DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 341

[Docket No. 76N-052T]

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for OTC Antitussive 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) antitussive drug products (drug products used to relieve cough) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal deals only with antitussive drug products and is part of the ongoing review of OTC drug products conducted by FDA.

DATE: Written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by December 19, 1983. New data by October 19, 1984. Comments on the new data by December 19, 1984. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determination by February 14, 1984.

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, National Center for Drugs and Biologics (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4960

SUPPLEMENTARY INFORMATION: In the **Federal Register** of September 9, 1976 (41 FR 38312) FA 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, 23 manufacturers, 1 consumer, 7 health care professionals, and 1 health care professional society submitted comments on antitussive. Copies of the comments received are on public display in the Dockets Management Branch.

FDA is issuing the tentative final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products in segments. This document on antitussive drug products is the third segment to be published. The first segment, on anticholinergic drug products and expectorant drug products, was published in the **Federal Register** of July 9, 1982 (47 FR 30002). The second segment, on bronchodilator drug products, was published in the **Federal Register** of October 26, 1982 (47 FR 47520). Subsequent segments, on antihistamines, nasal decongestants, and combination drug products and general comments, will be published in future issues of the **Federal Register.**

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

This tentative final monograph would amend Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations in Part 341 (as set forth in the tentative final monograph on anticholinergic drug products and expectorant drug products that was published in the **Federal Register** of July 9, 1982 (47 FR 30002)) in Subpart A, by adding in § 341.3, new paragraphs (j) and (k); in Subpart B, by adding § 341.14; and in Subpart C, by adding new § 341.74, and by adding in § 341.90, new paragraphs (o) and (p). This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC antitussive drug products, as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

The OTC procedural regulations (21 CFR 330.10) have been revised to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). (See the **Federal Register** of September 29, 1981; 46 FR 47730.) The Court in *Cutler* held that the OTC drug regulations were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision has been deleted from the regulations, which now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III

classification, and submission to FDA of the results of that testing or any other data, must be done during the OCT drug rulemaking process, before the establishment of a final monograph.

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

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

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

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

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

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on Antitussive Drug Products

1. One comment questioned whether any "medicine" should be allowed on the market simply for coughs. The comment explained that the public should be taught that a cough can come from postnasal drip, in which case a decongestant or an antihistamine might be indicated, or that a cough can come from asthma, in which case aminophylline might be indicated. The comment concluded that "cough medicines" are mostly "fakes" and the public should not be encouraged "to believe that it is unwise to cough without cough medicine."

The Panel recognized in its report that cough is a protective, physiologic reflex occurring in both healthy and diseased individuals (41 FR 38321 and 38338). Coughing helps clear the respiratory tract of secretions and foreign materials. Coughing may be a symptom associated with a variety of disease states, and whether or not to use an antitussive depends on the particular disease state. For example, in asthma, bronchitis, cystic fibrosis, and other respiratory diseases, there is an overproduction of secretions, and the cough reflex is essential in maintaining an open airway by clearing the respiratory passages of excessive secretions. Therefore, the use of an antitussive in these conditions would be harmful. In order to discourage use of an antitussive in these type of respiratory conditions, the Panel recommended a warning in § 341.74(b)(2) that the product should not be taken for persistent or chronic cough such as occurs with smoking, asthma, emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a doctor. However, where cough is associated with a self-limiting respiratory tract infection, or from the inhalation of irritant gases, or dusts, an OTC antitussive would be useful. Coughs due to the common cold and coughs due to inhaled irritants are the only types of coughs for which the Panel specifically designated the use of antitussives. Cough suppressant therapy would be indicated in these cases to help relieve irritation to the respiratory tract, and to help an individual rest or sleep comfortabley. These self-limiting conditions would rarely last more than 1 week. Coughs lasting more than 1 week may be indicative of a serious disease and should be treated by a doctor; therefore, the Panel recommended a warning in § 341.74(b)(3) limiting use of

an antitussive to 1 week. The agency believes that the warnings proposed by the Panel to discourage the use of antitussives in other than self-limiting conditions and the required indication proposed by the agency are explicit and adequate. Antitussives can be beneficial in alleviating coughs in acute, self-limiting conditions and should be available for OTC use.

2. One comment pointed out what it considered to be an error in the Panel's description of the symptoms of asthma. The comment noted that the Panel's statement that an "irritative cough * * * with a self-limiting respiratory tract infection" is "associated with a dry, hacking nonproductive cough in which no sputum is expectorated" was set in contrast to "the cough of asthma" (41 FR 38321). The comment contended that a cough without wheezing, exactly fitting the above description of irritative cough, is often the first and sometimes the only symptom of asthma in children. The comment contended that the Panel's statement reflects the cough of adult asthma and that it contains a significant error when the symptoms of asthma in children are considered.

The agency has reviewed the Panel's discussion of cough in which the Panel compared "nonproductive" (no sputum produced) and "productive" (sputum produced) types of cough (41 FR 38321). The Panel stated that the cough associated with self-limiting respiratory tract infection or following the inhalation of irritant gases or dusts is usually a dry, hacking, nonproductive cough in which no sputum is expectorated, and this type of cough lends itself to self-medication with OTC antitussive drug products. On the other hand, the loose, productive type of cough frequently associated with asthma and bronchitis should not be treated with an antitussive drug because the suppression of retained bronchial secretions could lead to increasing disability. Moreover, the Panel qualified its statements by saying that inhalation of irritant gases and dusts is "usually associated with a dry, hacking nonproductive cough," whereas a loose, productive cough is "frequently associated with asthma and bronchitis." The agency believes that these statements were intended to be general guidelines to appropriate treatment of cough, not precise statements of symptomology. More importantly, the Panel's statement and resulting label warning provide that any cough that persists for longer than 1 week should be diagnosed by a doctor. This limitation provides a safety factor in the use of antitussive drug products in children in treating cough without wheezing, should such a cough be a symptom of asthma.

3. One comment, citing the Panel's discussion that topical anesthetics and analgesics may be effective as "peripherally acting antitussives" by decreasing the sensitivity of special nerve endings or cough receptors in the mucosa of the respiratory tract (41 FR 38338), recommended that topical anesthetics, such as benzocaine, be placed in Category III as antitussives. The comment cited a study showing that a two-lozenge dose of 15 milligrams (mg) dextromethorphan and 5 mg benzocaine provided an antitussive effect, as measured by citric acid-induced cough, for 8 hours (Ref. 1). Based on the Panel's recommended 10- to 20-mg dose of dextromethorphan every 4 hours, the comment pointed out that the total dose of 15 mg dextromethorphan contained in the two lozenges should have been effective for only 3 to 4 hours, and thus attributed the extended duration of the antitussive effect to the presence of the benzocaine in the lozenge.

The Panel did not evaluate any topical anesthetic ingredients as antitussives. Three topical anesthetics, benzocaine, benzyl alcohol, and hexylresorcinol, were submitted to the Panel, but all three of these ingredients were deferred to other advisory review panels, including the Advisory Review Panel on OTC Oral Cavity Drug Products, which evaluated all three of these ingredients as topical analgesic/anesthetics for use in the oral cavity.

The study cited by the comment did not evaluate the contribution of either dextromethorphan or benzocaine to the antitussive effect shown by the combination of these ingredients, and the comment provided no new data to substantiate its argument. In the absence of any data on which to base a conclusion with regard to the effectiveness of topical anesthetics, such as benzocaine, for antitussive use, a Category III classification is not warranted. Anyone wishing to submit data demonstrating the antitussive effect of topical analgesic/anesthetic ingredients may do so during the period following publication of this proposed rule or may submit data through the new drug application (NDA) procedures.

Reference

(1) OTC Volume 040131.

B. Comment on Switching Prescription Antitussive Active Ingredients to OTC Status

4. One comment requested that chlophedianol hydrochloride be reclassified from prescription to OTC status as an antitussive. The comment claimed that this ingredient generally satisfies the conditions recommended by the Panel for OTC antitussive products and submitted copies of published studies to substantiate its claim (Refs. 1 through 10). Chlophedianol hydrochloride was not reviewed by the Panel.

The agency has evaluated the data submitted to support the safety and effectiveness of chlophedianol hydrochloride and concludes that these data justify reclassification of this ingredient from prescription status to Category I as an OTC antitussive active ingredient.

In the **Federal Register** of April 29, 1971 (36 FR 8071), FDA indicated that it had evaluated a report received from the National Academy of Science/National Research Council (NAS/NRC), Drug Efficacy Study Group, as well as other available evidence on a prescription cough syrup containing chlophedianol hydrochloride, and conclude that this drug is effective for symptomatic relief of cough. The NAS/NRC report cited studies by Chen, Biller, and Montgomery (Ref. 1), Noel (Ref. 3), and Simon (Ref. 9) in classifying this ingredient as effective for the relief of cough. The cough syrup containing chlophedianol hydrochloride had been previously approved in 1960, based only on safety data, for prescription antitussive use.

In determining the safety of chlophedianol hydrochloride for OTC, use, the agency reviewed the side effects reported in the clinical studies included in the NDA; the annual adverse reaction summary listing for the years 1974 to 1982 (Ref. 11); the summary of side effects in the comment's submission—32 cases reported between August 10, 1959 and December 16, 1974; and the side effects reported in studies by Schweem and Haden (Ref. 2), Noel (Ref. 3), Schechter and Rasansky (Ref. 4), Richter et al. (Ref. 6), and Saunders (Ref. 8). On the basis of the NDA reports and the studies cited above, the agency concludes that chlophedianol hydrochloride is safe for use as an OTC antitussive.

Therefore, the agency is proposing to reclassify chlophedianol hydrochloride from prescription to OTC use as a Category I oral antitussive at the following dosages, based on the currently approved NDA for this product: Adults: oral dosage is 25 mg every 6 to 8 hours, not to exceed 100 mg in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 mg every 6 to 8 hours, not to exceed 50 mg in 14 hours, or as

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

The agency's detailed comments and evaluations of the data are on file in the Dockets Management Branch (Ref. 12).

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

References

(1) Chen, J. Y. P., H. F. Biller, and E. G. Montgomery, Jr., "Pharmacological Studies of a New Antitussive, *Alpha* (Dimethylaminoethyl) *Ortho*-Chlorobenzhydrol Hydrochloride (SL-501, Bayer B-186)," *The Journal of Pharmacology and Experimental Therapeutics*, 128:384–391, 1960.

(2) Schweem, H. H., and H. M. Haden, "Control of Cough with Chlophedianol Hydrochloride a New Nonnarcotic Antitussive Agent," *The Journal of the Florida Medical Association*, 49:302–304, 1962.

(3) Noel, P. R., "The Evaluation of a New Cough Suppressant, 'Detigon', in General Practice," *The British Journal of Diseases of the Chest*, 56:70–77, 1962.

(4) Schechter, F. R., and H. N. Rasansky, "Cough—A New Nonnarcotic Antitussive Agent for its Control," *Medical Times*, 90:155–156, 1962.

(5) Nathan, L. A., "Clinical Evaluation of Chlophedianol a New Nonnarcotic Antitussive," *Applied Therapeutics*, 4:830–831, 1962.

(6) Richter, I. B., et al., "New Nonnarcotic Antitussive Agent," *Western Medicine*, 3:138–139, 1962.

(7) Vogel, G., "A New Nonnarcotic Antitussive," *General Practice*, 25:9–10, 1962.

(8) Saunders, D. C., "Trial of an Anti-Tussive Preparation in Droplet Form," *The Practitioner*, 186:367–369, 1961.

(9) Simon, S. W., "The Effectiveness of Non-narcotic Antitussive Drugs," *Journal of the American Geriatrics Society*, 10:653–657, 1962.

(10) Casey, V. J., "Treatment of 'Common Cold' in School Children without Narcotics or Antibiotics," *Medical Record and Annals*, 56:2–4, 1963.

(11) Department of Health and Human Services, Food and Drug Administration. "Annual Adverse Reaction Summary Listing," pertinent pages for the years 1974–1982, OTC Volume 04TTFM, Docket No. 76N–052T, Dockets Management Branch.

(12) Letter from, W. E. Gilbertson, FDA, to T. C. McPherson, Riker Laboratories, Inc., coded LETO 76, Docket No. 76N–052T, Dockets Management Branch.

C. Comments on Specific Antitussive Active Ingredients

5. One comment requested reclassification of camphor from Category III to Category I as an antitussive for topical use in an ointment to be rubbed on the chest and submitted data from two new studies (Refs. 1 and 2), as well as a reanalysis of data from a study reviewed by the Panel (Ref. 3), to show the effectiveness of this ingredient.

The agency has reviewed the data and concludes that two of the studies are adequate to support the reclassification of camphor to Category I for this use (Refs. 1 and 3). In the first study, the antitussive effectiveness of 4.73 percent camphor in petrolatum was compared with petrolatum alone as a control in 48 patients with chronic cough due to bronchopulmonary disease (Ref. 1). The data indicated that camphor decreased the number of coughs and cough components to a significantly greater degree than the petrolatum control. The agency concludes that this study is acceptable in demonstrating the effectiveness of 4.73 percent camphor as an antitussive in a suitable ointment vehicle to be rubbed on the chest.

The agency's review of the second study (Ref. 3) indicates that the original tabulations reviewed by the Panel appear to have been incorrect and that the revised statistical analyses of the induced cough studies show statistical evidence of the superiority of 5.3 percent camphor over petrolatum alone in reducing cough counts.

A third study was reviewed by the agency and found not to be supportive of camphor as an antitussive ingredient because there were no significant differences among the four treatment groups studied (Ref. 2).

Based on the evaluation of the first two studies, the agency proposes to reclassify camphor in concentrations of 4.7 to 5.3 percent for topical use in an ointment to be rubbed on the chest from Category III to Category I in this tentative final monograph. The directions for camphor are being proposed as follows: Adults and children 2 to under 12 years of age: rub on the throat and chest as a thick layer. The area of application may be covered with a warm, dry cloth if desired. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to three times daily or as directed by a doctor. Children under 2 years of age: consult a doctor.

The agency notes that in the submitted studies the ointment was used on the anterior chest and not on the back. Therefore, the Panel's recommended direction for use that provides for camphor to be "rubbed on the back" is not being reclassified as Category I, but remains in Category III. Because no data were submitted on camphor for use as an antitussive in a steam vaporizer, camphor for this use also remains in Category III.

The warning "For external use only. Do not take by mouth or place in nostrils" is being proposed in the "Warnings" section of this tentative final monograph. The Panel recommended that such warning be included in the required labeling for antitussive drug products containing camphor that are used in the form of an ointment, and the agency concurs.

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

References

(1) Finkel, S., and S. Zuckerman, "Antitussive Effectiveness: Chronic Cough Counting," (Study CRD 78–13), draft of unpublished study, Comment No. SUP008, Docket No. 76N–0052, Dockets Management Branch.

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

(3) Packman, E. W., "Antitussive Screening: Citric Acid Aerosal Technique," (Study CRD 74–19/A and B), reanalysis of data, Comment No. CR0004, Docket No. 76N–0052, Dockets Management Branch.

(4) Letter form W. W. Gilbertson, FDA, to G. F. Hoffnagle, Vick Health Care Division of Richardson-Merrell, Inc., coded LET078,

Docket No. 76N–052T, Dockets Management Branch.

6. One comment submitted a new study to support the reclassification of caramiphen edisylate from Category III to Category I as an antitussive (Refs. 1 and 2). Several comments requested that the Panel's recommended 80-mg maximum daily dosage for caramiphen edisylate be increased to 120 mg. One of the comments stated that no significantly greater incidence of adverse effects occurred with the 120-mg dosage when compared with placebo or 60 mg of caramiphen edisylate. This comment cited material previously submitted to FDA under an Investigational Exemption for a New Drug in support of the 120-mg maximum daily dosage.

The agency has reviewed the submitted study (Study PM–252) and determined that the data do not support the reclassification of caramiphen edisylate from Category III to Category I as an OTC antitussive. Study PM–252 was a multidose, triple-crossover, double-blined study designed to demonstrate the effectiveness of caramiphen edisylate. Thirteen patients with chronic cough served as subjects for the study; two patients were not included in the final analysis. Each patient received a full dosage schedule treatment with 20 mg caramiphen edisylate, 10 mg caramiphen edisylate, and a placebo.

The agency performed a statistical analysis of the raw data submitted using the same statistical methods used in the submission. The p-values found by the agency did not agree with those submitted by the comment. The agency's analysis produced a p-value >0.20 for the 20-mg dose of caramiphen edisylate when compared with the placebo and a p-value >0.10 for the 10-mg dose of caramiphen edisylate when compared with the placebo, indicating that there was not a statistically significant decrease in cough counts in favor of the 20-mg or the 10-mg dose. In addition, the statistical analysis submitted by the comment ignored a comparison of the drug cough counts with the baseline cough counts which would tend to bias the results in favor of the active drug. When the baseline cough counts were used for comparison with the drug cough counts, the agency's analysis of the treatments produced no statistically significant differences among the three treatments ($p>0.15$). Thus, there is no statistical evidence that caramiphen edisylate is superior to placebo in reducing cough counts. In addition, an examination of the cough counts for each patient revealed that no drug effect was noted in 7 of the 11 patients.

The agency concludes that the submitted data do not provide evidence that caramiphen edisylate is superior to placebo in reducing cough counts. The agency is proposing Category III status at this time because caramiphen edisylate has not been shown to be effective at the 10- or 20-mg does levels. The agency will not address the comment's request for an increase in the maximum daily does at this time.

Studies to demonstrate the effectiveness of caramiphen edisylate must be done in the target population, i.e., patients with acute upper respiratory infections, or if studies are done in a patient population other than the target population, such as patients with chronic cough, the mechanism of action must be shown conclusively to act specifically on the cough center of the brain.

The agency's detailed comments and evaluations of the data are on file in the Dockets Management Branch (Ref. 3).

References

(1) Comment No. C0169, Docket No. 76N–0052, Dockets Management Branch.

(2) Comment No. AMD003, Docket No. 76N–0052, Dockets Management Branch.

(3) Letter form W. E. Gilbertson, FDA, to J. F. Cassin, Smith Kline & French Laboratories, code LET075, Docket No. 76N–052T, Dockets Management Branch.

7. One comment objected to the Panel's finding that there were no well-controlled studies of the effectiveness of carbetapentance citrate as an antitussive. The comment stated that there are two controlled studies cited by the Panel as Refs. 6 and 13 at 41 FR 38346 (Refs. 1 and 2). The comment also referred to two studies in a submission to the Panel that compared cough syrups containing carbetapentance citrate with cough syrups containing dextromethorphan and placebo, using the citric acid aerosol challenge cough-counting technique (Refs. 3 and 4). The comment claimed that these studies confirmed the antitussive activity of 15 mg of carbetapentane citrate.

The agency has reviewed the studies cited in the comment, i.e., a clinical study by Carter and Maley (Ref. 1) and the summary of the Katz study (Ref. 2); and the two studies using the citric acid aerosol challenge cough-counting technique (Refs. 3 and 4). These studies were submitted to the Panel and were part of the basis for its Category III classification of carbetapentane citrate. The comment did not submit any new data relating to these studies.

In the Carter and Maley study, 557 patients were treated with the medication, and the remaining 134 patients were given placebos (Ref. 1). However, there is no indication as to whether patients were randomly assigned to the treatment or control groups, nor is there any indication of any blinding of the investigator or patients. Although a placebo was used, it connot be said that the study was well controlled.

In the Katz study, 22 patients with pulmonary tuberculosis received medication (Ref. 2). Six patients received 25 mg carbetapentane citrate. Nine patients received 30 mg of codeine as a positive control. These same nine patients, as well as seven other patients, received varying doses of carbetapentane citrate. However, there was no evidence of randomization or any blinding in the study. In the agency's view, the study was not well controlled, and tuberculosis patients are not an appropriate OTC target population.

With respect to the two studies using the citric acid aerosol challenge cough-counting technique, the medications administered were combination products containing carbetapentane citrate as one of the active ingredients (Refs. 3 and 4). In the agency's view, it is not possible to prove the effectiveness of carbetapentane citrate as a single ingredient antitussive agent is such a study design. The agency agrees with the Panel's conclusions that there are insufficient data to permit a determination of the effectiveness of carbetapentane citrate for OTC antitussive use. Therefore, the agency concludes that carbetapentane citrate should remain in Category III.

Studies to demonstrate the effectiveness of carbetapentane citrate must be done in the target population, i.e., patients with acute upper respiratory infections, or if studies are done in a patient population other than the target population such as patients with chronic cough, the mechanism of action must be shown conclusively to act specifically on the cough center of the brain.

The agency's detailed comments and evaluations of the data are on file in the Dockets Management Branch (Refs. 5 and 6).

References

(1) Carter, C. H., and M. C. Maley, "The Clinical Value of Toclase in Suppressing the Cough Reflex," *American Journal of the Medical Sciences*, 233:77–79, 1957.

(2) Letter from S. Katz to K. Dumas, OTC Volume 040298.

(3) Packman, E. W., draft of unpublished study, OTC Volume 040075, Section V. C.aa.

(4) Packman, E. W., draft of unpublished study, OTC Volume 040075, Section V.C.bb.

(5) Letter from W. E. Gilbertson, FDA, to G. F. Hoffnagle, Vick Health Care Division of Richardson-Merrell, Inc., coded ANS/LETO70, Docket No. 76N–052T, Dockets Management Branch.

(6) Letter from W. E. Gilbertson, FDA, to G. F. Hoffnagle, Vick Health Care Division of Richardson-Merrell, Inc., coded LET082, Docket No. 76N–052T, Dockets Management Branch.

8. One comment stated that codeine-containing cough remedies should be available OTC. The comment pointed out that due to the abuse of codeine-containing cough syrups, they connot be obtained without a prescription. The comment also stated that senior citizens, who are living on a fixed income and who are not likely to become addicted to these products with limited use, should be allowed to obtain these drugs without a prescription. Another comment strongly disagreed with the OTC status of codeine because the abuse potential is high. This comment recommended that codeine antitussive preparations be available only by prescription.

The agency notes that Federal regulations currently permit the OTC sale of codeine antitussives with certain restrictions and that the Panel's recommendations are consistent with these regulations. In many cases, State Laws are more stringent and do not permit the OTC sale of these preparations within the state. Because codeine may be abused, present Federal Drug Enforcement Administration (DEA) regulations place restrictions on the OTC sale of codeine, as set forth in 21 CFR 1306.32. This regulation provides for the OTC dispensing of codeine provided that such dispensing is made only be a pharmacist; not more than 120 milliliters (mL) (4 ounces), nor more than 24 dosage units may be dispensed to the same purchaser in any given 48-hour period; the purchaser is at least 18 years of age; the pharmacist requires every purchaser not known to him to furnish suitable identification; the pharmacist maintains a record book containing the name and address of the purchaser, name and quantity of substance purchased, the date of each purchase, and name or initials of the dispensing pharmacist; and other Federal, State, or local laws do not require a prescription for distribution or dispensing of the substance. FDA regulations at § 329.20(a)(3) (21 CFR 329.20(a)(3)) limit the amount of codeine or its salts that may be marketed without prescription at one time to not more than 64.8 mg per 29.5729 mL or per 28.3 grams (g). In addition, under DEA regulations at § 1308.15(b) (21 CFR 1308.15(b)) and FDA regulations at § 329.20(a) products containing narcotic drugs such as codeine must include one or more nonnarcotic active medicinal ingredients in sufficient proportion to confer upon the product valuable medicinal qualities other than those possessed by the narcotic drugs alone. Category I status of codeine ingredients for OTC use is restricted to drug products containing codeine in combination with one or more nonnaroctic active ingredients in accordance with §§ 329.20(a), 341.40, and 1308.15(b).

Although some individuals may abuse these products, the Panel felt that under conditions of normal therapeutic use, codeine has low dependency liability (41 FR 38339). Codeine may cause addiction, but it requires a consistently high daily dose to do so (Ref. 1). Therefore, the agency is proposing that codeine be generally recognized as safe and effective for OTC use as an antitussive agent under the restrictions noted above.

Reference

(1) Himmelsbach, C. K., et al., "Studies on Codeine Addiction," *Public Health Reports (supplement)*, 158: 1–67, 1940.

9. One comment requested that a "careful look" be taken at antitussive medications currently marketed OTC, especially dextromethorphan. The comment stated that, as is the case with any medication for children, the potential for accidental overdosing in children must be considered in any final evaluation.

The agency has reviewed the Panel's discussion pertinent to antitussives. Dextromethorphan has a wide margin of safety with respect to its potential to cause poisoning through accidental overdose. The Panel stated that no fatalities have been reported even with doses in excess of 100 times the normal adult dose (41 FR 38340). A review of the annual adverse reaction summary listing for the years 1969 to 1981 indicated 15 cases of reactions in children aged 1 to 10 years (Ref. 1). The adverse reactions reported included such side effects as hallucination, urticaria, nausea, insomnia, and hysteria, but no fatalities. Ataxia, edema of the face, and urticaria were reported in an apparent overdosing case involving a child 2 years of age who received a total of 225 mg dextromethorphan contained in 2.5 ounces of an antitussive drug product. While the potential for accidental overdosing and subsequent effects must be considered for any drug, in the case of dextromethorphan, the potential for toxicity to occur from accidental overdose is extremely low. The Panel concluded, and the agency concurs, that because of its low order of toxicity, dextromethorphan is probably the safest antitussive presently available. The comment did not present any data to alter these conclusions.

Reference

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

10. Several comments questioned the safety of diphenhydramine hydrochloride for OTC use and stated that studies have shown this ingredient can cause an unacceptable level of drowsiness. Some comments also contended that the available data do not adequately demonstrate antitussive effectiveness. A comment requested that the Commissioner reconsider a decision published in the **Federal Register** of November 30, 1976 (41 FR 52536) in which FDA dissented from the Panel's recommended Category I classification of diphenhydramine hydrochloride for OTC antitussive use and announced that any marketed product containing diphenhydramine hydrochloride for OTC antitussive use would be subject to immediate regulatory action.

At the time the Panel's report was published, September 9, 1976 (41 FR 38312), the Commissioner deferred a decision on the Panel's recommendation to place diphenhydramine hydrochloride in Category I as an OTC antitussive ingredient. FDA stated that the agency would wait until it had made a decision concerning a then pending supplemental NDA that had been submitted under 21 U.S.C. 355 seeking FDA approval for marketing of diphenhydramine hyrochloride as an OTC antitussive for the drug product Benylin. Subequently, on November 30, 1976, the agency announced in the **Federal Register** that the Commissioner did not accept the Panel's recommendation that diphenhydramine hydrochloride be classified in Category I for OTC antitussive use (41 FR 52536). In the **Federal Register** the Commissioner concluded that the recommended antitussive dose of diphenhydramine hydrochloride (25 mg) causes an unacceptable level of drowsiness for OTC use, even with a warning statement in the labeling as recommended by the Panel. Furthermore, although agreeing with the Panel that some data indicated that this ingredient has an antitussive effect, the Commissioner found a lack of

substantial evidence consisting of adequate and well-controlled studies, as required by § 314.111(a)(5)(ii) (21 CFR 314.111(a)(5)(ii)), on which to base a determination of the effectiveness of diphenhydramine hydrochloride as an antitussive. Because diphenhydramine hydrochloride had been limited to prescription use, the agency announced that under 21 CFR 330.13(b)(2) any marketed product containing diphenhydramine hydrochloride for OTC antitussive use was subject to immediate regulatory action.

With respect to the proceeding involving the supplemental NDA for Benylin, on August 31, 1979, FDA published in the **Federal Register** a final decision on the issues that had been presented in a formal evidentiary public hearing (44 FR 51512). In the Benylin decision the Commissioner extensively reviewed the safety and effectiveness data submitted by the manufacturer in support of an NDA for Benylin as an antitussive. This review also included a reevaluation of the findings of the Cough-Cold Panel regarding the general recognition of diphenhydramine hydrochloride's safety and effectiveness as an antitussive agent. In this decision, the Commissioner stated that studies to demonstrate the effectiveness of an antitussive must be done in the target population, i.e., patients with acute upper respiratory infections, and if studies are done in a patient population other than the target population, such as patients with chronic cough, the mechanism of action must be shown conclusively to act specifically on the cough center of the brain. The Commissioner also stated that induced cough studies are not a substitute for adequate and well-controlled studies in the target population and determined that the available data did not show that diphenhydramine hydrochloride was effective as an antitussive by the above criteria.

With regard to the safety of diphenhydramine hydrochloride, the Commissioner stated:

> I believe that, if Benylin were shown to be an effective antitussive drug, it might be possible to devise labeling that would provide adequate warnings of the risk of drowsiness and other ill effects and that, coupled with child resistant packaging, would enable the product to be safely used as an OTC drug. In devising any such labeling [it would be necessary] to consider inclusion of some or all of the information in the approved labeling for prescription Benylin as well as that recommended by the * * * Panel (footnote omitted). The risk to patients from a drug that causes drowsiness is indirect. The drowsiness itself does not cause harm. It is only when the patient tries to undertake a task that requires alertness such as driving a car, that the drug's sedative qualities pose a risk to the patient and to other members of the public. Suitable labeling of an OTC drug may provide sufficient safeguards for a drug that presents serious direct risks (e.g., of cancer or other serious disease), adequate labeling for any use without medical supervision generally cannot be written (44 FR 51524, 51525).

After publication of this notice, new data on the mechanism of action of diphenhydramine hydrochloride as an antitussive were submitted to the agency by the manufacturer of Benylin. These data were provided in response to an October 5, 1979 notice of opportunity for hearing on a proposal to withdraw approval of the NDA for Benylin (41 FR 57497). The new data contained unpublished studies which are considered to be confidential information covered by 21 CFR 20.61 and are not publicly available. Based on the agency's review of these studies and a reevaluation of two studies that had been reviewed by the Panel (Refs. 1 and 2) and included in a "Supplemental Medical Review" (Ref. 3), the agency approved a supplemental NDA for the marketing of Benylin as an OTC antitussive (Ref. 4). In essence, this action constituted the FDA's determination that diphenhydramine hydrochloride had been shown to be safe and effective as an antitussive in this particular product. However, even though FDA approved a supplemental NDA for this product, diphenhydramine hydrochloride as an OTC antitussive continues to be a "new drug" within the meaning of 21 U.S.C. 321(p) because of a lack of general recognition of effectiveness. A determination by FDA that a new drug is safe and effective and the approval of a NDA for the drug are not, of course, synonymous with a determination that a drug is generally recognized as safe and effective. See *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 651 (1973).

The new data accepted by the agency as demonstrating a central mechanism of action for diphenhydramine hydrochloride as an antitussive are not in the public domain. General recognition of the effectiveness of a drug, however, must be based on adequate published or publicly available medical and scientific data. (*United States* v. *41 Cases * * * Naremco*, 420 F. 2d 1126 (C.A. 5, 1970); *United States* v. *An Article of Drug * * * Mykocert*, 345 F. Supp. 571 (D.C. 1972); *United States* v. *An Article of Drug * * * Asper Sleep*, CCH F.D. and Cosm. L. Rep. 40,821 Civil No. 70–C–196 (N.D. Ill. 1971); *United Stated* v. *An Article of Drug * * * Furestrol Vaginal Suppositories* 294 F. Supp. 1307 (N.D. Ga. 1968).) Therefore, even though diphenhydramine hydrochloride has been shown, on the basis of proprietary information, to be safe and effective as required by 21 U.S.C. 355(d), there is not adequate information publicly available at this time to demonstrate that it is generally recognized as effective. Because the agency is unable to conclude at this time that diphenhydramine hydrochloride is generally recognized as effective as an OTC antitussive, FDA is proposing that it be Category III. Category III status at the tentative final stage of this rulemaking or nonmonograph status at the final stage of this rulemaking will not affect the legal OTC marketing of this drug under an approved NDA. Therefore, the present OTC marketing of Benylin under an approved supplemental NDA will not be changed by this rulemaking.

With respect to the issue of safety, the agency continues to agree with the Commissioner's discussion in the Benylin matter quoted above. Therefore, FDA tentatively concludes that diphenhydramine hydrochloride, with appropriate warnings, can be generally recognized as safe.

In a related matter, the agency recently responded to a petition seeking FDA's determination that diphenhydramine hydrochloride as an active ingredient in OTC antitussive drug products is generally recognized as safe and effective (Refs. 5 through 8). The agency advised the petitioner that diphenhydramine hydrochloride as an ingredient in OTC antitussive drug products at this time is not generally recognized as safe and effective and continues to be a "new drug" as defined in 21 U.S.C. 321(p). Therefore, at present diphenhydramine hydrochloride cannot be lawfully marketed as an OTC antitussive in the absence of an approved NDA (Ref. 9).

References

(1) Lilienfield, L.S., Protocol 184–35, draft of unpublished data, OTC Volume 040298.

(2) Summers, W. R., Protocol 184–36, draft of unpublished data, OTC Volume 040298.

(3) Walters, P. G., Supplemental Medical Review of January 22, 1981, NDA 6–514, OTC Volume 04TTFM, Dockets Management Branch.

(4) Letter from M. J. Finkel, FDA, to Warner-Lambert Company, NDA 6–514, OTC Volume 04TTFM, Dockets Management Branch.

(5) Comment No. CP, Docket No. 76N–052T, Dockets Management Branch.

(6) Comment No. C00190, Docket No. 76N–052T, Dockets Management Branch.

(7) Comment No. RC, Docket No. 76N–052T Dockets Management Branch.

(8) Comment No. RC0002, Docket No. 76N–052T, Dockets Management Branch.

(9) Letter from J. P. Hile, FDA, to R. N. Anderson, Vicks Health Care Division of Richardson-Vicks, Inc., coded PDN001, Docket No. 76N–052T, Dockets Management Branch.

11. One comment objected to permitting antitussive preparations containing ethylmorphine hydrochloride to be available for OTC use. The comment argued that ethylmorphine should be restricted to prescription status because the abuse potential would be high if it is permitted in OCT antitussive drug products.

The agency disagrees with the comment and concurs with the Panel's conclusion that ethylmorphine hydrochloride is safe "in the dose range used as an antitussive" (41 FR 38347). The agency recognizes, as did the Panel, that the possibility of abuse of ethylmorphine hydrochloride exists. Ethylmorphine is the ethyl ether of morphine and its pharmacologic properties, including its abuse potential, are similar to codeine, which is the methyl ether of morphine. Because of this, ethylmorphine hydrochloride is currently subject to DEA and FDA regulations. The regulations at 21 CFR 329.20 and at CFR 1306.32 provide for the OTC dispensing of ethylmorphine without a prescription under the same conditions that codeine may be dispensed OTC. (See comment 8 above.) In addition, § 329.20(a)(5) limits the amount of ethylmorphine or its salts that may be marketed without prescription to not more than 16.2 mg per 29.5729 mL or per 28.3 g.

Based on these regulations and the Panel's recommendations, the agency concludes that it is not necessary to restrict ethylmorphine hydrochloride to prescription status as proposed by the comment. However, the Panel questioned the effectiveness of ethylmorphine hydrochloride for use as an OTC antitussive and determined that additional data are needed to demonstrate its effectiveness. The agency agrees with this conclusion and is classifying ethylmorphine hydrochloride in Category III in this document.

12. One comment submitted data from two new studies and requested that eucalyptus oil be reclassified from Category III to Category I for OTC topical antitussive use in the form of a lozenge (Ref. 1).

The agency has reviewed the two studies (CFD 76–49R and CFD 77–59) and concludes that the data do not justify reclassifying eucalyptus oil from Category III to Category I for OCT antitussive use in the form of a lozenge because they do not conclusively demonstrate the effectiveness of eucalyptus oil.

Study CRD 76–49R was a singly-blind, induced-cough, crossover study involving 36 normal subjects challenged with acetic acid aerosol. The study compared the antitussive effect of eucalyptus oil alone, menthol alone, the combination of menthol and eucalyptus oil, and a vehicle control. The agency's analysis of the results showed that eucalyptus oil in a lozenge produced significant reductions in cough counts as compared with placebo at time intervals of 10, 30, and 50 minutes. The agency concludes that study CRD 76–49R is supportive, but it does not establish the antitussive effectiveness of eucalyptus oil in a lozenge dosage form. The Panel determined that induced-cough studies of this kind are not adequate alone to demonstrate the effectiveness of an antitussive ingredient, and the agency concurs.

In the second study, CRD 77–59, the antitussive effectiveness of 0.15 percent eucalyptus oil was compared with a control lozenge in 48 chronic bronchitis patients using cough-recording procedures. The agency's analysis of the results indicated that the antitussive effectiveness of eucalyptus oil was not adequately demonstrated. The study showed a reduction in cough of approximately 2 percent with the eucalyptus oil as compared to the control, but this reduction occurred only in the afternoon and amounted to approximately one less cough per hour. A statistical evaluation showed no significant differences in the reduction of cough counts or cough components at any time.

Based on these data, the agency concludes that the topical antitussive effectiveness of eucalyptus oil has not been established and that this ingredient does not cause a significant reduction in cough. Therefore, the agency is proposing in this tentative final monograph that eucalyuptus oil as an antitussive in lozenge form remain in Category III.

The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Refs. 2 and 3).

References

(1) Comment Nos. SUP009, SUP011, and SUP012, Docket No. 76N–0052, Dockets Management Branch.

(2) Letter from W. E. Gilbertson, FDA, to G. F. Hoffnagle, Vick Health Care Division of Richardson-Merrell, Inc., coded LET069, Docket No. 76N–052T, Dockets Management Branch.

(3) Letter from W. E. Gilbertson, FDA, to G. F. Hoffnagle, Vick Health Care Division of Richardson-Merrell, Inc., coded LET080, Docket No. 76N–052T, Dockets Management Branch.

13. One comment requested reclassification of eucalyptus oil from Category III to Category I as an antitussive for topical use in an ointment to be rubbed on the chest and submitted new data from two studies to show the effectiveness of this ingredient (Ref. 1).

The agency has reviewed the data and concludes that they are insufficient to support the reclassification of eucalyptus oil as a single ingredient from Category III to Category I for this use. Neither study dealt specifically with eucalyptus oil as a single ingredient and instead dealt with an ointment containing the volatile substances menthol, spirits of turpentine, camphor, cedar leaf oil, myristical oil, thymol, and 1.3 percent eucalyptus oil; camphor in petrolatum ointment; and menthol in petrolatum ointment. Consequently, these data do not demonstrate the effectiveness of eucalyptus oil alone as an antitussive.

In addition to reviewing the new data, the agency has reevaluated the data and information that were submitted to the Panel concerning the antitussive effectiveness of eucalyptus oil in an ointment to be rubbed on the chest. The agency's analyses of these data agree with the Panel's evaluation that the effectiveness of eucalyptus oil in ointment form has not been demonstrated. Only two of the studies (CRD 74–19/B and CRD 74–64) submitted to the Panel evaluated the antitrussive effective of eucalyptus oil as a single ingredient in the form of an ointment (Refs. 2 and 3).

Study CRD 74–19/B was a single-blind, placebo-controlled, crossover, induced-cough study involving 32 normal subjects. The Panel concluded that study CRD 74–19/B is supportive but not sufficient evidence of the claimed antitussive effectiveness of eucalyptus oil used in the form of an ointment. The Panel determined that induced-cough studies of this kind are not adequate alone to demonstrate the effectiveness of an antitussive ingredient, and the agency concurs.

Study CRD 74–64 was a single-blind, placebo-controlled, crossover study involving 27 patients with chronic bronchitis considered to have been stable for 6 months. The Panel concluded that the results did not demonstrate the antitussive effectiveness of eucalyptus oil in ointment form and the agency concurs with this finding.

The agency concludes that eucalyptus oil should remain in Category III for

topical antitussive use in the form of an ointment. Because no data were submitted on eucalyptus oil for use as an antitussive in a steam vaporizer, eucalyptus oil for this use also remains in Category III.

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

References

(1) Comment No. SUP008, Docket No. 76N–0052, Dockets Management Branch.

(2) Packman, E. W., "Antitussive Screening: Citric Acid Aerosol Technique," (Studies CRD 74–19/A and B), draft of unpublished data, OTC Volume 040298, Dockets Management Branch.

(3) Dennis, S. R. K., et al., "Medical Report on a Study to Evaluate the Effects of Vicks VapoRub as Compared to Those of Oil of Eucalyptus and a Petrolatum Placebo," (Study CRD 76–64), Draft of unpublished data, OTC volume 040298, Dockets Management Branch.

(4) Letter from W. E. Gilbertson, FDA, to G. F. Hoffnagle, Vick Health Care Division of Richardson-Merrell, Inc., coded LET077, Docket No. 76N–052T, Dockets Management Branch.

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

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

The response in this document addresses only the antitussive use of these ingredients. The nasal decongestant use will be addressed in a future issue of the **Federal Register**. The agency has reviewed the FTC's opinion and supporting evidence (Ref. 1). Medical and scientific experts testified at the FTC hearing that there is an absence of literature showing that the combination of eucalyptol, menthol, and thymol in a mouthwash dosage form is effective in preventing colds and alleviating cold symptoms such as nasal congestion and cough. These experts in the fields of respiratory and infectious diseases, virology, pharmacology, and microbiology further stated, based upon their knowledge in their respective areas, that it is doubtful that these ingredients would be effective in treating symptoms of the common cold.

Although the Panel did not have access to the FTC's opinion and supporting evidence, it did review the St. Barnabas study, which was one of the studies discussed during the FTC hearing (Ref. 2). The St. Barnabas study was undertaken to demonstrate the effect of rinsing and gargling twice daily with an aqueous mixture of 0.91 mg/mL eucalyptol, 0.42 mg/mL menthol, and 0.63 mg/mL thymol on the incidence, duration, and severity of the common cold and its symptoms. It was a 4-year subjective study in over 4,800 schoolchildren. The experts who testified at the FTC hearing agreed that the deficiencies in the design and execution of the study precluded any meaningful interpretation of the results. The FTC concluded that the design and execution of the tests heavily biased the results in favor of the manufacturer, and therefore the tests could not support the advertising claims. The Panel concluded that although the study was not well-controlled and could not be considered proof of effectiveness, the results did reveal milder nasal symptoms and cough symptoms in individuals using the medicated mouthwash as compared with these symptoms in individuals using the placebo. Because this study did not demonstrate the effectiveness of the individual antitussive ingredients, the Panel recommended that data to demonstrate effectiveness of each ingredient alone be required in accordance with its guidelines for testing OTC antitussive drug products (41 FR 38354 to 38355). Because safety was not at issue, and the data suggested the possibility that the combination of eucalyptol, menthol, and thymol was effective as an antitussive in a mouthwash dosage form, the Panel believed that a Category III classification was justified.

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

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

References

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

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

15. Two comments requested that 1 to 15 mg of menthol as an antitussive in a

lozenge dosage form be reclassified from Category III to Category I. One comment submitted new data in support of a dosage range of 5 to 10 mg of menthol (Refs. 1 through 8). The second comment contained data in support of a 10-mg menthol lozenge (Ref. 9). Another comment requested Category I status for lozenges containing less than 5 mg of menthol based on data previously reviewed by the Panel (Refs. 10 through 13).

Based on the data above, the agency proposes to classify menthol as a Category I antitussive at a dosage of 5 to 10 mg in a lozenge or compressed tablet dosage form. (See comment 20 below regarding compressed tablets.) The agency concludes that the two studies conducted by Finkel and Zuckerman (Refs. 6 and 7) show menthol to be effective in a lozenge at doses of 5.2 mg and 7.8 mg, respectively. In addition, the data submitted by the second comment show that menthol in a lozenge, at a dose of 10 mg, is an effective topical antitussive (Ref. 9). Based on the results of the studies, the agency concludes that the dosage frequency for lozenges or compressed tablets containing 5 to 10 mg menthol should be every hour instead of the Panel's recommended fequency of every 30 minutes to an hour.

The four studies, submitted in support of a dosage of less than 5 mg of menthol (Refs. 10 through 14), are not acceptable to prove the effectiveness of menthol at this dosage. The major problem in all four studies is that menthol was not studied as a single ingredient. All of the test lozenges contained other ingredients (benzyl alcohol, citric acid, eucalyptus oil, camphor, thymol, tolu balsam) in addition to menthol; thus, any therapeutic effect obtained from the use of the lozenge cannot be attributed to menthol only. The control lozenges did not contain these additional ingredients. Therefore, these studies cannot be considered supportive of the effectiveness of lozenges containing less than 5 mg of menthol. Menthol at less than 5 mg will remain in Category III until adequate data are presented to warrant reclassification to Category I.

In conclusion, the agency proposes to reclassify menthol in a lozenge or compressed tablet at a dose of 5 to 10 mg from Category III to Category I as an antitussive. The directions for menthol are being proposed as follows: Adults and children 2 to under 12 years of age: allow (lozenge or compressed tablet) to dissolve slowly in the mouth. May be repeated every hour as needed or as directed by a doctor. Children under 2 years of age: consult a doctor. Because no data were submitted to support a menthol dose greater than 10 mg, such a dose will remain in Category III.

The agency's detailed comments and evaluations of the data are on file in the Dockets Management Branch (Refs. 15 through 18).

References

(1) Dennis, S. R. K., P. Bass, and G. doPico, "Victors," (Study CRD No. 75–21), draft of unpublished study, Comment No. SUP009, Docket No. 76N–0052, Dockets Management Branch.

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

(3) Dennis, S. R. K., P. Bass, and G. doPico, "Victors," (Study CRD No. 75–50), draft of unpublished study, Comment No. SUP009, Docket No. 76N–0052, Dockets Management Branch.

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

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

(6) Finkel, S., and S. Zuckerman, "Victors," (Study CFD No. 77–58), draft of unpublished study, Comment No. SUP009, Docket No. 76N–0052, Dockets Management Branch.

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

(8) Comment No. SUP012, Docket No. 76N–0052, Dockets Management Branch.

(9) Comment No. CO181 (Volume 1), Docket No. 76N–0052, Dockets Management Branch.

(10) Packman, E. W., "Vicks Cough Drops," (Study CRD No. 72–64), draft of unpublished study, OTC Volume 040257.

(11) Packman, E. W., "Vick Cough Drops," (Study CRD No. 73–7), draft of unpublished study, OTC Volume 040257.

(12) Packman, E. W., "Vick Cough Drops," (Study CRD No. 73–8), draft of unpublished study, OTC Volume 040257.

(13) Packman, E. W., and S. J. London, "Vicks Cough Drops," (Study CRD No. 71–19), draft of unpublished study, OTC Volume 040063.

(14) Comment Nos. LET067 and SUP011, Docket No. 76N–0052, Dockets Management Branch.

(15) Letter from W. E. Gilbertson, FDA, to G. F. Hoffnagle, Vick Health Care Division of Richardson-Merrell, Inc., coded ANS 81/01/29 to SUP009, Docket No. 76N–052T, Dockets Management Branch.

(16) Letter from W. E. Gilbertson, FDA, to J. D. Clark, Warner-Lambert Company, coded NAS 81/01/29 to SUP009, Docket No. 76N–052T, Dockets Management Branch.

(17) Memorandum of Meeting, coded MM0003, Docket No. 76N–052T, Dockets Management Branch.

(18) Letter from W. E. Gilbertson, FDA, to G. F. Hoffnagle, Vick Health Care Division of Richardson-Merrell, Inc., coded LET081, Docket No. 76N–052T, Dockets Management Branch.

16. One comment requested reclassification of menthol from Category III to Category I as an antitussive for topical use in an ointment to be rubbed on the chest and submitted new data from two studies (Refs. 1 and 2), as well as a reanalysis of data from a study reviewed by the Panel (Ref. 3), to show the effectiveness of this ingredient.

The agency has reviewed the data and concludes that two of the studies are adequate to support the reclassification of menthol to Category I for this use (Refs. 1 and 3). In the first study, the antitussive effectiveness of 2.6 percent menthol in petrolatum was compared with petrolatum alone as a control in 48 patients with chronic cough due to bronchopulmonary disease (Ref. 1). The data indicated that menthol decreased the number of coughs and cough components to a significantly greater degree than the petrolatum control. The agency concludes that this study is acceptable in demonstrating the effectiveness of 2.6 percent menthol as an antitussive in a suitable ointment vehicle to be rubbed on the chest.

In the second study, the antitussive effectiveness of 2.8 percent menthol in petrolatum on artificially induced cough was compared with 5.3 percent camphor in petrolatum; 2.82 percent menthol in a mixture with camphor, eucalyptus oil, thymol, turpentine oil, myristica oil, and cedarleaf oil in petrolatum; and a petrolatum control. Menthol in petrolatum was significantly more effective than petrolatum alone in reducing coughs at 0.5, 1, and 3 hours and marginally more effective at 1.5 hours. The agency's analysis of the studies indicates statistical evidence of the superiority of 2.8 percent menthol over petrolatum alone in reducing cough counts (Ref. 3).

A third study was reviewed by the agency and found not to be supportive of menthol as an antitussive ingredient because there were no significant differences among the four treatment groups studied (Ref. 2).

Based on the evaluation of the first two studies, the agency proposes to reclassify menthol in concentrations of 2.6 to 2.8 percent for topical use in an ointment to be rubbed on the chest from Category III to Category I in this tentative final monograph. The directions for menthol are being proposed as follows: Adults and children 2 to under 12 years of age: rub on the throat and chest as a thick layer. The area of application may be covered

with a warm, dry cloth if desired. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to three times daily or as directed by a doctor. Children under 2 years of age: consult a doctor.

The agency notes that in the submitted studies the ointment was used on the anterior chest and not on the back. Therefore, the Panel's recommended direction for use that provides for menthol to be "rubbed on the back" is not being reclassified as Category I, but remains in Category III. Because no data were submitted on menthol for use as an antitussive in a steam vaporizer, menthol for this use also remains in Category III.

The warning "For external use only. Do not take by mouth or place in nostrils" is being proposed in the "Warnings" section of this tentative final monograph. The Panel recommended that such a warning be included in the required labeling for antitussive drug products containing menthol that are used in the form of an ointment, and the agency concurs.

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

References

(1) Finkel, S., and S. Zuckerman, "Antitussive Effectiveness: Chronic Cough Counting," (Study CRD 78–14), draft of unpublished study, Comment No. SUP008, Docket No. 76N–0052, Dockets Management Branch.

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

(3) Packman, E. W., "Antitussive Screening: Citric Acid Aerosol Technique," (Studies CRD 74–19/A and B), reanalysis of data, Comment CR0004, Docket No. 76N–0052, Dockets Management Branch.

(4) Letter from W. E. Gilbertson, FDA, to G. F. Hoffnagle, Vick Health Care Division of Richardson-Merrell, Inc., coded LET079, Docket No. 76N–052T, Dockets Management Branch.

17. One comment disagreed with the Panel's conclusion that there are insufficient data to determine the effectiveness of noscapine for OTC use as an antitussive and requested that it be reclassified from Category III to Category I. The comment contended that a lack of current studies persuaded the Panel to place noscapine in Category III and to recommend that two additional studies be conducted to establish its effectiveness. The comment argued that, although the current studies may have been lacking in quantity, the quality of existing studies clearly shows that noscapine is an effective antitussive. The comment added that, because of the very unusual pharmacological properties of noscapine, the Panel should have considered it as an expectorant as well as an antitussive. (A discussion of this ingredient as an expectorant is included in comment 16 in the proposed rule for anticholinergic and expectorant drug products published in the **Federal Register** of July 9, 1982 (47 FR 30007).) The comment pointed out that noscapine has been shown to have the significant advantage of facilitating expectoration and stimulating the production of bronchial mucus, while suppressing nonproductive cough in certain disease states such as asthma, and cited a study in support of this activity (Ref. 1).

The agency has reviewed the Panel's findings regarding the Category III status of noscapine as an antitussive and notes that the Panel concluded that effectiveness has not been established by objective methods (41 FR 38352). The Panel cited six references (Refs. 2 through 7) and noted that, although the majority of these reported clinical trials indicate that noscapine is equal to codeine in clinical effectiveness, these studies are subjective. The Panel recommended that objective studies employing cough-counting techniques be required to demonstrate the effectiveness of antitussives, and the agency concurs. The agency's evaluation of the six studies cited by the Panel confirmed that none of these studies include objective cough-counting methods.

The agency has reviewed the reference cited by the comment in which noscapine hydrochloride was administered intravenously to 50 surgical patients in a dosage of 3 milligrams per kilogram (mg/kg) body weight (Ref. 1). Doses were administered before the induction of anesthesia or at the end of anesthesia. The cough reflex was not completely removed, and foreign matter in the laryngeal or bronchial areas was coughed up. The researchers concluded that "It appears that this drug should be given an extended trial in any situation where a reduction of the cough reflex is desirable."

The study assessed only the intravenous use of noscapine in surgical patients as an antitussive. The study did not use cough-counting techniques. The agency does not consider this study appropriate to demonstrate the effectiveness of noscapine taken orally as an OTC antitussive. The agency also notes that "AMA Drug Evaluations" states that noscapine has been shown to be effective in some studies, but evidence is insufficient to determine its relative effectiveness conclusively (Ref. 8). "AMA Drug Evaluations" cited a report by Eddy et al. (Ref. 9), which states that clinical reports and judgments of noscapine as an antitussive have been few and trials have generally been poorly controlled. Those that are availabe represent mainly the impressions gained by the investigators.

The agency is unaware of any recent studies which would establish the effectiveness of noscapine as an antitussive; therefore, based on the available evidence, the agency is proposing that noscapine remain in Category III for OTC use as an antitussive.

References

(1) Loder, R. E., "Safe Reduction of the Cough Reflex with Noscipine," *Anaesthesia,* 24:355–358, 1969.

(2) Segal, M. S., M. M. Goldstein, and E. O. Attinger, "The Use of Noscapine (Narcotine) as an Antitussive Agent," *Diseases of the Chest,* 32:305–309, 1957.

(3) Janschulte, B., "Experience with Narcompren, a New Antitussive," (English translation), ("Erfahrungen mit Narcompren, einem neuen Hustenmittel"), *Medizinische Klinik,* 42:1788–1789, 1955.

(4) Peeters, E. G., "Antitussive Properties of Noscapine," (English translation), ("Les Proprietes Antitussives de la Noscapine"), *Le Scalpel,* 114:945–954, 1961.

(5) General Practitioner Research Group, Report No. 21, "General Practitoner Clinical Trials. A Long Acting Antitussive Preparation," *The Practitioner,* 188:249–252, 1962.

(6) Bergmann, M., and H. Stolzer, "Clinical Experience with Narcotine as a Cough Suppressant," (English translation), ("Klinische Erfahrungen mit 'Narkotin' als hustenreizstillendes Mittel"), *Wiener Medizinische Wochenschrift,* 106:232–233, 1956.

(7) Blankart, R., "Clinical Experience with an Antitussive Containing Narcotine," (English translation), ("Klinische Erfahrungen mit einem narcotinhaltigen Hustenmittel"), *Therapeutische Umschau,* 20:403–406, 1963.

(8) "AMA Drug Evaluations," 4th Ed., John Wiley and Sons, Inc., New York, p. 468, 1980.

(9) Eddy, N. B., et al., "Codeine and Its Alternatives for Pain and Cough Relief. 4. Potential Alternates for Cough Relief," *Bulletin of the World Health Organization,* 40:639–719, 1969.

D. Comments on Dosages for Antitussive Active Ingredients

18. One comment cited articles on camphor poisoning in children (Refs. 1 and 2) and recommended that the camphor content of OTC antitussives be limited to less than 0.75 g camphor per 30 g of final product or to less than 2.5 percent (weight/volume). The comment stated that there is no evidence that warning statements deter childhood

poisoning and concluded that this lower concentration would reduce the risk of serious accidental poisoning while still permitting an adequate concentration of camphor.

The Panel found camphor safe when applied topically or as an inhalant at certain concentrations, but recommended a Category III classification based on insufficient data to permit final classification of its effectiveness when labeled for use as an antitussive (41 FR 38344). For adults and children 2 to under 12 years of age, the Panel recommended Category III labeling for the use of camphor in the form of a 5-percent ointment preparation, a 7-percent solution for steam inhalation, or a lozenge containing 0.02 to 15 mg camphor. Following publication of the Panel's recommendations on camphor, the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel) also reviewed camphor. The Miscellaneous External Panel, however, concluded that OTC products containing greater than 2.5 percent camphor have a low benefit-to-risk ratio and recommended that camphor be limited in OTC drug products for external use to less than 2.5 percent (45 FR 63874). The Miscellaneous External Panel also recommended that the total quantity of camphor in a package be limited to 360 mg and stated that a child-proof container would deter childhood poisoning.

Because of the conflicting recommendations on camphor-containing drug products, the agency announced in the **Federal Register** of September 26, 1980 (45 FR 63874) that it is treating the data and information on camphor received from the Miscellaneous External Panel as a petition to reopen the administrative record on cold, cough, allergy, bronchodilator, and antiasthmatic drug products. The agency subsequently granted this petition by allowing those data and information to be included in the administrative record for these drug products. This notice served to inform interested persons of the existence of these recommendations and also invited persons or firms to submit any comments they may have. One manufacturer submitted a comment in response to the data information received from the Miscellaneous External Panel and requested that this Panel's recommendations concerning reduction in the concentration of camphor and limitation of the amount of camphor contained in a package be rejected (Ref. 3). This reopening of the administrative record related only to the ingredient camphor in OTC drug products.

The agency is proposing to classify camphor in concentrations for 4.7 to 5.3 percent in an ointment to be rubbed on the chest in Category I as an antitussive. (See comment 5 above.) The agency has reviewed the Panel's varying recommendations and determined that there is little likelihood of childhood poisonings occurring from camphor being available OTC in a 4.7 to 5.3 percent concentration in an ointment dosage form. Most of the poisonings that have occurred with camphor preparations have occurred with liquid products and not with camphor in an ointment. Therefore, the agency sees no reason to limit the quantity of camphor to 360 mg in such products labeled for antitussive use. Manufacturers are, however, encouraged voluntarily to use child-proof containers to reduce the possibility of young children inadvertently getting into such products.

References

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

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

(3) Comment No. C00185, Docket No. 76N–0052, Dockets Mangement Branch.

19. One comment from a pediatrician objected to the use of codeine antitussives in children. The comment stated that there is little, if any, indication for cough suppression in respiratory diseases of children. The comment recommended that the labeling of codeine antitussives should not allow their use in children under 12 years of age. Another pediatrician has expressed concern to FDA about the use of codeine-containing antitussives in young children (Ref. 1).

The agency recognizes that antitussives should not be used indiscriminately in children. The Panel stated that antitussives are beneficial to suppress an irritative cough associated with a self-limiting respiratory tract infection that is usually viral in nature or that follows the inhalation of irritant gases or dusts (41 FR 38321). The Panel believed that OTC antitussive drug products could be rationally used for this type of cough and used safely in children over 2 years of age.

In response to the two pediatricians' concerns about the use of codeine-containing antitussives in young children, the agency requested the American Academy of Pediatrics (AAP) to make recommendations on this issue. The AAP based its recommendations on a poll of the members of its Committee on Accident and Poison Control and a number of directors of pediatric outpatient departments in hospitals and on a review of case histories of adverse reactions to codeine in young children (Ref. 2). AAP stated in its report to FDA that "We believe there is a preponderance of evidence that codeine-containing cough syrups can be hazardous to young children, even in prescribed doses."

Young children 2 to 5 years of age appear to be most vulnerable to serious adverse reactions to codeine. Respiratory arrest, coma, and death have been reported in this age group following codeine doses of 5 to 12 mg/kg body weight (Refs. 3, 4, and 5). Although the Panel provided recommended doses of codeine for children 2 to under 12 years of age, the AAP's belief that "codeine-containing cough syrups can be hazardous to young children, even in prescribed doses" and the data on adverse reactions in children 2 to 5 years of age raise questions concerning the safety of administering codeine to children under 6 years of age on an OTC basis.

Because the agency has received two varying recommendations on this dose, at this time the agency is taking a more conservative approach and is proposing that a codeine dose for children 2 to under 6 years of age be provided in professional labeling only. Labeling of OTC codeine-containing antitussives would not contain a recommended dose for this age group, but would include the following statement: Children 2 to under 6 years of age: consult a doctor. The agency invites specific comment on this proposal.

The AAP has recommended a codeine dose for young children of 1 mg/kg body weight in four divided doses, not to exceed 60 mg/day. The agency notes that there are no documented cases of serious adverse reactions in children at the AAP's recommended dose in the literature, in the National Clearinghouse for Poison Control Center data, or in the FDA adverse reaction reporting system (Ref. 3). The AAP also recommended including a calibrated measuring device in the package of a codeine-containing antitussive drug product that is intended to be used in young children. The agency agrees with the AAP that codeine should be used in children under 6 years of age at no higher dose than 1 mg/kg body weight per day and that because of the seriousness of possible adverse reactions due to inadvertent overdose caused by inaccurate measuring of the dose, the use of a calibrated measuring device to

administer this dose is necessary. Accordingly, the agency is proposing the following paragraphs under § 341.90(p) of the professional labeling section of the monograph.

(1) Children 2 to under 6 years of age: oral dosage is 1 milligram per kilogram body weight per day administered in four equal divided doses. The average body weight for each age may also be used to determine dosage as follows: for children 2 years of age (average body weight, 12 kilograms), the oral dosage is 3 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours; for children 3 years of age (average bodyweight, 14 kilograms), the oral dosage is 3.5 milligrams every 4 to 6 hours, not to exceed 14 milligrams in 24 hours; for children 4 years of age (average body weight, 16 kilograms), the oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 16 milligrams in 24 hours; for children 5 years of age (average body weight, 18 kilograms), the oral dosage is 4.5 milligrams every 4 to 6 hours, not to exceed 18 milligrams in 24 hours. If age is used to determine the dose, the directions must include instructions to reduce the dose for low-weight children.

(2) Parents should be instructed to use a calibrated measuring device to give the drug to the child, to use extreme care in measuring the dosage, and not to exceed the recommended daily dosage.

(3) A dispensing device (such as a dropper calibrated for age or weight) for use in children 2 to under 6 years of age must be distributed to all professionals (doctors and pharmacists) to be dispensed along with the product to prevent possible overdose due to improper measuring of the dose.

References

(1) Letter from L. Finburg, Montefiore Hospital and Medical Center, Albert Einstein College of Medicine of Yeshiva University, to M. J. Finkel, FDA, OTC Volume 04TTFM, Docket No. 76N–052T, Dockets Management Branch.

(2) Letter to M. M. Freeman, FDA, from J. D. Lockhart, American Association of Pediatrics, OTC Volume 04TTFM, Docket No. 76N–052T, Dockets Management Branch.

(3) Segal, S., et al., American Academy of Pediatrics, Committee on Drugs, "Use of Codeine- and Dextromethorphan-Containing Cough Syrups in Pediatrics," *Pediatrics*, 62:118–121, 1978.

(4) Von Muhlendahl, K. E., et al., "Codeine Intoxication in Childhood," *Lancet*, 2:303–305, 1976.

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

20. One comment objected to the Panel limiting eucalyptol, menthol, and thymol to lozenge and mouthwash dosage forms when these ingredients are present in products used as "oral (topical)" antitussives. The comment contended that this limitation is arbitrary since viscous syrups and compressed tablets (in contrast to boiled candy base lozenges) are just as effective as mouthwashes and lozenges. The comment recommended that an "oral (topical) dosage" form of eucalyptol, menthol, and thymol include any oral dosage form that is topically effective and that can be formulated to contain the same concentrations of these ingredients which are allowed for lozenges.

The agency agrees that compressed tablets and syrups could also be used as dosage forms for antitussive products containing eucalyptol, menthol, or thymol, in addition to the lozenge and mouthwash dosage forms recommended by the Panel once these ingredients in specific dosage forms have been reclassified in Category I. It should be noted that the Panel concluded that these ingredients are peripherally acting antitussive agents acting on the nerve receptors within the respiratory tract (41 FR 38338). The local anesthetic effect of these ingredients have been the justification for their inclusion in various products for alleviation of cough (41 FR 38350). However, the agency points out that eucalyptol and thymol are Category III ingredients, which, although found safe by the Panel, lack adequate data to demonstrate their effectiveness as antitussives. Data to demonstrate effectiveness are required in order to permit final classification of these ingredients in the monograph for this use. Menthol for topical antitussive use as a lozenge or compressed tablet in a dosage of 5 to 10 mg has been reclassified from Category III to Category I (see comment 15 above); however, additional data are necessary to demonstrate the antitussive effectiveness of menthol in other dosage forms, e.g., a syrup.

21. One comment pointed out that the Panel's recommended dosage ranges for menthol in lozenge form when used as an antitussive (dosage range—1 to 15 mg), as an expectorant (dosage range—1 to 12 mg), and as a nasal decongestant (dosage range—1 to 10 mg) do not have the same maximum dosage. The comment stated that the dosage range for these three uses were based substantially on the same reference information and that the relative safety in lozenge form between these three maximum doses was not commented upon by the Panel. The comment recommended that 15 mg per lozenge be the maximum dosage recognized for these three uses at the Category III stage.

Menthol for use as a topical antitussive in a lozenge or compressed tablet dosage form has been reclassified as Category I in a dosage range of 5 to 10 mg. (See comment 15 above.) However, menthol remains a Category III ingredient for nasal decongestant and expectorant use. Because further testing is necessary to determine the effective dosages and/or final classification for these two indications, the agency finds no need to change the Panel's recommended dosages for these uses at this time.

E. Comments on Labeling of Antitussive Drug Products

22. One comment contended that manufacturers should be able to include in the labeling of antitussive drug products terms that are included in the Panel's definition of an "antitussive" in § 341.3(f). The comment pointed out that of the three verbs in the definition—"inhibits," "controls," and "suppresses"—no form of "inhibits" is allowed in the indications labeling for antitussives.

The agency agrees that manufacturers should have the option to use the verbs "controls" and "suppresses" in addition to the terms "alleviates," "decreases," "relieves," "quiets," "calms," and "reduces," and the phrase "helps you cough less" in the indications for antitussives when they are appropriate and has included them in the proposed monograph. However, the agency believes that the term "inhibits" may imply to consumers that an OTC antitussive has the ability to eliminate cough completely and is therefore not including the term "inhibits" in the indications section of the proposed monograph.

The agency is also simplifying the definition of "antitussive drug" in the monograph to include definitions for "oral antitussive" and "topical antitussive" respectively, to read as follows: "A drug that is taken by mouth and acts systemically to relieve cough" and "a drug that relieves cough when applied topically to the throat or chest in the form of an ointment or dissolved in the mouth in the form of a lozenge or compressed tablet." The agency believes that the simplification and separation of definitions for oral and topical antitussives provides clearer and more concise definitions for these drug products.

23. One comment quoted the Panel's statement on cough as follows:

"Medications which suppress the act of coughing by reducing * * * the intensity of coughing are known as antitussive drugs (41 FR 38321)," and complained that the Panel's recommended monograph stated that a manufacturer may not make a labeling claim that refers to a reduction "in the intensity of coughing" although the Panel used this phrase in its discussion of cough.

The agency agrees that a phrase referring to the reduction of the intensity of coughing is appropriate in the labeling of antitussive drug products and has therefore added a statement including this phrase in the indications section of the proposed monograph.

24. One comment stated that the Panel allowed a claim for "cooling" to be made for topical nasal decongestants for which the effect can be substantiated, e.g., menthol or other volatile oils (41 FR 38422). The comment contended that if the "cooling" claim is allowed for methol used as a topical nasal decongestant, it should also be allowed for methol used as an antitussive. The comment recommended that this claim be added to the monograph.

The agency has no objection to the use of terms, such as "cooling," that describe certain physical and chemical qualities of a drug, as long as these terms do not imply that any therapeutic effect might occur, are true and not misleading, and are distinctly separated from labeling indications. Terms describing product characteristics (e.g., color, odor, flavor, and feel) appear in the labeling for consumers' information. The agency concludes that it is not necessary to include terms such as these in the antitussive or nasal decongestant monographs. Accordingly, § 341.80(a)(13) of the Panel's proposed monograph which refers to the cooling sensation demonstrated by topical nasal decongestants will not be included in the tentative final monograph for nasal decongestant drug products which will be published in a future issue of the **Federal Register.**

25. One comment objected to the Panel's classification of the following statement as Category III in its labeling discussion (41 FR 38354): "Terms relating to sleep such as 'quiets annoying coughs and lets you sleep.' An antitussive is capable of quieting annoying coughs, but has not been demonstrated to be directly related to sleep." The comment stated that, on first inspection, a Category III classification of this claim is inconsistent with the Panel's statement that treatment of cough symptoms is likely to allow normal sleep. However, the comment concluded that this sleep-related claim suggests that the antitussive drug is also a sedative and contended that such claims are unjustified for these drug products at antitussive doses. The comment stated that products containing antitussives and other active ingredients which are not generally recognized as effective sedatives at the recommended doses should not be labeled with a sedative claim.

The Panel stated that terms relating to sleep such as "Quiets annoying cough and lets you sleep" are Category III, and that "An antitussive is capable of quieting annoying cough, but has not been demonstrated to be directly related to sleep" (41 FR 38354). The agency does not believe that the direct relationship between an ingredient and sleep that is required for Category I nighttime sleep-aid claims is necessary to permit this type of useful information to appear in the labeling of OTC antitussive drug products. A statement that clearly relates the ability of an antitussive to quiet an annoying cough that prevents an individual from falling asleep, thereby helping the individual to fall asleep, is reasonable. The agency is therefore proposing the following statement in this tentative final monograph under "Other allowable statements": (Select one of the following: "Alleviates," "Decreases," "Relieves," "Reduces," "Controls," or "Suppresses") (select one of the following: "cough," "the impulse to cough," or "your cough") "to help you get to sleep."

The agency recognizes that there might be a secondary pharmacological action of an antitussive, tantamount to a sedative effect, that helps an individual to sleep. The scientific literature describes slight drowsiness as a side effect for both codeine and dextromethorphan preparations (Refs. 1 through 7). However, the Panel stated that the drowsiness caused by a 20-mg oral dose of codeine, which it placed in Category I as an antitussive, is not significantly greater than that of a placebo (41 FR 38339). The Panel made no mention of drowsiness in its discussion of dextromethorphan, also a Category I antitussive (41 FR 38340). The agency is not aware of data demonstrating that the antitussive ingredients codeine and dextromethorphan could be classified as Category I nighttime sleep-aids or that they require a drowsiness warning. Therefore, sleep-aid claims directly related to the ability of an antitussive ingredient to cause drowsiness, e.g., "For relief of occasional sleeplessness." will remain in Category III.

References

(1) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Littleton, MA, pp. 662–664 and 666–667, 1977.

(2) Bickerman, H. A., "Antitussive Drugs," *in* "Drugs of Choice 1978–1979," edited by W. Modell, C. V. Mosby Co., St. Louis, pp. 461–475, 1978.

(3) Blacow, N. W., and A. Wade, editors, "Martindale: The Extra Pharmacopoeia," 26th Ed., The Pharmaceutical Press, London, pp. 1107–1109 and 1495, 1972.

(4) Cormier, J. F., and B. G. Bryant, "Cold and Allergy Products," *in* "Handbook of Nonprescription Drugs," 6th Ed., American Pharmaceutical Association, Washington, pp. 89–90, 1979.

(5) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 331 and 406, 1973.

(6) Swinyard, E. A., "Analgesics and Antipyretics," *in* "Remington's Pharmaceutical Sciences," 16th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, pp. 1046–1047, 1980.

(7) Swinyard, E. A., "Respiratory Drugs," *in* "Remington's Pharmaceutical Sciences," 16th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, pp. 808–809, 1980.

26. One comment was opposed to the Panel's recommended restriction of OTC antitussives 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 productive cough due to a cold will become debilitating if treated with an antitussive, nor that the recommended OTC doses of the antitussives considered by the Panel restrict the physiological cough stimulated by such mucous secretions."

The agency agrees with the Panel's recommendations. The purpose of a productive cough is to remove irritants, such as mucus, or foreign material from the respiratory tract. The agency's primary concern in limiting the use of antitussives to nonproductive cough is to decrease the possibility that OTC cough suppressants will be used in the presence of serious diseases such as asthma, emphysema, chronic bronchitis, and cystic fibrosis. In diseases such as these, there is an over-production of secretions which accumulate in the airway. The suppression of cough in these circumstances would impair clearing of the airway and could be harmful.

Furthermore, 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. 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 the use of

antitussives in cough accompanied by excessive phlegm (mucus) is warranted.

The Panel recommended the following warning in § 341.74(b)(2) for antitussive drug products: "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 this tentative final monograph) has been revised for clarity and to conform to the current format of recently published tentative final monographs to read as follows: "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, emphysema, or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor." In addition, the agency recognizes that children under 12 years of age are unlikely to have a chronic cough due to smoking or emphysema and has therefore deleted the words "smoking" and "emphysema" from the above warning for drug products labeled only for children under 12 years of age.

F. Comments on Testing Guidelines

27. One comment from a research laboratory requested that FDA not accept the statement in the Panel's report that questions the accuracy and reliability of the high speed automatic electronic cough counter used in a study on the effectiveness of caramiphen edisylate as an antitussive (41 FR 38345). The comment claimed that the automatic electronic cough counter is reliable and accurate when used to assess the effectiveness of antitussives in patients with chronic, spontaneous cough and requested that this electronic cough-counting system be included as a recommended method in the final guidelines for testing the effectiveness of antitussive drug products.

The agency believes it is not appropriate for it to recommend the use of a particular instrument to evaluate the effectiveness of OCT antitussive drug products. As stated in the **Federal Register** notice of May 13, 1980 (45 FR 31423), tentative final and final monographs will no longer contain recommended testing guidelines. The Panel's testing criteria are considered to be recommendations to the agency; however, studies submitted in support of the effectiveness and safety of a Category III condition are evaluated on their own merits rather than on how well they meet the Panel's requirements. For example, two studies designed to demonstrate the effectiveness of menthol as an antitussive active ingredient were submitted in response to the advance notice of proposed rulemaking. (See Comment Nos. C0018, SUP009, SUP011, and SUP012, Docket No. 76N–0052, Dockets Management Branch.) The agency has reviewed these studies, which included the use of automatic cough-counting systems, and accepted them as demonstrating the effectiveness of menthol as an OTC antitussive active ingredient. The agency emphasizes that each study submitted to support a request for reclassification of a Category III condition to Category I status must substantiate the reclassification whether or not the Panel's recommended guidelines are followed. It is an individual decision of a manufacturer or sponsor of the test whether or not to use an automatic cough-counting system to test antitussives for effectiveness. Before utilizing an electronic high speed automatic counter to test antitussive drug products, the sponsor of such testing may discuss the use of the counter with the agency.

28. One comment pointed out that the Panel indicated that antitussives are best assessed by objective cough-counting techniques and that these drugs can be tested by decreasing induced cough or by decreasing the cough in patients with chronic cough (41 FR 38336). However, in its testing guidelines (41 FR 38355), the Panel described procedures for testing antitussives in patients with a cough due to an acute self-limiting illness, as well as in patients with a cough due to chronic lung disease. The comment recommended that patients with "acute" cough be included in both discussions of the patient populations that the Panel considered appropriate for testing antitussives.

The agency has reviewed the Panel's statement regarding objective cough-counting techniques and notes that it was provided as one of the examples of the different types of studies used by the Panel to assess different drug groups and was merely a statement of fact. The agency believes that the Panel did not intend that this statement should apply to its recommendations concerning the selection of patients for further study of antitussive active ingredients. The agency believes that it is not necessary to relate this statement to the description of patients to be selected for testing the effectiveness of antitussives in the Panel's recommended testing guidelines. Therefore, there is no need to add the term "acute" to the Panel's statement in the testing guidelines. As noted in comment 27 above, and in part II. paragraph A.2. below, the Panel's testing guidelines are considered recommendations to the agency, and manufacturers are not restricted to these guidelines in testing Category II or Category III conditions.

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

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

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and is proposing to reclassify two antitussive active ingredients from Category III to Category I. In addition, two antitussive active ingredients (benzonatate and chlophedianol hydrochloride), previously marketed as prescription drugs, that were not reviewed by the Panel are being proposed as Category I ingredients. (See agency change 2 below and comment 4 above.) For the convenience of the reader, the following table is included as a summary of the categorization of antitussive active ingredients by the Panel and the proposed classification by the agency.

Antitussive active ingredients	Panel	Agency
Beechwood creosote	III	III.
Benzonatate	(1)	I.
Camphor (topical inhalant):		
Ointment	III	I.
Lozenge	III	III.
Steam inhalation	III	III.
Caramiphen edisylate	III	III.
Carbetapentane citrate	III	III.
Chlophedianol hydrochloride	(1)	I.
Cod liver oil	III	III.
Codeine	I	I.
Codeine phosphate		
Codeine sulfate		
Dextromethorphan	I	I.
Dextromethorphan hydorbromide		
Diphenhydramine hydrochloride	I	III.
Elm bark	III	III.
Ethymorphine hydrochloride	III	III.
Eucalyptol/eucalyptus oil:		
Topical/inhalant		
Ointment	III	III.
Lozenge	III	III.
Mouthwash	III	III.
Steam inhalation	III	III.
Horehound (horehound fluid extract)	III	III.
Hydrocodone bitartrate	II	II.
Menthol/peppermint oil (topical/inhalant):		
Ointment	III	I.
Lozenge or compressed tablets:		
(a) 5 to 10 mg	III	I.
(b) less than 5 mg, greater than 10 mg.	III	III.
Mouthwash	III	III.
Steam inhalation	III	III.
Noscapine	III	III.
Noscapine hydrochloride		
Thymol (topical/inhalant):		
Ointment	III	III.
Lozenge	III	III.
Room spray	III	III.
Mouthwash	III	III.
Steam inhalation	III	III.
Turpentine oil (spirits of turpentine):		
(a) Oral	II	II.
(b) Topical/inhalant:		
Ointment	III	III.
Steam inhalation	III	III.

(1) Not reviewed.

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for antitussive drug products (41 FR 38329 and 38355). 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 antitussive ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). This clarified policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes

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

1. The agency has modified the Panel's definition of "antitussive drug" in § 341.3(f) (redesignated as § 341.3(j) and (k)) to include a definition of an "oral antitussive drug" and a "topical antitussive drug." (See comment 22 above.) Also, the agency is modifying the required statement of identity for labeling of oral and topical antitussive drug products from "antitussive" to "cough suppressant" or "antitussive (cough suppressant)." The agency believes that the terms "cough suppressant" or "antitussive (cough suppressant)" will be better understood by consumers than the term "antitussive."

2. Benzonatate has been marketed under an approve NDA for 24 years as a prescription antitussive drug product at a dosage for adults and children over 10 years of age of 100 mg three times daily as required. The package insert states that, if necessary, up to 600 mg daily may be given (Ref. 1). The agency has reviewed the literature concerning the safety and effectiveness of benzonatate as an antitussive ingredient. Based on this review, and the review by the Drug Efficacy Study Implementation Group (DESI) published in the **Federal Register** of April 29, 1971 (36 FR 8071), the agency is proposing that benzonatate be generally recognized as safe and effective for OCT antitussive use.

The agency has reviewed studies by Herzog (Ref. 2); Naegeli (Ref. 3); Simon (Ref. 4); Wilson, Farber, and Mandel (Ref. 5); Gregoire, Thibaudeau, and Comeau (Ref. 6); Shane, Krzyski, and Copp (Ref. 7); Bickerman and Itkin (Ref. 8); and Simon (Ref. 9) concerning the safety and effectiveness of benzonatate. Several of these studies evaluated products that are marketed under the approved NDA (Refs. 5, 6, 8, and 9). The studies were performed in patients suffering from various acute and chronic pulmonary dysfunctions, such as asthmatic bronchitis and pulmonary emphysema (Refs. 3, 4, 5, and 9), Pleural and bronchial irritation (Refs. 2 and 3), and chronic cough due to tuberculosis (Refs. 3, 5 and 6). One study was concerned with acute lower respiratory tract infections that produce an irritative cough (Ref. 3). All of the above studies showed benzonatate to be effective in reducing the frequency of cough in a significant number of patients. Three of the studies were double-blinded (Refs. 5, 6, and 8). One study using a double-blind crossover design showed that benzonatate caused a distinct diminution in cough for a group of tuberculosis patients (Ref. 6).

Three of the studies tested benzonatate against experimentally induced cough in healthy subjects (Refs 6, 7, and 8). One study used a citric acid aerosol to induce the cough and showed that 100 mg of benzonatate was more effective at reducing the frequency of induced cough than one-half grain of codeine (Ref., 7). Benzonatate reduced the frequency of induced cough by 80 percent, while codeine reduced the frequency by 50 percent. A second study using citric acid aerosol was double-blinded and compared benzonatate with 12 other drugs or placebos over a 4-hour test period (Ref. 8). The agency concludes that benzonatate was shown to be an effective antitussive ingredient.

A review of FDA adverse reaction summary reports since 1970 indicated that only a few adverse reactions have been reported in cases when benzonatate was the only drug given (Ref. 11). In only one case (anaphylactoid reaction as a result of the drug dissolving in the mouth) was enough information available to indicate a possible cause-and-effect relationship between benzonatate and the reaction. Because benzonatate has a secondary pharmacologic effect as a local anesthetic, orpharyngeal anesthesia will develop rapidly if the drug is released in the oral cavity. The drug should be marketed in an appropriate dosage form that does not release it into the oral cavity and consumers should be directed not to chew or dissolve the drug product in the mouth. Therefore, the agency is proposing the following directions: "Swallow woithout chewing or dissolving in the mouth. May produce temporary numbness if dissolved in the mouth."

Based on the above data and information and a record of safe and effective use of up to 600 mg daily for 24 years under an approved NDA, the agency believes that benzonatate can be generally recognized as safe and effective for OTC use as an antitussive. However, because benzonatate's effects last for 3 to 8 hours (Ref. 1), the maximum proposed OTC dose will be limited to 400 mg in 24 hours. Therefore, the agency is proposing to include this ingredient in the OTC antitussive tentative final monograph at a dose for adults and children 12 years of age and older of 100 mg in a suitable dosage form that prevents release of the drug in the mouth every 4 to 6 hours, not to exceed 400 mg in 24 hours. The labeling directions and warnings are consistent with the other Category I antitussives.

Although the agency is proposing to switch benzonatate to OTC availability from its present status as a prescription drug, OTC marketing may not begin at this time. Like chlophedianol hydrochloride (see comment 4 above), benezonatate was not considered by the advisory review panel and, therefore, does not meet the terms of the enforcement policy in § 330.13. The agency has also determined that benzonatate is not otherwise appropriate for OTC marketing at this time. FDA believes that public comments submitted in response to the proposed switch in status should be evaluated before OTC markteting is begun. Accordingly, until such comments are reviewed, benezonatate remains a prescription drug subject to the terms and conditions specified in its approved NDA.

References

(1) Copy of FDA-approved labeling from NDA 11–210, OTC Volume 04TTFM, Docket No. 76N–052T, Dockets Management Branch.

(2) Herzog, H., "Polyathylenglykolderivate mit hustenstillender Wirkung, insbesondere Tessalon," *Schweizerische Medizinische Wochenschrift*, 86: 96–99, 1956.

Naegeli, H. R., "Klinische Untersuchungen mit einem neuen Hustenbekampfungsmittel," *Praxis*, 45:56–58, 1956.

(4) Simon, S. W., "A New Non-Narcotic, Antitussive Drug," *Annals of Allergy*, 15:521–525, 1957.

(5) Wilson, R. H., S. M. Farber, and W. Mandel, "A New Agent of Therapeutic Value in Pulmonary Insufficiency and Irritative Cough," *Antibiotic Medicine and Clinical Therapy*, 5:567–572, 1958.

(6) Gregoire, F., Y. Thibaudeau, and M. Comeau, "The Treatment of Cough by a Non-Narcotic Antitussive," *Canadian Medical Association Journal*, 79:180–184, 1958.

(7) Shane, S. J., T. K. Krzyski, and S. E. Copp, "Clinical Evaluation of a New Antitussive Agent," *Canadian Medical Association Journal*, 77:600–602, 1957.

(8) Bickerman, H. A., and S. E. Itkin, "Further Studies on the Evaluation of Antitussive Agents Employing Experimentally Induced Cough in Human Subjects," *Clinical Pharmacology and Therapeutics*, 1:180–191, 1960.

(9) Simon, S. W., "The Effectiveness of Non-Narcotic Antitussive Drugs," *Journal of the American Geriatrics Society*, 10:653–657, 1962.

(10) Lineback, M., "Benzonatate as Cough and Gag Reflex Suppressive," *Clinical Medicine*, 69:1806–1808, 1962.

(11) Department of Health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listings," pertinent pages for the years 1970–82, OTC Volume 04TTFM, Docket No. 76N–052T, Dockets Management Branch.

3. The agency has reclassified the antitussive active ingredient camphor from Category III to Category I for topical use in an ointment containing 4.7 to 5.3 percent camphor and added directions for this use to the tentative final monograph. The agency has also added a specific warning relevant to the topical use by adults and children of camphor in ointment preparations (§ 341.74(c)(4) (i) and (ii)). "Directions" for the antitussive use of camphor in an ointment have been added to § 341.74(d)(2)(i) in the tentative final monograph. (See comment 5 above.)

4. The agency has classified chlophedianol hydrochloride in Category I as an OTC antitussive. (See comment 4 above.)

5. The agency has deleted the labeling for OTC use of codeine-containing drug products for use in children 2 to under 6 years of age and has placed revised directions for use in children 2 to under 6 years of age in the professional labeling section of the tentative final monograph. (See comment 19 above.)

6. The agency has deleted § 341.14(c), the reference to § 341.14(c) in § 341.74(a)(7), § 341.74(b)(5) and § 341.90(c)(2) of the Panel's recommended monograph. These sections provided dosages, indications, warnings, and professional labeling for diphenhydramine hydrochloride for use as an antitussive. The agency concludes that general recognition of the effectiveness of this ingredient as an antitussive has not been adequately established. Consequently, the agency has reclassified diphenhydramine hydrochloride in Category III for antitussive use. (See comment 10 above.)

7. The agency has reclassified the antitussive active ingredient menthol from Category III to Category I for use as a lozenge or compressed tablet at a dosage of 5 to 10 mg every hour and in an ointment containing 2.6 to 2.8 percent menthol, and added directions for these uses to the tentative final monograph. The agency has also added a specific warning relevant to the topical use by adults and children of menthol in ointment preparations (§ 341.74(c)(4) (i) and (ii)). "Directions" for the antitussive use of menthol in the form of a lozenge or compressed tablet and an ointment have been added to § 341.74(d)(2) (i), (ii), and (iii) in the tentative final monograph. (See comments 15 and 16 above.)

8. The agency has added to § 341.74 a "Statement of identity" paragraph (designated as § 341.74(a)) and a "Directions" paragraph (designated as § 341.74(d)) to conform with the format of other recently published advance notices of proposed rulemaking and tentative final monographs. Inclusion of the "Statement of identity" paragraph has necessitated a redesignation of the Panel's recommended § 341.74(a) to § 341.74(b), and § 341.74(b) to § 341.74(c). The agency is also redesignating Subpart D as Subpart C and placing the labeling sections of the monograph in Subpart C.

9. Portions of the indications recommended by the Panel have been revised by the agency into statements that may be included in labeling at the manufacturer's option. These statements appear in §341.74(b)(2) in this tentative final monograph under the heading "Other allowable statements." In addition, the agency has also added to monograph under "Other allowable statements," a statement that clearly relates the ability of an antitussive to quiet an annoying cough that prevents an individual from falling asleep, thereby helping the individual to fall asleep. (See comment 25 above).

10. In § 341.74(b) (3) and (5)(iv) the Panel recommended the use of the signal word "Caution" in a section of the labeling where the heading "Warnings" is also recommended. The agency notes that historically there has not been a consistent usage of the signal words "warning" and "caution" in OTC drug labeling. For example, in §§ 369.20 and 369.21 (21 CFR 369.20 and 369.21), which list "warning" and "caution" statements for drugs, the signal words "warning" and "caution" are both used. In some instances either of these signal words is used to convey the same or similar precautionary information.

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

11. The agency has added warnings that are appropriate for products that are labeled for children under 12 years of age. The agency acknowledges that some warnings which the Panel recommended for all antitussive drug products are inappropriate for products which are labeled for children under 12 years of age. In addition, the warnings for products labeled for children under 12 years of age have been worded to reflect the administration of the product by adults rather than self-administration.

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

13. The agency has revised § 341.74(c) for clarity by listing the warnings according to ingredient and dosage form (i.e., oral or topical antitussives).

14. The agency has deleted § 341.74(b)(1) and (5)(v) of the Panel's recommended monograph. These sections provided warnings not to give antitussives to children under 2 (or 6) years of age except under the advice and supervision of a physician. The directions provided under new

§ 341.74(d) state clearly that a doctor should be consulted for the use of a particular antitussive drug product in children under certain ages. The agency believes that the Panel's proposed warnings are therefore repetitious and unnecessary.

The agency proposes to revoke the existing warning and caution statements in §§ 369.20 and 369.21, and exemptions for certain drugs limited by NDAs to prescription sale in § 310.201(a)(14) for antitussive drug products at the time that this monograph becomes effective. The agency proposes to revoke § 310.201(a)(20) and to delete carbetapentane citrate from bearing the warning and caution statements required by § 369.21 at the time that this monograph becomes effective if this ingredient is reclassified in Category I as an OTC antitussive in the final monograph.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** 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 antitussive drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Public Law 96-354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC antitussive drug products is not expected to pose such an impact on small business. 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 antitussive 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 antitussive 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 antitussive drug products, a period of 120 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

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

List of Subjects in 21 CFR Part 341

OTC drugs, Anticholinergics, Expectorants, Bronchodilators, Antitussives.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 341 (proposed in the **Federal Register** of July 9, 1982; 47 FR 30002) to read as follows:

PART 341—[AMENDED]

1. In Subpart A, § 341.3 is amended by adding and reserving paragraphs (d)–(i) and by adding new paragraphs (j) and (k), to read as follows:

§ 341.3 Definitions.

* * * * *

(d)–(i) [Reserved]

(j) *Oral antitussive drug.* A drug that is taken by mouth and acts systemically to relieve cough.

(k) *Topical antitussive drug.* A drug that relieves cough when applied topically to the throat or chest in the form of an ointment or dissolved in the mouth in the form of a lozenge or compressed tablet.

2. In Subpart B, new § 341.14 is added, to read as follows:

§ 341.14 Antitussive active ingredients.

The active ingredients of the product consist of any of the following when used within the dosage limits and in the dosage forms established for each ingredient in § 341.74(d):

(a) *Oral antitussives.* (1) Benzonatate.

(2) Chlophedianol hydrochloride.

(3) Codeine ingredients.

(i) The following ingredients may be used only in combination in accordance with §§ 329.20(a), 341.40, and 1308.15(b).

(*a*) Codeine.

(*b*) Codeine phosphate.

(*c*) Codeine sulfate.

(4) Dextromethorphan.

(5) Dextromethorphan hydrobromide.

(b) *Topical antitussives.* (1) Camphor.

(2) Menthol.

3. In Subpart C, new § 341.74 is added.

§ 341.74 Labeling of antitussive drug products.

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

(b) *Indications.* (1) The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following phrase: "Temporarily" (select one of the following: "alleviates," "decreases," "relieves," "reduces," "controls," "suppresses," "quiets," or "calms") "cough due to minor throat and bronchial irritation as may occur with" (select one of the following: "the common cold" or "a cold") "or inhaled irritants."

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

(i) "Cough suppressant which temporarily" (select one of the following: "alleviates," "decreases," "relieves," "reduces," "controls," or "suppresses") "the impulse to cough."

(ii) "Temporarily helps you cough less."

(iii) "Temporarily helps to" (select one of the following: "alleviate," "decrease," "relieve," "control," "suppress," or

"reduce") "the cough reflex that causes coughing."

(iv) "Temporarily" (select one of the following: "alleviates," "decreases," "relieves," "reduces," "controls," or "suppresses") "the intensity of coughing."

(v) (Select one of the following: "Alleviates," "Decreases," "Relieves," "Reduces," "Controls," or "Suppresses"] (select one of the following: "cough," "the impluse to cough," or "your cough") "to help you get to sleep."

(vi) *For products containing chlophedianol hydrochloride, codeine ingredients, dextromethorphan, or dextromethorphan hydrobromide identified in § 341.14 (a)(2), (3), (4), and (5):* "Calms the cough control center and relieves coughing."

(vii) *For products containing benzonatate, chlophedianol hydrochloride, dextromethorphan, dextromethorphan hydrobromide, camphor, or menthol identified in § 341.14(a)(1), (2), (4), and (5) and (b)(1) and (2):*

(*a*) "Nonnarcotic cough suppressant for the temporary" (select one of the following: "relief," "alleviation," "decrease," "reduction," "suppression." or "control") "of cough."

(*b*) (Select one of the following: "Alleviates," "Decreases," "Reduces," "Controls," or "Suppresses") "cough impulses without narcotics."

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

(1) *For antitussives labeled for adults.* (i) "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."

(ii) "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 high fever, rash, or persistent headaches, consult a doctor."

(2) *For antitussives labeled for children under 12 years of age.* (i) "Do not give this product for persistent or chronic cough such as occurs with asthma or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

(ii) "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 high fever, rash, or persistent headaches, consult a doctor."

(3) *Oral antitussives*—(i) *For products containing codeine ingredients identified in § 341.14(a)(3) when labeled for adults*

(*a*) "May cause or aggravate constipation."

(*b*) "Do not take this product if you have a chronic pulmonary disease or shortness of breath unless directed by a doctor."

(ii) *For products containing codeine ingredients identified in § 341.14(a)(3) when labeled for children under 12 years of age.*

(*a*) "May cause or aggravate constipation."

(*b*) "Do not give this product to children who have a chronic pulmonary disease, shortness of breath, or who are taking other drugs unless directed by a doctor."

(4) *Topical antitussives*—(1) *For products containing camphor or menthol identified in § 341.14(b) (1) and (2) in a suitable ointment vehicle when labeled for adults.* "For external use only. Do not take by mouth or place in nostrils."

(ii) *For products containing camphor or menthol identified in § 341.14(b) (1) and (2) in a suitable ointment vehicle when labeled for children under 12 years of age.* "For external use only. Do not take by mouth or place in nostrils."

(5) *For antitussive products labeled for both adults and for children under 12 years of age.* The labeling of the product contains the applicable warnings identified in paragraphs (c)(1), (3) (i), and (ii)(*b*), and (4)(i) of this section.

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

(1) *Oral antitussives*—(i) *For products containing benzonatate identified in § 341.14(a)(1).* Adults: oral dosage is 100 milligrams in a suitable dosage form every 4 to 6 hours, not to exceed 400 milligrams in 24 hours, or as directed by a doctor. Swallow without chewing or dissolving in the mouth. May produce temporary numbness if dissolved in the mouth. Children under 12 years of age: consult a doctor.

(ii) *For products containing chlophedianol hydrochloride identified in § 341.14(a)(2).* Adults: oral dosage is 25 milligrams every 6 to 8 hours, not to exceed 100 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 12.5 milligrams every 6 to 8 hours, not to exceed 50 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(iii) *For products containing codeine ingredients identified in § 341.14(a)(3)* Adults: oral dosage is 10 to 20 milligrams every 4 to 6 hours, not to exceed 120 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 5 to 10 milligrams every 4 to 6 hours, not to exceed 60 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(iv) *For products containing dextromethorphan or dextromethorphan hydrobromide identified in § 341.14(a) (4) and (5).* Adults: oral dosage is 10 to 20 milligrams every 4 hours or 30 milligrams every 6 to 8 hours, not to exceed 120 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: oral dosage is 5 to 10 milligrams every 4 hours or 15 milligrams every 6 to 8 hours, not to exceed 60 milligrams in 24 hours, or as directed by a doctor. Children 2 to under 6 years of age: oral dosage is 2.5 to 5 milligrams every 4 hours or 7.5 milligrams every 6 to 8 hours, not to exceed 30 milligrams in 24 hours, or as directed by a doctor. Children under 2 years of age: consult a doctor.

(2) *Topical antitussives*—(1) *For products containing camphor identified in § 341.14(b)(1) in a suitable ointment vehicle.* The product contains 4.7 to 5.3 percent camphor. Adults and children 2 to under 12 years of age: rub on the throat and chest as a thick layer. The area of application may be covered with a warm, dry cloth if desired. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to three times daily or as directed by a doctor. Children under 2 years of age: consult a doctor.

(ii) *For products containing menthol identified in § 341.14(b)(2) in a suitable ointment vehicle.* The product contains 2.6 to 2.8 percent menthol. Adults and children 2 to under 12 years of age: rub on the throat and chest as a thick layer. The area of application may be covered with a warm, dry cloth if desired. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to three times daily or as directed by a doctor. Children under 2 years of age: consult a doctor.

(iii) *For products containing menthol identified in § 341.14(b)(2 in a lozenge or compressed tablet.* The product contains 5 to 10 milligrams menthol. Adults and children 2 to under 12 years of age: allow (lozenge or compressed tablet) to dissolve slowly in the mouth. May be repeated every hour as needed or as directed by a doctor. Children under 2 years of age: consult a doctor.

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

4. In § 341.90, reserve paragraphs (c)–(n) and add new paragraphs (o) and (p) to read as follows:

§ 341.90 Professional labeling.

* * * * *

(o) *For products containing chlophedianol hydrochloride identified in § 341.14(a)(2).* Children 2 to under 6 years of age: oral dosage is 12.5 milligrams every 6 to 8 hours, not to exceed 50 milligrams in 24 hours.

(p) *For products containing codeine ingredients identified in § 341.14(a)(3).*

(1) Children 2 to under 6 years of age: oral dosage is 1 milligram per kilogram body weight per day administered in four equal divided doses. The average body weight for each age may also be used to determine dosage as follows: for children 2 years of age (average body weight, 12 kilograms), the oral dosage is 3 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours; for children 3 years of age (average body weight, 14 kilograms), the oral dosage is 3.5 milligrams every 4 to 6 hours, not to exceed 14 milligrams in 24 hours; for children 4 years of age (average body weight, 16 kilograms), the oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 16 milligrams in 24 hours; for children 5 years of age (average body weight, 18 kilograms), the oral dosage is 4.5 milligrams every 4 to 6 hours, not to exceed 16 milligrams in 24 hours. If age is used to determine the dose, the directions must include instructions to reduce the dose for low-weight children.

(2) Parents should be instructed to use a calibrated measuring device to give the drug to the child, to use extreme care in measuring the dosage, and not to exceed the recommended daily dosage.

(3) A dispensing device (such as a dropper calibrated for age or weight) for use in children 2 to under 6 years of age must be distributed to all professionals (doctors and pharmacists) to be dispensed along with the product to prevent possible overdose due to improper measuring of the dose.

Interested persons may, on or before December 19, 1983, 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 February 14, 1984. 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 above office between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before October 19, 1984, 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 December 19, 1984. 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 above office between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on December 19, 1984. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register,** unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: September 26, 1983.

Mark Novitch,

Deputy Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

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