciences," 17th Ed., Mack Publishing Co., Easton, PA, p. 1280, 1985.

6. Several comments contended that certain OTC cough-cold drug products should be sold only in pharmacies and that general marketing of these products in places such as grocery stores, newspaper stands, and train stations should not be permitted. Some of the comments recommended that certain OTC drug products be dispensed by pharmacists and designated in a third class, separate from OTC or prescription, to be called "Pharmacy OTC Only." These comments maintained that the public should have the expert advice of pharmacists to make effective choices of OTC drug products.

One comment opposed a "pharmacy only" restriction and referred to the agency's conclusion on this "druggist monopoly concept" that was published in the **Federal Register** of June 4, 1974; 39 FR 19880–19881. This comment agreed with the position stated by the Department of Justice that the restriction of OTC drug product sales to pharmacies would have severe anticompetitive effects and inhibit the efficient distribution of OTC drug products to the consumer.

The issue of "a third class of drugs" (drugs that are available only in a pharmacy) has been considered previously in the OTC drug review, and the agency stated its position on this matter at that time. (See the **Federal Register** of June 4, 1974; 39 FR 19880.) The agency noted that although the Federal Food, Drug, and Cosmetic Act (the act) "permits imposition of whatever limitations or restrictions are necessary to assure the safe use of any drug, including restrictions on the channels of distribution, no controlled studies or other adequate research data have been supplied to support the position that any class of OTC drugs must be dispensed only by pharmacists in order to assure their safe use." Additionally, "restricting the sale of some or all OTC drugs only to pharmacies would decrease the number of outlets where the consumer could purchase OTC products, limit competition, and raise some OTC drug prices, with no attendant public benefit." The agency concluded that "it would be inappropriate to restrict the sale of OTC drugs to pharmacies based on anything less than proof that a significant safety issue was involved" (39 FR 19881) and that, because there was no public health concern at that time to justify the creation of a third class of drugs, the issue was solely an economic one.

More recently, the agency addressed the issue of a third class of drugs in response to two citizen's petitions that requested FDA to issue regulations to establish sale-by-pharmacist only of certain OTC drug ingredients. The agency denied the petitions, stating that a class of drugs for sale-by-pharmacist only is unnecessary because a public health need for such a limitation has not been demonstrated. OTC drug products must be adequately labeled for safe and effective use by laypersons, and if the agency were to find that the labeling for a particular drug product did not provide sufficient information for a layperson to use that product safely, it would take appropriate action. Further, the agency stated that the legal authority to create a sale-by-pharmacist class of drugs is questionable because under the act, there is no provision for an intermediate class of drugs between OTC and prescription products. The statutory requirement that a drug either be limited to prescription dispensing or available OTC with adequate directions for use seems to preclude the agency from establishing a class of drugs whose labeling would need to be supplemented by a pharmacist's instructions (Refs. 1 and 2).

The comments did not provide any controlled studies or other data adequate to demonstrate that a safety issue exists with respect to marketing OTC drug products in general, and certain OTC cough-cold drug products in particular, in places other than pharmacies. The agency is not aware of any such data, and therefore its position on a "third class of drugs," as stated above, is unchanged.

References

(1) Letter from F.E. Young, FDA, to D.C. Huffman, American College of Apothecaries, in OTC Volume 04GTFM, Docket No. 76N–052G, Dockets Management Branch.

(2) Letter from F.E. Young, FDA, to C.M. West, The National Association of Retail Druggists, in OTC Volume 04GTFM, Docket No. 76N–052G, Dockets Management Branch.

7. A number of comments objected to the continued marketing of many OTC cough-cold drug products which have not been proven safe and effective. These comments referred to 58 cough-cold active ingredients placed in Category III by the Panel. One comment stated that cough-cold drug products containing such ingredients are legally required to be either generally recognized as safe and effective or the subject of a new drug application and concluded that drugs which do not meet these criteria are not marketable; i.e., they are illegal.

FDA has stated that it is agency policy to take regulatory action prior to a final monograph against products that present a potential health hazard or a significant and substantial question of effectiveness (45 FR 31425 and 46 FR 47737). At this time, the agency is not aware of any information to show that any of the ingredients in question fits either of these criteria. Therefore, the agency will continue to review these ingredients under the standard OTC drug review process. The Panel's "placement" of ingredients in Category III represents only the Panel's recommendations to the agency regarding their safety and effectiveness. The agency's determination whether the ingredients are generally recognized as safe and effective, and not misbranded, will not be completed until the agency has finished its review and a final monograph has been issued. Until then, Category III ingredients may continue to be marketed. As originally promulgated, the OTC drug review procedural regulations permitted continued marketing of Category III ingredients after a final monograph became effective. However, FDA has revised the OTC drug review regulations so that an ingredient that is not included in the appropriate final monograph (nonmonograph condition) will be subject to regulatory action if marketed once that final monograph becomes effective. (See the **Federal Register** of September 29, 1981; 46 FR 47730.)

8. One comment stated that the Panel used an inappropriate standard in categorizing some Category II claims and placed claims such as "used by," "most recommended by doctors," and "improved" in Category II because they are difficult to substantiate. The comment contended that a claim is not false or misleading because it is difficult to substantiate, and that if it is factual, a claim should be permitted regardless of whether it can be demonstrated in controlled studies. The comment questioned whether the Panel was saying that a product cannot be

improved, adding that one would expect that a number of products would be "improved" as a result of the OTC drug review.

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

The agency believes terms such as "used by" and "most recommended by doctors" are unrelated to the characteristics of the drugs in question and, therefore, do not relate in a significant way to the drugs' safe and effective use. Accordingly, the terms "used by" and "most recommended by doctors" are outside the scope of the OTC drug review. The agency emphasizes that even though terms such as "most recommended by doctors" are outside the scope of the OTC drug review, they are subject to the prohibitions in section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading. Such terms will be evaluated by the agency in conjunction with normal enforcement activities relating to that section of the act. Moreover, any term that is outside the scope of the review, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information. (See comment 23 below.)

A number of cough-cold drug products will be "improved" as a result of the OTC drug review. Such improvements may include replacement of a Category III ingredient with a Category I ingredient, a change in the dosage of an ingredient to provide a safe and effective product, and new indications, warnings, or directions for use that are clearer to the consumer and protect against misuse.

In May 1977, The Proprietary Association (the trade association of manufacturers of nonprescription drugs) initiated a "Flag the Label" program, partially as a result of the OTC drug review, to alert consumers to significant changes in the ingredients or labeling of an OTC drug product (Ref. 1). This "Flag the Label" program informs consumers of changes in indications, dosages, active ingredients, directions, warnings, contraindications, or any other significant new information by using an attention-getting visual device (a flag) on the label. The agency endorses this program because it directs consumers' attention to important new product information, much of which results from the OTC drug review, without using words such as "improved," which could mislead consumers into thinking that the product is therapeutically superior to other comparable products.

Reference

(1) "Flag the Label Guidelines," The Proprietary Association, Washington, DC, in OTC Volume 04GTFM.

9. One comment requested that the following description of coryzal rhinitis be added to the Panel's discussion of rhinitis under the heading *Diseases and Related Symptoms Relieved by OTC Cold, Cough, Bronchodilator and Antiasthmatic Products* at 41 FR 38321: "Coryzal rhinitis results in the symptoms of sneezing, rhinorrhea, and nasal congestion due to edema of the nasal mucosa. The discharge is serous at first and may subsequently become mucoid or mucopurulent. The feeling of nasal congestion may intensify from suppression of the sense of smell."

The agency has reviewed the Panel's discussions of the common cold and the reduction of nasal secretions and believes that the symptoms of coryzal rhinitis as described by the comment and the symptoms of the common cold as described by the Panel are similar. The Panel concluded that the effectiveness of OTC antihistamine cough-cold products in relieving the symptoms of the common cold had not been demonstrated (41 FR 38380). However, based on new data submitted in response to the Panel's report, the agency has proposed a Category I indication for antihistamine drug products for the relief of the symptoms of sneezing and runny nose associated with the common cold. (See the tentative final monograph for OTC antihistamine drug products at 50 FR 2203.) Based on this proposed Category I indication, the agency does not see the need to expand the Panel's discussion of rhinitis, as requested by the comment.

B. General Comments on the Switch of Prescription Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drugs to OTC Status

10. Several comments disagreed with the agency's dissent from the Panel's recommendations to switch several ingredients from prescription to OTC marketing status, arguing that this dissent was based on comparative safety and effectiveness. The comments contended that the agency used criteria that were not mandated by statute or the OTC drug review in determining whether these drugs could be switched to OTC status. The comments concluded that the statutory criterion for prescription status is whether the drug may be safely used without the supervision of a licensed practitioner, and the fact that there are more effective drugs available OTC or even that there are less toxic drugs already available OTC is irrelevant to the determination required by the statute.

The agency agrees that it is not within the scope of the OTC drug review regulations to use comparative safety and comparative effectiveness as criteria for switching a drug from prescription to OTC status. In dissenting from or accepting the recommendations of advisory review panels to switch ingredients from prescription to OTC marketing status, the agency has judged these ingredients individually on whether they can be generally recognized as safe and effective for OTC use. General recognition of safety and effectiveness is not based on comparison.

In 1976, while considering the Panel's recommendations to switch certain prescription drugs to OTC marketing status, the agency considered the safety of these drugs for OTC use and did not believe at that time that they were safe for switching. For example, the agency concluded that the marketing status of diphenhydramine hydrochloride as an antitussive should be resolved by first considering the approvability of the pending supplemental NDA for OTC use of a cough syrup product containing this ingredient (41 FR 38313). The agency also concluded at that time that diphenhydramine hydrochloride as an antihistamine should remain a prescription drug because of its pronounced tendency to produce sedation in a high proportion of those persons using it. The agency pointed out that no diphenhydramine hydrochloride product was being marketed OTC as an antihistamine at any dosage level. Subsequently, the agency determined that the risk of drowsiness presented by

diphenhydramine hydrochloride did not provide sufficient reason to restrict this ingredient to prescription status so long as adequate warnings concerning drowsiness are included in the labeling of the product. (See the tentative final monograph for OTC antihistamine drug products, 50 FR 2206; and the amendment to the tentative final monograph for OTC antihistamine drug products, 52 FR 31913.)

The other ingredients the Panel recommended switching from prescription to OTC drug use have also been judged by the agency in accordance with the standards set forth in the act and the OTC drug review regulations in § 330.10(a)(4). For example, the agency has proposed that promethazine hydrochloride, as a single ingredient, be classified in Category III in the tentative final monograph for OTC antihistamine drug products because of the lack of safety data on long-term use, not because of comparison with other OTC drug ingredients (50 FR 2202). (See also the discussion of promethazine combinations in "Summary of the Agency's Changes in the Panel's Recommendations," in Part II. paragraph B. below.) Thus, the agency is applying the statutory criterion referred to by the comment.

11. One comment objected to FDA's allowing the OTC marketing, immediately following publication of the advance notice of proposed rulemaking, of the ingredients that the Panel recommended be switched from prescription to OTC status. The comment stated that no opportunity was permitted for public objections to this change in marketing status. Further, the comment stated that allowing the immediate OTC sale of these ingredients causes confusion and a dilemma in the drug distribution system because if these ingredients are now considered OTC items by FDA, then all such drug products currently in distribution containing these ingredients and bearing the prescription legend are misbranded and in violation of federal law.

The proposed policy for interim OTC marketing of ingredients previously limited to prescription use immediately following the publication of a panel's report and proposed monograph was published in the **Federal Register** of December 4, 1975 (40 FR 56675), and public comment was invited. Subsequently, a final policy statement regarding the marketing status of prescription ingredients recommended for OTC use was published in the **Federal Register** of August 4, 1976 (41 FR 32580). Briefly, the policy set forth in § 330.13 provides that an OTC drug product containing an active ingredient limited to prescription use on May 11, 1972, or an active ingredient at a dosage level higher than that available in an OTC drug on December 4, 1975, may be marketed OTC after the date of publication of an advance notice of rulemaking proposed in the **Federal Register**, if the Panel has classified the ingredient in Category I and the Commissioner has not dissented. Such marketing is subject to the risk that the Commissioner may not accept the Panel's recommendations and may instead adopt another position that may require relabeling, recall, or other regulatory action.

The agency does not agree with the comment that interested persons did not have ample opportunity to express their points of view prior to the Panel's recommendations affecting the prescription status of cough-cold drug products. During the 3½ years of the Cough-Cold Panel's deliberations, each Panel meeting was announced in the **Federal Register** and, at each session, an opportunity was afforded to any interested person to present his or her views relevant to the Panel's work. Those portions of the Panel's deliberations not open to the public were attended by a consumer and an industry liaison, and summary minutes of each Panel session were put on public display in the Dockets Management Branch (address above). Furthermore, an information copy of the Panel's report was made available to the public prior to publication in the **Federal Register**.

It may happen, as the comment points out, that during the pendency of the rulemaking some manufacturers may choose to market previously prescription ingredients OTC, while others choose to continue marketing the same ingredients with the prescription legend. As noted, these ingredients are marketed OTC subject to the risk that the agency may not accept the Panel's recommendation and may instead adopt a different position at any time prior to the effective date of a final monograph at which time products containing any of these ingredients may be subject to relabeling, recall, or other regulatory action. FDA does not believe that this interim marketing enforcement policy, which affords manufacturers some choice while the rulemaking is ongoing, has been unduly disruptive of the marketplace.

12. One comment requested that the agency permit the continued sale of drugs switched from prescription to OTC status as prescription drugs for a specified period of time.

As discussed in comment 11 above, when an advisory review panel recommends that a prescription ingredient be included in an OTC drug monograph for the same indication, OTC marketing under the terms of 21 CFR 330.13 may occur. However, during the pendency of the rulemaking, manufacturers may choose instead to continue prescription marketing of the ingredient in light of the possibility that the agency may ultimately decide that OTC marketing is not appropriate. However, after the effective date of the final OTC drug monograph (usually 12 months after its publication in the **Federal Register**), if the ingredient and indication are included in the monograph, a drug product containing the ingredient as switched to OTC status may not be marketed as a prescription product. The agency believes that manufacturers will have ample opportunity to prepare for the change in marketing status from prescription to OTC marketing.

13. Several comments were opposed to the OTC sale of certain antihistamine, nasal decongestant, and bronchodilator drugs (which were previously available only by prescription) unless these drugs are packaged in child-resistant containers. One of the comments stated that prescription drugs are subject to the requirements of the safety packaging law and are required to be dispensed in safety packaging. However, once prescription drugs are allowed to be sold OTC, they are not required to be dispensed in safety packaging. The comments stated that children will be exposed to potential poisoning from these drugs without the safety packaging requirements. The comments urged that FDA not allow these drugs to be sold OTC unless they are packaged in child-resistant containers.

FDA agrees that these and all OTC drugs should be safe for consumer use. However, statutory authority to require child-resistant closures rests with the Consumer Product Safety Commission (CPSC) under the Poison Prevention Packaging Act of 1970. That act provides that hazardous or potentially hazardous products must be sold in safety packaging that most children under 5 years of age cannot open. FDA's Division of Epidemiology and Surveillance in the Center for Drugs and Biologics compiles poison control case reports and statistics and forwards them to CPSC for review. If the poison control data indicate that a particular drug or class of drugs presents a poisoning hazard to children due to its packaging,

CPSC may determine if child-resistant closures should be required. Additionally, consumers may petition the CPSC to study hazardous drugs that could be toxic to young children and to determine whether child-resistant closures are warranted.

FDA is aware that CPSC has reviewed the available data on antihistamines to determine if child-resistant closures are warranted for OTC drug products containing these ingredients. CPSC published a final rule requiring that drug products containing more than 75 mg diphenhydramine hydrochloride in a single package and in a dosage form intended for oral administration have child-resistant packaging. (See CPSC Requirements for Child-Resistant Packaging; Diphenhydramine Hydrochloride, published in the **Federal Register** on February 15, 1984; 49 FR 5737.) CPSC found that serious toxic effects can be produced with doses of diphenhydramine hydrochloride as low as 100 mg. In the **Federal Register** of August 15, 1984 (49 FR 32565), CPSC amended the regulation to broaden its scope by requiring child-resistant packaging for preparations containing more than 66 mg diphenhydramine base in any oral dosage form. Although CPSC reviewed the toxicity of other antihistamines, it did not propose that any antihistamine other than diphenhydramine be required to be packaged with child-resistant closures. Because of the lack of significant toxicity data for antihistamines other than diphenhydramine, CPSC concluded that child-resistant closures were not necessary for these drugs, regardless of the amount of drug contained in each package. At this time, CPSC is not reviewing the other drug products mentioned by the comments.

FDA urges that manufacturers voluntarily place child-resistant closures on any OTC drug product that could be toxic to young children.

C. General Comments on Miscellaneous OTC Ingredients

14. One comment suggested that an upper limit of menthol as a flavoring agent in syrups, lozenges, sprays, etc., is needed to clearly distinguish between menthol used as an active ingredient and menthol used as an inactive ingredient.

Menthol is generally recognized as safe for use as a flavoring substance in foods. (See 21 CFR 172.515 and 182.20.) Section 172.515 specifies that such flavoring substances be "used in the minimum quantity required to produce their intended effect and otherwise in accordance with all the principles of good manufacturing practice." These regulations do not specify an upper concentration for menthol used as a flavoring agent, and the agency is not proposing such a limit for OTC drug products at this time. However, the agency invites information and comments on: (1) The minimum concentration of menthol needed to achieve a flavoring effect and (2) the minimum concentration of menthol needed to achieve a therapeutic effect. The agency will consider such information in determining how to distinguish between menthol as an active ingredient and menthol as an inactive ingredient and whether to establish minimum levels. In any case, if menthol is present at a therapeutic level in a product, the agency would consider it to be an active ingredient in that product.

15. One comment requested that topical analgesics be included in item 8 of the Panel's table at 41 FR 38320, which listed symptoms and the corresponding pharmacologic groups of drugs for the treatment of these symptoms. The comment suggested that item 8, "Generalized aching," be expanded to include the Category I labeling indications for topical analgesics, counterirritants, and rubefacients recommended by the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (the Topical Analgesic Panel).

The agency discussed this use of topical analgesics in the notice of proposed rulemaking for OTC external analgesic drug products published in the **Federal Register** of February 8, 1983 (comment 18 at 48 FR 5859).

16. One comment expressed concern about the synergistic effect that occurs when alcohol is combined with ingredients of cough-cold products, such as antihistamines, and that the Panel's report ignored the use of alcohol in marketed cough-cold products that contain antihistamines.

The synergism between alcohol and antihistamine that heightens the drowsiness side effect of most antihistamines has been reported in the literature (Refs. 1 and 2). However, because alcohol is an excellent solvent and stabilizer and may provide palatability to distasteful ingredients, it is used in OTC antihistamine-containing cough-cold products as a pharmaceutical necessity (Ref. 3). The agency finds that the concentrations of alcohol commonly used in antihistamine-containing cough-cold products are sufficiently low that the quantity of alcohol consumed with a single dose of antihistamine does not constitute a hazard (Ref. 4). The agency finds that the benefits of using alcohol in this manner outweigh the minimal risk presented.

The Panel recognized the synergistic effects of the interaction between alcohol and antihistamines and in its recommended warning in § 341.72(b)(4) cautioned adult consumers not to drink alcoholic beverages while taking antihistamines. The agency also recognizes that alcohol potentiates central nervous system depressants and interacts with certain drugs. The agency shares the Panel's concern regarding additional central nervous system effects, such as drowsiness, that can occur if alcoholic beverages are used simultaneously with antihistamine drug products (Ref. 5). However, drowsiness itself is not a sufficient reason to prohibit the OTC use of such products when the labeling provides appropriate warnings and essential information. In the tentative final monograph for OTC antihistamine drug products (50 FR 2209), the agency proposed a stronger warning than the one recommended by the Panel—"May cause marked drowsiness; alcohol may increase the drowsiness effect. Avoid alcoholic beverages while taking this product * * *." (See § 341.72(c)(4) at 50 FR 2216.)

The Panel also recommended in § 341.50(c) that products containing concentrations of alcohol greater than 10 percent (weight/weight) not be given to children under 6 years of age except under the supervision of a doctor. Alcohol depresses the central nervous system over a wide range of doses. Threshold effects are observed at blood levels of 20 to 50 milligrams (mg) per 100 milliliters (mL), and a detectable impairment of vision occurs at a blood level of about 15 mg per 100 mL (Ref. 6). In its report of March 1982, the American Academy of Pediatrics (AAP) recommended limiting the amount of alcohol in a container of an OTC drug product labeled for use in children to an amount that, if entirely consumed accidentally by a 2-year-old child as a single dose or accumulated over a period of time, would not produce a blood ethanol concentration level in excess of 25 mg per 100 mL of blood (Ref. 4). The AAP also recommended that drug products be required to have safety closures if they contain alcohol in concentrations greater than 5 percent (volume/volume).

The AAP's report was published in March 1984 (Ref. 7). In the published report, the AAP reiterated the concerns expressed in its 1982 report and stated that it is desirable that no ethanol be

included in medicinal products intended for use in children. However, if ethanol is required to solubilize the active ingredients the following recommendations should be met: (1) OTC liquid preparations should be limited to a maximum of 5 percent (volume/volume) ethanol, (2) physician supervision is suggested for children less than 6 years using OTC preparations containing alcohol, (3) the amount of ethanol contained in any medicinal preparation should not be able to produce a blood concentration greater than 25 mg per 100 mL after a single recommended dose, (4) appropriate intervals between doses should be prescribed to prevent the accumulation of blood alcohol, (5) the packaged volume of ethanol-containing products should be kept to a reasonable minimum to prevent potential lethal ingestions, and (6) safety closures should be recommended for medications with greater than a 5 percent ethanol content (Ref. 7).

FDA's position regarding safety closures has been discussed in comment 13 above. The agency is considering the adoption of the recommendations made by the AAP regarding limitations in the alcohol content of drug products labeled for use by children and invites specific comment on these recommendations. Pending a final decision, the Panel's recommendation to limit the alcohol content to less than 10 percent in cough-cold drug products labeled for use in children under 6 years of age is not being included in this tentative final monograph. The agency urges manufacturers to use the least possible amount of alcohol to achieve solubility, stability, and palatability for all cough-cold drug products.

References

(1) Martin, E., "Hazards of Medication," J.B. Lippincott Co., Philadelphia, pp. 430–439, 1971.

(2) Forney, B.R., and W. Hughes, "Combined Effects of Alcohol and Other Drugs," Charles C. Thomas, Springfield, IL, pp. 101–102, 1968.

(3) Gennaro, A.R., editor, "Remington's Pharmaceutical Sciences," 17th Ed., Mack Publishing Co., Easton, PA, p. 219, 1985.

(4) "Ethanol in Over-the-Counter Drugs for Children," Report to the Food and Drug Administration, Bureau of Drugs, by the Committee on Drugs, American Academy of Pediatrics, March 1982.

(5) Food and Drug Administration, "Alcohol-Drug Interactions," *FDA Drug Bulletin*, Vol. 6, p. 11, Nov. 5, 1979.

(6) Maling, H.M., "Toxicology of Single Doses of Ethyl Alcohol," *in* "International Encyclopedia of Pharmacology and Therapeutics," Pergamon Press, Elmsford, NY 2:277–299, 1970.

(7) Committee on Drugs, American Academy of Pediatrics, "Ethanol in Liquid Preparations Intended for Children," *Pediatrics*, 73:405–407, 1984.

17. One comment objected to the Panel's Category III classification of ascorbic acid (vitamin C), considering that the Panel recommended the switch of more potent drugs from prescription to OTC marketing status. Another comment objected to reports that state there is no scientific justification for the claim that vitamin C is beneficial in preventing the common cold. This comment personally attested to the benefits of vitamin C in preventing the common cold or alleviating its uncomfortable effects, particularly runny nose. The comment added that this vitamin is also beneficial if taken in the "very beginning" stages of a sore throat.

The Panel placed vitamin C in Category III after reviewing a number of studies and concluding that "the published data support a beneficial effect of ascorbic acid on the severity and perhaps frequency of the 'common cold' when given in dosages exceeding the daily requirement," but that "it is not yet clear that this effect is clinically significant." The Panel also stated that "the magnitude of the dosages needed and the optimum schedule for prophylaxis and therapy remain to be determined" (41 FR 38417).

The Advisory Review Panel on OTC Vitamin, Mineral, and Hematinic Drug Products also reviewed vitamin C and stated that the OTC drug use of vitamin C for its protective or therapeutic effect on the course of the common cold is presently not supported by adequate controlled clinical studies. Although claims have been made for the beneficial effects of 500 to 1,000 mg or more of vitamin C daily for the treatment and/or prevention of the common cold, double-blind studies have not adequately demonstrated this effect and are required to evaluate fully the validity of the claim (44 FR 16142).

The Cough-Cold Panel's recommendations to switch several drugs from prescription to OTC status were based on the available safety and effectiveness data, and dosage information. Similar data and information were not available regarding the use of vitamin C to prevent and/or treat the common cold.

In order for vitamin C to be classified as Category I for prevention and/or treatment of the common cold, there must be data demonstrating the ingredient to be safe and effective for these uses. Such data for vitamin C have not yet been submitted, nor did the comment provide such data. Accordingly, vitamin C remains in Category III in this tentative final monograph.

D. General Comments on Dosages for OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drugs

18. One comment stated that the Panel's recommended dosage statements are inconsistent with regard to equivalent dosages for different salts of a drug. The comment explained that the dosage for phenylpropanolamine preparations in § 341.20(e) of the Panel's recommended monograph is based on the phenylpropanolamine hydrochloride equivalent; however, the Panel did not differentiate the active moiety content of the salts of other drugs such as codeine, dextromethorphan, and ephedrine. The comment recommended that the agency adopt the format used for phenylpropanolamine, selecting a particular salt as the representative form of that drug and identifying the dosage for that salt with a statement similar to that used for phenylpropanolamine. The comment suggested that the sulfates be used as the representative forms for codeine and ephedrine, and that the hydrobromide salt be the representative form for dextromethorphan.

The Panel recommended that the dosage for phenylpropanolamine preparations be "based on the phenylpropanolamine hydrochloride equivalent" because data were submitted to the Panel to support this dosage (Refs. 1 and 2). In its report, when dosages for drugs were not based on representative forms, the Panel determined that the same doses for various salts of these drugs were generally equivalent based on historical usage and the Panel's experience with the various drugs. Moreover, this approach using the same dose for codeine sulfate and phosphate, and ephedrine hydrochloride and sulfate is consistent with standards established in USP XXI (Ref. 3). At this time, the agency is not aware of any data showing that the dosages recommended by the Panel for codeine and ephedrine and their salts should be stated differently, and the comment did not submit any data demonstrating the need for establishing particular salts of these drugs as representative drug forms. With regard to dextromethorphan and dextromethorphan hydrobromide, the agency has determined that the dosage should be equivalent to dextromethorphan hydrobromide. (See the final monograph for OTC antitussive drug products published in the Federal

Register of August 12, 1987; 52 FR 30042.) The agency will consider identifying representative forms of drugs on a case-by-case basis if data are submitted showing that a change is necessary.

References

(1) OTC Volume 040273.
(2) OTC Volume 040285.
(3) "The United States Pharmacopeia XXI—National Formulary XVI," United States Pharmacopeial Convention, Rockville, MD, pp. 243–244, and 372, 1985.

E. General Comments on Labeling and Advertising for OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drugs

19. One comment stated that OTC drugs should be proven safe and effective, and have true, clear, understandable, and more detailed labeling.

The agency agrees with the comment. Upon completion of the OTC drug review, OTC drug monograph standards of safety, effectiveness, and labeling will be developed for all OTC active ingredients, assuring safe and effective OTC drug products. Moreover, the agency has given serious consideration to the importance of accurate labeling and the consumer's comprehension of the intended message in the labeling. The expertise of the various panels was directed toward assuring informative, medically accurate OTC labeling. The agency, on its own initiative and in response to public comments, is modifying labeling proposed by the panels, where necessary, to make it clearer and more understandable to consumers.

20. Five comments objected to the Panel's recommendation that all inactive ingredients be listed in the labeling of OTC cough-cold drug products. The comments argued that a list of inactive ingredients in the labeling would be meaningless, confusing, and misleading to most consumers. The comments noted that the Federal Food, Drug, and Cosmetic Act does not require that the inactive ingredients of drug products be included on a label and argued that listing these ingredients would crowd out information that is more meaningful to consumers. Two comments agreed with the Panel's recommendation.

The Federal Food, Drug, and Cosmetic Act specifies the requirements for ingredient labeling of OTC drug products. Section 502(e) of the act (21 U.S.C. 352(e)) requires that all active ingredients and certain other ingredients, whether included as active or inactive, be disclosed in the labeling. The act also limits the requirement for stating quantity of ingredients in OTC drug products to those specifically mentioned in section 502(e). Although the act does not require the disclosure of all inactive ingredients in the labeling of OTC drug products, the agency agrees with the Panel that listing of inactive ingredients in OTC drug product labeling would be useful information for some consumers. Consumers with known allergies or intolerances to certain ingredients would then be able to identify substances that they may wish to avoid.

The Proprietary Association, the trade association that represents approximately 85 OTC drug manufacturers who reportedly market between 90 and 95 percent of the volume of all OTC drug products sold in the United States, has established guidelines (Ref. 1) for its member companies to list voluntarily inactive ingredients in the labeling of OTC drug products. Under another voluntary program begun in 1974, the member companies of The Proprietary Association have been including the quantities of active ingredients on OTC drug labels. The agency is not at this time proposing to require the listing of inactive ingredients in OTC drug product labeling. However, the agency commends these voluntary efforts and urges all other OTC drug manufacturers to similarly label their products.

Reference

(1) "Guidelines for Disclosure of Inactive Ingredients in OTC Medicines," The Proprietary Association, Washington, DC, July 12, 1984, in OTC Volume 04GTFM.

21. One comment agreed with the Commissioner's statement in the preamble to the advance notice of proposed rulemaking that manufacturers should include information concerning changes in dosages and reformulation in the labeling of drug products (41 FR 38313), but objected to placing this information on the principal display panel of the label. The comment also requested a time limit on how long a manufacturer would be required to continue providing such information in the labeling, stating that 1 year after reformulation of the product would be an appropriate limit.

Currently, there are no regulations requiring the inclusion of information concerning changes in dosages and reformulation in the labeling of OTC drug products, and the agency is not proposing any at this time. However, The Proprietary Association has instituted a program in which manufacturers of OTC drug products are encouraged to inform consumers voluntarily in the labeling of changes in dosages and formulations. (See comment 8 above.) The agency commends the program and encourages its continuation.

22. Several comments were opposed to the number and type of warnings proposed by the Panel for OTC cough-cold products. One comment stated that terms such as "monoamine oxidase inhibitor," "enlargement of the prostate gland," "glaucoma," "antihypertensive," and "antidepressant" are meaningless to all but a limited number of consumers. The comment further stated that it is redundant to use such terms in addition to "except under the advice and supervision of a physician" when the consumer has already been diagnosed by a physician as having these conditions. Several comments stated that warnings which contain specific contraindications should be based on sound epidemiological data, and that the addition of extensive warnings tends to reduce the impact of the important labeling statements. The comments recommended that FDA accept only those warnings which are necessary and important, and which are applicable to a significant portion of the target population.

The agency agrees that too many warning statements reduce the impact of important statements. The agency also believes that the warnings it has proposed provide important information to consumers. As each segment of the monograph for cough-cold drug products was proposed, many of the Panel's recommended warnings were revised, simplified, combined, or eliminated. For example, the phrase "except under the advice and supervision of a physician" has been shortened to "unless directed by a doctor." Some information recommended by the Panel in *"Warnings,"* such as age restrictions, is now included in the *"Directions"* section. Contraindications for specific populations, e.g., people with hypertension or glaucoma, have been included only when there is evidence to support these contraindications.

With regard to the terms in the Panel's warnings which the comment believed would be meaningless to consumers, the agency stated in the tentative final monograph for OTC nasal decongestant drug products that terms such as "monoamine oxidase inhibitor," "antihypertensive," and "antidepressant" may be confusing to consumers and deleted "monoamine oxidase inhibitor," substituted "high blood pressure" for "antihypertensive," and substituted "depression" for "antidepressant" (50 FR 2231). Similar changes will be made in other monographs as appropriate. Because antihypertensive and antidepressant

drugs are widely prescribed, persons taking these medications should be alerted to drug interactions that can occur if they are taken simultaneously with some OTC drugs. Likewise, although consumers may have been diagnosed by a physician as having enlargement of the prostate gland or glaucoma, they may not be aware that a particular OTC drug product contains ingredients that they should not use.

The agency believes that, with the above changes, the proposed warning statements for OTC cough-cold products will provide important, understandable information to the consumer in a concise manner.

23. Two comments contended that FDA does not have the authority to legislate the exact wording of OTC labeling claims. The comments stated that limiting the indications to the exact terminology of the monograph is overly restrictive because the Panel itself had used alternate terminology throughout the report in discussing the indications for these products. One comment requested that more flexibility in labeling be permitted by adding to the approved indications a statement as follows: "* * * or similar indications statements which are in keeping with the Panel's report."

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 in an applicable monograph or other regulation, e.g., 21 CFR 201.63 or 330.1(g).

In this tentative final monograph, supplemental language relating to indications has been proposed and captioned as *Other Allowable Statements.* Under FDA's revised labeling policy (51 FR 16258), such statements are included at the tentative final stage as examples of other truthful and nonmisleading language that would be allowed elsewhere in the labeling. In accordance with the revised labeling policy, such statements would not be included in a final monograph. However, the agency has decided that, because these additional terms have been reviewed by FDA, they should be incorporated, wherever possible, in final OTC drug monographs under the heading "Indications" as part of the indications developed under the monograph.

24. Two comments objected to limiting the terminology in the indication statements to "temporarily relieves" or "temporary relief of" when the actual duration of action is known in hours. These comments requested that a statement of a definite duration of action (e.g., "12 hours of relief") replace a term such as "temporary relief" in the labeling of drug products with a known duration of action.

Information on duration of action is provided by the dosage intervals given in the directions for use in the cough-cold monograph, e.g., 2 or 3 drops or sprays every 12 hours. The agency believes that it is unnecessary to repeat this information in the indications. A manufacturer may use a term such as "12 hours of relief" elsewhere in the labeling if the term is true and not misleading, but such terms are not being proposed in the tentative final monograph.

25. One comment, noting that the Panel restricted product identification to the terms defined in § 341.3 of its recommended monograph, requested that definitions of the terms "cold (common cold) product" and "sinus congestion product" be included in the monograph, so that these terms could be used to identify products. Other comments objected to the Panel's recommendation that product names or labeling claims that contain the words "cough" or "cold," such as "cough syrup," "common cold," "cold tablets," "cold capsules," "cold formula," and "cold medicine," not be allowed in OTC drug product labeling. These comments contended that such terms are truthful in the context of the total label and are meaningful to consumers. Several comments added that the Panel's recommendations conflict with existing trademark laws and arbitrarily prohibit the use of lawfully registered trademarks.

Although the Panel restricted product identifications to those terms defined in § 341.3 of its recommended monograph, the agency is including in each monograph a "statement of identity" paragraph that sets forth acceptable terms for product identification. As stated in § 201.61 (21 CFR 201.61), the statement of identity of an OTC drug is limited to the established name of the drug, if any, followed by an accurate statement of the general pharmacological category(ies) of the drug or the principal intended action(s) of the drug. The established name of a drug, as defined in section 502(e)(3) of the act (21 U.S.C. 352(e)(3)) is: (1) The official name designated pursuant to section 508 of the act, (2) the official name recognized in an official compendium, if the drug has no designated official name, or (3) the common or usual name of the drug if neither (1) nor (2) apply. Terms employed to describe the general pharmacological category(ies) or principal intended action(s) of the drugs covered by this monograph are "antihistamine," "antitussive," "bronchodilator," "expectorant," and "nasal decongestant." An example of a statement of identity for an antihistamine drug product containing chlorpheniramine maleate to relieve hay fever would be "chlorpheniramine maleate" followed by the term "antihistamine," i.e., the established name of the drug and its pharmacological category. Wherever possible, the agency prefers to use the general pharmacologic category as the statement of identity because information on the principal intended action is provided in the indications. However, in instances where the pharmacologic category is not appropriate as the statement of identity, the principal intended action is used. For example, the statement of identity for an antihistamine used as a nighttime sleep-aid is "nighttime sleep-aid."

The agency believes that, while naming the symptom or condition for which the product is used, terms such as "cold tablets," "cold capsules," "cold formula," "cold medicine," "cold (common cold) product," "cough syrup," or "sinus congestion product" convey a general use but do not convey the drug's principal intended action as well as the terms "antihistamine," "nasal decongestant," etc. The agency does not oppose the inclusion of such terms in the names of products; however, these terms are not required and are not being included in the labeling in the

monograph. Product names, which may include terms such as "cold formula," are considered to be outside the scope of the OTC drug review, but are subject to the prohibitions in section 502 of the act relating to labeling that is false or misleading. Such terms, whether used in product names or in other parts of the labeling that are not covered by the monograph, will be evaluated by the agency in conjunction with normal enforcement activities relating to that section of the act.

In reviewing the terms defined by the Panel in recommended § 341.3, the agency concludes that "antihistamine" in paragraph (e) conveys the pharmacological category, but "allergy product" in paragraph (b) or "hay fever product" in paragraph (k), do not convey the pharmacological category or principal intended action of the product. Thus, the term "antihistamine" has been proposed as the statement of identity in the tentative final monograph for OTC antihistamine drug products (50 FR 2216), but "allergy product" and "hay fever product" have not been included. However, these terms are similar to the terms "cold tablets," "cold formula," "sinus congestion product," etc. in that they name the condition or symptom for which the product is used, and may be used in the names of products as discussed in the preceding paragraph.

26. One comment objected to the Panel's recommendation against the use of the words "works internally" and stated that these words clearly and directly tell the consumer the difference between products which have different routes of administration, such as products for external application or for intranasal use, as opposed to products for systemic absorption by an oral or rectal route.

The agency believes that the term "works internally" provides little useful information to the consumer and, in fact, can be misleading. When self-administering a medication, it is important for the consumer to know how to use the drug, the nature of any side effects that can occur, and any contraindications for its use. This information is contained in the label directions and warnings on the product. Further, the label warnings will inform the consumer of any systemic or internal effects which might occur from using the drug.

The term "works internally" does not provide specific information that facilitates safe and effective use of an OTC drug product or prevents misuse and might well serve to confuse consumers. Many topically applied products have systemic effects. The agency believes that it would be confusing to consumers to have label directions that state that the product is to be used topically, while elsewhere on the label it states that the product "works internally." Therefore, the agency agrees with the Panel that the term "works internally" should be classified in Category II.

27. One comment requested that advertising claims for the effectiveness of OTC drug products containing ingredients that are placed in Category III for lack of data to show effectiveness not be allowed during the testing period of these ingredients. The comment recognized that this request may come under the jurisdiction of the Federal Trade Commission (FTC).

As discussed below, the FTC has the primary responsibility for regulating OTC drug advertising. FDA has forwarded copies of the comments concerning cough-cold advertising to the FTC for its consideration. Manufacturers are responsible for adhering to applicable statutory and regulatory standards with respect to advertising claims regardless of whether there is ongoing testing. FDA notes that, since the comment was submitted, the regulations concerning OTC drug review procedures have been revised to delete the provision that had allowed continued marketing of an OTC drug product with a condition classified in Category III after publication of a final monograph pending further testing (see 46 FR 47730; September 29, 1981). (See comment 28 below.)

28. Several comments asserted that the Panel went beyond its charter by making statements concerning the advertising of the products under its review. The comments stated that FDA did not grant such authority in the procedures established for OTC panels. The comments further argued that the Panel's statements on OTC drug advertising were not only inappropriate for inclusion in the report, but were also based on inadequate information because, according to FDA procedures, data and information pertaining to advertising were not submitted to the Panel.

The OTC drug review procedures do not preclude a panel from expressing its concern about OTC drug advertising. The Panel's statements and recommendations on OTC drug advertising (41 FR 38334) were partly based on a presentation made to the Panel by a representative of the Council on Children, Media and Merchandising in April 1975. The presentation included a film and documentation on the use of the package and labeling of OTC drugs in advertising and the possible effect of advertising on children (Ref. 1). FTC has the primary responsibility for regulating OTC drug advertising, and FDA has forwarded copies of the comments concerning cough-cold advertising to the FTC for its consideration (Ref. 2). FDA does, however, have the authority to regulate OTC drug advertising that constitutes labeling under the Federal Food, Drug, and Cosmetic Act. See, e.g., *United States* v. *Article of Drug * * * B-Complex Cholinos Capsules*, 362 F.2d 923 (3d Cir. 1966); *V.E. Irons, Inc.* v. *United States*, 244 F.2d 34 (10th Cir.), *cert. denied*, 354 U.S. 923 (1957). In addition, for an OTC drug to be generally recognized as safe and effective and not misbranded, the advertising for the drug must satisfy the FDA regulations at § 330.1(d) (21 CFR 330.1(d)), which state that the advertising may prescribe, recommend, or suggest the drug's use only under the conditions stated in the labeling. If advertising for an OTC cough-cold drug product offers the product for conditions not included in the final monograph labeling, the drug product may be subject to regulatory action by FDA.

References

(1) Summary Minutes of the 18th Meeting of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products, April 3, 4, and 5, 1975, Dockets Management Branch.

(2) Letter from S. Bader, FDA, to W. Snyder, FTC, May 6, 1982, in OTC Volume 04GTFM, Docket No. 76N-052G, Dockets Management Branch.

F. General Comments on Testing Guidelines

29. Several comments expressed concerns about the testing guidelines recommended by the Panel for Category III OTC single drug ingredients and combinations. The comments urged the Commissioner not to shorten the period of time within which studies must be completed as recommended by the Panel (41 FR 38312) but instead to expand the period of time where good cause can be shown. Other comments stated that the clinical testing time allotted for drugs in Category III is "excellent" or entirely appropriate because of a lack of specific proven methods for some of the studies being recommended. Some comments expressed concern about the competition for a limited number of investigational facilities and trained research personnel which could result from testing of each type of Category III ingredient and combination.

The agency has not addressed specific testing procedures in this document. In revising the OTC drug review procedures relating to Category III,

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

30. Referring to the testing of Category III drugs for effectiveness, one comment stated that government agencies should perform absolutely essential testing on prototype drug products and provide industry with the results. According to the comment, the cost of testing could be prorated to the companies marketing the drugs. The comment objected to the testing of OTC drug products by industry because of duplication of studies of the same drug by many companies and because of the moral, ethical, and economic issues involved in utilizing human subjects in testing Category III drugs for effectiveness.

In the preamble to the final rule revising the procedures relating to Category III conditions, the agency stated that "it is the responsibility of the manufacturer of a drug to have adequate tests that meet the statutory requirements before marketing the drug." (See the **Federal Register** of September 29, 1981; 46 FR 47732.) In this document, the agency also stated that "FDA will require adequate and well-controlled studies except where the agency waives this requirement as unnecessary or inappropriate. The agency advises that § 330.10(a)(4)(ii) does permit reports of significant human experience during marketing to be used as corroborative support for general recognition of effectiveness" (46 FR 47731).

Regarding other considerations mentioned by the comment in connection with Category III testing, as discussed in comment 29 above, the agency emphasizes its intention to meet with manufacturers at their request to discuss protocols and other testing issues involving conditions that industry is interested in upgrading. In many instances, reformulation of products to replace Category III ingredients with Category I ingredients will also eliminate a large portion of the costs of testing products containing Category III drugs.

31. Two comments requested modification of the Panel's recommended guidelines for the evaluation and standardization of cough-cold timed-release formulations (41 FR 38331).

These guidelines were published as the Panel's recommendations, but the agency is not adopting them or commenting on them at present. In the **Federal Register** of October 28, 1977 (42 FR 56756), the agency stated that dosage recommendations in the Panel's monograph apply only to conventional formulations. Timed-release formulations are considered new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)). Timed-release formulations are complex such that the state of the art does not permit adequate standardization of them for inclusion in an OTC drug monograph (42 FR 56756). In order to market a timed-release formulation, an approved NDA containing appropriate bioavailability data is required under section 505 of the act (21 U.S.C. 355) and FDA regulations in 21 CFR Part 314. Persons interested in testing or marketing such products should consult with the Office of Drug Research and Review (formerly the Office of New Drug Evaluation), Center for Drug Evaluation and Research.

G. General Comments on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Combination Drug Products

32. One comment contended that the Panel endorsed combination products which did not meet the "normal FDA standards." The comment pointed out that currently marketed cough-cold products may contain as many as 12 or more chemicals (including therapeutic ingredients and cosmetic chemicals such as flavors and dyes) and that the Panel recommended the continued marketing of products containing eight or more "active" chemicals. The comment argued that because most cough-cold drug products are combinations of a number of ingredients, their safety depends not only on the safety of individual ingredients for individual symptoms but also on the safety of the ingredients taken together. These ingredients, the comment stated, may interact with each other to enhance toxicity, inhibit effectiveness, or simply expose the consumer to unwanted side effects without providing an overriding benefit.

The agency disagrees with the comment's claim that the Panel endorsed combination products that did not meet "normal FDA standards." These standards are set forth in § 330.10(a)(4)(iv), which states that "an OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients, * * *" The Panel concurred with the requirements of the regulation that each active ingredient in a combination product must contribute to the claimed effects and must be necessary for the rational therapy of concurrent symptoms. The Panel was also aware of the inclusion of inactive (nontherapeutic) ingredients which are used for various purposes, such as preservatives and flavors, in cough-cold preparations. The Panel also recognized that some inactive ingredients may be necessary for marketing purposes (41 FR 38323). The Panel recommended that marketed products should contain only those active and inactive ingredients that are essential to the product.

The Panel evaluated the submitted data on active ingredients in combination products from the standpoint of safety and effectiveness and, based on its evaluation, recommended specific combinations of ingredients from the same and different pharmacologic groups. The Panel classified a number of combinations as Category II (41 FR 38326) and considered medical rationale and drug interactions in making these recommendations. For example, the Panel stated that combinations containing an anticholinergic and an expectorant are medically irrational because an expectorant promotes the production of secretions whereas the anticholinergic produces an opposite effect, i.e., antisecretory action.

After the Panel's report was published in September 1976, the agency published "General Guidelines for OTC Drug Combination Products" (Ref. 1). The guidelines outline the conditions for combinations of Category I active ingredients from the same and different therapeutic categories where each type of combination meets the OTC drug combination policy in all other respects. The guidelines also outline the conditions for the combination of Category I active ingredients from the same therapeutic category having the same or different mechanisms of action.

The agency believes that the Panel's recommendations and the agency's guidelines have adequately addressed the comment's concern as to the continued marketing of products containing several "active" chemicals and the safety of these ingredients when

taken together in a combination drug product.

Reference

(1) Food and Drug Administration "General Guidelines for OTC Drug Combination Products, September 1978," Docket No. 78D-0322, Dockets Management Branch.

33. One comment was opposed to OTC combination drug products because they contain fixed doses of ingredients and do not allow latitude for titrating the dose of the various ingredients. The comment cited one medical expert who stated that "fixed combinations prevent establishing an effective dose of individual constituents without affecting the dose of other ingredients (in the combination) * * * which not only may not be necessary, but which may cause undesirable toxic effects."

The comment also referred to a 1969 opinion of the National Academy of Sciences that "It is a basic principle of medical practice that more than one drug should be administered only for the treatment of a given condition only if the physician is persuaded that there is substantial reason to believe that each drug will make a positive contribution to the effect he seeks * * * each drug should be given at the dose level that may be expected to make its optimal contribution to the total effect, taking into account the status of the individual patient and any synergistic or antagonistic effects that one drug may be known to have on the safety or efficacy of the other."

The OTC combination drug products under consideration in this rulemaking are intended to relieve two or more concurrent symptoms. The convenience of being able to take one combination product instead of two or more single ingredient products appeals to many individuals. In fact, the Panel's report acknowledges that cough-cold combination drug products are widely used by consumers (41 FR 38322). Nevertheless, the agency recognizes that OTC combination drug products contain fixed doses of ingredients which do not allow the consumer to adjust the doses of the individual ingredients.

The agency believes that combinations of the cough-cold ingredients specified in this tentative final monograph provide a convenient and rational approach for relief of concurrent symptoms which so frequently accompany the common cold. The agency also believes that combination products formulated in accordance with the tentative final monograph will be safe and effective in a large percentage of the general population.

For consumers who do not believe that the doses of ingredients in fixed combinations represent the optimal titrations for them, the agency believes that appropriate single ingredient products will remain available.

34. One comment disagreed with what it described as the two ways in which the Panel justified its recommendation of cough-cold combinations: first, the requirement that each active ingredient belong to a different pharmacologic class; and second, the fact that "marketing experience" of cough-cold combination products showed that the incidence of consumer complaints for such products was relatively low. The comment contended that the Panel did not consider drug interactions when approving combinations which contain ingredients from different pharmacologic groups, e.g., nasal decongestant, expectorant, cough suppressant, etc. The comment also asserted that the fact that ingredients are added for different purposes is no assurance that they will not have a detrimental effect when combined. The comment further contended that "marketing experience" is worthless in determining the safety and effectiveness of combination products or any other products, because consumers cannot evaluate the special merits of each separate ingredient in the product and are unlikely to keep records and file complaints with the manufacturer.

The agency believes that the comment overlooks other important considerations in the Panel's evaluation of combinations. The Panel did not base its recommendation for cough-cold combinations on different pharmacological categories for each ingredient and marketing experience alone. The Panel specified that only one ingredient from a pharmacological category could be included in a combination and based its classification of the individual ingredients in combinations on data submitted to it for evaluation. It was not the Panel's intention to permit random combinations of ingredients in single products (a "shotgun" approach); however, because the symptoms of the common cold or hay fever often include nasal congestion, runny nose, and coughing, for example, the Panel believed it would be justifiable to combine active ingredients to treat these separate symptoms if the combination met the Panel's and the agency's requirements (41 FR 38323).

In its "General Guidelines for OTC Drug Combination Products" (cited above), published after publication of the Panel's report, the agency provided that Category I active ingredients from different therapeutic categories may be combined to treat different symptoms concurrently only if each ingredient is present within its established safe and effective dosage range and the combination meets the OTC drug combination policy in all other respects. The OTC drug combination policy, as stated in § 330.10(a)(4)(iv) of the OTC drug regulations, includes the provisions that combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients, and the combination provides rational concurrent therapy for a significant proportion of the target population.

The agency concludes that the Panel's Category I recommendations, as adopted by the agency, the application of the OTC drug regulations (21 CFR 330.10), and the agency's guidelines are adequate to insure that those combinations of ingredients permitted in the monograph would be generally recognized as safe, effective, and not misbranded. Regarding "marketing experience," the Panel considered marketing data submitted to it for review. The Panel indicated, based on the data, that there appeared to be a low incidence of adverse reactions. The Panel concluded, and the agency concurs, that while marketing data are limited and difficult to interpret they tend to support the safety of combinations of active ingredients reviewed by the Panel (41 FR 38325).

H. Comments on Specific OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Combination Drug Products

35. One comment requested that the agency not impose a limit on the number of ingredients from a single pharmacological group which may be combined in an OTC drug product. The comment contended that the Panel used purely theoretical reasons in categorizing combinations containing two ingredients from the same pharmacologic group as Category III and combinations containing more than two such ingredients as Category II. The comment stated that products combining multiple ingredients from a single pharmacologic group as well as from several pharmacologic groups have been widely sold for many years. The comment requested that the FDA's combination policy for OTC drug products in § 330.10(a)(4)(iv) be the governing criteria for these products without a limitation on the number of ingredients.

Section 330.10(a)(4)(iv) specifies the criteria for OTC combination drug

products. The agency's "General Guidelines for OTC Drug Combination Products" (cited above) state that ingredients from the same therapeutic category that have different mechanisms of action may be combined to treat the same symptoms or condition if the combination meets the OTC drug combination policy in 21 CFR 330.10(a)(4)(iv) in all respects and the combination is, on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose. The guidelines also state that Category I active ingredients from the same therapeutic category that have the same mechanism of action should not ordinarily be combined unless there is some advantage over the single ingredient in terms of enhancing effectiveness, safety, patient acceptance, or quality of formulation. Thus, the agency's combination policy does not set limits on the number of ingredients from the same pharmacologic group that may be combined, provided data are presented to show the combination meets the necessary criteria. Combinations containing ingredients from the same pharmacologic group will be permitted if adequate data are presented to the agency.

36. Several comments favored the Panel's recommendation to limit combination products to ingredients from three pharmacological groups. In addition, the comments stated that single ingredient products should be available to the consumer so that a specific drug can be used to treat a specific symptom without the consumer having to take unnecessary ingredients that may cause undesirable side effects.

Other comments disagreed with the Panel's proposal to limit combination products to ingredients from three pharmacological groups, arguing that this recommendation was an unscientific and arbitrary judgment inconsistent with the FDA guidelines for combination products (21 CFR 330.10(a)(4)(iv)), inconsistent with data submitted to the Panel on combination products containing ingredients from more than three pharmacological groups, and inconsistent with the Panel's allowance of Category I status for products containing ingredients from more than three pharmacological groups provided a suitable target population can be identified. One comment stated that the requirement that additional evidence that a significant target population exists for a combination containing ingredients from four pharmacologic groups is unwarranted, and that the imposition of a limit of a specific number of ingredients may curtail the flexibility of the formulator and frustrate the principle of combination products. Several comments recommended that no fixed limit be placed upon the number of active ingredients in a combination if the combination can be shown to be a rational, safe, and effective combination with a suitable target population.

The agency agrees that no fixed limit need be placed upon the number of active ingredients in a combination product if it can be shown to be a rational, safe, and effective combination with a suitable target population. This position is consistent with the FDA policy for OTC drug combination products in 21 CFR 330.10(a)(4)(iv) and with the "General Guidelines for OTC Drug Combination Products" (cited above). The Panel placed certain two and three ingredient combination products in Category I because data were presented to support their safety and effectiveness. The agency will consider any combination for Category I, regardless of the number of ingredients, provided adequate data are presented in accordance with the regulation and guidelines mentioned above.

The agency also agrees that single ingredient products are desirable and should be available. However, the agency recognizes that a significant target population exists for some OTC cough-cold combination products to treat concurrent symptoms and has proposed that such combinations be classified as Category I. Allowable combinations are listed in § 341.40 of the tentative final monograph.

37. One comment disagreed with the Panel's conclusions on combining active ingredients from the same pharmacological group at less than the minimum effective dose. The comment contended that requiring such combinations to show some special benefit is not in accord with the FDA policy for combination products (21 CFR 330.10(a)(4)(iv)). The comment recommended that such combinations not be required to show some special benefit beyond substantial support of safety and effectiveness.

After the Panel's report was published, the agency developed its "General Guidelines for OTC Drug Combination Products" (cited above). In part, the guidelines pertain to the combination of two or more active ingredients from the same pharmacological (therapeutic) category that have the same or different mechanisms of action. Paragraph 3 of the guidelines provides that "Category I active ingredients from the same therapeutic category that have the same mechanism of action should not ordinarily be combined unless there is some advantage over the single ingredients in terms of enhanced effectiveness, safety, patient acceptance, or quality of formulation. They may be combined in selected circumstances to treat the same symptoms or conditions if the combination meets the OTC combination policy (in § 330.10(a)(4)(iv)) in all respects, the combination offers some advantage over the active ingredients used alone, and the combination is, on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose." Paragraph 2 of the guidelines provides that: "Category I active ingredients from the same therapeutic category that have different mechanisms of action may be combined to treat the same symptoms or condition if the combination meets the OTC combination policy in all respects and the combination is on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose. Such combinations may utilize each active ingredient in full therapeutic dosage or sub-therapeutic dosage, as appropriate."

The agency developed these guidelines to clarify the existing regulation in 21 CFR 330.10(a)(4)(iv). Both the guidelines and the regulation will be used in evaluating data regarding combination products. The comment did not present any data that would lead the agency to change its general guidelines for OTC drug combination products described above.

38. One comment pointed out an error at 41 FR 38326 concerning combinations containing an antitussive and a local anesthetic or a local analgesic-antipyretic as a lozenge, and combinations containing a nasal decongestant and a local anesthetic or a local analgesic-antipyretic as a lozenge. The comment stated that the word "antipyretic" should be deleted from these statements because the "compounds" being referred to in these combinations are not antipyretics.

The agency points out that the Panel did not include the word "antipyretic" in § 341.40 (j) and (o) of its recommended monograph, which correspond to the statements at 41 FR 38326 cited by the comment. It appears that the word "antipyretic" was erroneously included at 41 FR 38326 and that the Panel intended the statements on that page to be consistent with its recommended

monograph. The Panel's report at 41 FR 38326 is amended accordingly.

39. One comment suggested that § 341.40 (j) and (o) in the advance notice of proposed rulemaking do not accurately reflect the intent of the Panel. The comment pointed out that § 341.40(j) permits combining any single Category I antitussive active ingredient with any single generally recognized as safe and effective local anesthetic or local analgesic active ingredient and that § 341.40(o) permits combining any single Category I nasal decongestant active ingredient with any single generally recognized as safe and effective local anesthetic or local analgesic active ingredient. The comment argued that not all topical analgesic ingredients that are generally recognized as safe and effective should be used on the oral mucosa and that the Panel actually intended to permit combinations of an antitussive or nasal decongestant ingredient with any ingredient that is generally recognized as safe and effective for the relief of sore throat pain.

The comment also indicated that the monograph for OTC oral cavity drug products [which has been renamed oral health care drug products] will determine which pharmacologic categories and ingredients are generally recognized as safe and effective for the relief of sore throat pain and that ingredients from pharmacologic groups other than analgesics, e.g., demulcents, may be appropriate. The comment therefore recommended that paragraphs (j) and (o) of § 341.40 be revised to provide for combinations of an antitussive or a nasal decongestant ingredient with any single ingredient from any pharmacologic group which is designated in the monograph for OTC oral cavity drug products as being generally recognized as safe and effective for the relief of sore throat pain. In addition, the comment suggested that § 341.40(o) be limited specifically to oral nasal decongestant ingredients because § 341.40(o), as currently written, permits combining a topical nasal decongestant with a local anesthetic active ingredient.

In the first segment of the tentative final monograph for OTC oral health care drug products, published in the **Federal Register** of January 27, 1988 (53 FR 2436), the agency deferred consideration of the following combinations to this tentative final monograph: Expectorants and demulcents; expectorants and oral anesthetic/analgesics; oral nasal decongestants and demulcents, oral anesthetic/analgesics, or antimicrobials; antihistamines and oral anesthetic/analgesics, antimicrobials, astringents, debriding agent/oral wound cleansers, or demulcents; and oral antitussives and oral anesthetic/analgesics, antimicrobials, astringents, debriding agent/oral wound cleansers, or demulcents.

The agency agrees with the comment that combinations containing a single antitussive or nasal decongestant ingredient and a single local anesthetic or local analgesic ingredient should be limited to those anesthetic/analgesic ingredients which are generally recognized as safe and effective for use on the oral mucosa. Such ingredients have been proposed in § 356.10 of the tentative final monograph for OTC oral health care drug products (53 FR 2458). To be consistent with the language used in the oral health care drug products tentative final monograph, the term "oral anesthetic/analgesic" is used in this document rather than the term "local anesthetic or local analgesic."

In addition, the agency concurs with the comment's suggestion that § 341.40(o) be restricted to oral nasal decongestants. The agency believes that such a restriction was originally intended by the Panel because it indicated that such a combination should be used only in lozenge form. Topical nasal decongestants are intended for application directly to the nasal mucosa while oral nasal decongestants act through systemic absorption. Antitussives and bronchodilators may also be used as oral or topical drugs. Therefore, for clarity, the agency is specifying in the monograph in § 341.40 and § 341.85 whether antitussives, bronchodilators, and nasal decongestants are for oral or topical (i.e., inhalant or ointment) use.

The comment requested a Category I classification for combination drug products containing an antitussive or a nasal decongestant ingredient with any generally recognized safe and effective ingredient for sore throat pain. In this tentative final monograph the agency evaluates the comments requested combination drug products and other cough-cold and oral health care combination drug products which were deferred from the oral health care rulemaking to the cough-cold rulemaking.

The combination of a local anesthetic or local analgesic (oral anesthetic/analgesic) with an oral antitussive or an oral nasal decongestant was placed in Category I by the Cough-Cold Panel provided that the product is available in the form of a lozenge (41 FR 38326). The agency agrees with the Panel.

In addition, the agency believes that a demulcent can be combined with an oral antitussive or an oral nasal decongestant in a solid dosage form. In several submissions to the Cough-Cold Panel, the demulcent attributes of the products were mentioned (Ref. 1). The Oral Cavity Panel's definition of a demulcent is that it is a bland, inert agent that soothes and relieves irritation of inflamed or abraded surfaces such as mucous membranes. An anesthetic blocks pain receptors resulting in a sensation of numbness and abolition of response to painful stimuli (47 FR 22927). Dry or sore throat is a generally recognized symptom of the common cold (Refs. 2 and 3). In discussing combination drug products containing local anesthetics or other agents for the relief of sore throat, the Cough-Cold Panel stated that because symptoms of sore throat often accompany cough and the "common cold," combination drug products containing cough-cold ingredients and agents to relieve minor irritations are rational (41 FR 38325).

The Cough-Cold Panel reviewed data relating to combination products containing cough-cold ingredients and oral health care ingredients with claims for relief of sore throat. The majority of these data concerned anesthetic/analgesics combined with cough-cold ingredients. The Panel determined that products containing an antitussive or a nasal decongestant combined with an oral anesthetic/analgesic in a lozenge dosage form are rational, identified a target population that would benefit from such products, and placed such combinations in Category I (41 FR 38325). The Panel did not do an extensive review of all possible oral health care and cough-cold combination drug products; thus, it did not identify any other specific cough-cold and oral health care combination products as meeting its requirements for Category I classification. The Panel established specific criteria for the treatment of symptoms with combination products and based its Category I recommendations on whether the combination product is rational concurrent therapy for a significant and existing target population that can benefit from such use (41 FR 38322). Similarly, justification for classifying a 4-ingredient combination product was based on these principles, i.e., identification of a significant target population that required treatment for concurrent symptoms (see comment 47 below). Because of the similarities in the use of oral anesthetic/analgesics and oral demulcents in relieving pain and irritation, the agency believes that the

target populations for products containing an oral nasal decongestant or an oral antitussive combined with an oral anesthetic/analgesic would be the same as that for combination products containing an oral nasal decongestant or an oral antitussive combined with a demulcent ingredient. In addition, in § 356.20(b) of the tentative final monograph for OTC oral health care drug products (January 27, 1988; 53 FR 2458), the agency proposed that an oral anesthetic/analgesic and an oral demulcent was an acceptable combination. Therefore, the agency is proposing that an oral nasal decongestant and/or an oral antitussive can be combined with an oral anesthetic/analgesic and an oral demulcent. The Cough-Cold Panel recognized that most sore throat remedies are applied topically while other symptoms of the cold are usually treated internally by products ingested orally (41 FR 38325). Thus, the type of epidemiological data considered acceptable by the Panel to place a combination of an oral antitussive or oral nasal decongestant and an oral anesthetic/analgesic in Category I can be extrapolated to allow a demulcent or a demulcent and anesthetic/analgesic combination to be combined with similar cough-cold ingredients. Therefore, the agency is classifying in Category I in this tentative final monograph the following combinations provided the product is in a solid dosage form to be dissolved in the mouth and swallowed: (1) An oral antitussive or an oral nasal decongestant and an oral anesthetic/analgesic, (2) an oral nasal decongestant, an oral antitussive, and an oral anesthetic/analgesic, (3) an oral antitussive or an oral nasal decongestant and an oral demulcent, (4) an oral nasal decongestant, an oral antitussive, and an oral demulcent, (5) an oral antitussive or an oral nasal decongestant, an oral anesthetic/analgesic, and an oral demulcent, and (6) an oral nasal decongestant, an oral antitussive, an oral anesthetic/analgesic, and an oral demulcent.

In its report on OTC oral health care drug products, the Oral Cavity Panel classified the combination of an expectorant with an anesthetic/analgesic in Category II because it believed that an anesthetic would be diluted and removed from the mucous membranes of the mouth and throat by the action of the expectorant (47 FR 22792). However, the final monograph for OTC expectorant drug products, to be published in a future issue of the **Federal Register**, will provide for expectorants to be taken orally to promote or facilitate the removal of secretions from the respiratory airways. Further, the indications for expectorants are "helps loosen phlegm (sputum) and bronchial secretions and rid the bronchial passageways of bothersome mucus" or "drain bronchial tubes by thinning mucus." Thus, contrary to the Oral Cavity Panel's statements, the expectorant ingredient included in the monograph is not intended to exert an effect in the mouth and throat, but is intended to have a systemic effect. It could be expected that when a combination drug product in a solid dosage form containing an expectorant and an oral anesthetic/analgesic or a combination containing an expectorant and an oral demulcent is dissolved in the mouth and then swallowed, the oral anesthetic/analgesic or the oral demulcent will have exerted its topical therapeutic effect before the expectorant exerts its systemic effect. Therefore, in such combination drug products, the action of the expectorant would not interfere with the sore throat relief provided by the anesthetic/analgesic or the demulcent ingredient; thus, the agency believes that the combination of an expectorant with an oral anesthetic/analgesic in a solid dosage form and the combination of an expectorant and an oral demulcent in a solid dosage form could be rational. A product containing an expectorant and an anesthetic/analgesic was submitted to the Cough-Cold Panel, but the product is no longer marketed (Ref. 4). The agency is not aware of any currently marketed products containing these combinations of ingredients in a solid dosage form. Moreover, no data were submitted to demonstrate a significant target population with concurrent symptoms that would benefit from such combinations. Therefore, the agency is proposing a Category III classification in this tentative final monograph for the combination of an expectorant with an oral anesthetic/analgesic and the combination of an expectorant with an oral demulcent in a solid dosage form.

Likewise, the agency believes that the combination of an antihistamine and an oral anesthetic/analgesic or an oral demulcent could be rational if the combination drug product is in a solid dosage form so that the anesthetic/analgesic ingredient or the demulcent ingredient may exert its topical effect and the antihistamine can be ingested. The symptoms of allergic rhinitis and minor throat irritation that may result from the nasal congestion that often occurs with allergic rhinitis and subsequent breathing through the mouth could be treated concurrently by a combination drug product containing an antihistamine and an oral health care active ingredient. However, the agency is not aware of any currently marketed OTC drug products that contain such a combination of ingredients, and no data were submitted to demonstrate a significant target population with concurrent symptoms that would benefit from such combinations. Therefore, the agency is proposing a Category III classification in this tentative final monograph for the combination of an antihistamine with an oral anesthetic/analgesic and the combination of an antihistamine and an oral demulcent.

The agency has considered the combination of a debriding agent/oral wound cleanser with an antitussive or antihistamine active ingredient. The Oral Cavity Panel classified several combinations containing debriding agents in Category II stating that a debriding agent, because of its mechanical cleansing action, would wash away or dilute the other active ingredients in the combination and thus prevent them from acting as intended or from exerting their therapeutic effects (47 FR 22792). In addition, in the first segment of the tentative final monograph for OTC oral health care drug products, the agency proposed a Category II classification for the combination of a debriding agent/oral wound cleanser and a demulcent (53 FR 2452). The agency notes that a debriding agent/oral wound cleanser is designed to be swished around in the mouth for at least a minute and then spat out; it should not be swallowed. In a combination drug product containing a debriding agent/oral wound cleanser and an antitussive or an antihistamine, the antitussive or antihistamine could not exert its therapeutic effect because it would not be ingested. The agency concludes that the combination of a debriding agent/oral wound cleanser with an oral antitussive or an antihistamine is not rational. Therefore, the agency is proposing a Category II classification for the combination of a debriding agent/oral wound cleanser with an antitussive or an antihistamine.

Regarding the combination of an oral health care astringent with an oral antitussive or an antihistamine, the agency notes that, as is the case for debriding agent/oral wound cleansers, the directions for an astringent require that the ingredient be in the mouth for at least one minute and then spat out. The agency concludes that these directions are incompatible with the effective use of an oral antitussive or an antihistamine active ingredient. Therefore, in this tentative final

monograph the agency is proposing a Category II classification for the combination of an astringent with an oral antitussive or an antihistamine.

Because the Oral Cavity Panel did not propose any Category I indications for oral antimicrobials, the agency will discuss combinations that include oral antimicrobials in the antimicrobial segment of the tentative final monograph for OTC oral health care drug products, to be published in a future issue of the **Federal Register**. If necessary, the cough-cold combinations tentative final monograph will be amended at a later date to include any combinations identified as being Category I.

Accordingly, in this tentative final monograph, proposed § 341.40(j) reads as follows: "Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral anesthetic/analgesic active ingredient identified in § 356.10 provided that the product is available only in a solid dosage form to be dissolved in the mouth and swallowed," and § 341.40(p) reads as follows: "Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any single oral anesthetic/analgesic active ingredient identified in § 356.10 provided that the product is available only in a solid dosage form to be dissolved in the mouth and swallowed."

In addition, the agency is adding the following Category I combinations to the designated paragraphs in § 341.40:

(u) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral demulcent active ingredient identified in § 356.18 provided that the product is available only in a solid dosage form to be dissolved in the mouth and swallowed.

(v) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any single oral demulcent active ingredient identified in § 356.18 provided that the product is available only in a solid dosage form to be dissolved in the mouth and swallowed.

(w) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any single oral demulcent active ingredient identified in § 356.18 provided that the product is available only in a solid dosage form to be dissolved in the mouth and swallowed.

(x) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral anesthetic/analgesic active ingredient identified in § 356.10 and any single oral demulcent active ingredient identified in § 356.18 provided that the product is available only in a solid dosage form to be dissolved in the mouth and swallowed.

(y) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any single oral anesthetic/analgesic active ingredient identified in § 356.10 and any single oral demulcent active ingredient identified in § 356.18 provided that the product is available only in a solid dosage form to be dissolved in the mouth and swallowed.

(z) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any single oral anesthetic/analgesic active ingredient identified in § 356.10 and any single oral demulcent active ingredient indentified in § 356.18 provided that the product is available only in a solid dosage form to be dissolved in the mouth and swallowed.

References

(1) OTC Volumes 040061, 040104, and 040248.

(2) "Handbook of Nonprescription Drugs," 8th Ed., American Pharmaceutical Association, Washington, pp. 127, 130, and 131, 1986.

(3) Berkow, R., editor, "The Merck Manual of Diagnosis and Therapy," 14th Ed., Merck and Co., Rahway, NJ, p. 189, 1982.

(4) OTC Volume 040104.

40. One comment noted a possible oversight in the Panel's classification of Category I combinations. The comment pointed out that the Panel placed in Category I combinations containing an antitussive and a local anesthetic or local analgesicantipyretic in a lozenge dosage form and combinations containing a nasal decongestant and a local anesthetic or local analgesic-antipyretic in a lozenge dosage form. The Panel did not, however, classify combinations of an antitussive, a nasal decongestant, and a local anesthetic or local analgesic-antipyretic. The comment requested Category I classification of such combinations in a lozenge dosage form, stating that there should be no difficulty in recognizing the target population with concurrent symptoms necessitating treatment with the three pharmacologically different Category I ingredients.

The agency has reviewed the Panel's recommended criteria for classifying cough-cold combinations and agrees that there is a target population that has the symptoms of nasal congestion, cough, and sore throat concurrently. As noted in comment 38 above, the term "antipyretic" should not be included for combinations such as these. As noted in comment 39 above, the anesthetic/analgesic ingredients in these combinations are limited to those that are generally recognized as safe and effective for use on the oral mucosa, and the nasal decongestants in these combinations are limited specifically to any oral nasal decongestants that are identified in § 341.20(a) as generally recognized as safe and effective (50 FR 2238). The agency is including in this tentative final monograph combinations containing an oral antitussive, an oral nasal decongestant, and an anesthetic/analgesic provided the product is available only in a solid dosage form to be dissolved in the mouth and swallowed.

41. One comment opposed the Panel's Category II classification of a combination product containing an antihistamine for the exclusive purpose of sedation and a second antihistamine for relief of the symptoms of allergic rhinitis. The comment referred to the Panel's discussion regarding nighttime cough-cold products which are promoted for use at bedtime to provide a restful sleep (41 FR 38415, paragraph B.1.a). The Panel stated that the duration of drug effects in nighttime cold products which are recommended to be taken once at bedtime is not fully documented, and it recommended the use of antihistamines in cough-cold products only for the relief of symptoms of allergic rhinitis. The comment contended that the Panel's determination that a combination of two antihistamines is "not rational" is a "conclusionary statement" and that the Panel provided no data to support this conclusion. The comment recommended that such combinations be placed in Category I in the absence of any supporting data to prove irrationality.

The agency agrees with the Panel that it is irrational to add an additional antihistamine primarily for the purpose of sedation when treating the symptoms of allergic rhinitis. When using an antihistamine to relieve the symptoms of allergic rhinitis, the desired therapeutic effect is to alleviate the symptoms of allergy, i.e., runny nose, sneezing, and itchy and watery eyes. Addition of a second antihistamine to the product to promote sleep is unnecessary because if allergic rhinitis symptoms are relieved at night by using an antihistamine, most individuals will sleep normally. Antihistamines as a class produce varying degrees of drowsiness as a side effect. The agency is not convinced that there is a need to compound the drowsiness effect of one antihistamine

by adding a second antihistamine to the product. The comment also implies that there is a target population for which an OTC drug product consisting of two antihistamines would be appropriate. However, the comment did not submit any supporting data. For these reasons, the combination of an antihistamine for the relief of the symptoms of allergic rhinitis and an antihistamine added solely for sedation purposes remains in Category II.

42. One comment expressed concern that adverse reactions have been reported with some antihistamine/decongestant combination products containing central nervous system stimulants or sympathomimetic-like agents. The comment stated that good data are not available concerning adverse reactions caused by such combinations; therefore in-depth review is needed. No additional information was submitted by the comment.

The agency notes that the Panel reviewed the available data to determine the rationale and appropriateness of cough-cold combination drug products and to determine the potential for these combinations to cause side effects and adverse reactions. Based on its review, the Panel recommended that any Category I antihistamine could be combined with any Category I nasal decongestant provided each ingredient in the combination was present in amounts within the effective dosage range and the appropriate Category I labeling was used (41 FR 38326).

The data reviewed by the Panel included the marketing history and adverse reaction reports (Ref. 1) for currently marketed drug products containing antihistamines and nasal decongestants. The Panel found that these data showed a low incidence of adverse effects for these combinations (41 FR 38325) and therefore did not recommend any additional warning statements beyond those recommended for individual antihistamine and oral nasal decongestant active ingredients. The agency has reviewed the adverse reaction reports for the years 1969 to 1988 for various combination drug products containing antihistamines and nasal decongestants. These data show that there is a relatively low incidence of central nervous system stimulant adverse effects caused by these combinations (Ref. 2).

Because the pharmacologic actions of the various Category I antihistamines are similar, and because the pharmacologic actions of the various Category I oral nasal decongestants are similar, the agency agrees with the Panel that any Category I antihistamine and any Category I oral nasal decongestant may be safely combined. All warning statements that are required for individual antihistamine and oral nasal decongestant active ingredients will be required for combination drug products containing those ingredients, and the agency believes that the proposed warnings in §§ 341.72(c) and 341.80(c) are adequate to warn consumers of the possibility of adverse effects of a combination product. Therefore, no further in-depth review is necessary at this time.

References

(1) OTC Volumes 040287 and 040287A.

(2) Department of Health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listing," pertinent pages for the years 1969 to 1988, OTC Volume 04GTFM, Docket No. 76N-052G, Dockets Management Branch.

43. One comment argued that it was inappropriate for the Panel to recommend a Category II classification for a combination containing a drug recognized as both an antitussive and an antihistamine combined with another antitussive and/or antihistamine. The comment argued that the Panel expressed only theoretical concerns regarding the safety of this combination and did not document the incidence of side effects it envisaged as occurring. The comment urged that such a combination be placed in Category III.

The agency believes that the combination drug products described by the comment and classified by the Panel in Category II (41 FR 38326) should be considered to be combinations containing two ingredients from the same pharmacologic group and that a Category II classification is inconsistent with the Panel's recommendation that such combinations containing two ingredients from the same pharmacologic group should be in Category III. The agency's "General Guidelines for OTC Drug Combination Products" (cited above), which were made available after publication of the Panel's report, state that Category I active ingredients from the same therapeutic category that have the same mechanism of action should not ordinarily be combined unless there is some advantage over the single ingredients in terms of enhanced effectiveness, safety, patient acceptance, or quality of formulation. However, these guidelines also state that such ingredients may be combined in selected circumstances to treat the same symptoms or conditions if the combination meets the OTC drug combination policy in all respects, the combination offers some advantage over the active ingredients used alone, and the combination is, on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose. Accordingly, based on the Panel's position concerning combinations containing two ingredients from the same pharmacologic group and the agency's general combination guidelines, the agency has placed these types of oral antitussive-antihistamine combinations in Category III.

44. One comment was opposed to the proposed restriction of OTC antitussive-antihistamine combinations to nonproductive cough when the underlying disease stimulating the cough is a cold. The comment stated that it was not aware of any "evidence that the combining of OTC doses of antitussives and antihistamines results in any negative effect on patients with productive cough due to a cold." The comment contended that consumer and clinical experience, including clinical studies reported to the Panel, provided evidence that the use of antitussive-antihistamine combinations for cough due to a cold are both safe and beneficial to the patient.

The agency does not agree with the comment that antitussive-antihistamine combinations should be allowed as a treatment for productive cough, i.e., cough associated with excessive phlegm, when the underlying disease stimulating the cough is a cold. Antitussives, as single ingredient products, have also been restricted to non-productive cough (i.e., cough that is not associated with excessive secretions) because cough suppression in certain diseases with productive cough may impair clearing of the airway (48 FR 48589). Antihistamines have a drying effect and may cause thickening of the secretions in the larynx, pharnyx, and lower respiratory tract. Retention of these secretions may also lead to the potentially harmful effect of airway obstruction (Ref. 1). A productive cough may be associated with a wide variety of diseases, ranging from a mild self-limiting disease to a very serious disease (Ref. 1). The symptoms of the common cold in its early stages are very similar to the early stages of diseases such as pneumonia, tuberculosis, pertussis, or measles, and are not readily distinguishable (Refs. 2, 3, and 4). It is not possible for the consumer to recognize the cause of a productive cough, and the agency believes that, in the interest of safety, a generalized warning against use of antitussives in cough accompanied by excessive phlegm (mucus) is warranted.

The Panel recommended the following warning in § 341.74(b)(2) for all products containing an antitussive: "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician." This warning (redesignated as § 341.74(c)(1)(i) in the antitussive tentative final monograph (48 FR 48594)) has been slightly revised for clarity to read as follows:

Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor.

References

(1) Calvert, J.C., "Cough Differential Diagnosis and Treatment," *Drug Intelligence and Clinical Pharmacy*, 10:640–650, 1976.

(2) Keefer, C.S., and R.W. Wilkins, editors, "Medicine-Essentials of Clinical Practice," Little, Brown and Co., Boston, pp. 103, 113, 125, and 127, 1970.

(3) Conn, H.F., and R.B. Conn, Jr., editors, "Current Diagnosis," W.B. Saunders Co., Philadelphia, pp. 116 and 180, 1974.

(4) Talso, P.J., and A.P. Remenchik, editors, "Internal Medicine Based on Mechanisms of Disease," C.V. Mosby Co., St. Louis, pp. 382 and 394, 1968.

45. One comment pointed out a discrepancy between the Panel's report and the Panel's recommended monograph regarding the combination of an oral bronchodilator and an antitussive. The comment stated that the Panel indicated in its report that a combination product containing an oral bronchodilator and an antitussive when labeled only for cough associated with asthma is a Category II combination because the antitussive suppresses cough, and the cough reflex is essential in asthma to maintain an open airway by clearing the respiratory passages of excessive secretions. However, such a combination was included as a Category I combination in § 341.40(f) and § 341.85(b) of the advance notice of proposed rulemaking.

The agency previously recognized this discrepancy and corrected it in the **Federal Register** of October 28, 1977 (42 FR 56756) by proposing to delete § 341.40(f) and § 341.85(b). Interested persons were invited to comment on this proposed deletion, but no comments were received. Therefore, the combination of an oral bronchodilator and an oral antitussive labeled for cough associated with asthma is classified as Category II and is not included in this tentative final monograph.

46. One comment disagreed with the Panel's recommendation that a combination containing an antitussive and an expectorant that is labeled for a productive cough be placed in Category III and requested that such a combination be classified in Category I. The comment agreed with what it contended was the Panel's concern that chronic bronchitic, asthmatic, and emphysematous patients not drown in their own secretions when taking such a combination, but argued that this is not a problem with OTC use of this combination. The comment claimed that: (1) OTC antitussives at their recommended dosages do not prevent physiological coughing, i.e., coughing to clear the airways of mucus, but merely reduce excessive irritative cough; (2) there is no evidence that increasing the volume of mucus in productive cough due to a cold by the action of an expectorant represents a hazard to a person with a cold; and (3) when the recommended use of the combination is for cough due to a cold, the great majority of the population desiring cough relief do not have bronchitis, asthma, or emphysema. The comment stated that there is a growing body of clinical acceptance that OTC antitussives reduce excessive irritative cough but not physiological coughing and therefore would not present a problem in patients with productive cough. It also stated that clinical studies of cough syrups containing antitussives and expectorants in patients with cough due to a cold have usually involved patients with productive and nonproductive cough indiscriminately, without evidence of lack of safety.

The Panel specifically stated that "additional studies are necessary to assess the combined effects of an antitussive and an expectorant in the presence of excessive or more fluid bronchial secretions" (41 FR 38328). Accordingly, the Panel concluded that an OTC cough-cold combination of an antitussive and an expectorant, when indicated for a productive cough, be classified in Category III. The agency agrees with the Panel's conclusion and does not consider the information contained in the comment sufficient to support a Category I classification for a combination of an oral antitussive and an expectorant. The comment failed to provide specific documentation, in the form of data from well-controlled clinical studies, to justify its claims. Without such data, the agency concludes that a combination containing an oral antitussive and an expectorant labeled for productive cough will not be reclassified to Category I and will remain in Category III.

47. One comment objected to the Panel's decision to place combination drug products containing ingredients from four different pharmacologic groups in Category III until a significant target population requiring such a combination was identified and argued that data were submitted to the Panel concerning the existence of such a population (Ref. 1). Another comment submitted new data from an unpublished epidemiological study (Ref. 2) conducted to comply with the Panel's recommendation that a significant target population be identified for an OTC four-ingredient combination drug product containing an analgesic-antipyretic, an antitussive, an antihistamine, and a nasal decongestant for treatment of concurrent cold symptoms (41 FR 38328). Six comments, noting that the Panel did not categorize a combination consisting of ingredients from three of the four pharmacologic groups, i.e., an analgesic-antipyretic, an antihistamine, and a nasal decongestant, requested that this three-ingredient combination be classified in Category I, based on submissions made for the combination containing ingredients from the four pharmacologic groups (Ref. 3).

The data referred to by the first comment included several literature references, a consumer research study, and a retrospective analysis of four clinical studies, none of which was originally conducted to determine the existence of the applicable target population. The Panel concluded that these data did not support the existence of a significant target population with concurrent cold symptoms of sufficient duration and severity to require a four-ingredient combination drug product.

The new data submitted by the second comment consisted of an epidemiological study conducted by seven investigators who followed a protocol consisting of a physical examination, including a nasal turbinate observation; a characterization of complaints; and a retrospective survey of subjects who had head colds and had been accepted for pharmacological assay experiments. The agency's analysis of the data indicated that the seven investigators identified a total of 695 patients, of whom 308, or 44.32 percent, had symptoms in all four treatment categories, i.e., (1) analgesic-antipyretic for pain, such as muscle ache and headache, and fever; (2) antitussive for wet or dry cough; (3) antihistamine for watery eyes, runny nose, and itchy nose; and (4) nasal decongestant for congestion. The retrospective survey confirmed the epidemiological study by identifying another large population of

individuals with symptoms in all four categories.

The agency accepts the results of the epidemiological study as evidence of the existence of a significant target population with concurrent cold symptoms of sufficient duration and severity to require a combination product containing an analgesic-antipyretic (as a single ingredient identified in § 343.10 or as a combination containing an analgesic-antipyretic identified in § 343.20 (a) or (b)(3), an oral antitussive, an antihistamine, and an oral nasal decongestant. Based on this evidence, the agency proposes to reclassify such a combination from Category III to Category I in this tentative final monograph.

Based on its evaluation of the data submitted for use of a combination product containing ingredients from the four pharmacological groups, the agency proposes to classify the following as Category I in this tentative final monograph: (1) a combination consisting of an analgesic-antipyretic (as a single ingredient or as a combination containing an analgesic-antipyretic as identified above), an oral antitussive, and an oral nasal decongestant and (2) a combination consisting of an oral antitussive and an analgesic-antipyretic (as a single ingredient or as a combination containing an analgesic-antipyretic as identified above). The agency's detailed comments and evaluation on the data are on file in the Dockets Management Branch (Refs. 4 and 5).

The labeling for the analgesic-antipyretic component of combination drug products containing cough-cold ingredients and analgesic-antipyretic ingredients may include indications for the "temporary relief of minor aches, pains, headache, muscular aches, and fever associated with the common cold." (See comment 61 below.) These indications, consistent with the symptoms reported in the epidemiological study (Ref. 2), are commonly found on currently marketed products and are also consistent with the intended use of a combination drug product containing cough-cold and analgesic-antipyretic ingredients.

References

(1) Comment No. C0111, Docket No. 76N-0052, Dockets Management Branch.

(2) Comment No. C0180, Docket No. 76N-0052, Dockets Management Branch.

(3) Comment Nos. C0109, C0110, C0134, C0144, C0161, C0188, Docket No. 76N-0052, Dockets Management Branch.

(4) Letter from W.E. Gilbertson, FDA, to G.F. Hoffnagle, Richardson-Vicks, Inc., coded LET077, Docket No. 76N-052G, Dockets Management Branch.

(5) Letter from W.E. Gilbertson, FDA, to B.M. Lanman, Bristol-Myers Products, Division of Bristol-Myers Co., coded LET078, Dockets No. 76N-052G, Dockets Management Branch.

48. One comment suggested that the list of ingredients deferred to the Advisory Review Panel on OTC Oral Cavity Drug Products (Oral Cavity Panel) (41 FR 38319) should be supplemented to include benzocaine. The comment pointed out that there are several currently marketed combination drug products containing benzocaine and an antitussive or a nasal decongestant and that such combinations have been classified as Category I by the Cough-Cold Panel (41 FR 38326).

Benzocaine was reviewed and included in the Oral Cavity Panel's report published in the **Federal Register** of May 25, 1982 (47 FR 22712). Benzocaine should have been listed at 41 FR 38319 with the other ingredients deferred by the Cough-Cold Panel to the Oral Cavity Panel, and the agency now corrects the omission.

49. One comment objected to the Panel's classification of phenobarbital 8 mg in Category III as a stimulant corrective to counteract the adverse central nervous system stimulant effects of drugs such as ephedrine in antiasthmatic preparations and requested Category I classification instead. The comment cited Goodman and Gilman (Ref. 1), as reflecting the experience of clinicians, to support its contention that there are sufficient data to permit final classification of phenobarbital as safe and effective for OTC use as a stimulant corrective. The comment presented the following medical arguments to justify the use of phenobarbital at a low dose to counteract the central nervous system stimulant effects of other drugs: (1) Barbiturates are respiratory depressants, (2) the hypoxic and chemical drives to respiration are decreased as the barbiturate dose increases, and (3) the medical treatment of asthma must provide for maximum breathing capacity and velocity of air movement, especially in the expiratory phase. In addition, the comment noted that the Panel used the term "sedative corrective" instead of "stimulant corrective" in its statement on the effectiveness of phenobarbital (41 FR 38418).

The agency has reviewed the Panel's recommendations on phenobarbital (41 FR 38417) and on combination products containing stimulant and sedative correctives (41 FR 38325), as well as the information provided in the comment. The agency has also reviewed the findings of the Pulmonary-Allergy Drugs Advisory Committee, which stated unanimously that there was no evidence that formulation with a barbiturate reduces the incidence of side effects caused by ephedrine-theophylline combinations (Ref. 2).

Sims, do Pico, and Reed (Ref. 3) reported in a recent double-blind, randomized, placebo-controlled study that phenobarbital 8 mg, in combination with theophylline 130 mg and ephedrine 25 mg, did not reduce the central nervous system stimulant side effects of tremor, nervousness, or nausea induced by theophylline or ephedrine. As the Panel noted, phenobarbital and other barbiturates are subject to abuse (41 FR 38417), phenobarbital is a potent hepatic microsomal enzyme-inducer which alters corticosteroid metabolism (prescription corticosteroid drugs are sometimes used in patients with bronchial asthma), and phenobarbital has a known enzyme-inducing effect with many other commonly used drugs (Refs. 4, 5, and 6).

As indicated in the comment, phenobarbital and the barbiturates have a respiratory depressant effect, which would be a specific hazard to a large segment of the population with diminished pulmonary function as a result of chronic obstructive pulmonary disease, and a possible hazard to individuals with other diseases.

These adverse effects could occur with the proposed adult oral dosage regimen of 8 to 16 mg of phenobarbital every 4 hours (41 FR 38418). The daily (24 hour) dose of phenobarbital could be as high as 96 mg. Lecamwasam et al. (Ref. 5), Landay et al. (Ref. 6), and Brooks et al. (Ref. 7) have reported significant effects of phenobarbital on the metabolism of other drugs when administered at a level of 90 mg daily. Thus, phenobarbital used at this dosage could create the potential for a significant incidence of adverse drug interactions by affecting the metabolism of many other commonly used drugs.

Goodman and Gilman (Ref. 1), whom the comment cited, state that "the central nervous system stimulant action of ephedrine tends to cause wakefulness and irritability, and a barbiturate is commonly given in addition." However, the "reference" in Goodman and Gilman does not provide any indication of a phenobarbital dosage for this purpose, nor does it indicate that phenobarbital should be used in combination with ephedrine or theophylline for self-medication. On the contrary, Goodman and Gilman state that barbiturates in

mixtures offer little advantage and that the physician should prescribe such drugs separately for concurrent use, adjusting doses to specific patient needs (Ref. 8). In fact, data show that phenobarbital 8 mg is not effective as a stimulant corrective in combination with ephedrine and theophylline (Ref. 2).

Based on its review of available data, the agency concludes that phenobarbital is not generally recognized as safe and effective for OTC use as a stimulant corrective in combination products with central nervous system stimulant drugs such as ephedrine or the theophyllines and is reclassifying phenobarbital 8 mg as a stimulant corrective from Category III to Category II.

Regarding the use of the term "sedative corrective" in the Panel's report at 41 FR 38325, the agency agrees with the comment that the term "stimulant corrective" should have been used.

References

(1) "The Pharmacological Basis of Therapeutics," 4th Ed., edited by L.S. Goodman and A. Gilman, The Macmillan Co., New York, p. 517, 1970.

(2) Minutes of the Pulmonary-Allergy Drugs Advisory Committee, December 6 and 7, 1979, p. 5, in OTC Volume 04GTFM, Docket No. 76N-052G, Dockets Management Branch.

(3) Sims, J.A., G.A. do Pico, and C.E. Reed, "Bronchodilating Effects of Oral Theophylline-Ephedrine Combination," *Journal of Allergy and Clinical Immunology*, 62:15–21, 1978.

(4) Thorn, G.W., et al., editors, "Harrison's Principles of Internal Medicine," 8th Ed., McGraw-Hill Book Co., New York, pp. 342–343, 1977.

(5) Lecamwasam, D.S., et al., "Effect of Phenobarbitone on Hepatic Drug-Metabolizing Enzymes and Urinary D-Glutaric Acid Excretion in Man," *British Journal of Clinical Pharmacology*, 2:257–262, 1975.

(6) Landay, R.A., et al., "Effect of Phenobarbital on Theophylline Disposition," *The Journal of Allergy and Clinical Immunology*, 62:27–29, 1978.

(7) Brooks, S.M., et al., "Adverse Effects of Phenobarbital on Corticosteroid Metabolism in Patients with Bronchial Asthmas," *New England Journal of Medicine*, 286:1125–1128, 1972.

(8) "The Pharmacological Basis of Therapeutics," 4th Ed., edited by L.S. Goodman and A. Gilman, The Macmillan Co., New York, pp. 112–113, 1970.

50. One comment indicated that "lethargy," a feeling of fatigue or tiredness, should have been included with the cold symptoms listed by the Panel at 41 FR 38320. The comment claimed that caffeine included in a cold preparation not containing an antihistamine would combat the lethargy that affects a significant target population of persons with cold symptoms. The comment recommended that, because of its stimulant action, caffeine at a dosage of 15 to 30 mg should be permitted in cold preparations to overcome symptoms of lethargy.

The agency agrees that lethargy may be a symptom which accompanies a cold. In the final monograph for OTC stimulant drug products, caffeine was included as a monograph drug for the indication "helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness" in a dose of 100 to 200 mg (53 FR 6105). The comment did not submit any data to support its suggested inclusion in a cough-cold combination of 15 to 30 mg (or a higher quantity) of caffeine to combat "lethargy" accompanying the common cold. Therefore, the agency is unable to accept the comment's request at this time.

51. One comment requested Category I classification for a combination product containing phenylephrine hydrochloride (a nasal decongestant) and methapyrilene hydrochloride (an antihistamine) in a nasal spray and submitted two clinical studies in support of its request (Ref. 1).

The Panel classified combination products containing a nasal decongestant and an antihistamine administered topically in a spray or drops in Category III. The Panel specified that additional studies are necessary to assess the contribution of an antihistamine administered by the topical route because there are inadequate studies demonstrating the effectiveness of topically applied antihistamines in such combinations (41 FR 38328). In the studies submitted by the comment, nasal sprays containing 0.125 percent methapyrilene hydrochloride alone, 0.50 percent phenylephrine hydrochloride alone, and 0.125 percent methapyrilene and 0.50 percent phenylephrine in combination were studied on a double-blind, parallel (non-crossover) basis in patients with allergic rhinitis (ragweed hay fever) and acute coryzal rhinitis. The agency's evaluation of the studies indicates that methapyrilene hydrochloride alone had no significant effect on the symptomatology of coryza or allergic rhinitis, and that there were no significant differences between phenylephrine alone and the combination of phenylephrine and methapyrilene in relieving the symptoms of coryza and allergic rhinitis.

In light of the finding by the National Cancer Institute that methapyrilene is a potent carcinogen in rats and therefore a potential carcinogen in man, manufacturers have voluntarily recalled all methapyrilene-containing products from the market, and FDA has withdrawn all NDA's for products containing methapyrilene. (See the preamble to the tentative final monograph for OTC antihistamine drug products published in the **Federal Register** of January 15, 1985; 50 FR 2200.) The agency has placed all OTC methapyrilene-containing drug products in Category II for safety, and the combination of phenylephrine hydrochloride and methapyrilene hydrochloride in a nasal spray or drops for OTC use will not be considered further in this document. However, the combination of a Category I antihistamine and a Category I nasal decongestant in a nasal spray or drops will remain in Category III until substantive data are submitted to demonstrate the effectiveness of such a combination.

Reference

(1) Comment COIII, Docket Number 76N-0052, Dockets Management Branch.

52. One comment objected to the reformulation of a specific cough-cold combination drug product, contending that the reformulated product is not "as effective as the one [FDA] forced to be taken off the market."

The combination product referred to in the comment was submitted to the Panel in October 1972 and at that time contained 1 mg chlorpheniramine maleate (an antihistamine), 5 mg phenylephrine hydrochloride (a nasal decongestant), 300 mg acetaminophen (an analgesic-antipyretic), and 30 mg caffeine (a stimulant) per tablet at an adult dosage of two tablets every 4 hours (Ref. 1). The presently marketed combination contains 2 mg chlorpheniramine maleate, 18.75 mg phenylpropanolamine (a nasal decongestant), and 325 mg acetaminophen per tablet at an adult dosage of two tablets every 4 hours. The reformulation of the combination product was probably due in part to the recommendations of the Panel, but was undertaken voluntarily by the manufacturer.

The Panel recommended 4 mg of chlorpheniramine as the minimum effective adult dose (41 FR 38384), and the agency adopted this dose in the tentative final monograph for OTC antihistamine drug products (50 FR 2217). The previous combination product formulation provided an adult dose of 2 mg chlorpheniramine in two tablets, only half the Panel's recommended effective dose. The new combination provides an effective adult dose of 4 mg chlorpheniramine in two tablets.

The previous combination also provided an oral adult dose of 10 mg phenylephrine hydrochloride as a nasal decongestant in two tablets. The new combination provides an adult dose of 37.5 mg phenylpropanolamine as a nasal decongestant in two tablets. Both the dose of phenylephrine in the previous combination and the dose of phenylpropanolamine in the new combination were found by the Panel to be effective as nasal decongestants. Therefore, the change in the nasal decongestant ingredients included in the combination would not appear to be based on the Panel's recommendations. After the Panel's report was published, FDA became aware of studies indicating that certain dosages of phenylpropanolamine may cause elevation of blood pressure. For this reason, the agency has decided to address the safety of phenylpropanolamine for nasal decongestant use in a future **Federal Register** publication. Therefore, phenylpropanolamine is not categorized in the nasal decongestant tentative final monograph. (See the **Federal Register** of January 15, 1985; 50 FR 2220.)

The previous combination provided an adult dose of 60 mg caffeine in two tablets, while the new combination does not contain caffeine. The Panel recognized that caffeine may be included in cough-cold products that contain antihistamines as a "stimulant corrective" (41 FR 38417), but did not find sufficient data to support the effectiveness of caffeine for this use and placed caffeine in Category III. (The agency notes that the Panel used the terms "stimulant corrective" in referring to caffeine; however, the term "sedative corrective" should have been used. The agency hereby makes the correction.) No further data have been submitted to the agency to demonstrate the effectiveness of caffeine as a "sedative corrective." Caffeine will, therefore, remain in Category III for this use.

The previous combination provided an adult dose of 600 mg acetaminophen in two tablets, while the new combination provides an adult dose of 650 mg acetaminophen in two tablets. The Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products recommended an adult dosage range of 325 to 650 mg acetaminophen as safe and effective in the advance notice of proposed rulemaking published in the **Federal Register** of July 8, 1977 (42 FR 35346) at 42 FR 35416. That Panel's recommendations would not require a change in the formulation of the combination.

The agency disagrees with the comment's contention that agency actions have resulted in a less effective cough-cold combination drug product. The key change in the formulation of the combination, based on the recommendations of the Cough-Cold Panel and the Internal Analgesic Panel, was an increase in the dose of chlorpheniramine to an effective dose (from 2 mg to 4 mg). Further changes in dosage or ingredients may be required when the final monograph for OTC cough-cold products is published depending on the outcome of the agency's review of data on the safety of phenylpropanolamine as a nasal decongestant. However, combinations of an antihistamine, an oral nasal decongestant, and an analgesic-antipyretic ingredient have been placed in Category I in this tentative final monograph. The agency believes that its decisions, which are based on the review of data, marketing experience, and the recommendations of experts regarding the safety and effectiveness of cough-cold drug products, will result in the marketing of only those OTC cough-cold drug products that are safe and effective.

Reference

(1) OTC Volume 040027.

53. One comment pointed out that a marketed combination drug product containing belladonna alkaloids (an anticholinergic), phenylpropanolamine hydrochloride (a nasal decongestant), and chlorpheniramine maleate (an antihistamine) was similar to a combination drug product that was deemed "irrational" by the AMA Council on Drugs, 1971. The comment expressed its concern about the safety of this combination drug product because of reported cases of urinary retention, dizziness, blurring of vision, etc. The comment stated that in short-term animal studies on this combination drug product the ingredients taken in combination "potentiated" the toxic effects of the individual ingredients. The comment objected to the Panel's report for permitting marketing of this combination drug product pending study and for not recommending study for "long term" effects.

The Panel did not specifically classify the combination product mentioned by the comment, i.e., an anticholinergic, a nasal decongestant, and an antihistamine. It did, however, classify combinations containing atropine, an anticholinergic drug that is a component of belladonna alkaloids, and an oral nasal decongestant as Category III, stating that the available safety data were insufficient to make a final determination and that additional studies were necessary to assess the potential additive central nervous system stimulant side effects (41 FR 38328). Similarly, the Panel classified combinations containing an antihistamine and an anticholinergic as Category III, stating that additional studies are necessary to assess the nature and extent of additive anticholinergic side effects (41 FR 38328).

Based on the Panel's classification of these combinations (atropine with an oral nasal decongestant, and an antihistamine with an anticholinergic), the combination of an anticholinergic, an oral nasal decongestant, and an antihistamine would satisfy the criteria for Category III combination drug products. However, because there are no monograph anticholinergic ingredients at this time, all OTC combination drug products containing an anticholinergic ingredient are considered Category II (nonmonograph) conditions. (See the final rule for OTC anticholinergic drug products published in the **Federal Register** of November 8, 1985; 50 FR 46582.)

The agency has evaluated the safety of this combination drug product by considering the safety of the individual active ingredients. The Panel recognized the problem of urinary retention associated with belladonna alkaloids and recommended that an appropriate warning "Do not take this product if you have * * * difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician" be included in the labeling of products containing this ingredient. The agency concurred at 47 FR 30009 in the tentative final monograph for OTC anticholinergic drug products and expectorant drug products published on July 9, 1982.

Sympathomimetic drugs such as phenylpropanolamine, a nasal decongestant, may also cause urinary retention problems, and the agency has proposed the following warning for nasal decongestant drugs at 50 FR 2227 in the tentative final monograph for OTC nasal decongestant drug products: "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." The labeling for combination drug products will include the applicable warning statements for the individual ingredients contained in the product. The warnings may be combined where appropriate to eliminate

repetition. Therefore, warnings will be adequately provided.

The Panel recognized blurring of vision and other side effects which can occur with the use of belladonna alkaloids and recommended in § 341.70(b)(2) that the labeling for products containing anticholinergics bear a warning that consumers should stop taking this product if any of these side effects occur. However, the Panel did not include dizziness as one of the side effects identified in this section. The agency previously recognized dizziness as a possible side effect of belladonna alkaloids and added "dizziness" to the warning statement in § 341.70(c)(2) in the tentative final monograph for OTC anticholinergic drug products and expectorant drug products (47 FR 30009). Because these specific warning statements will be required in the labeling for the combination drug product should it obtain monograph status, the agency believes that the concern expressed by the comment regarding safety has been adequately addressed.

The agency concludes that animal studies for long-term toxic effects as urged by the comment are not needed based on the Panel's evaluation of belladonna alkaloids (41 FR 38378). The Panel believed that it was not necessary to recommend such studies because belladonna alkaloids have been marketed and widely used for many years.

The Panel stated that, in determining the safety of a drug or combination of drugs, it considered both animal and human studies (41 FR 38335). Although animal studies were of interest, the Panel pointed out that they were seldom very helpful because it would have been unusual for a drug to reach the market without satisfactory animal safety data. The agency is unaware of any data generated by animal studies to support the comment's contention that ingredients such as belladonna alkaloids, phenylpropanolamine hydrochloride, and chlorpheniramine maleate when taken together in a combination product produced a potentiation of toxic effects. No new data were submitted by the comment.

The combination drug product discussed by the comment has been marketed OTC since 1961 with an approved NDA for safety. In 1980, the manufacturer reformulated the product to delete the anticholinergic ingredient. Therefore, there has been no need for regulatory action prior to publication of a final rule.

As mentioned above, the agency believes that the combination of an anticholinergic, an oral nasal decongestant, and an antihistamine satisfies the criteria for Category III combination drug products. However, because at this time, there are no Category I (monograph) anticholinergic ingredients in the final rule for OTC anticholinergic drug products (published in the **Federal Register** of November 8, 1985; 50 FR 46582), all combination drug products containing an anticholinergic ingredient are Category II (nonmonograph) and may not be shipped in interstate commerce after November 10, 1986, the effective date of the final rule for OTC anticholinergic drug products. Thus, in this tentative final monograph, the combination of an anticholinergic, an oral nasal decongestant, and an antihistamine; the combination of an antihistamine and an anticholinergic; and the combination of atropine and an oral nasal decongestant are being classified in Category II because all anticholinergic ingredients are nonmonograph. If, in the future, any ingredient is determined to be generally recognized as safe and effective as an OTC anticholinergic, and if adequate data support the safety and effectiveness of a combination of an anticholinergic, an oral nasal decongestant, and an antihistamine, or any of the other combinations mentioned above, such combinations may be proposed for inclusion in the final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products.

54. Several comments questioned the safety and effectiveness of bronchodilator drug products containing a combination of theophylline and ephedrine, and opposed the OTC availability of such combinations. The comments stated that the addition of ephedrine to theophylline results in synergistic toxicity without significant additive therapeutic effect, and that these combination products contain suboptimal dosages of theophylline. Another comment requested that a combination of a methylxanthine (theophylline) bronchodilator, a sympathomimetic (ephedrine) bronchodilator, and an expectorant be classified as Category I.

In the **Federal Register** of December 10, 1976 (41 FR 54032), the Commissioner disagreed with the Panel's recommendation to allow the use of theophylline as a single ingredient in OTC drug products and limited the use of theophylline as a single ingredient to prescription drug products. The Commissioner also advised that the use of theophylline, both as a single ingredient and in combination, in both prescription and OTC drug products, was undergoing extensive review in FDA.

In the tentative final and final monographs for OTC bronchodilator drug products, published in the **Federal Registers** of October 26, 1982 (47 FR 47520) and October 2, 1986 (51 FR 35338), respectively, the agency confirmed its earlier decision that theophylline as a single ingredient is Category II, i.e., nonmonograph, as an OTC bronchodilator. In this present document, the agency is proposing that combinations containing theophylline also be classified in Category II.

Currently marketed OTC combinations of theophylline and ephedrine usually contain theophylline (100 to 130 mg), ephedrine (24 mg), and either guaifenesin (100 mg), or phenobarbital (8 mg). Questions have been raised whether the low dose of theophylline in these combination products is therapeutically effective, and whether the addition of the ephedrine to theophylline increases the risk of central nervous system side effects without increasing the effectiveness of the product.

The agency has reviewed many studies on theophylline as a single ingredient and in combination with other ingredients. Weinberger and Bronsky (Refs. 1 and 2), Jenne (Ref. 3), and Piafsky and Ogilvie (Ref. 4) recommended dosage titration with serum level control to insure a safe and effective dose because of the wide individual response to orally administered theophylline. Piafsky and Ogilvie commented that effectiveness and toxicity are better correlated with plasma theophylline concentrations than with dosage. Frequently, toxic effects associated with elevated serum levels of theophylline are not preceded by minor adverse effects (Refs. 5, 6, and 7).

Sims et al. (Ref. 8) and Tinkelman and Avner (Ref. 9) reported evidence of an additive effect of the theophylline and ephedrine combination. Sims et al. reported that a single dose of the combination of ephedrine (25 mg) and theophylline (130 mg) produced a bronchodilator effect in patients with mild to moderate asthma, that the combination was more effective than either drug alone, and that the combination tended to cause slightly more side effects (tremor, nervousness, nausea), but found that these differences were not striking. The authors noted that, although a low dose of theophylline and a low dose of ephedrine produced a greater improvement, this result did not preclude the possibility that similar improvement could have been achieved with a larger dose of theophylline alone.

Tinkelman and Avner reported that ephedrine enhanced bronchodilation when added to the treatment of theophylline-titrated children, but noted that the improvement was not overwhelming. In addition, they reported that the prolonged administration of ephedrine did not cause either tolerance or toxicity during an 8-week study. Although no significant increase in adverse effects was observed, it should be noted that in this study, the ephedrine dose was independently administered and 40 percent less than if administered in fixed combination.

Riegelman et al. (Ref. 10) designed a study to determine whether plasma levels of theophylline in the range of 12 to 18 micrograms per milliliter (μ/mL) (i.e, plasma levels comparable to a high dose of theophylline) are necessary to obtain a satisfactory therapeutic effect, or whether a satisfactory therapeutic effect is obtained at a lower plasma theophylline range of 4 to 8 μ/mL (i.e., plasma levels comparable to a low dose of theophylline). The study was also designed to determine whether a beneficial additive effect is demonstrated with a combination of ephedrine, phenobarbital, and theophylline at a low dose (i.e., plasma concentration of theophylline of 4 to 8 μ/mL). In the study, plasma theophylline levels for each patient were calculated, and the exact amount of theophylline required to achieve low and high dose concentrations for each patient was determined. The results indicated that ephedrine has no beneficial additive effect in combination with theophylline, but that theophylline given at a low dose was associated with subjective and objective superiority (over no therapy) in 27 of the 28 patients that were studied. It should be noted that the range of dosage required to achieve the low plasma concentration was extremely wide and associated with only a variable degree of success in attaining the desired level. Accordingly, the study demonstrates the need for individual titration of theophylline.

On July 20 and 21, 1981, the FDA Pulmonary-Allergy Drugs Advisory Committee met to discuss the completed Riegelman study and the status of theophylline and ephedrine combination drug products. The Committee agreed that there is a lack of clinically documented evidence of an additive effect with the theophylline and ephedrine combination drug product (Ref. 11). On November 4, 1982, the Committee continued its discussion of theophylline and ephedrine combination drug products, reporting that there is a lack of adequate evidence of an additive or synergistic effect of theophylline and ephedrine in combination, that the combination of the two ingredients does not permit using a lower dosage of either ingredient to produce bronchodilation, that there is an increase in incidence of side effects from use of the combinations, and that it did not favor the continued OTC or prescription marketing of theophylline and ephedrine fixed combination drug products (Ref. 12).

Disadvantages of theophylline and ephedrine combination products have been reported by Weinberger and Bronsky (Refs. 1 and 2), who stated that there was no significant clinical benefit from using the combination product. They reported that ephedrine in combination with theophylline appeared to add little benefit to that of theophylline when the latter is provided in a dosage titrated for the individual patient. Moreover, the studies indicated that ephedrine increased the frequency of such side effects as insomnia, nervousness, and gastrointestinal complaints, suggesting toxicity. Jenne (Ref. 3) commented that theophylline and ephedrine combinations provide one-fourth to one-half the optimum dose of theophylline and less bronchodilation than the full theophylline regimen. Piafsky and Ogilvie (Ref. 4) reported that the use of the combination is not warranted because the theophylline dose should be individualized. They added that when theophylline therapy is unsatisfactory, other oral medications such as ephedrine may be added, but only small increases in efficacy and some increase in toxicity should be expected. Plummer (Ref. 5) noted the importance of monitoring serum theophylline levels and the inadequacy of the dose of theophylline in these combination drug products. Webb-Johnson and Andrews (Ref. 13) commented that ephedrine often produces side effects, and tolerance to its action develops. Rachelefsky et al. (Ref. 14) studied a sustained-release theophylline preparation (260 mg administered every 12 hours) and ephedrine (30 mg) and found that ephedrine did not add significantly to improvement in pulmonary function, nor did it influence serum theophylline levels.

Other investigators have studied theophylline in combination with other ingredients. Deutsch et al. (Ref. 15), demonstrated that a low dose of oral theophylline (130 mg) failed to produce acute bronchodilatation or to produce additive bronchodilatation when combined with terbutaline (2.5 mg), a potent long-acting beta-2 adrenergic stimulant used in the treatment of asthma. Cohen (Ref. 16) compared terbutaline tablets to a sustained-release combination tablet containing theophylline, ephedrine, and phenobarbital and concluded that, although terbutaline was effective, the combination of theophylline, ephedrine, and phenobarbital produced greater bronchodilation. Lyons et al. (Ref. 17) commented on the Weinberger and Bronsky data (Ref. 1), stating that mild-to-moderate asthmatics (as opposed to severe and chronic asthmatics) may benefit from the conventional doses found in theophylline and ephedrine combinations.

Piafsky and Ogilvie (Ref. 4) reported that phenobarbital added to a theophylline and ephedrine combination in the doses commonly used in these combination products does not effectively counteract the central nervous system effect of theophylline. Webb-Johnson and Andrews (Ref. 13) and Plummer (Ref. 5) reported that theophylline, ephedrine, and phenobarbital combinations should not be used because phenobarbital may cause respiratory depression, particularly if the patient is suffering from hypoxemia (deficient oxygen in the blood) and hypercarbia (excess carbon dioxide in the blood). As discussed in comment 49 above, combinations containing theophylline, ephedrine, and phenobarbital have been classified as Category II.

The agency believes there is insufficient evidence to support the use of theophylline and ephedrine combinations. Although several investigators (Refs. 8, 9, and 16) have found theophylline and ephedrine combinations to be beneficial, in one study ephedrine was added to the treatment of theophylline-titrated children (Ref. 9); in another study, although the theophylline dose was low, it was only a single dose study and, as noted by the investigator, did not preclude the possibility of similar improvement with a higher dose of theophylline given alone (Ref. 8); and in the third study, phenobarbital was included in the combination (Ref. 16).

The data that have been reviewed indicate that ephedrine adds little benefit to the theophylline and ephedrine combination when the theophylline is provided in a dosage that is titrated for the individual patient (Refs. 1 through 5). Additionally, a number of investigators have pointed out the need for individual titration of theophylline (Refs. 1 through 4, and 10). An increase in adverse effects has also

been associated with the use of theophylline and ephedrine combination drug products (Refs. 1, 2, 5, and 12). For several years, the agency has been reviewing the use of theophylline in both prescription and OTC drugs. In a Drug Efficacy Study Implementation (DESI) notice and Notice of Opportunity for Hearing (see the **Federal Register** of February 29, 1984; 49 FR 7454), the agency discussed the safety and effectiveness of certain combination drug products containing xanthine derivatives. FDA discussed new information in that notice and concluded that there is a lack of substantial evidence that each ingredient of the theophylline and ephedrine combination drug product makes a contribution to the claimed effects of the product. Moreover, as the Commissioner stated in the **Federal Register** of December 10, 1976 (41 FR 54032), careful titration based on measurement of theophylline serum levels is necessary. In the bronchodilator tentative final monograph (47 FR 47520), the agency reaffirmed its position that theophylline should be Category II and should not be available OTC as a single ingredient product because it is essential that a physician titrate theophylline dosage, based on individual patient measurements of theophylline serum levels. The agency believes that dosage titration is necessary whether theophylline is administered as a single ingredient or in combination with another drug. Therefore, the agency concludes that theophylline should be administered under professional supervision and is classifying any combination drug product containing theophylline as Category II in this tentative final monograph.

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(14) Rachelefsky, G.S., et al., "A Sustained Release Theophylline Preparation," *Annals of Allergy*, 40:252–257, 1978.

(15) Deutsch, R.I., et al., "Bronchodilator Effects of Low Doses of Oral Theophylline and Terbutaline in Asthmatic Subjects," *Annals of Allergy*, 45:137–143, 1980.

(16) Cohen, B.M., "The Cardiorespiratory Effects of Oral Terbutaline and an Ephedrine-Theophylline-Phenobarbital Combination: Comparison in Patients with Chronic Obstructive Ventilatory Disorders," *Annals of Allergy*, 40:233–239, 1978.

(17) Lyons, H.A., et al., "Theophylline and Ephedrine in Asthma," *Current Therapeutic Research*, 18:573–577, 1975.

55. One comment (Ref. 1) submitted new data from three controlled clinical studies on the combination of 1-desoxyephedrine and aromatics (camphor (54 mg), menthol (80 mg), methyl salicylate (11 mg), bornyl acetate (0.2 mg), and lavender oil (4 mg)) used as a topical nasal decongestant (administered by a nasal inhaler) (Refs. 2, 3, and 4). The comment requested Category I status for the combination based on these data, some of the data reviewed by the Panel (Refs. 5 and 6), and the manufacturer's marketing experience.

On the basis of the above data (Refs. 2 through 6) and an additional study (Ref. 7), the agency proposed Category I status for 1-desoxyephedrine as a single-ingredient topical nasal decongestant in the tentative final monograph for OTC nasal decongestant drug products (50 FR 2225). Four of these same studies also support the Category I classification of 1-desoxyephedrine combined with aromatics by showing that the combination of 1-desoxyephedrine and aromatics is superior to placebo, aromatics alone, and 1-desoxyephedrine alone (Refs. 2 through 6). The aromatic mixture when tested alone had little effect. The combination of 1-desoxyephedrine and the aromatic mixture did not cause rebound nasal congestion when inhaled every 2 hours six times daily for a 7-day period (Ref. 4).

Based on the data reviewed, the agency proposes to classify the 150 mg aromatic mixture in combination with 50 mg of 1-desoxyephedrine as a Category I topical nasal decongestant combination to be administered by a nasal inhaler. The agency is unaware of a marketed product containing the aromatic mixture alone and proposes to classify the aromatic mixture alone in Category II. This approach is consistent with paragraph 5 of the agency's "General Guidelines for OTC Drug Combination Products, September 1978" (cited above), which provides that "in some cases an ingredient may be appropriate for use only in a specific combination or data may be available only to support the use of the ingredient in combination but not as a single ingredient. In such cases the ingredient will be placed in Category I for use only in permissible combinations and not as a single ingredient." The studies indicate that the aromatic mixture enhances the effectiveness of the 1-desoxyephedrine.

The proposed adult dosage of the combination is two inhalations in each nostril not more often than every 2 hours from an inhaler that delivers in each 800 mL of air 0.04 to 0.15 mg of 1-desoxyephedrine. In keeping with the guidelines established by the Panel (41 FR 38333), the dosage for children 6 to under 12 years of age is one-half of the adult dosage. (See 41 FR 38328, paragraph C.10.i.). Because the results of one study showed that rebound congestion did not occur in 52 subjects who inhaled the combination of 50 mg of 1-desoxyephedrine and 150 mg of aromatic ingredients from an inhaler every 2 hours six times daily for a 7-day period (Ref. 4), the agency is proposing in this tentative final monograph that the use of the combination of 1-desoxyephedrine and aromatics as a topical nasal decongestant be limited to not more than 7 days instead of the 3-day limit for other topical nasal decongestants that cause rebound congestion.

The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Refs. 8 and 9).

References

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

(2) Connell, J. T., "Inhaler," (Study CRD 74–30), draft of unpublished study in Comment No. CO111, Docket No. 76N–0052, Dockets Management Branch.

(3) Connell, J. T., "Inhaler," (Study CRD 74–58), draft of unpublished study in Comment No. CO111 (Volume 4), Docket No. 76N–0052, Dockets Management Branch.

(4) Connell, J. T., "Nasomucosal Rebound Delta–P," (Study CRD 75–45), draft of unpublished study in Comment No. CO111, Docket No. 76N–0052, Dockets Management Branch.

(5) Turgeon, R. F., "Vick Inhaler," (Study CRD 70–24), draft of unpublished study in OTC Volume 040298.

(6) Memo to W. E. Burke, from E. B. Cohen, "Vick Inhaler: Vick Rhinorheometer Study—Maine Research" (supersedes Study CRD 70–24, dated February 11, 1971), in OTC Volume 040298.

(7) Connell, J. T., "Nasal Decongestant Delta-'P' Method," (Study CRD 74–10A), draft of unpublished study in Comment No. CO111, Docket No. 76N–0052, Dockets Management Branch.

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

(9) Letter from W. E. Gilbertson, FDA, to G. F. Hoffnagle, Richardson-Vicks, Inc., coded LET080, Docket No. 76N–052N, Dockets Management Branch.

56. One comment submitted data to support the reclassification of a combination of volatile substances, i.e, menthol, camphor, eucalyptus oil, thymol, oil of turpentine, cedarleaf oil, and myristica oil, in a petrolatum ointment from Category III to Category I as an antitussive for topical application to the chest. The data included statistical reevaluations of four citric acid aerosol induced cough studies reviewed by the Panel (Refs. 1, 2, and 3) (these statistical reevaluations were not available to the Panel for review), one study in chronic bronchitis that was originally reviewed by the Panel (Ref. 4), and one new study in patients with chronic cough (Ref. 5).

Four of the studies show that the combination of menthol, camphor, eucalyptus oil, thymol, oil of turpentine, cedarleaf oil, and myristica oil applied to the chest as an ointment in a petrolatum base is more effective in reducing coughs than each individual ingredient in the combination when tested separately (Refs. 1, 3, and 4). The antitussive effect lasted for up to 2.5 hours. The data provide no evidence that the individual ingredients thymol, oil of turpentine, cedarleaf oil, or myristica oil have a statistical advantage over the petrolatum control. Study CRD 74–19/B supports the effectiveness of 1.3 percent eucalyptus oil (Ref. 1), and study CRD 74–64 shows that 1.3 percent eucalyptus oil tended to produce a lower cough count than did the petrolatum control (Ref. 4). Study CRD 75–40 provides evidence that the combination of 2.6 percent menthol, 4.7 percent camphor, and 1.2 percent eucalyptus oil in a petrolatum base is more effective in reducing coughs than a combination of 0.38 percent cedarleaf oil, 0.485 percent myristica oil, 0.076 percent thymol, and 4.5 percent oil of turpentine in a petrolatum base (Ref. 2). At various time points, the combination of menthol, camphor, eucalyptus oil, thymol, oil of turpentine, cedarleaf oil, and myristica oil in a petrolatum base was more effective in reducing the number of coughs as compared to the other formulations. All formulations were more effective than the petrolatum alone.

Based on the data, the agency concludes that there is sufficient evidence to place the combination of menthol, camphor, and eucalyptus oil in a suitable ointment vehicle in Category I as an antitussive. Concentrations of 4.7 to 5.3 percent camphor and 2.6 to 2.8 percent menthol, as single antitussive ingredients, have previously been proposed for Category I for use in a suitable ointment vehicle (48 FR 48594). Eucalyptus oil as a single ingredient currently remains in Category III as an antitussive drug (48 FR 48583). While studies CRD 74–19/B and 74–64 are not sufficient to reclassify eucalyptus oil in Category I, the studies do indicate that eucalyptus oil makes a contribution to the effectiveness of the combination product. The Panel concluded that study CRD 74–19/B is supportive but does not provide sufficient evidence of the claimed antitussive effectiveness of eucalyptus oil as a single active ingredient in an ointment.

Thymol (0.1 percent) and oil of turpentine (4 percent) were reviewed by the Panel and placed in Category III as antitussives because additional effectiveness data were needed. The data that have been reviewed thus far by the agency do not show that thymol and oil of turpentine are effective antitussives, nor do the data adequately show the contribution of thymol and oil of turpentine to the effectiveness of the combination product. Based on the concentrations of these ingredients in the product, the agency considers thymol to be an inactive ingredient; however, the oil of turpentine would not be considered an inactive ingredient. Although cedarleaf oil and myristica oil were tested, the agency also considers these ingredients to be inactive ingredients.

Although this combination product contains more than two antitussive active ingredients from the same pharmacologic group (i.e., menthol, camphor, and eucalyptus oil), paragraph 3 of the agency's "General Guidelines for OTC Drug Combination Products" (cited above) permits such a combination " * * * if the combination offers some advantage over the active ingredients used alone, and the combination is, on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose." Eucalyptus oil may be included in the combination based on paragraph 5 of the agency's "General Guidelines," which states that "in some cases an ingredient may be appropriate for use only in a specific combination or data may be available only to support the use of the ingredient in combination but not as a single ingredient. In such cases the ingredient will be placed in Category I for use only in permissible combinations and not as a single ingredient."

Based on the above guidelines, the agency proposes that the combination containing menthol (2.6 to 2.8 percent), camphor (4.7 to 5.3), and eucalyptus oil (1.2 to 1.3 percent) in a suitable ointment vehicle be classified as a Category I topical antitussive combination drug product.

The labeling that is proposed for menthol and camphor in § 341.74 of the final monograph for antitussive drug products will also be proposed for the combination of menthol, camphor, and eucalyptus oil. (See 52 FR 30055.)

The agency's detailed comments on the data are on file in the Dockets Management Branch (Ref. 6).

References

(1) Cash, W., and K. Martin, "Recalculation of Significance Levels (P-values) for the VapoRub CAA Studies CRD No. 74–19/A and 74–19/B—Dr. Packman," in Comment No. CR0004, Docket No. 76N–0052, Dockets Management Branch.

(2) Cash, W., and K. Martin, "Recalculation of Significance Levels (P-values) for the VapoRub CAA Study CRD No. 75–40—Dr. Packman," in Comment No. CR0004, Docket No. 76N–0052, Dockets Management Branch.

(3) Cash, W., and K. Martin, "Recalculation of Significance Levels (P-values) for the VapoRub CAA Study CRD No. 74–52–Dr. Packman," in Comment No. CR0004, Docket No. 76N–0052, Dockets Management Branch.

(4) Dennis, S.R.K., et al., "A Study for the Measurement of the Antitussive Effects of Vicks VapoRub Compared to Eucalyptus Oil and Compared to Placebo in Stabilized Patients with Chronic Cough," (Study CRD 74–64), draft of unpublished study in OTC Volume 040060A, Docket No. 76N–0052, Dockets Management Branch.

(5) Dennis, S.R.K., P. Bass, and G. doPico, "VapoRub," (Study CRD 76–41), draft of unpublished study in Comment No. SUP008, Docket No. 76N–0052, Dockets Management Branch.

(6) Letter from W.E. Gilbertson, FDA, to G.F. Hoffnagle, Richardson-Vicks, Inc., coded LET079, Docket No. 76N-052G, Dockets Management Branch.

57. Two comments requested reclassification of a combination of eucalyptus oil and menthol from Category III to Category I as an antitussive in lozenge form. One comment contended that the written submissions and oral presentations to the Panel included adequate data to support a Category I classification of lozenge products containing this combination for antitussive use. The other comment submitted data from additional studies to show the effectiveness of a combination of not less than 5 mg eucalyptus oil and menthol for topical use as an antitussive in lozenge form.

In the final monograph for OTC antitussive drug products (52 FR 30055), menthol (5 to 10 mg) as a single ingredient has been classified as a monograph condition when used in a lozenge or compressed tablet dosage form, and eucalyptus oil as a single ingredient in a lozenge dosage form has been classified as a nonmonograph condition.

The agency has reviewed the data submitted to the Panel and concurs with its conclusion that a combination of eucalyptus oil and menthol for topical use as an antitussive in lozenge form is appropriately classified in Category III.

The agency has also reviewed the additional data and concludes that they are insufficient to support the reclassification from Category III to Category I of a combination of menthol and not less than 5 mg eucalyptus oil for topical use in lozenge form. In two studies (Refs. 1 and 2), the following were compared to a control lozenge containing only the candy base and to a lactose capsule placebo: A 9.3 mg menthol lozenge (study CRD 77-58) and a combination product containing 5.27 mg menthol and 0.6 mg eucalyptus oil (CRD 78-19). Although the studies indicate the antitussive effectiveness of the lozenges, the data are not supportive of eucalyptus oil because no comparisons to eucalyptus oil as a single ingredient were made.

Study CRD 76-49R, a single-blind crossover study, was conducted in subjects with artificially induced cough to compare the antitussive effectiveness of a combination product containing 8.8 mg menthol and 6 mg eucalyptus oil, with 9.8 mg menthol alone, 5.7 mg eucalyptus oil alone, and a vehicle control, all in a lozenge dosage form. Although this study is supportive of the effectiveness of eucalyptus oil as an antitussive, the agency did not find any evidence that eucalyptus oil contributes to the effectiveness of the combination lozenge. The menthol lozenge produced numerically greater reductions in cough counts at all three challenge times and overall ($P < .05$) than did the combination lozenge (Ref. 3).

Study CRD 75-26, a single-blind crossover study, was conducted in patients with chronic cough due to bronchopulmonary disease to compare the antitussive effectiveness of a combination product containing 7.5 mg menthol and 5.4 mg eucalyptus oil with a 7.5 mg menthol lozenge, a 5.1 mg eucalyptus oil lozenge, and a control lozenge. There were no significant differences among these four treatments in reducing cough counts. Thus, this study does not demonstrate that eucalyptus oil contributes to the antitussive effectiveness of menthol in a combination product (Ref. 4).

Study CRD 76-43, a single-blind parallel study, was conducted in patients with chronic cough due to bronchopulmonary disease to compare the antitussive effectiveness of a combination product containing menthol and eucalyptus oil, a menthol lozenge, a eucalyptus oil lozenge, and a control lozenge (Ref. 5). A significant reduction in overall cough counts was reported for these four treatments ($P < .05$). However, comparisons of pairs of tested lozenges did not show any significance; for example, menthol compared to the combination product or the control compared to the combination product. The agency concludes that, in addition to the lack of difference shown between eucalyptus oil and the control, the results obtained with the combination lozenge were virtually the same as those obtained with the menthol lozenge.

The agency concludes that the data from studies CRD 76-49R, CRD 75-26, and CRD 76-43 do not demonstrate that eucalyptus oil contributed to the antitussive effectiveness of the combination lozenge because the combination lozenge did not reduce cough counts in subjects more significantly than did the menthol lozenge alone. Therefore, the agency proposes to classify the combination of menthol and eucalyptus oil in a lozenge form as Category III in this tentative final monograph.

The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (Refs. 6 and 7).

References

(1) Finkel, S., and S. Zuckerman, "Victors," (Study CRD 77-58), draft of unpublished study in Comment No. SUP009, Docket No. 76N-0052, Dockets Management Branch.

(2) Finkel, S., and S. Zuckerman, "Vicks Medicated Cough Drops," (Study CRD 78-19), draft of unpublished study in Comment No. SUP009, Docket No. 76N-0052, Dockets Management Branch.

(3) Packman, E.W., "Victors Cough Drops," (Study CRD 76-49R), draft of unpublished study in Comment No. SUP009, Docket No. 76N-0052, Dockets Management Branch.

(4) Dennis, S.R.K., P. Bass, and G. doPico, "Victors Squares," (Study CRD 75-26), draft of unpublished study in Comment No. SUP009, Docket No. 76N-0052, Dockets Management Branch.

(5) Dennis, S.R.K., P. Bass, and G. doPico, "Victors," (Study CRD 76-43), draft of unpublished study in Comment No. SUP009, Docket No. 76N-0052, Dockets Management Branch.

(6) Letter from W.E. Gilbertson, FDA, to G.F. Hoffnagle, Vicks Health Care Division of Richardson-Merrell, Inc., coded ANS 81/01/29 to SUP009, Docket No. 76N-0052, Dockets Management Branch.

(7) Letter from W.E. Gilbertson, FDA, to G.F. Hoffnagle, Richardson-Vicks Inc., coded LET080, Docket No. 76N-052G, Dockets Management Branch.

58. One comment requested that a combination of menthol, camphor, eucalyptus oil, tincture of benzoin, and polyoxyethylene dodecanol (wetting agent) be classified in Category I for use as an antitussive in a steam vaporizer. The comment stated that the Panel reviewed studies on this combination drug product and indicated that the studies show a statistically significant reduction in cough counts compared to steam alone, even beyond the duration of exposure to the vapors (41 FR 38350). However, because the Panel was concerned only with individual drugs, the comment assumed that the Panel felt it inappropriate to place this combination in Category I. The comment added that the combination of menthol, camphor, eucalyptus oil, tincture of benzoin, and polyoxyethylene dodecanol should be in Category I because the safety of the product is not in question and because the route of administration (inhalation of vapors) and the ratio of ingredients is the same for this combination product as for the antitussive combination of menthol, camphor, and eucalyptus oil in an ointment that the agency has classified in Category I. In support of the effectiveness of this combination drug product, the comment cited and summarized a number of studies that were reviewed by the Panel (Ref. 1).

The agency has reviewed the data and concludes that they are insufficient to support a Category I classification of menthol, camphor, eucalyptus oil, tincture of benzoin, and polyoxyethylene dodecanol as antitussives in a steam vaporizer.

The data consist of three citric acid aerosol induced cough studies and eleven active disease state studies (Refs. 2 through 15).

The citric acid aerosol studies had the same objective and design. Each study involved 24 normal volunteers who were divided equally into three groups and given two treatment regimens (medicated and non-medicated steam) in cross-over fashion. The objective was to evaluate the efficacy of the combination drug product in reducing the frequency of cough induced by citric acid aerosol challenge. The results of the citric acid aerosol induced cough studies (CRD 68–49, CRD 72–26, and CRD 71–32) are equivocal (Refs. 2, 3, and 4). The sponsor's own conclusions indicate that only in study CRD 68–49 (phase two) was there any difference between medicated and unmedicated steam. Additionally, the number of coughs recorded after exposure to unmedicated steam was greater than the number reported at baseline, prompting the sponsor's comment that the differences between treatments "may be attributable to position bias because the 1 hour runs were done first." The results of study CRD 72–26 indicate that both treatments (medicated and unmedicated) were effective, but when compared to each other, the differences (favoring medicated steam) were only apparent at the 30 minute evaluation point. The sponsor's statement that the differences between treatments was only apparent at the 30 minute challenge time needs clarification because only Group I subjects (8 subjects) were challenged at that time. In study CRD 71–37, the sponsor states that there were no differences between regimens at any observation point and both treatments appeared effective. However, the sponsor's statistician notes that the overall values (3 way analysis of variance) favor unmedicated steam primarily due to its superiority at 4½ hours.

The agency does not consider the disease state studies adequate to demonstrate the effectiveness of the combination of ingredients contained in the product (Refs. 5 through 15). Objective cough counting was not employed in any of the studies. Study CRD 71–51 was the only study in which superiority of medicated over nonmedicated steam was reported to exist. There were no accompanying data for analysis to confirm this claim and the study design requires a comparison of values which were not included with the submitted material. In the published Larkin study, it was reported that treatment with medicated steam and polyoxyethylene dodecanol resulted in fewer coughs; however, the study was uncontrolled and subjective (Ref. 6). In the other studies, no differences in cough reduction were observed.

In reference to the Panel's statement on page 38350 of its report that two of the citric acid aerosol challenge studies provided statistically significant reductions in cough counts compared to steam alone, even beyond the duration of exposure to the vapors, the agency has found that the Panel's statement is inconsistent with the results of those studies. The agency also notes that although the combination drug product contains menthol, camphor, eucalyptus oil, tincture of benzoin, and polyoxyethylene dodecanol, and although the combination of menthol, camphor, and eucalyptus oil in an ointment as an antitussive has been proposed for Category I, tincture of benzoin and polyoxyethylene dodecanol have not been individually tested. Thus, the submitted studies cannot be used in support of the effectiveness of the combination of menthol, camphor, eucalyptus oil, tincture of benzoin, and polyoxyethylene dodecanol. The data generated from the studies using menthol, camphor, and eucalyptus oil as antitussives in an ointment also cannot be used as support for the effectiveness of the combination of menthol, camphor, and eucalyptus oil as antitussives in a steam vaporizer because the superiority of steam with aromatics over unmedicated steam has not been established. When aromatics are added to water in a vaporizer which generates steam, the superiority of medicated steam over unmedicated steam requires substantiation.

Camphor and menthol individually are monograph drugs for steam inhalation use for antitussive claims (see the **Federal Register** of August 12, 1987 (52 FR 30042)). Therefore, further effectiveness data are not needed for these ingredients. In order for the combination of camphor and menthol to be placed in Category I, data are needed that establish that the combination has some advantage over the single ingredients (see comment 37 above). If other active ingredients, such as eucalyptus oil, tincture of benzoin, or polyoxyethylene dodecanol are included, any additional ingredient must be tested alone versus placebo (steam) to demonstrate a therapeutic effect, and the entire combination must be tested versus unmedicated steam. The agency recognizes that steam is not a placebo since it has a recognized benefit, but for the proposed type of product formulation, there is no known suitable control; thus, steam appears to be the only viable alternative. The Panel classified tincture of benzoin as a Category III expectorant (as a steam inhalant). If tincture of benzoin is to be considered as an expectorant in the product, the objective measurements of sputum volume and sputum viscosity should be done and correlated with subjective evaluations. Polyoxyethylene dodecanol, a surfactant, is listed as an active ingredient in the labeling of the combination product. If this ingredient is intended as active, its enhancing of the effect of steam in reducing coughs, as claimed in the comment's submission, must be demonstrated. For a combination product containing menthol, camphor, and eucalyptus oil as antitussives, and tincture of benzoin as an expectorant, objective cough counting, sputum volume, and viscosity measurements should be performed. The studies should be conducted in patients with cough due to respiratory disease.

The agency also notes that ingredients that might indirectly relieve cough (and for which there may be no measurable antitussive activity) may actually have other pharmacologic effects such as expectorant or nasal decongestant action. In the Litchfield study (Ref. 14), there was improvement in relief of symptoms of nasal congestion with medicated steam and no differences were found for coughs. The Panel provided for a Category III classification of combination products containing several claimed active ingredients which are mixtures of volatile substances with overlapping pharmacologic activities for which a minimum effective dosage cannot be established for one or more of the ingredients when tested alone. The Panel recommended a testing procedure for such combinations and suggested that the drug effect should demonstrate a 10 percent or greater difference from placebo (41 FR 38328).

In conclusion, the data on the combination of menthol, camphor, eucalyptus oil, tincture of benzoin, and polyoxyethylene dodecanol as antitussives for use in a steam vaporizer remain inadequate and, therefore, this combination is classified in Category III for this use.

The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (Ref. 16).

References

(1) Comment No. LET065, Docket No. 76N–052G, Dockets Management Branch.

(2) Packman, E.W., "Vaposteam," (Study CRD 68–49), draft of unpublished data, OTC Volume 040266, Dockets Management Branch.

(3) Packman, E.W., "Vaposteam," (Study CRD 72–26), draft of unpublished data, OTC Volume 040266, Dockets Management Branch.
(4) Packman, E.W., "Vaposteam," (Study CRD 71–37), draft of unpublished data, OTC Volume 040266, Dockets Management Branch.
(5) Carter, V.H., "Vaposteam," (Study CRD 71–51), draft of unpublished data, OTC Volume 040267, Dockets Management Branch.
(6) Larkin, V.D., "Polyoxyethylene Dodecanol Vaporization in the Treatment of Respiratory Infections of Infants and Children," *New York State Journal of Medicine*, 57:2667–2672, 1957.
(7) Larkin, V.D., "Broad Clinical," draft of unpublished data, OTC Volume 040267, Dockets Management Branch.
(8) Amler, A.B., "Broad Clinical," draft of unpublished data, OTC Volume 040267, Dockets Management Branch.
(9) Mund, A., "Broad Clinical," draft of unpublished data, OTC Volume 040267, Dockets Management Branch.
(10) Goodall, R.E., "Broad Clinical," draft of unpublished data, OTC Volume 040267, Dockets Management Branch.
(11) Berman, M., "Broad Clinical," draft of unpublished data, OTC Volume 040267, Dockets Management Branch.
(12) Singer, A., "Broad Clinical," draft of unpublished data, OTC Volume 040267, Dockets Management Branch.
(13) Williams, H.J., "Broad Clinical," draft of unpublished data, OTC Volume 040267, Dockets Management Branch.
(14) Litchfield, H.R., "Vaposteam, (Commercial Product)," draft of unpublished data, OTC Volume 040267, Dockets Management Branch.
(15) Ghadimi, H., "Vaposteam," (Study CRD 70–34), draft of unpublished data, OTC Volume 040267, Dockets Management Branch.
(16) Letter from W.E. Gilbertson, FDA to G.F. Hoffnagle, Richardson-Vicks, Inc., coded ANS, Docket No. 76N–052G, Dockets Management Branch.

59. One comment stated that a combination of volatile aromatic oils, i.e., menthol, camphor, eucalyptus oil, thymol, cedar leaf oil, and nutmeg oil have been historically combined in a number of products for the relief of symptoms of the common cold and have gained consumer acceptance (Ref. 1). The comment considered this combination of volatile oils as a single active ingredient rather than as a list of aromatics as single drug entities. The comment stated that well-controlled studies supporting the nasal decongestant effectiveness of the mixture of aromatics and a study on the individual aromatics are contained in the OTC volumes that were submitted to the Panel. The comment added that these studies are in keeping with the Panel's criterion that such products are mixtures of volatile substances with overlapping pharmacologic activities for which a minimum effective dosage cannot be established for one or more of the ingredients when tested alone (41 FR 38328). The comment urged FDA to consider such combinations of aromatic oils a special situation with regard to drug combinations.

The agency has reviewed the information cited by the comment and notes that the Panel specifically addressed the studies on combinations of aromatic oils as nasal decongestants referred to by the comment. The Panel pointed out that varying degrees of decongestion were noted with use of the combination product but that there were no well-controlled studies conducted on the individual ingredients to demonstrate their effectiveness as nasal decongestants (41 FR 38406–38414). Therefore, the Panel placed these ingredients in Category III. The Panel also reviewed a draft of an unpublished study by T. C. Grubb, entitled "The Nasal Decongestant Effect of Aromatic Substances" (41 FR 38407–38409). In this study, which was not placebo-controlled or double-blinded, a number of aromatic ingredients were individually tested. The ingredients were inhaled from an apparatus containing a cotton wick that was impregnated with the aromatic substance. The test was not conducted in the same manner that the product would actually be used. The Panel did not, nor does the agency, consider this study adequate to demonstrate the nasal decongestant effect of the individual aromatic ingredients. The comment did not submit any new data to support the nasal decongestant effectiveness of the individual ingredients or the combination product.

The Panel proposed a Category III classification for combination drug products containing several claimed active ingredients which are mixtures of volatile substances with overlapping pharmacologic activities for which a minimum effective dosage cannot be established for one or more of the ingredients when tested alone (41 FR 38328). The agency does not believe that the entire combination of aromatic ingredients in an ointment or steam vaporizer formulation should be considered to be this type of combination. The "antitussive" effectiveness of a combination of menthol, camphor, eucalyptus oil, thymol, oil of turpentine, cedar leaf oil, and myristica (nutmeg) oil is discussed in this document (see comment 56 above). The combination of menthol, camphor, and eucalyptus oil in a suitable ointment vehicle is proposed as a Category I combination for use as a topical antitussive. Thymol, cedarleaf oil, and myristica oil were considered inactive ingredients, based on their concentrations in the combination product; however, oil of turpentine was not considered an inactive ingredient. A final decision on oil of turpentine depends on its status in the final monograph or on any position on inactive ingredients that the agency may take in the future.

The agency points out that the combination of aromatics for antitussive use was not considered as a "single active ingredient." Data on the aromatic ingredients were reviewed and demonstrated the antitussive effectiveness of menthol and camphor individually (as well as in combination with other aromatic ingredients), and the supportive contribution of eucalyptus oil. Likewise, in order to achieve Category I status for the combination of aromatic ingredients as nasal decongestants, the individual ingredients must be tested to show that they do provide a significant nasal decongestant effect when compared to a control. Additionally, in accordance with the agency's "General Guidelines for OTC Drug Combination Products, September 1978" cited above, Category I ingredients from the same therapeutic category that have the same mechanism of action may be combined in selected circumstances to treat the same symptoms or conditions if the combination meets the OTC combination drug policy in all respects, the combination offers some advantage over the active ingredients used alone, and the combination is, on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose.

In conclusion, the agency agrees with the Panel that the data for the combination of menthol, camphor, eucalyptus oil, thymol, cedar leaf oil, and nutmeg oil as nasal decongestants for application as an ointment or for steam inhalation are inadequate and, therefore, the combination is classified as Category III.

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

References

(1) Comment No. LET083, Docket No. 76N–052G, Dockets Management Branch.
(2) Letter from W.E. Gilbertson, FDA to G.F. Hoffnagle, Richardson-Vicks, Inc., coded LET084, Docket No. 76N–052G, Dockets Management Branch.

I. Comments on Dosages for OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Combination Drug Products

60. Two comments pointed out a number of problems in combining an oral nasal decongestant with an analgesic-antipyretic because of what they described as "irreconcilable"

dosage schedules recommended by the Cough-Cold and the Internal Analgesic Panels. The comments stated that this situation existed because the Cough-Cold Panel had recommended fixed single dosages for the nasal decongestants phenylephrine and phenylpropanolamine for children 2 to under 6 years and 6 to under 12 years of age, and the Internal Analgesic Panel (in the draft of its report available at the time the Cough-Cold Panel's report was published) was recommending dosages for children 2 to under 4 years, 4 to under 7 years, 7 to under 9 years, 9 to under 11 years, and 11 to under 12 years of age.

In order to combine an oral nasal decongestant with an analgesic-antipyretic for use in children 2 to under 12 years of age, the Cough-Cold Panel's two fixed single dosages for children 2 to under 6 and 6 to under 12 years of age would have to be expanded to include an intermediate dosage for children 4 to under 6 years of age, or a dosage range would have to be allowed. For this reason, one comment proposed increasing the 12.5 mg-every-4-hour dosage of phenylpropanolamine recommended by the Panel for children 6 to under 12 years of age to 12.5 to 25 mg every 4 hours (or 25 mg every 8 hours), and increasing the dosage of 6.25 mg every 4 hours recommended by the Panel for children 2 to under 6 years of age to 6.25 to 12.5 mg every 4 hours (or 12.5 mg every 8 hours). The second comment recommended a dosage for phenylephrine every 4 hours of 2.5 mg for children 2 to under 4 years of age; 3.75 mg for children 4 to under 7 years of age; and 5 mg for children 7 to 9 years of age. This proposal would increase the 2.5 mg dosage of phenylephrine recommended by the Panel for children 4 and 5 years of age to 3.75 mg, and decrease the 5 mg dosage of phenylephrine recommended by the Panel for children 6 years of age to 3.75 mg.

As for the first comment's suggested dosage for phenylpropanolamine of 25 mg every 8 hours for children 6 to 12 years of age, and 12.5 mg every 8 hours for children 2 to under 6 years of age, the agency published a notice concerning the Panel's recommendation on the dosages of phenylpropanolamine in the **Federal Register** on October 28, 1977 (42 FR 56756). The notice stated that the adult dosage of 50 mg every 8 hours and equivalent children's dosages were provided only for timed-release dosage forms which would not be included in the monograph. Therefore, the Panel's recommended monograph was corrected to include only the dosages for conventional, immediate-release formulations. The reference to a dosage of 50 mg every 8 hours and equivalent children's dosages was deleted from the Panel's recommendations by the October 28, 1977 notice.

Because of studies indicating that certain dosages of phenylpropanolamine can cause elevations in blood pressure, the agency has not categorized phenylpropanolamine as a nasal decongestant in the tentative final monograph for OTC nasal decongestant drug products (50 FR 2220), but will, instead, address the safety of phenylpropanolamine for weight control use and nasal decongestant use in a future **Federal Register** publication. Before there can be any resolution of the "irreconcilable" dosage issue concerning combinations containing phenylpropanolamine preparations, the safety and effectiveness issues that have been raised must be addressed.

The agency recognizes that a problem of irreconcilable dosages would also occur with combinations containing an analgesic-antipyretic with pseudoephedrine, a Category I oral nasal decongestant, if the dosages are not changed. In the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products (to be published in a future issue of the **Federal Register**), the agency will propose that the minimal effective dose of 325 mg of aspirin, acetaminophen, and sodium salicylate for children 6 to 9 years of age can also be used as the minimal effective dose for children over 9 years of age (i.e., 9 to under 12). Because of the extension of the 325-mg minimal effective dose of aspirin, acetaminophen, and sodium salicylate to children over 9 years of age, combinations of an analgesic-antipyretic with pseudoephedrine are possible for children 6 to under 12 years of age with no changes in the Cough-Cold Panel's recommended dosages. Combinations are also possible for children 2 to under 4 years of age based on the Cough-Cold Panel's recommended dosages. However, no dosage formulation of the combination product could be used for children 4 to under 6 years of age because, in one case, if the analgesic is given at the recommended dosage, then the pseudoephedrine dosage would be too high for this age group, and in the other case, if pseudoephedrine is given at the recommended dosage, then the analgesic dosage would be too low. A similar situation exists for combination products containing phenylephrine hydrochloride and an analgesic-antipyretic, i.e., the recommended dosages could be used for children 2 to under 4 and 6 to under 12 years of age, but there would be a problem of irreconcilable dosages for children 4 to under 6 years of age.

The agency is not modifying the dosages for oral nasal decongestants at this time, but is inviting comments from interested persons on the problem of currently irreconcilable dosages for these combination products. The agency invites comments and the submission of data on dosage ranges for children for products containing oral phenylephrine, or pseudoephedrine for use in combination with analgesics, or for any other cough-cold ingredients for which there might be a problem concerning irreconcilable dosages when combined with analgesics. Other comments have been received in response to the tentative final monograph for OTC antihistamine (50 FR 2200), antitussive (48 FR 48576), and nasal decongestant (50 FR 2220) drug products, requesting that the agency revise pediatric dosages for combination drug products containing ingredients in these pharmacologic classes including when these ingredients are combined with internal analgesic-antipyretic ingredients. Because several rulemakings are affected by this issue, the agency has published a separate document discussing pediatric dosages for OTC cough-cold drug products and deferred all issues regarding pediatric dosages to that document. (See the **Federal Register** of June 20, 1988; 53 FR 23180.) Any amendments to currently proposed tentative final monographs will be addressed at that time.

J. Comments on Labeling for OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Combination Drug Products

61. One comment objected to the Panel's recommendation "that combination products must be labeled to reflect all of the proven pharmacologic activities of each active ingredient in the combination" (41 FR 38325). The comment pointed out that such labeling would conflict with the Panel's recommendation that labeling include only those indications that are for concurrent symptoms. The comment stated that labeling that includes use of the product for a nonconcurrent symptom would confuse consumers and possibly encourage them to use a combination drug product when a single-ingredient product would suffice. The comment also objected to the Internal Analgesic Panel's recommendation that the labeling of

such combination products emphasize use of the product only when all such symptoms are present (42 FR 35370). The comment maintained that such labeling would be confusing and that a product containing an analgesic-antipyretic ingredient should not be avoided because a single symptom of only pain or fever is present rather than both symptoms. To clarify the apparent inconsistency in both the Panels' recommendations, the comment requested that the phrase "consistent with the recommended use of the product" be added to the Cough-Cold Panel's statement concerning the inclusion of all proven pharmacologic activities in the labeling of a drug product and that the phrase in § 343.20(d) (1), (2), (3), and (4) of the advance notice of proposed rulemaking for OTC internal analgesic drug products that states "* * * the product is labeled for the concurrent symptoms involved * * *" be replaced by the following statement: "The product must be labeled to reflect all of the proven pharmacological activities of the active ingredient(s) consistent with the recommended use of the product."

A second comment contended that drug products should be labeled with all the pharmacologic activities of a drug. The comment maintained that knowing all the activities of a drug causes consumers less confusion and is less expensive because there are times when a single drug can be used to relieve several symptoms. Thus, the consumer can avoid spending twice the money for two products when one product would suffice.

The agency notes there is no legal restriction that prevents "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. 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 in addition to the labeling requirements for OTC drugs in Subpart C of 21 CFR Part 201. Because of the labeling requirements and the need to provide information that is not confusing to consumers, the agency invites manufacturers to consult with FDA before labeling their products with multi-use labeling.

In the case of an OTC drug product that contains an ingredient with different pharmacologic actions that can treat related symptoms, those pharmacologic actions that are consistent with the intended use of the product appropriately may appear in the labeling but are not required to appear. Diphenhydramine hydrochloride is an example of such a drug. If diphenhydramine hydrochloride were reclassified as a Category I antitussive in the final monograph, a drug product containing diphenhydramine hydrochloride for the treatment of symptoms associated with the common cold could be labeled both as an antihistamine and an antitussive because these actions are consistent with the intended use of the product. However, if a manufacturer chose to promote only one of the pharmacologic actions of diphenhydramine (e.g., its antitussive action), the product would not be required to be labeled as both an antihistamine and an antitussive. In such a case, because the product is intended only for use as an antitussive, only information on the use of the drug as an antitussive need be included in the labeling.

Diphenhydramine hydrochloride also has another pharmacologic action (i.e., causes drowsiness) that allows it to be marketed OTC as a nighttime sleep-aid. For cough-cold combination drug products, the use of multi-use labeling is limited because it is unlikely that a specific combination of ingredients, e.g., an antihistamine-antitussive-internal analgesic combination (which relieves cold symptoms such as runny nose, sneezing, cough, and fever) could also be used to relieve other symptoms not related to the common cold, e.g., nighttime sleep-aid. Further, if combinations are labeled with multi-use labeling, all of the labeled uses must be indications that are consistent with Category I combinations. There are currently no Category I combinations involving cough-cold ingredients and nighttime sleep-aid ingredients.

The agency believes that the labeling for OTC analgesic-antipyretic and cough-cold ingredient combination drug products should reflect the principal intended use(s) of the product (e.g., pain reliever-fever reducer and nasal decongestant.) Such labeling must be consistent with the approved indications for all of the ingredients but should not necessarily contain all of the indications, particularly those indications that are not consistent with the concurrent use of the ingredients in the combination product.

In adopting an indications statement for an analgesic-antipyretic active ingredient with the indications statement(s) for the possible cough-cold active ingredients it could be combined with (e.g., an antihistamine, an antitussive), the agency has determined that an appropriate indications statement for the analgesic-antipyretic ingredient of a cough-cold product would be "For the temporary relief of minor aches, pains, headache, muscular aches, and fever associated with" (select one of the following: "the common cold" or "a cold") which would then be followed by the appropriate indication(s) for the cough-cold ingredient(s).

The agency recognizes that products containing an analgesic-antipyretic combined with an antihistamine, or a nasal decongestant, or both, may also be marketed for use in a target population that has hay fever/allergic rhinitis or sinusitis symptoms, but not cold symptoms. The agency has determined that an appropriate indications statement for the analgesic-antipyretic ingredient for such products would be "For the temporary relief of minor aches, pains, and headache" (followed by the labeling for antihistamines in § 341.72(b)(1) and/or the labeling for nasal decongestants in § 341.80(b)(1) (ii) or (iii), as appropriate).

Therefore, in § 341.85(b)(1) of this tentative final monograph, the agency is proposing that all permitted combinations of analgesic-antipyretic and cough-cold active ingredients, identified in § 341.40 that are marketed and labeled for relief of cough-cold symptoms must bear the following indications statement: "For the temporary relief of minor aches, pains, headache, muscular aches, and fever associated with the common cold" (followed by the appropriate indication(s) for the cough-cold active ingredient(s)). In addition, permitted combinations containing an analgesic-antipyretic and an antihistamine identified in § 341.40(a); an analgesic-antipyretic, an antihistamine, and an oral nasal decongestant identified in § 341.40(c); and an analgesic-antipyretic and an oral nasal decongestant identified in § 341.40(n) may also bear this indication. However, for products which are promoted for use in individuals with hay fever/allergic rhinitis or sinusitis symptoms, the following indications statement in § 341.85(b)(2) should be used: "For the temporary relief of minor aches, pains, and headache," (followed by the labeling for antihistamines in § 341.72(b)(1) and/or the labeling for nasal decongestants in § 341.80(b)(1) (ii) or (iii), as appropriate). Products which are promoted for relief of cough-cold symptoms in addition to hay fever/allergic rhinitis and/or sinusitis

symptoms must include both labeling statements in § 341.85(b) (1) and (2).

In conclusion, the agency believes that combination drug products may contain only those active ingredients that treat concurrent symptoms consistent with the intended use of the product. The agency finds it unnecessary to adopt the comment's suggestion that product labeling should be "consistent with the recommended use of the product," because the proposed labeling for combination products ensures that each component of the combination product conforms to the intended use of the product. The agency does not agree with the comment that the product must be labeled to reflect *all* of the proven pharmacological activities of the active ingredient(s) consistent with the recommended use of the product. There is no agency requirement that an OTC drug product be labeled with all of the proven pharmacological activities of its active ingredients. On the other hand, there is no regulation that prohibits multi-use labeling, i.e., the labeling of products to reflect all of the proven pharmacologic activities of its active ingredients. However, for combination drug products to be labeled with multi-use labeling, all of the labeled uses must be for Category I combinations. The OTC drug monographs provide the acceptable labeling of the product for OTC use, and the agency believes that the labeling proposed for combination products in this tentative final monograph adequately describes for consumers the appropriate concurrent symptoms for which the product is to be used.

62. One comment stated that warnings for combination products containing ingredients from several different pharmacologic groups should be consolidated in order to decrease the number of different statements that would be required for such products. Another comment requested that provision be made for combining indications for combination products containing ingredients from several different pharmacologic groups so that the resulting statement of indications is clear and understandable.

The agency agrees with the comments. For combination products that contain ingredients from several different pharmacologic groups, manufacturers may combine warnings, indications, and directions, respectively, to eliminate duplicative words or phrases so that the resulting information is clear and understandable. To clarify how this can be done, the agency is proposing a paragraph in the labeling section (§ 341.85) for permitted combinations in this tentative final monograph which states that indications, warnings, and directions, respectively, applicable to each active ingredient in the combination drug product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable. For example, the warning for an antihistamine in proposed § 341.72(c)(2) (50 FR 2216) "Do not take this product if you have asthma, glaucoma, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor," and the warning for an oral nasal decongestant in proposed § 341.80(c)(1)(i)(*c*) (50 FR 2239) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor" may be combined for an antihistamine-nasal decongestant combination product as follows: "Do not take this product if you have asthma, glaucoma, heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

In reviewing the warnings for different ingredients that could be present in possible combination products, the agency has determined that a conflict exists between the warning proposed for oral nasal decongestants (labeled for adult use) in § 341.80(c)(1)(b) that states: "Do not take this product for more than 7 days. If symptoms do not improve or are accompanied by fever, consult a doctor," and the warning to be proposed in a future issue of the **Federal Register** for internal analgesic ingredients (adult dosages) in § 343.50(c) that will state not to take this product for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor; and if pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition. A similar conflict exists between the warning proposed for oral nasal decongestants (labeled for children under 12 years of age) in § 341.80(d)(ii)(b) and the warning to be proposed for internal analgesic ingredients (children's dosages) in § 343.50(c)(2), which will limit the use of an internal analgesic for pain in children to 5 days. Because of the conflict between the respective warnings, the agency is proposing that the following specific warning be used for combinations containing an analgesic-antipyretic ingredient(s) and an oral nasal decongestant ingredient identified in § 341.40 (c), (f), (k), and (n) when labeled for adult use: "Do not take this product for more than 10 days. If symptoms do not improve or are accompanied by fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor."

The agency is also proposing the following warning for this combination when labeled for children 2 years to under 12 years of age, "Do not give this product to children for more than 5 days. If symptoms do not improve or are accompanied by fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor." The agency is further proposing a warning for this combination product when labeled for both adults and children 2 years of age to under 12 years of age: "Do not take this product for more than 10 days (for adults) or 5 days (for children). If symptoms do not improve or are accompanied by fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor."

An incompatibility also exists between the analgesic-antipyretic warnings discussed above and the warning for antitussives in § 341.74(c)(1) "A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by fever, rash, or persistent headache, consult a doctor" (52 FR 30056). The agency is proposing that the following warning be used for combination drug products containing an antitussive and an analgesic-antipyretic ingredient(s) identified in § 341.40 (f) and (k) when labeled for adult use: "Do not take this product for more than 10 days. A persistent cough may be a sign of a serious condition. If cough persists for more than 7 days, tends to recur, or is accompanied by rash, persistent headache, fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor." The combined warning for children reads as follows: "Do not give this product to children for more than 5 days. A persistent cough may be sign of a serious condition. If cough persists for more than 7 days, tends to recur, or is accompanied by rash, persistent headache, fever that last for more than 3 days, or if new symptoms occur, consult a doctor." For products labeled for both adults and children, the proposed combined warning reads as follows: "Do not take this product for more than 10 days (for adults) or 5 days (for children). A persistent cough may be sign of a serious condition. If cough persists for more than 7 days, tends to recur, or is accompanied by rash, persistent

headache, fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor."

The warning proposed for expectorants in § 341.78(c)(3) in the tentative final monograph for OTC expectorant drug products "A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by fever, rash, or persistent headache, consult a doctor," also conflicts with the warning for analgesic-antipyretics discussed above. The combined warnings to be used for combinations containing an expectorant and an analgesic-antipyretic ingredient(s) identified in § 341.40(m) when labeled for adults and/or children are the same warnings proposed above for combinations of an antitussive and an analgesic-antipyretic ingredient(s). The warnings for specific cough-cold combination drug products which differ from the warnings required for the individual ingredients are included in § 341.85(d) in this tentative final monograph.

The agency has also identified conflicts in that portion of the directions that deal with the lower age limits of use for children's dosages for some of the combinations identified in § 341.40. For example, the directions for an OTC antihistamine advises that a doctor be consulted for use in children under 6 years of age, while OTC analgesic-antipyretic ingredients may be given to a child as young as 2 years of age without consulting a doctor. The agency is concerned that when a combination product containing analgesic-antipyretic and cough-cold ingredients is labeled for use in children of a particular age group that each individual ingredient be generally recognized as safe for use in that particular age group. Therefore, the agency is proposing that when there is a difference in the directions established for the individual ingredients in a combination drug product, e.g., when the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph. Thus, in the above example, the product can be labeled only for use in children 6 years of age and over.

63. One comment disagreed with the Panel's classification of the word "multiaction" as a claim having no scientific foundation or meaning, or as being meaningless to the consumer as a labeling claim for cough-cold products (41 FR 38337). In the comment's opinion, this term is meaningful in a labeling claim for a combination product recommended for the relief of more than one symptom because such a product would have multiple actions and the term "multiaction" would indicate to the consumer a need to consider these actions. Therefore, the comment contended that it is inconsistent "to prohibit the use of one of the clearest, most direct words available to describe the product's potential" to the consumer. In view of this, the comment recommended that the word "multiaction" not be rejected as a term to be used in labeling claims for combination cough-cold products.

The word "multiaction" is not sufficiently specific to be included in the "statement of identity" or "indications" portions of the labeling required for OTC drug products. However, the agency has no objection to use of this word as a general, descriptive term in the labeling of drug products that combine ingredients from different therapeutic categories. Considering that the specific identity and use(s) of the drug product are spelled out in the statement of identity and indications, the word "multiaction" used elsewhere in the labeling would not be misleading and should be available to manufacturers as a matter of choice. Although this term does not appear in this tentative final monograph, the agency has no objection to its use in other portions of the labeling that are not regulated by the monograph.

64. A number of comments objected to the warning recommended by the Panel in § 341.85(d) for combination products containing aspirin: "This product contains aspirin and should not be taken by individuals who are sensitive to aspirin." Several of the comments stated that the warning was redundant and unnecessary because the listing of the active ingredients on the label suffices to disclose the presence of aspirin. Another comment stated that the labeling for aspirin should be addressed as part of the internal analgesic monograph and not in the cough-cold monograph. Two of the comments suggested that the word "allergic" be used instead of "sensitive" because the latter is misleading and the Panel intended to use the term "allergic."

The agency agrees that the labeling for aspirin should be addressed in the internal analgesic monograph and, therefore, is not addressing the specific requests stated by the comments in this document. The agency's conclusions on aspirin labeling will be stated as part of the rulemaking for OTC internal analgesic drug products. For these reasons, the Panel's recommendation in § 341.85(d) is not being included in this tentative final monograph.

The agency points out, however, that combination products containing cough-cold ingredients plus internal analgesic ingredients would need to conform to both monographs.

In addition, combination products that have aspirin or aspirin-containing drugs as the internal analgesic ingredient must bear the Reye syndrome warning in accord with 21 CFR 201.314(h) (1) through (4). The regulation also states that OTC drug products covered by the regulation and labeled solely for use by children (pediatric products) shall not recommend the product for use in treating flu or chicken pox. In the **Federal Register** of June 9, 1988 (53 FR 21633), the agency published a final rule making this Reye syndrome labeling provision permanent. Therefore, even though this tentative final monograph is only a proposed rule, any currently marketed cough-cold combination product that contains aspirin or an aspirin-containing ingredient must bear the appropriate Reye's syndrome labeling in accord with 21 CFR 201.314(h).

65. One comment expressed concern that products recommended by the Panel in § 341.40 (a), (c), (j), (m), and (o) containing cough-cold ingredients in combination with analgesic-antipyretic ingredients or local anesthetic ingredients might require reformulation and relabeling more than once. The comment explained that this could happen if the a cough-cold monograph became final before the other applicable monograph(s). Thus, cough-cold combinations containing internal analgesic ingredients such as aspirin might have to be reformulated and relabeled to comply with the subsequent internal analgesic final monograph. To avoid this, the comment proposed that the effective date for reformulation and relabeling of combination products containing ingredients from more than one monograph should be the effective date of the last applicable final monograph.

The agency's policy is that an OTC drug product, whether single ingredient or combination, must conform to an applicable monograph on the effective date of the final monograph. Thus, the cough-cold component of a combination product described above would have to meet all of the requirements of the cough-cold monograph upon its effective date. The agency acknowledges that a combination product containing ingredients covered by different monographs might require reformulation

and relabeling more than once. However, the comment's suggested approach could result in the continued marketing of an ingredient of questionable safety or an ingredient not proven effective (nonmonograph condition) past the effective date of an applicable final monograph, or the failure to include required labeling on the product, only because the ingredient was included in a combination product with another ingredient covered by a monograph that had yet to take effect. Therefore, the comment's proposal is not accepted.

66. One comment pointed out "an apparent contradiction in the labeling requirements for a bronchodilator combined with an expectorant." The Panel's recommended warning for bronchodilator-expectorant combinations in § 341.85(c) states "This product should be used only for cough associated with asthma" (41 FR 38423). The comment noted, however, that the following warning is included in the labeling requirements for expectorant drug products in § 341.78(b)(2): "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema or where cough is accompanied by excessive secretions except under the advice and supervision of a physician" (41 FR 38422). The comment requested that the word "asthma" be deleted from the Panel's recommended warning in § 341.78(b)(2) to resolve an apparent inconsistency concerning the use of the combination by asthmatics that would result from placing both label warnings {§§ 341.85(c) and 341.78(b)(2)} on the combination product.

The inclusion of the word "asthma" in the warning in § 341.78(b)(2) does not conflict with the warning for bronchodilator-expectorant combinations in § 341.85(c). The Panel's inclusion of the word "asthma" in its warning in § 341.78(b)(2) only emphasizes that products containing expectorants, even in combination with a bronchodilator, should not be used in patients with asthma "unless directed by a doctor." This is consistent with the Panel's recommended warning for bronchodilators in § 341.76(b)(1) that states "Do not take this product unless a diagnosis of asthma has been made by a physician." In addition, the agency agrees with the Panel that cough-cold drug products which contain an expectorant but do not contain a bronchodilator should not be available OTC for use by consumers with asthma except as directed by a doctor. Therefore, the agency does not agree that the word "asthma" should be deleted from the warning recommended by the Panel in § 341.78(b)(2).

However, after reviewing all of the warnings proposed for bronchodilator drug products (47 FR 47527), the agency concludes that the Panel's recommended warning in § 341.85(c) "This product should be used only for cough associated with asthma," in addition to the agency's proposed warning in § 341.76(b)(1) "Do not take this product unless a diagnosis of asthma has been made by a physician," is unnecessarily repetitious. Therefore, the warning recommended by the Panel in § 341.85(c) is not being proposed in this tentative final monograph.

K. Comments on Testing Guidelines for OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Combination Drug Products

67. Several comments disagreed with the Panel's testing procedures for Category III combination products. One comment stated that the Panel had omitted a criterion for the testing of some combinations containing ingredients with overlapping pharmacologic activities, e.g., an antihistamine and an anticholinergic. The comment submitted a proposed criterion and testing procedure for such combinations.

As noted in comment 29 above, tentative final and final monographs will no longer contain recommended testing guidelines. Therefore, comments regarding Category III testing guidelines will not be addressed in this document. However, the agency will meet with industry representatives at their request to develop testing guidelines for those conditions which industry is interested in upgrading, and to advise industry on the adequacy of proposed protocols. (See also part II. paragraph A.2. below—*Testing of Category II and Category III conditions.*)

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

A. Summary of Combinations Categorizations and Testing of Category II and Category III Conditions

1. *Summary of combinations categorizations.* The agency has reviewed all claimed active ingredients and combinations submitted to the Panel, as well as other data and information available at this time, and is proposing the recategorization of eight combinations, i.e., the combination of an analgesic-antipyretic(s), an oral antitussive, an oral nasal decongestant, and an antihistamine; the combination of an antihistamine (if the antihistamine is also a Category I antitussive) and an oral antitussive; the combination of an oral antitussive (if the antitussive is also a Category I antihistamine) and an antihistamine; the combination of theophylline and a sympathomimetic bronchodilator; combinations containing more than two active ingredients from the same pharmacologic group; combinations containing phenobarbital and any central nervous system stimulant cold, cough, allergy, bronchodilator, or antiasthmatic ingredient(s); the combination of 1-desoxyephedrine and aromatics in a inhaler as a topical nasal decongestant; and the combination of menthol, camphor, and eucalyptus oil in an ointment as a topical antitussive. The agency is proposing the classification of seven combinations that were not classified by the Panel, i.e., the combination of an analgesic-antipyretic(s), an oral antitussive, and an oral nasal decongestant; the combination of an oral antitussive and an analgesic-antipyretic(s); the combination of an analgesic-antipyretic(s) and an expectorant; the combination of an oral nasal decongestant, an oral antitussive, and an anesthetic/analgesic in a solid dosage form; the combination of an anticholinergic, an antihistamine, and an oral nasal decongestant; combinations containing caffeine (to combat lethargy) and cough-cold preparations not containing antihistamines; and the combination of phenylpropanolamine, ephedrine, and caffeine. In addition, the agency is proposing the classification of the following fourteen combinations containing cough-cold and oral health care active ingredients that were not classified by either the Cough-Cold or Oral Cavity Panels: a debriding agent/oral wound cleanser and an oral antitussive; a debriding agent/oral wound cleanser and an antihistamine; an astringent and an oral antitussive; an astringent and an antihistamine; an oral antitussive and an oral demulcent; an oral nasal decongestant and an oral demulcent; an oral nasal decongestant, an oral antitussive, and an oral demulcent; an expectorant and an oral anesthetic/analgesic; an expectorant and an oral demulcent; an antihistamine and an oral anesthetic/analgesic; an antihistamine and an oral demulcent; an oral antitussive or an oral nasal decongestant, an oral anesthetic/analgesic, and an oral demulcent; and an oral nasal decongestant, an oral antitussive, an oral anesthetic/analgesic, and an oral demulcent. The last ten of these combinations are for products in a solid dosage form to be dissolved in the mouth and swallowed.

For the convenience of the reader, the following table is included as a summary of the categorizations by the Panel and the proposed classification by the agency.

The combination drug products that are listed below are intended for oral use unless otherwise stated. Because antitussives, bronchodilators, and nasal decongestants may be administered orally or topically, the agency is identifying these drugs as oral or topical for clarity.

Cough-cold combinations	Panel	Agency
Analgesic-antipyretic(s) and antihistamine	I	I
Analgesic-antipyretic(s) and oral antitussive	[1] N.C.	I
Analgesic-antipyretic(s) and expectorant	N.C.	I
Analgesic-antipyretic(s) and oral nasal decongestant	I	I
Analgesic-antipyretic(s) and oral nasal decongestant and antihistamine	I	I
Analgesic-antipyretic(s) and oral antitussive and oral nasal decongestant	N.C.	I
Analgesic-antipyretic(s) and oral antitussive and oral nasal decongestant and antihistamine	III	I
Antihistamine and oral antitussive (if labeled "May cause market drowsiness")	I	I
Antihistamine and oral nasal decongestant	I	I
Antihistamine and oral antitussive and oral nasal decongestant	I	I
Oral antitussive and expectorant (if labeled for nonproductive cough)	I	I
Oral antitussive and oral nasal decongestant	I	I
Oral antitussive and expectorant and oral nasal decongestant (if labeled for nonproductive cough)	I	I
Oral antitussive and anesthetic/analgesic (if available only in a solid dosage form)	I	I
Oral bronchodilator and expectorant (if labeled for cough associated with asthma)	I	I
Expectorant and oral nasal decongestant	I	I
Oral nasal decongestant and oral anesthetic/analgesic (if available in a solid dosage form)	I	I
Oral nasal decongestant and oral antitussive and oral anesthetic/analgesic (if available in a solid dosage form)	N.C.	I
Oral antitussive and oral demulcent (if available in a solid dosage form)	N.C.	I
Oral nasal decongestant and oral demulcent (if available in a solid dosage form)	N.C.	I
Oral nasal decongestant and oral antitussive and oral demulcent (if available in a solid dosage form)	N.C.	I
Oral antitussive and oral anesthetic/analgesic and oral demulcent (if available in a solid dosage form)	N.C.	I
Oral nasal decongestant and oral anesthetic/analgesic and oral demulcent (if available in a solid dosage form)	N.C.	I
Oral nasal decongestant and oral antitussive and oral anesthetic/analgesic and oral demulcent (if available in a solid dosage form)	N.C.	I
Oral antitussive and debriding agent/oral wound cleanser	N.C.	II
Antihistamine and debriding agent/oral wound cleanser	N.C.	II
Oral antitussive and astringent	N.C.	II
Antihistamine and astringent	N.C.	II
Analgesic-antipyretic(s) and oral bronchodilator	II	II
Anticholinergic and expectorant	II	II
Antihistamine and expectorant	II	II
Antihistamine (if antihistamine is also a Category I antitussive) and oral antitussive	II	III
Oral antitussive (if antitussive is also a Category I antihistamine) and antihistamine	II	III
Oral bronchodilator and anticholinergic	II	II
Oral bronchodilator and antihistamine	II	II
Oral bronchodilator and oral antitussive (if labeled for cough associated with asthma)	II	II
Theophylline and sympathomimetic bronchodilator (e.g., ephedrine)	I	II
Antihistamine and anticholinergic	III	[2] II
Antihistamine and oral anesthetic/analgesic	N.C.	III
Antihistamine and oral demulcent	N.C.	III
Expectorant and oral anesthetic/analgesic	N.C.	III
Expectorant and oral demulcent	N.C.	III
Antihistamine and nasal decongestant (administered topically as spray or drops)	III	III
Oral antitussive and bronchodilator used as an antitussive (if labeled for cough not associated with asthma)	III	III
Oral antitussive and expectorant (if labeled for productive cough)	III	III
Oral antitussive and expectorant and oral nasal decongestant (if labeled for productive cough)	III	III
Analgesic-antipyretic(s) and oral antitussive and expectorant and oral nasal decongestant	III	III
Anticholinergic and antihistamine and oral nasal decongestant	N.C.	[2] II
Atropine and oral nasal decongestant	III	[2] II
Expectorant and oral bronchodilator used as an antitussive (if labeled for cough not associated with asthma)	III	III
Combinations containing Category I ingredients from different pharmacologic groups if any ingredient is at less than the minimum effective dosage (unless the ingredient(s) are being used to treat the same symptom).	II	II
Combinations containing 2 or more ingredients at less than the minimum effective dosage and used to treat the same symptom (labeling claim) (even if it contains Category I ingredients from different pharmacologic groups).	III	III
Combinations containing more than 2 active ingredients from the same pharmacologic group	II	III
Combinations containing an antihistamine for the relief of symptoms of allergic rhinitis and an additional antihistamine which is added exclusively for sedation, and the product contains labeling which represents the additional antihistamine as a sleep-aid.	II	II
Combinations containing an antihistamine with a sleep-aid claim	III	III
Combinations containing a Category III ingredient or labeling and no Category II ingredient or labeling	III	III
Combinations containing 2 Category I ingredients from the same pharmacologic group	III	III
Combinations containing 2 Category I ingredients from the same pharmacologic group if either or both ingredients are at less than the minimum effective dosage.	III	III
Combinations containing a corrective (an active ingredient specifically intended to counteract a side effect of other ingredients in the product), e.g., caffeine, and any cold, cough, allergy, bronchodilator, or antiasthmatic ingredient(s) (except for the combination immediately below).	III	III
Combinations containing phenobarbital (8 mg) (as a stimulant corrective) and any central nervous system stimulant cold, cough, allergy, bronchodilator, or antiasthmatic ingredient(s) such as theophylline and ephedrine.	III	II
Combinations containing several claimed active ingredients which are mixtures of volatile substances with overlapping pharmacologic activities for which a minimum effective dosage cannot be established for one or more of the ingredients when tested alone (except for the combination immediately below).	III	III
1-Desoxyephedrine and aromatics (camphor, menthol, methyl salicylate, bornyl acetate, and lavender oil) in an inhaler as a topical nasal decongestant.	III	I
Combinations containing 4 or more ingredients from different pharmacologic groups (except for the combination of an analgesic-antipyretic and oral antitussive and oral nasal decongestant and antihistamine described above).	III	III

Cough-cold combinations	Panel	Agency
Combinations containing a stimulant, e.g., caffeine (at a fully effective level), and any cold, cough, allergy, bronchodilator, or antiasthmatic ingredient(s).	II	II
Combinations containing caffeine (15–30 mg) to combat lethargy (not as a sedative corrective) and cold preparations not containing antihistamines.	N.C.	II
Combinations containing vitamin C and cold, cough, allergy, bronchodilator, or antiasthmatic ingredient(s) for prevention or treatment of the common cold.	III	III
Combinations containing any vitamins with labeling claims for prevention or treatment of the common cold	II	II
Phenylpropanolamine and ephedrine and caffeine	N.C.	II
Caffeine and ephedrine or pseudoephedrine	N.C.	II
Caffeine and phenylpropanolamine	N.C.	II
Menthol and camphor and eucalyptus oil and thymol and cedar leaf oil and nutmeg oil (myristica oil) in a suitable vehicle for steam inhalation or topical use as a nasal decongestant.	III	III
Menthol and camphor and eucalyptus oil in a suitable ointment vehicle as a topical antitussive	III	I
Menthol and eucalyptus oil in a lozenge as a topical antitussive	III	III
Methol and camphor and eucalyptus oil and tincture of benzoin and polyoxyethylene dodecanol for use in a steam vaporizer as an antitussive.	III	III
Promethazine hydrochloride (if labeled for relief of symptoms of the common cold) may be used as the antihistamine in the above Category I combinations that contain cough-cold and/or analgesic-antipyretic ingredients.	I	I

[1] N.C.—Not classified by Panel.
[2] Combination is classified as Category II because of nonmonograph status of anticholinergics (50 FR 46587).

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products (41 FR 38327 and 38418). The agency is offering these guidelines as the Panel's recommendations without adopting them or making any formal comment on them. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any active ingredient or combination included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

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

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

1. For clarity, the agency is specifying in the tentative final monograph in § 341.40 and § 341.85 whether antitussives, bronchodilators, and nasal decongestants are for oral or topical use. (See comment 39 above.)

2. The agency is amending § 341.40 (j) and (o) to state that any single ingredient in § 356.10 (Category I anesthetic/analgesic active ingredients identified in the monograph for oral health care drug products) may be combined with an oral antitussive or an oral nasal decongestant in a solid dosage form to be dissolved in the mouth and swallowed. Additionally, to be consistent with the language used in the oral health care drug products report, the term "oral anesthetic/analgesic" is used in this document rather than the term "local anesthetic or local analgesic."

Additionally, the agency has examined other combination drug products containing cough-cold and oral health care active ingredients which were not reviewed by the Panel and is proposing to include the following as Category I combinations in new paragraphs u through z in § 341.40: an oral antitussive and an oral demulcent in a solid dosage form; an oral nasal decongestant and an oral demulcent in a solid dosage form; an oral antitussive, an oral nasal decongestant, and an oral demulcent in a solid dosage form; an oral antitussive, an oral anesthetic/analgesic, and an oral demulcent in a solid dosage form; an oral nasal decongestant, an oral anesthetic/analgesic, and an oral demulcent in a solid dosage form; and an oral nasal decongestant, an oral antitussive, an oral anesthetic/analgesic, and an oral demulcent in a solid dosage form. The following combinations are proposed as Category II: an antihistamine and an astringent; an oral antitussive and an astringent; an antihistamine and a debriding agent/oral wound cleanser; and an oral antitussive and a debriding agent/oral wound cleanser. The following combinations in a solid dosage form are proposed as Category III: an antihistamine and an oral anesthetic/analgesic; an antihistamine and an oral demulcent; an expectorant and an oral anesthetic/analgesic; and an expectorant and an oral demulcent. The agency will discuss combinations that include oral antimicrobials in the antimicrobial segment of the tentative final monograph for OTC oral health care drug products, to be published in a future issue of the **Federal Register**. (See comment 39 above.)

3. The agency is proposing a Category I classification of combination drug products containing an oral antitussive, an oral nasal decongestant, and an anesthetic/analgesic, provided that the product is available only in a solid dosage form to be dissolved in the mouth and swallowed. (See comment 40 above.)

4. The agency is reclassifying from Category II to Category III combination drug products containing an oral antitussive (if the antitussive is also a Category I antihistamine) and an antihistamine and combination drug products containing an antihistamine (if the antihistamine is also a Category I antitussive) and an oral antitussive. (See comment 43 above.)

5. The agency is classifying in Category III combination drug products containing a nasal decongestant and an antihistamine administered topically in a nasal spray or drops. However, the specific combination product containing phenylephrine hydrochloride (a nasal decongestant) and methapyrilene hydrochloride (an antihistamine) in a nasal spray has been placed in Category II because methapyrilene-containing drug products are not generally recognized as safe. (See comment 51 above.)

6. The agency concludes that the combination of an anticholinergic, an oral nasal decongestant, and an antihistamine satisfies the criteria for a Category III combination. However, because at this time, there are no Category I (monograph) anticholinergics

in the final rule for OTC anticholinergic drug products (published in the **Federal Register** of November 8, 1985; 50 FR 46582), all OTC combination drug products containing anticholinergic ingredients (including the above mentioned combination) are classified as Category II (nonmonograph) conditions in this tentative final monograph. (See comment 53 above.)

7. Based on the Internal Analgesic Panel's Category I classification of a combination drug product containing an expectorant and an analgesic-antipyretic (42 FR 35493), the agency is proposing that the combination be classified in Category I in this tentative final monograph. [This combination was not classified by the Cough-Cold Panel.]

8. The Internal Analgesic Panel, stating that there is a small percentage of the population for whom buffered aspirin produces a lower incidence of gastric intolerance and who might therefore derive some benefit from buffered aspirin, classified in Category I buffered aspirin products, i.e., those containing aspirin combined with buffering ingredients (correctives) and those containing aspirin combined with antacids (42 FR 35469). In the tentative final monograph for OTC internal analgesic drug products, to be published in a future issue of the **Federal Register**, the agency will include buffered aspirin and aspirin and antacid combinations in the monograph. This tentative final monograph for cough-cold combination drug products proposes that buffered aspirin and aspirin and antacid combination drug products may be combined with cough-cold active ingredients as identified in § 341.40 "Permitted combinations of active ingredients" provided the product is labeled according to § 341.85.

Additionally, this document proposes that for combination drug products containing an analgesic-antipyretic ingredient(s) and a cough-cold active ingredient(s), that are marketed and labeled for relief of cough-cold symptoms, the indications statement for the analgesic-antipyretic portion of the product is as follows: "For the temporary relief of minor aches, pains, headaches, muscular aches, and fever associated with" (select one of the following: "the common cold" or "a cold") (followed by the appropriate indication(s) for the cough-cold ingredient(s).) However, for drug products containing an analgesic-antipyretic combined with an antihistamine and/or an oral nasal decongestant as identified in § 341.40 (a), (c), and (n) which are promoted for use in individuals with hay fever/allergic rhinitis or sinusitis symptoms, the following indication should be used: "For the temporary relief of minor aches, pains, and headaches" (followed by the labeling for antihistamines in § 341.72(b)(1) and/or the labeling for nasal decongestants in § 341.80(b)(1) (ii) or (iii), as appropriate). Products which are promoted for relief of cough-cold symptoms in addition to hay fever and/or sinusitis symptoms must include both labeling statements. (See comment 61 above.)

9. The agency is reclassifying from Category III to Category I combination drug products containing analgesic-antipyretic(s), an oral antitussive, an antihistamine, and an oral nasal decongestant. Additionally, based on the data on the above combination, the agency is also classifying in Category I combination drug products containing analgesic-antipyretic(s) (as identified above), an oral antitussive, and an oral nasal decongestant and combination drug products containing an oral antitussive and analgesic-antipyretic(s) (as identified above). (See comment 47 above.)

10. The agency is reclassifying from Category III to Category I combination drug products containing menthol (2.6 to 2.8 percent), camphor (4.7 to 5.3 percent), and eucalyptus oil (1.2 to 1.3 percent) in a suitable ointment vehicle as a topical antitussive combination drug product. (See comment 56 above.)

11. The agency is reclassifying from Category III to Category I combination drug products containing 1-desoxyephedrine and aromatics (camphor, menthol, methyl salicylate, bornyl acetate, and lavender oil) as a topical nasal decongestant (administered by a nasal inhaler). (See comment 55 above.)

12. The agency is reclassifying from Category I to Category II combination drug products containing theophylline and ephedrine. Therefore, the Panel's recommendation in § 341.40(k) is not being included in this tentative final monograph. Additionally, the agency is classifying in Category II any combination drug product that contains theophylline. This includes, but is not limited to, combinations of theophylline and ephedrine; combinations of theophylline, ephedrine, and phenobarbital; and combinations of theophylline, ephedrine, and an expectorant. (See comment 54 above.)

13. The agency is classifying the following combination drug products in Category II: phenylpropanolamine, ephedrine, and caffeine; caffeine in combination with ephedrine or pseudoephedrine; and phenylpropanolamine in combination with caffeine. FDA determined that such products are new drugs and are required to be the subject of an approved NDA. (See the **Federal Registers** of August 13, 1982 (47 FR 35344), November 18, 1983 (48 FR 52513), and June 29, 1984 (49 FR 26814).)

14. The agency is reclassifying phenobarbital 8 mg from Category III to Category II as a stimulant corrective. (See comment 49 above.)

15. The agency is classifying caffeine at a dosage of 15 to 30 mg in Category III when included in cough-cold drug preparations to combat lethargy. (See comment 50 above.)

16. The Panel recommended a Category I classification for the prescription drug promethazine hydrochloride as an antihistamine in its advance notice of proposed rulemaking (41 FR 38390). Because of concerns regarding adverse reactions on the central nervous system, the agency dissented from this recommendation in the preamble to the Panel's report (41 FR 38312). Subsequently, data were submitted to the agency to alleviate these concerns, but not sufficient to justify agreeing with the Panel's Category I classification of promethazine hydrochloride as a single ingredient (Ref. 1). Therefore, general recognition of the safety of promethazine hydrochloride as a single ingredient has not been adequately established.

Promethazine hydrochloride has not been used extensively on a long-term basis as a single ingredient for antihistamine/allergic rhinitis/anti-allergy use. The agency believes that consumers who use OTC antihistamines to treat the symptoms of allergic rhinitis use these products on a long-term basis because the symptoms of allergic rhinitis usually occur for extended periods of time. The major use of promethazine hydrochloride as a prescription drug is in combination drug products for relief of acute cough/cold symptoms on a short-term basis. The possibility that the rare, but serious adverse reaction of the central nervous system known as tardive dyskinesia will not occur if promethazine hydrochloride is used on a long-term basis in a single ingredient OTC antihistamine drug product has not been adequately demonstrated. Therefore, the agency proposed a Category III classification for promethazine hydrochloride in the tentative final monograph for OTC antihistamine drug products published in the **Federal Register** on January 15, 1985 (50 FR 2206). The agency will address the comments received in

response to that tentative final monograph on single ingredient use of promethazine in the final monograph for OTC antihistamine drug products in a future issue of the **Federal Register.**

The agency has also reviewed data and information on combination drug products containing promethazine hydrochloride that are used extensively on a prescription basis for treating symptoms of the common cold (Refs. 1 and 2). These data and information indicate that such short-term use of promethazine hydrochloride in these products is safe. Under conditions of short-term use for the relief of cold symptoms, the possibility that tardive dyskinesia might occur is no longer a concern. Therefore, the agency is proposing a Category I classification of promethazine hydrochloride in combination with other cough-cold and/or analgesic-antipyretic ingredients as provided for antihistamine active ingredients in § 341.40 (a) through (f) of this tentative final monograph. (See § 341.40(t) in this document.)

In accordance with the enforcement policy set out in 21 CFR 330.13, and with FDA's Compliance Policy Guide (Ref. 3), promethazine hydrochloride combinations may now be marketed OTC under the conditions set out in this tentative final monograph. Such marketing, pending issuance of the final monograph, is subject to the risk that the Commissioner may adopt a different position in the final monograph that could require relabeling, recall, or other regulatory action. Marketing of such a product with labeling not in accord with the tentative final monograph also may result in regulatory action against the product, the marketer, or both.

As with other combination drug products, the labeling of combination drug products containing promethazine hydrochloride must include those indications and pharmacologic actions that are consistent with the intended use of the product; however, labeling indications related to the antihistamine (promethazine hydrochloride) component of the combination product may indicate use only for the treatment of symptoms of the common cold. Such indications are specified in § 341.72(b)(2) of the tentative final monograph for OTC antihistamine drug products. The agency recognizes that combinations of an antihistamine and a nasal decongestant are often used on a long-term basis to treat symptoms of allergic rhinitis. In the case of a combination drug product containing promethazine hydrochloride and a nasal decongestant, the labeling cannot contain indications for allergic rhinitis specified in § 341.72(b)(1) nor any other labeling in any area of the label or packaging that might imply use in treating symptoms of allergic rhinitis. Such labeling restriction will ensure short-term rather than long-term use on an OTC basis of products containing promethazine.

The Panel recommended the following oral dosage schedule for promethazine hydrochloride: For adults, the dosage is 6.25 to 12.5 mg every 8 to 12 hours, not to exceed 37.5 mg in 24 hours. For children 6 to under 12 years, the dosage is 3.125 to 6.25 mg every 8 to 12 hours, not to exceed 18.75 mg in 24 hours. The Panel recommended that a dosage of 1.56 to 3.125 mg every 8 to 12 hours, not to exceed 9.375 mg in 24 hours be included under professional labeling for children 2 to under 6 years of age. For children under 2 there is no recommended dosage except under the advice and supervision of a physician (41 FR 38390).

The Panel's recommended dosage interval (i.e., 8 to 12 hours) does not allow promethazine hydrochloride in an immediate release dosage form to be combined with other cough-cold active ingredients. However, based on the Panel's conclusion that 6.25 mg is the minimum effective OTC dose for promethazine (41 FR 38390), and past FDA approved labeling for promethazine-containing drug products that recommend a dosage of up to 4 times daily (Ref. 4), and the current approved NDA labeling for the innovator promethazine-containing combination drug product that provides for a dosage of 6.25 mg every 4 to 6 hours (Ref. 4), the agency is proposing an adult dosage for promethazine hydrochloride of 6.25 mg every 4 to 6 hours, not to exceed 37.5 mg in 24 hours (and corresponding children's dosages). This revised dosage schedule will allow promethazine hydrochloride to be combined with other cough-cold active ingredients, as proposed in this tentative final monograph.

In addition to the general labeling required for antihistamine drug products in § 341.72 (a) and (c)(1) (see 50 FR 2216 and 52 FR 31913), the following labeling statements and revisions are required for combination drug products containing promethazine hydrochloride:

(1) Based on approved labeling for prescription drug products containing promethazine hydrochloride, the warning in § 341.72(c)(2) is modified to read "Do not take this product if you have asthma, glaucoma, emphysema, liver disease, seizures, 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," and the warning in § 341.72(c)(6)(i) is modified to read "Do not give this product to children who have asthma, liver disease, seizures, or glaucoma unless directed by a doctor" (Ref. 4).

(2) The warning concerning drowsiness in § 341.72(c)(4) or (6)(iii) is required (see 52 FR 31913).

(3) The directions for use are "Adults: Oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours. Children 6 to under 12 years of age: oral dosage is 3.125 milligrams every 4 to 6 hours, not to exceed 18.75 milligrams in 24 hours. Children under 6 years of age: Consult a doctor."

The modified warnings and directions for drug products containing promethazine hydrochloride appear in this document in § 341.85(d)(4) and § 341.85(e), respectively.

In addition, dosage information for the promethazine hydrochloride component of combination drug products containing promethazine hydrochloride for use in children 2 to under 6 years of age is included under professional labeling in § 341.90(r). Such dosage information is provided to health professionals but not to the general public as follows:

(r) *For combination drug products containing promethazine hydrochloride as identified in § 341.40(s).* Children 2 to under 6 years of age: oral dosage is 1.56 milligrams every 4 to 6 hours, not to exceed 9.36 milligrams in 24 hours.

References

(1) Comment Nos. C00188 and CP0002, Docket No. 76N-052H, Dockets Management Branch.

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

(3) Food and Drug Administration Compliance Policy Guide 7132b.16, Docket No. 78D-0322, Dockets Management Branch.

(4) Copies of FDA-approved labeling from NDA 8-306, and 8-306/S-010 and S-011, OTC Volume 04GTFM, Docket No. 76N-052G, Dockets Management Branch.

17. The agency is adding to § 341.85 a "Statement of identity" paragraph (designated as § 341.85(b)), an "Indications" paragraph (designated as § 341.85(c)), a "Warnings" paragraph (designated as § 341.85(d)), and a "Directions" paragraph (designated as § 341.85(e)) to conform with the format of other recently published tentative final monographs. Inclusion of the new paragraphs has necessitated a redesignation of the Panel's warning in § 341.85(a) to 341.85(d)(5). The agency is also redesignating Subpart D as Subpart

C and placing the labeling sections of the monograph in Subpart C.

18. In § 341.85(a) the agency is proposing that indications, warnings, and directions, respectively, applicable to each active ingredient of the combination product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable. For combination products for which the labeling (i.e., statement of identity, indications, and warnings) in the individual applicable monographs conflicts or is inappropriate, the agency is proposing specific labeling for such combinations in § 341.85. Further, the agency is also proposing that when there is a difference in the directions established for the individual ingredients in the combination drug product, e.g., when the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph. (See comment 62 above.)

19. The agency is deleting the signal word "Caution" from the Panel's warning in § 341.85(a) (redesignated as § 341.85(d)(5)) for an antihistamine combined with an antitussive, i.e., "Caution: May cause marked drowsiness." In addition, upon petition, the agency will consider deletion of the word "marked" from this warning provided adequate data are submitted to demonstrate that the combination product does not cause a significant increase in drowsiness as compared with each active ingredient when tested alone. The petition and the data it contains will be maintained in a permanent file for public review in the Dockets Management Branch.

20. The agency is deleting the warning for bronchodilator-expectorant combination drug products recommended by the Panel in § 341.85(c), "This product should be used only for cough associated with asthma." (See comment 66 above.)

21. The agency is deleting the warning recommended by the Panel in § 341.85(d), "This product contains aspirin and should not be taken by individuals who are sensitive to aspirin." (See comment 64 above.)

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC cold, cough, allergy, bronchodilator, and antiasthmatic combination 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 cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

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

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday. This action was considered under FDA's final rule implementing the National Environmental Policy Act (21 CFR Part 25).

Interested persons may, on or before December 12, 1988, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before December 12, 1988. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

Interested persons, on or before August 14, 1989, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written, comments on the new data may be submitted on or before October 12, 1989. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on October 14, 1989. Data submitted after the closing of

the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 341

Labeling; Over-the-counter drugs; Cold, cough, allergy, bronchodilator, and antiasthmatic combinations.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, and under 21 CFR 5.11, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 341 as follows:

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for Part 341 continues to read as follows:

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

2. In Subpart B, new § 341.40 is added, to read as follows:

§ 341.40 Permitted combinations of active ingredients.

The following combinations are permitted provided each active ingredient is present within the established dosage limits and the product is labeled in accordance with § 341.85:

(a) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or aspirin and antacid combinations.

(b) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a).

(c) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any single analgesic-antipyretic active ingredients, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or aspirin and antacid combinations.

(d) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral antitussive active ingredient identified in § 341.14(a) provided that the product is labeled according to § 341.85(d)(5).

(e) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral antitussive active ingredient identified in § 341.14(a) and any single oral nasal decongestant active ingredient identified in § 341.20(a).

(f) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral antitussive active ingredient identified in § 341.14(a) and any single oral nasal decongestant active ingredient identified in § 341.20(a) and any single analgesic-antipyretic active ingredients or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or aspirin and antacid combinations.

(g) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single expectorant active ingredient identified in § 341.18.

(h) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a).

(i) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any single expectorant active ingredient identified in § 341.18.

(j) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral anesthetic/analgesic active ingredient identified in § 356.10 of this chapter provided that the product is available in a solid dosage form to be dissolved in the mouth and swallowed.

(k) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any single analgesic-antipyretic active ingredients or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or aspirin and antacid combinations.

(l) Any single oral bronchodilator active ingredient identified in § 341.16 (a), (b), (c), and (h) may be combined with any single expectorant active ingredient identified in § 341.18.

(m) Any single expectorant active ingredient identified in § 341.18 may be combined with any single analgesic-antipyretic active ingredients or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or aspirin and antacid combinations.

(n) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any single analgesic-antipyretic active ingredients or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or aspirin and antacid combinations.

(o) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any single expectorant active ingredient identified in § 341.18.

(p) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any single oral anesthetic/analgesic active ingredient identified in § 356.10 of this chapter provided that the product is available in a solid dosage form to be dissolved in the mouth and swallowed.

(q) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any single oral antitussive active ingredient identified in § 341.14(a) and any single anesthetic/analgesic active ingredient identified in § 356.10 of this chapter provided that the product is available in a solid dosage form to be dissolved in the mouth and swallowed.

(r) Camphor identified in § 341.14(b)(1) may be combined with menthol identified in § 341.14(b)(2) and eucalyptus oil (1.2 to 1.3 percent) provided that the product is available only in a suitable ointment vehicle.

(s) 1-desoxyephedrine identified in § 341.20(b)(1) may be combined with aromatics (camphor (54 mg), menthol (80 mg), methyl salicylate (11 mg), bornyl acetate (0.2 mg), and lavender oil (4 mg)) provided that the product is available only as an inhaler.

(t) Promethazine hydrochloride identified as an antihistamine (if labeled for relief of symptoms of the common cold as identified in § 341.72(b)(2)) may be used in combination with other cough-cold and/or analgesic-antipyretic ingredients as provided for antihistamine active ingredients in § 341.40 (a) through (f) of this section.

(u) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral demulcent active ingredient identified in § 356.18 of this chapter provided that the product is in a solid dosage form to be dissolved in the mouth and swallowed.

(v) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any single oral demulcent active ingredient identified in § 356.18 of this chapter provided that the

product is in a solid dosage form to be dissolved in the mouth and swallowed.

(w) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any single oral demulcent active ingredient identified in § 356.18 of this chapter provided that the product is in a solid dosage form to be dissolved in the mouth and swallowed.

(x) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral anesthetic/analgesic active ingredient identified in § 356.10 of this chapter and any single oral demulcent active ingredient identified in § 356.18 of this chapter provided that the product is available only in a solid dosage form to be dissolved in the mouth and swallowed.

(y) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any single oral anesthetic/analgesic active ingredient identified in § 356.10 of this chapter and any single oral demulcent active ingredient identified in § 356.18 of this chapter provided that the product is available only in a solid dosage form to be dissolved in the mouth and swallowed.

(z) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any single oral anesthetic/analgesic active ingredient identified in § 356.10 of this chapter and any single oral demulcent active ingredient identified in § 356.18 of this chapter provided that the product is available only in a solid dosage form to be dissolved in the mouth and swallowed.

3. In Subpart C, new § 341.85 is added to read as follows:

§ 341.85 Labeling of permitted combinations of active ingredients.

Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs. For a combination drug product that does not have an established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph (a).

(1) *For permitted combinations identified in § 341.40 (a), (c), (f), (k), (m), and (n) containing an analgesic-antipyretic active ingredient.* The analgesic-antipyretic component of the product shall be identified as a "pain reliever" or "analgesic (pain reliever)." If the product is also labeled to relieve fever, then the analgesic-antipyretic component is identified as a "pain reliever-fever reducer" or "analgesic (pain reliever)-antipyretic (fever reducer)."

(2) [Reserved]

(b) *Indications.* The labeling of the product states, under the heading "Indications," the indication(s) for each ingredient in the combination, as established in the indications sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph (b). Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in the applicable OTC drug monographs or listed in this paragraph, may also be used, as provided in § 330.1(d)(2), subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For permitted combinations containing an analgesic-antipyretic active ingredient identified in § 341.40 (a), (c), (f), (k), (m), and (n) when labeled for relief of cough-cold symptoms.* The following indication for analgesic-antipyretic ingredients should be used. "For the temporary relief of minor aches, pains, headache, muscular aches, and fever associated with" (select one of the following: "the common cold" or "a cold") (followed by the appropriate indication(s) for the cough-cold ingredient(s).)

(2) *For permitted combinations containing an analgesic-antipyretic active ingredient identified in § 341.40 (a), (c), and (n) when labeled for relief of hay fever/allergic rhinitis and/or sinusitis symptoms.* The following indication for analgesic-antipyretic ingredients should be used. "For the temporary relief of minor aches, pains, and headache" (followed by the labeling for antihistamines in § 341.72(b)(1) and/or the labeling for nasal decongestants in § 341.80(b)(1) (ii) or (iii), as appropriate).

(3) *For permitted combinations containing an analgesic-antipyretic active ingredient identified in § 341.40 (a), (c), and (n) when labeled for relief of cough-cold symptoms and for relief of hay fever/allergic rhinitis and/or sinusitis symptoms.* Both indications in § 341.85(b) (1) and (2) must be used.

(4) *For permitted combinations containing an anesthetic-analgesic active ingredient identified in § 341.40 (j), (p), (q).* The indication for anesthetic/analgesics in § 356.55(b)(1) of this chapter should be used.

(5) *For permitted combinations containing the antihistamine promethazine hydrochloride identified in § 341.40(t).* The indication for antihistamines in § 341.72(b)(2) should be used.

(6) *For permitted combinations containing 1-desoxyephedrine and aromatics (camphor, menthol, methyl salicylate, bornyl acetate, and lavender oil) as a topical nasal decongestant administered by a nasal inhaler.* The indications for nasal decongestants in § 341.80(b) should be used.

(7) *For permitted combinations containing menthol, camphor, and eucalyptus oil as topical antitussives in an ointment.* The indication for antitussives in § 341.74(b) should be used.

(8) *Other allowable statements.* In addition to the required information identified in this section (b), the labeling of the combination drug product may contain any of the "other allowable statements" (if any), that are identified in the applicable monographs, provided such statements are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

(c) *Warnings.* The labeling of the product states, under the heading "Warnings," the warning(s) for each ingredient in the combination, as established in the warnings sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph (c). [All citations that refer to § 343.50 of this chapter will be published in a future issue of the **Federal Register**.]

(1) *For permitted combinations containing an antitussive and an analgesic-antipyretic identified in § 341.40 (f) and (k).* The following products are to be labeled, accordingly.

(i) *For products labeled for adults.* The following warning should be used instead of the warnings in § 343.50(c)(1)(i) of this chapter and

§ 341.74(c)(1)(ii). "Do not take this product for more than 10 days. A persistent cough may be a sign of a serious condition. If cough persists for more than 7 days, tends to recur, or is accompanied by rash, persistent headache, fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor."

(ii) *For products labeled for children under 12 years of age.* The following warning should be used instead of the warnings in § 343.50(c)(2)(i) of this chapter and § 341.74(c)(2)(ii). "Do not give this product to children for more than 5 days. A persistent cough may be a sign of a serious condition. If cough persists for more than 7 days, tends to recur, or is accompanied by rash, persistent headache, fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor."

(iii) *For products labeled for both adults and for children under 12 years of age.* The following warning should be used instead of the warnings in § 343.50(c)(3) of this chapter and §§ 341.74 (c)(1)(ii) and (c)(2)(ii). "Do not take this product for more than 10 days (for adults) or 5 days (for children). A persistent cough may be a sign of a serious condition. If cough persists for more than 7 days, tends to recur, or is accompanied by rash, persistent headache, fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor."

(2) *For permitted combinations containing an expectorant and an analgesic-antipyretic identified in § 341.40(m).* The following products are to be labeled, accordingly.

(i) *For products labeled for adults.* The following warning should be used instead of the warnings in § 343.50(c)(1)(i) of this chapter and § 341.78(c)(3). "Do not take this product for more than 10 days. A persistent cough may be a sign of a serious condition. If cough persists for more than 7 days, tends to recur, or is accompanied by rash, persistent headache, fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor."

(ii) *For products labeled for children under 12 years of age.* The following warning should be used instead of the warnings in § 343.50(c)(2)(i) of this chapter and § 341.78(c)(3). "Do not give this product to children for more than 5 days. A persistent cough may be a sign of a serious condition. If cough persists for more than 7 days, tends to recur, or is accompanied by rash, persistent headache, fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor."

(iii) *For products labeled for both adults and for children under 12 years of age.* The following warning should be used instead of the warnings in § 343.50(c)(3) of this chapter and § 341.78(c)(3). "Do not take this product for more than 10 days (for adults) or 5 days (for children). A persistent cough may be a sign of a serious condition. If cough persists for more than 7 days, tends to recur, or is accompanied by rash, persistent headache, fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor."

(3) *For permitted combinations containing a nasal decongestant and an analgesic-antipyretic identified in § 341.40 (c), (f), (k), and (n).* The following products are to be labeled, accordingly.

(i) *For products labeled for adults.* The following warning should be used instead of the warnings in § 343.50(c)(1)(i) of this chapter and § 341.80(c)(1)(i)(b). "Do not take this product for more than 10 days. If symptoms do not improve or are accompanied by fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor."

(ii) *For products labeled for children under 12 years of age.* The following warning should be used instead of the warnings in § 343.50(c)(2)(i) of this chapter and § 341.80(c)(1)(ii)(b). "Do not give this product to children for more than 5 days. If symptoms do not improve or are accompanied by fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor."

(iii) *For products labeled for both adults and children under 12 years of age.* The following warning should be used instead of the warnings in § 343.50(c)(3) of this chapter and § 341.80(c)(iii). "Do not take this product for more than 10 days (for adults) or 5 days (for children). If symptoms do not improve or are accompanied by fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor."

(4) *For permitted combinations containing promethazine hydrochloride identified in § 341.40(t).* The following products are to be labeled, accordingly.

(i) *For products labeled for adults.* The warnings for antihistamines in § 341.72(c) (1) and (4) must be used, in addition to the following: "Do not take this product if you have asthma, glaucoma, emphysema, liver disease, seizures, 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."

(ii) *For products labeled for children under 12 years of age.* The warnings for antihistamines in § 341.72(c)(1) and (6)(iii) must be used, in addition to the following: "Do not give this product to children who have asthma, liver disease, seizures, or glaucoma unless directed by a doctor."

(5) *For combination drug products containing an antihistamine combined with an oral antitussive.* The warning "May cause marked drowsiness," must be used. The word "marked" may be deleted from the warning upon petition under the provisions of § 10.30 of this chapter provided adequate data are submitted to demonstrate that the combination product does not cause a significant increase in drowsiness as compared with each active ingredient when tested alone. The petition and the data it contains will be maintained in a permanent file for public review by the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

(6) *For combination drug products containing 1-desoxyephedrine and aromatics (camphor, menthol, methyl salicylate, bornyl acetate, and lavender oil) as a topical nasal decongestant administered by a nasal inhaler.* The warnings for topical nasal decongestants in § 341.80(c) must be used.

(7) *For combination drug products containing menthol, camphor, and eucalyptus oil as topical antitussives in an ointment.* The warnings for topical antitussives in § 341.74(c) must be used.

(d) *Directions.* The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph (d). When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph.

(1) *For permitted combinations containing promethazine hydrochloride identified in 341.40(t).* Adults and children 12 years of age and older: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 milligrams in 24 hours. Children 6 to under 12 years of age: Oral dosage is 3.125 milligrams every 4 to 6 hours, not to exceed 18.75 milligrams in 24 hours. Children under 6 years of age: Consult a doctor.

(2) [Reserved]

(e) *Optional wording.* The word "physician" may be substituted for the

word "doctor" in any of the labeling statements in this section.

4. In § 341.90, new paragraph (r) is added to read as follows:

§ 341.90 Professional labeling.

* * * * *

(r) *For permitted combinations containing promethazine hydrochloride as identified in § 341.40(t).* Children 2 to under 6 years of age: Oral dosage is 1.56 milligrams every 4 to 6 hours, not to exceed 9.36 milligrams in 24 hours.

Dated: May 2, 1988.

Frank E. Young,

Commissioner of Food and Drugs.

[FR Doc. 88-18066 Filed 8-11-88; 8:45 am]

BILLING CODE 4160-01-M