DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 341

[Docket No. 76N-052C]

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Over-the-Counter Anticholinergic Drug Products and Expectorant 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) anticholinergic drug products and expectorant drug products are generally recognized as safe and effective and not misbranded. (Anticholinergics are drugs used in cough-cold products for the relief of excessive secretions of the nose and eyes, symptoms which are commonly associated with hay fever, allergy, rhinitis, and the "common cold" (cold); expectorants are drugs used to promote or facilitate the removal of secretions from the respiratory airways.) 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 anticholinergic drug products and expectorant drug products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by September 7, 1982. New data by July 11, 1983. Comments on the new data by September 9, 1983. 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). Written comments on the agency's economic impact determination by November 8, 1982.

ADDRESS: Written comments, objections, 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. New data and comments on new data should also be addressed to the Dockets Management Branch.

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

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

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

FDA is issuing the tentative final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products in segments. This document on anticholinergic drug products and expectorant drug products is the first segment. Subsequent segments on antitussives, bronchodilators, antihistamines, nasal decongestants, combinations, etc., 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) the FDA states for the first time its position on the establishment of a monograph for OTC anticholinergic drug products and expectorant 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 anticholinergic drug products and expectorant drug products.

In response to the advance notice of proposed rulemaking, two drug manufacturers, one consumer group, and one health professional submitted comments on anticholinergics. Two drug manufacturers, two health care professionals, and two consumer groups submitted comments on expectorants. Copies of the comments received are also on public display in the Dockets Management Branch.

This proposal to establish Part 341 (21 CFR Part 341) constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC anticholinergic drug products and expectorant 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'a responses to them. The agency emphasizes that no anticholinergic active ingredients and no expectorant active ingredients have been determined to be generally recognized as safe and effective and not misbranded. However, the agency is proposing Category I labeling in this document in the event that data are submitted which result in the upgrading of any ingredients to monograph status in the final rule.

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in

Cutler v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph (46 FR 47738).

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of 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. 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.

In the case of anticholineric drug products and expectorant drug products, there are currently no Category I conditions. The agency is aware that at least one expectorant ingredient is being tested and that data relating to that ingredient may be submitted before the final monograph is issued. Thus, the agency cannot at this time determine whether all expectorant drug products, or only some, may have to be reformulated. The agency is not aware that any anticholinergic ingredients are being tested. Thus, it appears that products containing anticholinergic ingredients 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.

In addition to reformulation, relabeling of products will be necessary in order for manufacturers to comply with the final regulation. New labels complying with the regulation 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 regulation. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with exension requests and related paperwork.

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 or reformulate their products and have them in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

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

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on Anticholinergic Drug Products

1. One comment contended that the amount of belladonna alkaloids contained in a particular OTC timed-release cough-cold product is too high for safe use, and another comment questioned whether this same product might be unsafe because the timed-release dosage form could release its ingredients inconsistently or all at once.

The product mentioned in the comments contains 0.2 milligrams (mg) belladonna alkaloids, 50 mg phenylpropanolamine hydrochloride, and 4 mg chlorpheniramine maleate in a 12-hour timed-release dosage form. The Panel concluded that the dosage of belladonna alkaloids in this timed-release dosage form is probably safe in OTC cough-cold products for anticholinergic use, but that further testing is needed to establish their effectiveness. The agency concurs with the finding, and points out that the product is the subject of a new drug application (NDA), approved on September 1, 1961 on the basis of safety. FDA is unaware of any data that would change the conclusion that the specific product subject to the NDA is safe. However, timed-release products are subject to the regulation in § 200.31(a) (21 CFR 200.31(a)), which requires that any timed-release dosage form that contains per dosage unit (e.g., capsule or tablet) a quantity of active drug ingredient that is not generally recognized as safe for administration as a single dose under the conditions suggested in its labeling is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)). This requirement is grounded on the agency's recognition that there is a possibility of overdosage if products that are designed

to release the active ingredient over a prolonged period are improperly made and the active ingredient is released all at once or over too short a time interval. An NDA for a timed-release product must contain bioavailability data that demonstrate that the active ingredient is released uniformly over the dosage duration of the product and not over too short or too long a time interval. Thus, timed-release products containing a quantity of active ingredient that is not generally recognized as safe for administration as a single dose may not be introduced into interstate commerce unless an NDA has been approved for the product. Because the Panel reviewed no data on belladonna alkaloids apart from the timed-release formulation, it made no recommendations as to a single dose amount that would be generally recognized as safe and effective. The agency is unaware of any data that would establish a generally recognized safe and effective single dose of belladonna alkaloids for use in non-timed-release cough-cold products.

2. One comment objected to FDA's permitting the marketing of the timed-release product containing belladonna alkaloids until FDA has evaluated data on the belladonna component and has found the ingredient to be effective for use in OTC cough-cold products.

It has been the agency's policy, since the initiation of the OTC drug review, to take regulatory action prior to a final monograph against only those products that present a potential health hazard or a significant and substantial effectiveness question. The product which the comment refers to has been marketed OTC since 1961 with an approved NDA for safety. FDA believes that with additional testing the belladonna alkaloids may be shown to be effective. Therefore, the agency sees no need for regulatory action toward this ingredient prior to publication of a final rule.

3. A comment objected to the Panel's not having required studies of belladonna alkaloids for "long-term" effects.

The Panel stated that "clinical experience has confirmed that belladonna alkaloids are safe in the dosage ranges used as anticholinergics" (41 FR 38373). Section 330.10(a)(4)(i) of the OTC drug regulations states that proof of safety "shall include results of significant human experience during marketing." Because belladonna alkaloids have been marketed in this and other products, and have been widely used for many years, the Panel did not believe it necessary to recommend studies for long-term effects. The agency agrees with the Panel and concludes that studies for long-term effects are not needed.

4. One comment requested that a dosage be established for belladonna alkaloids when they are used in combination drug products which are not time-released. The comment pointed out that the Panel recommended only an adult oral dose for belladonna alkaloids of 0.2 mg two times a day, based on review of a timed-release dosage form. Based on this timed-release dose, the comment requested that a dose of 0.067 mg every 4 hours or 0.1 mg every 6 hours also be allowed.

The Panel did not recommend a dosage for belladonna alkaloids to be administered every 4 to 6 hours because no data on such dosage forms were submitted for review. Because the comment submitted no new data, and because FDA is unaware of any such data, a generally recognized safe and effective dosage for belladonna alkaloids administered every 4 to 6 hours in cold, cough, and allergy products has not been established. Therefore, the agency denies this request.

5. Two comments expressed concern that belladonna alkaloids might cause urinary retention in males. The comments cited personal experiences where urinary retention has occurred after taking an OTC combination cough-cold product containing belladonna alkaloids.

It is well known that belladonna alkaloids and related drugs, particularly atropine, contribute to retention of urine (Ref. 1). The Panel recognized that urinary retention might become a problem in a male with an enlarged prostate. Such persons might develop urinary obstruction. For this reason, the Panel recommended an appropriate label warning which states in part *"Caution:* Do not take this product if you have * * * difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician." FDA concurs that this warning will adequately alert men who have an enlarged prostate gland and who may experience urinary retention problems following use of a product containing belladonna alkaloids. FDA has incorporated this warning into the tentative final monograph with two minor revisions, i.e., deletion of the signal word "Caution" and substitution of the word "doctor" for "physician." (See § 341.70(c)(3) below.

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 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 § 341.70(b)(3) (redesignated as § 341.70(c)(3) in the tentative final monograph).

The agency believes that the word "doctor" is more commonly used and better understood by consumers and, therefore, is substituting "doctor" for "physician" in the warnings appearing in the tentative final monograph. This change is being made as part of a continuing effort to achieve OTC labeling language that is simple, clear, and accurate, in keeping with § 330.10(a)(4)(v), (21 CFR 330.10(a)(4)(v)), which states in part:

Labeling * * * shall state the intended uses and results of the product; adequate directions for proper use; and warnings against unsafe use, side effects, and adverse reactions in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use.

Public comment on these proposed changes in labeling language is invited. The agency also invites public comment on ways to define the words "anticholinergic" and "expectorant" in lay language.

Reference

(1) Cullumbine, H., "Cholinergic Blocking Drugs," *in* "Drill's Pharmacology in Medicine," 4th Ed., edited by J. R. DiPalma, McGraw-Hill, New York, p. 616, 1971.

6. One comment expressed concern about belladonna alkaloids in OTC cough-cold (combination) products causing dizziness and blurring of vision, noting that such side effects have been reported with the use of belladonna alkaloids in these products.

The Panel recognized that blurring of vision, as well as constipation,

excessive dryness of the mouth, insomnia, excitement, confusion, and rapid pulse are side effects, which can occur with the use of belladonna alkaloids. The Panel recommended in § 341.70(b)(2) that the labeling of these products bear a warning that consumers should stop taking the product if any of these side effects occur. The Panel did not, however, specifically include dizziness as a possible side effect. Because the agency previously recognized dizziness as a possible side effect of belladonna alkaloid products, dizziness was included in the recommended warning statement set forth for belladonna preparations in § 369.20. Therefore, the agency agrees with the comment and has added dizziness to the warning in § 341.70(c)(2). Further, in the interest of clarity, the agency is changing the Panel's recommended wording "do not continue to take" to "stop taking." Thus, § 341.70(b)(2) which is redesignated as § 341.70(c)(2) in the tentative final monograph, reads as follows: "Stop taking this product if constipation, excessive dryness of the mouth, insomnia, excitement, confusion, dizziness, rapid pulse, or blurring of vision occurs."

7. One comment questioned the Panel's classification of an antihistamine and an anticholinergic combination drug product in Category III for safety. The comment contends that information presented to the Panel at its December 3, 1974 meeting showed that combining an anticholinergic with an antihistamine does not increase the nature or severity of the potential side effects of each ingredient. The comment requested elimination of the requirement of additional safety studies for such a combination.

The agency disagrees with the comment. The agency concludes that the data cited by the comment cannot be used to establish general recognition of the safety of OTC anticholinergic/antihistamine combinations because different antihistamines and anticholinergics have varying degrees of side effects. Moreover, because antihistamines have anticholinergic effects in varying degrees, when drugs from each class are combined it may be necessary to adjust the dose of each to prevent cumulative side effects. The agency therefore considers it important to require a measure of the side effects of any proposed antihistamine/anticholinergic combination. Effectiveness testing will be required for any such combinations that are proposed because there are no Category I anticholinergics, and the two anticholinergic ingredients in Category III were placed there because of a lack of effectiveness data. Measurement of side effects could be done in conjunction with this effectiveness testing in order to determine the overall benefit-to-risk ratio of the addition of the anticholinergic to the combination, as well as a safe dosage for the combination.

B. General Comments on Expectorant Drug Products

8. One comment agreed with the Panel's conclusion that oral expectorants lack proven effectiveness and that some of them are potentially dangerous as OTC drugs. The comment suggested, however, that wild cherry syrup or tea and honey preparations should be labeled as placebos and marketed for the treatment of mild, self-limited cough.

The Panel suggested that a number of currently marketed expectorant active ingredients required further testing to establish their effectiveness. A number of other expectorants reviewed by the Panel were placed in Category II because they were considered safe. The agency appreciates the comment's agreement with the Panel's conclusions.

As for the comment's suggestions that certain ingredients be labeled as placebos and marketed for the treatment of mild self-limited cough, in order for a product to be marked with OTC drug labeling it must be shown to be generally recognized as safe and effective for its labeled indication. There are no data available to the agency to demonstrate that tea and honey or wild cherry syrup are effective for the treatment of mild, self-limited cough. Therefore FDA disagrees with the comment.

9. One comment submitted a new clinical study (Protocol 14) in support of the effectiveness of guaifenesin (glyceryl guaiacolate). The comment also questioned specific statements made by the Panel and presented a reevaluation of previous studies (Protocols 06 and 08) discussed in the Panel's report at 41 FR 38362–38363. The data, rebuttal of the Panel's statements, and the reevaluation were submitted to establish the effectiveness (Category I status) of guaifenesin as an expectorant for OTC use (Ref. 1).

The agency has reviewed the new data (Protocol 14) and all of the data on guaifenesin which the Panel had previously reviewed. In summary, the studies performed under Protocol 08 were judged unacceptable by the Panel (41 FR 38363), and the agency concurs with the Panel's conclusions. Because the studies performed under Protocol 06 were essentially identical to Protocol 08, the agency finds that these studies are also unacceptable. The Protocol 14 study was inadequate for several reasons: (a) The lack of comparability between placebo and treatment groups with respect to age and characteristics of disease (i.e., the placebo group was older and produced more and thicker sputum), (b) the small sample of patients studied, and (c) the inadequate period of drug administration. Additionally, although the Panel required only subjective tests for determining the effectiveness of expectorants, the agency believes that objective measurements of sputum volume and sputum viscosity should be done. The data submitted were inadequate to establish whether the subjective improvement produced was the result of an expectorant action, i.e, reduced thickness or increased quantity of secretions. The agency concludes that the data do not support the reclassification of guaifenesin as an expectorant from Category III to Category I.

The agency's detailed comments and evaluations on the data and its recommendations for additional studies are on file in the Dockets Management Branch (Refs. 2, 3, and 4).

References

(1) Comment Nos. SUP013 and SUP014, Docket No. 76N–0052, Dockets Management Branch.

(2) Letter from William E. Gilbertson, FDA, to Frederick A. Clark, Jr., A. H. Robins Co., coded ANS and 81/01/14 to SUP013 and SUP014, Docket No. 76N–0052, Dockets Management Branch.

(3) Memoranda of meetings, coded MM0004, MM0005, and MM0006, Docket No. 76N–052C, Dockets Management Branch.

(4) Letter from William E. Gilbertson, FDA, to Frederick A. Clark, Jr., A. H. Robins Co., coded LET076, Docket No. 76N–052C, Dockets Management Branch.

10. One comment stated that several references concerning research on guaifenesin, which was conducted by the correspondent and his colleagues, were inappropriately used by the Panel in reaching its conclusions. The comment contended that, because the cited studies were performed in patients with chronic lung secretion problems and employed larger-than-usual doses, they should not have been used in drawing conclusions about the effectiveness of guaifenesin in acute conditions, for which guaifenesin is generally used as an OTC drug. The comment stated that it would have been more reasonable for the Panel to have distinguished the use of guaifenesin in acute illnesses from its use in chronic

illnesses, even though this distinction would not have resulted in a change in the Panel's recommendations.

The Panel's recommendations apply only to the use of guaifenesin in acute, self-limited conditions which are suited to OTC treatment. The agency notes that the data cited above were not the sole determining factor in the Panel's decision to place quaifenesin in Category III. The Panel recognized that the available data showed conflicting results regarding guaifenesin's effectiveness and noted that there is considerable dispute among experts as to the appropriate dosage for OTC use. The Panel therefore placed guaifenesin in Category III for further study. The agency concurs with this classification.

11. One comment objected to the Panel's review of ipecac fluidextract. The comment contends that ipecac fluidextract is not contained in any OTC preparation and that any reference to this ingredient in the OTC drug review is unnecessary.

The agency disagrees. The Panel received data on the use of ipecac fluidextract as a source of ipecac in an OTC preparation intended for use as an expectorant. These data comprise OTC Volume 040011 (Ref. 1). Therefore, it was necessary for the Panel to review this ingredient.

Reference

(1) OTC Volume 040011.

12. One comment questioned the omission of an article by Boyd, Palmer, and Pearson (Ref. 1) in the Panel's discussion of ipecac syrup as an expectorant at 41 FR 38363. The comment stated that this article is an excellent short paper showing favorable results of the use of ipecac syrup as an expectorant.

The Boyd, Palmer, and Pearson article reports a study concerning testing of a cough mixture containing theophylline ethylenediamine, potassium citrate, wine of ipecac, and chloroform in a syrup. The article reports the results of testing the expectorant action of this cough mixture in animals and humans, testing the effects of the separate ingredients in animals, investigating the mechanism of action of the cough mixture in animals, and measuring the effect of the cough mixture on volume output of respiratory tract fluid in animals. The agency notes that the Panel was aware of this article and cited it as a reference in its discussion of sodium citrate as an expectorant at 41 FR 38367 but not in the ipecac syrup section of the report.

The agency has reviewed the Boyd, Palmer, and Pearson article. Ipecac as a single expectorant ingredient was studied only in albino rats. The wine of ipecac was tested in a group of 11 albino rats at a dose of 0.4 milliliter per kilogram of body weight. Each of the active ingredients of the cough mixture when tested separately had an expectorant effect measured as a percentage increase in respiratory tract fluid output. The agency notes, however, that the Boyd, Palmer, and Pearson article does not provide the amount of ipecac contained in the wine of ipecac administered to the animals in the study. The data from the study are of little value in supporting a safe and effective single dose of ipecac for use as an expectorant in humans.

The only human data presented were on the whole cough mixture combining the four active ingredients. In this part of the study, the combination was tested in 43 patients for antitussive and not for expectorant properties.

The agency concludes that because of the lack of testing of ipecac as a single ingredient in humans the Boyd, Palmer, and Pearson article provides no additional significant data to establish general recognition of the effectiveness of ipecac syrup as an OTC expectorant.

Reference

(1) Boyd, E. M., B. Palmer, and G. Pearson, "Is There Any Advantage in Combining Several Expectorant Drugs in a Compound Cough Mixture?" *Canadian Medical Association Journal,* 54:216–220, 1946.

13. One comment noted that, in the Panel's discussion on the effectiveness of ipecac syrup as an expectorant, the Panel referred to several references (Refs. 1, 2, and 3 below—cited as Refs. 8, 9, and 10 in the Panel's report on page 38364 (41 FR 38364)) as "* * * controlled studies in humans with chronic cough * * *" as though they meet the Panel's criteria for controlled studies. The comment suggested that the Panel erred in referring to these studies as "controlled studies." Further, the comment stated that "none of the references cited to support the proposition of controlled studies showing no efficacy actually support that proposition."

Even though the Panel referred to these studies as "controlled," the agency believes that the Panel did not intend to mean that the studies met the Panel's testing criteria for establishing effectiveness of expectorants.

The Panel concluded that the available data were insufficient to make a determination that ipecac is effective. The agency has reviewed these studies and concurs with the Panel that they do not demonstrate that ipecac is effective as an expectorant and that further study is needed.

References

(1) Alstead, S., "Potassium Iodide and Ipecacuanha as Expectorants," *The Lancet,* 2:932–934, 1939.

(2) Hillis, B. R., and L. Stein, "The Assessment of Expectorant Drugs," *Scottish Medical Journal,* 3:252–263, 1958.

(3) Rose, I., "The Ineffectiveness of Expectorants," *Canadian Medical Association Journal,* 69:494–495, 1953.

14. One comment submitted individual patient data sheets for two studies previously submitted to the Panel (Ref. 1). The comment believed that these additional data would support the classification of ipecac as a Category I expectorant. One study was a single dose study in 72 subjects—24 received the comment's product (a liquid combination drug product containing ipecac as one of its ingredients), 24 received a product containing guaifenesin as its active ingredient, and 24 received placebo. The purpose of the study was to investigate the single-dose effect of the combination drug product in the relief of symptoms of upper respiratory congestion associated with the common cold. The study was conducted under double-blind conditions. Results were reported in terms of a decrease in nasal-airway resistance, relief of runny nose, relief of stuffy nose, reduction in sneezing, relief of coughing, and reduction of a number of other symptoms for which there were insufficient positive responses to carry out statistical evaluations. The second study assessed the effectiveness of a single-and multi-dose schedule of the combination drug product in 25 patients with chronic cough. The study was carried out as a double-blind, placebo-controlled trial with the random allocation of 13 patients to test drug treatment and 12 patients to placebo. Frequency, intensity, and distress of cough were evaluated subjectively by the patients, and reduction in the number of coughs was measured objectively.

The agency has reviewed the studies submitted by the comment and concludes that they were improperly designed and thus could not demonstrate the effectiveness of ipecac as an expectorant. The combination drug product contains ipecac, beechwood creosote, cascara, menthol, white pine, wild cherry, and alcohol. Ipecac, white pine, and beechwood creosote were classified by the Panel as Category III expectorants. Menthol and beechwood creosote were classified as Category III antitussives and as Category III nasal decongestants. The wild cherry and alcohol are considered inactive ingredients. Guaifenesin, used

as a comparative drug in the first study, was classified as a Category III expectorant by the Panel. As the combination drug product contains a number of ingredients with various pharmacologic actions (expectorant/antitussive/nasal decongestant), it is impossible to determine from the studies, as conducted, which of the active ingredients were contributing to or producing the pharmacologic actions that resulted in relief of the symptoms evaluated. Because the ingredients of the combination drug product were not studied individually, the agency cannot ascertain which ingredient(s) in the product were responsible for any of the effects obtained.

In addition, an expectorant drug product was defined by the Panel in § 341.3(j) as "a drug used to promote or facilitate the removal of secretions from the respiratory airways." The studies submitted by the comment did not include any objective measurements of the quality or thickness of sputum. The agency believes that such measurements (an increase in sputum volume and a decrease in viscosity) are necessary to establish the effectiveness of an expectorant ingredient (see comment 9 above). In order to establish the effectiveness of ipecac as an expectorant, it should be studied alone against a placebo (not guaifenesin) with the appropiate parameters being objectively evaluated. The agency concludes that the studies as conducted by the comments do not establish the effectiveness of ipecac as an expectorant active ingredient.

Reference

(1) OTC Volume 040289.

15. A comment disagreed with limiting the OTC use of ipecac syrup as an expectorant to Children 6 years of age and older. The comment contended that there is no basis in the literature for such a limitation. Furthermore, accordingly to the comment, ipecac syrup has a long history of safe usage in children between 2 and 6 years of age, and there is no basis to require the advice and supervision of a physician for its OTC use in children in this age range.

A committee composed of experts in pediatric drug therapy served as advisors to the Panel in determining pediatric dosages for OTC cough-cold drug ingredients. These experts reviewed the available data and recommended that ipecac syrup, as an OTC expectorant, be used only in children 6 years of age and over. The Panel also reviewed the available data and noted that there were no clinical studies substantiating the effectiveness of ipecac syrup as an expectorant and no data on the toxicity of ipecac syrup as a single ingredient for expectorant use in children under 6 years of age. Because of this lack of data, the Panel adopted the pediatric committee's recommendation limiting ipecac syrup as an expectorant to use in children 6 years of age and over. The comment provides not new information which would lead the agency to alter the Panel's recommendation.

16. One comment states that because of the very unusual pharmacological properties of noscapine the Panel should have considered it as an expectorant as well as an antitussive. 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 non-productive cough in certain disease states such as asthma. One study was referenced in support of this activity (Ref. 1). The comment requested that noscapine be considered as an expectorant or, alternatively, be placed in Category III so that further studies can confirm its unique qualities.

The agency has reviewed the reference cited in the comment in which noscapine hydrochloride was administered intravenously to 50 surgical patients in a dosage of 3 milligrams per kilogram of body weight. Doses were administered before the induction of anesthesia or at the end of anesthesia. The cough reflex was not completely removed but foreign matter in the laryngeal or bronchial areas was coughed up. Loder (Ref. 1) 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 agency concludes that the study only assessed the intravenous use of noscapine in surgical patients as an antitussive and was not designed to measure the expectorant activity of the drug. Data and information submitted to the Panel contained studies which were designed primarily to assess antitussive effectiveness (Ref. 2) but also contained unsupported statements that implied the effectiveness of noscapine as an expectorant. The agency has reviewed the Panel's statement on the Category III status of noscapine as an antitussive. (See 41 FR 38352.) The Panel concluded that "There are no well-controlled studies documenting the effectiveness of noscapine as an antitussive. Effectiveness has not been established by objective, controlled clinical trials." Because the comment provided no additional data and because the data and information reviewed by the Panel do not support the effectiveness of noscapine as an expectorant, the agency concludes that noscapine is Category II for OTC use as an expectorant.

References

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

(2) OTC Volumes 040001, 040002, 040003, 040004, and 040204.

17. Two comments objected to the Panel's recommendation that chloroform be permitted for use as a flavoring agent in cough-cold products. Both comments stated that the Panel's recommendation conflicts with the National Cancer Institute's finding that chloroform is an animal carcinogen having the potential for carcinogenesis in humans. The comments concluded that chloroform should not be allowed to be used as a flavoring agent.

This issue is addressed in this document because the Panel discussed the safety of chloroform as a flavoring agent as part of its evaluation of chloroform as an expectorant agent. One of the documents which the Panel reviewed pertaining to the possible carcinogenicity of chloroform was a preliminary report from the National Cancer Institute (NCI) entitled "Report on Carcinogenesis Bioassay of Chloroform" dated February 1976 (Ref. 1). After considering the dosage of chloroform administered in the study described in the NCI report, the Panel stated that it was unable to determine from the available data whether chloroform at a maximum allowable concentration of 0.4 percent proposed for use as a flavoring agent was safe.

The Panel's report was adopted and submitted to FDA during its last meeting on March 2 and 3, 1976. On March 1, 1976, the agency received the NCI's "Report On The Carcinogenesis Bioassay of Chloroform." FDA reviewed this report and, prior to publication of the Panel's report, published a proposal in the **Federal Register** of April 9, 1976 (41 FR 15026) and a final regulation in the **Federal Register** of June 29, 1976 (41 FR 26842), which has been codified in § 310.513 (21 CFR 310.513), stating that any human drug product containing chloroform as an ingredient is a new drug and is misbranded. The Panel's report was subsequently published in the **Federal Register** on September 9, 1976 (41 FR 38312), and was not changed to reflect the above regulation because it was not an agency proposal. The chloroform ban in § 310.513 is, of course, applicable to chloroform used as an

active (expectorant) or inactive (flavoring agent), and any drug product containing chloroform is considered to be a new drug.

Reference

(1) OTC Volume 040338.

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

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

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and has made no changes at this time in the Panel's categorization of ingredients. For the convenience of the reader, the following tables are included as summaries of the categorization of anticholinergic and expectorant active ingredients.

	Category
Anticholinergic Active Ingredients	
Atropine sulfate	III.
Belladonna alkaloids	III.
Belladonna alkaloids as contained in atropa belladonna and datura stramonia (inhalant).	II.
Expectorant Active Ingredients	
Ammonium chloride	III.
Antimony potassium tartrate	II.
Beechwood creosote	III.
Benzoin preparations (inhalant) (compound tincture of benzoin, tincture of benzoin).	III.
Camphor (topical/inhalant)	III.
Chloroform	II.
Eucalyptol/eucalyptus oil (topical/inhalant)	III.
Guaifenesin (glyceryl guaiacolate)	III.
Iodides (calcium iodide, anhydrous; hydriotic acid syrup; iodized lime; potassium iodide).	II.
Ipecac fluidextract	II.
Ipecac syrup	III.
Menthol/peppermint oil (topical/inhalant)	III.
Pine tar preparations (extract white pine compound, pine tar, syrup of pine tar, compound white pine syrup, white pine).	III.
Potassium guaiacolsulfonate	III.
Sodium citrate	III.
Squill preparations (squill, squill extract)	II.
Terpin hydrate preparations (terpin hydrate, terpin hydrate elixir).	III.
Tolu preparations (tolu, tolu balsam, tolu balsam tincture).	III.
Turpentine oil (spirits of turpentine) (oral)	II.
Turpentine oil (spirits of turpentine) (topical/inhalant)	III.

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for anticholinergic drug products and expectorant drug products (41 FR 38329, 38369, and 38379). The agency is offering these guidelines as the Panel's recommendations without adopting them or making any formal comment on them. The agency has some reservations about the Panel's testing guidelines for expectorants and suggests that manufacturers discuss their proposed protocol(s) with the agency prior to performing studies. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any anticholinergic or expectorant 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). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

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

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the anitcholinergic and expectorant sections of the Panel's report and recommended monograph with the changes described in FDA's response to the comments above and with other changes described in the summary below. A summary of the changes made in the Panel's conclusions and recommendations follows.

1. The agency has amended §§ 341.70 and 341.78 to include a "Statement of identity" paragraph and a "Directions" paragraph to conform to the format of other recently published proposed and tentative final monographs. Inclusion of new paragraphs has necessitated a redesignation of paragraphs within these sections as noted below. The agency is also redesignation proposed Subpart D as Subpart C and placing the labeling sections of the monographs under Subpart C.

2. The agency has combined the indications for anticholinergics that were included under § 341.70(a) (redesignated as § 341.70(b)). The agency has also combined several indications for expectorants that were inlcuded under § 341.78(a) (redesignated as § 341.78(b)). The agency believes that combining these respective indications presents them to the consumer in a clearer and more concise manner. Therefore, the Panel's indications in § 341.70(a) (1) through (5) have been revised, combined, and redesignated as new § 341.70(b). The Panel's indications in § 341.78(a) (1) through (4) have been combined, revised, and redesignated as new § 341.78(b)(1). Section 341.78(a)(5) has been redesignated as new § 341.78(b)(2).

3. The Panel's recommended warning in § 341.70(b)(2) has been redesignated as § 341.70(c)(2) and changed to include "dizziness" as described in comment 6 above.

4. In §§ 341.70(b)(3) and 341.78(b)(3) the Panel recommended use of the signal word "caution" in a section of the labeling where the heading "Warnings" is also recommended. FDA has determined that the signal word "warning," rather than the word "caution," will be used routinely in OTC drug labeling. Accordingly, the signal word "caution" has been deleted from §§ 341.70(b)(3) and 341.78(b)(3) (redesignated as §§ 341.70(c)(3) and 341.78(c)(3) respectively in the tentative final monograph). (See comment 5 above).

5. The agency has deleted the word "high" (in reference to fever) from the Panel's warning for expectorants in § 341.78(b)(3) (redesignated as § 341.78(c)(3)). Fever can be defined as a body temperature above the normal temperature of 98.6° F (37° C). In the same or different disease states, however, fevers may vary significantly. Fever may be low grade, moderate, high, intermittent, or sustained. The particular characteristics of a fever depend on the disease state, and, in many cases, the stage of development of the disease. The word "high" has been deleted from the warning because the agency believes that it is important for the consumer to recognize the presence of fever, regardless of whether the fever is high or low.

6. The Panel recommended use of the word "physician" in several warnings. Believing that the word "doctor" is more commonly used and better understood by consumers, the agency is substituting the word "doctor" for "physician" in the warnings appearing in the tentative final monograph. FDA is proposing that the term "doctor" be used instead of the term "physician" in all OTC drug monographs. (See comment 5 above).

The agency has examined the economic consequences of this proposed rulemaking and has determined that it does not require either a Regulatory Impact Analysis, as specified in Executive Order 12291, or a Regulatory Flexibility Analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96-354). Specifically, the proposal would necessitate some testing or reformulation as there are currently no Category I anticholinergic or expectorant ingredients. The agency is aware that one expectorant ingredient, guaifenesin, is being tested and that the data relating to that ingredient may be submitted before the final monograph is issued. If guaifenesin is placed in Category I, some minor relabeling will be necessary, resulting in minimal costs. The agency knows of no anticholinergic ingredients being tested, and it appears that cough-cold products containing these ingredients will have to be

reformulated after the final monograph is issued. Minimal impact is expected, however, as most of these products have already been reformulated voluntarily without the anticholinergic ingredient. Therefore, the agency concludes that the proposed rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that the proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have an OTC anticholinergic drug products and expectorant 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 anticholinergic drug products and expectorant 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 anticholinergic drug products and expectorant 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, contained in an environmental assessment (under 21 CFR 25.31, proposed in the **Federal Register** of December 11, 1979; 44 FR 71742), may be seen in the Dockets Management Branch, Food and Drug Administration.

List of Subjects in 21 CFR Part 341

OTC drugs: Anticholinergics, Expectorants.

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 as revised (see 47 FR 16010; April 14, 1982), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Part 341, to read as follows:

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

Subpart A—General Provisions

Sec.
341.1 Scope.
341.3 Definitions.

Subpart B—Active Ingredients [Reserved]

Subpart C—Labeling

341.70 Labeling of anticholinergic drug products.
341.78 Labeling of expectorant drug products.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–42 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); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 341.1 Scope.

(a) An over-the-counter cold, cough, allergy, bronchodilator, or antiasthmatic drug product in a form suitable for oral, inhalant, or topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this part in addition to each of the general conditions established in § 330.1.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 341.3 Definitions.

As used in this part:

(a) *Anticholinergic drug.* A drug used for the relief of excessive secretions of the nose and eyes, symptoms which are commonly associated with hay fever, allergy, rhinitis, and the "common cold" (cold).

(b) *Expectorant drug.* A drug used to promote or facilitate the removal of secretions from the respiratory airways.

Subpart B—Active Ingredients [Reserved]

Subpart C—Labeling

§ 341.70 Labeling of anticholinergic drug products.

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

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following phrase: "Temporarily" (selected one of the following: "suppresses" or "relieves" (select one of the following: "watery nasal discharge," "excessive nasal secretions," or "running nose") "and watery eyes as may occur in certain allergic conditions and infections of the upper respiratory tract."

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

(1) "Do not exceed recommended dosage unless directed by a doctor."

(2) "Stop taking this product if constipation, excessive dryness of the mouth, insomnia, excitement, confusion, dizziness, rapid pulse, or blurring of vision occurs."

(3) "Do not take this product if you have asthma, glaucoma, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(4) "Do not give this product to children under 12 years of age unless directed by a doctor."

(d) *Directions. [Reserved]*

§ 341.78 Labeling of expectorant drug products.

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

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to one or both of the following phrases:

(1) "Helps" (select one of the following: "Loosen phlegm) (sputum) and bronchial secretions and rid the bronchial passageways of bothersome mucus" or "drain bronchial tubes by thinning mucus.")

(2) "Relieves irritated membranes in the respiratory passageways by preventing dryness through increased mucus flow."

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

(1) "Do not give this product to children under 2 years of age unless directed by a doctor."

(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is

accompanied by excessive secretions unless directed by a doctor."

(3) "A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by fever, rash, or persistent headache, consult a doctor."

(d) *Directions.* [Reserved]

Interested persons may, on or before September 7, 1982 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 November 8, 1982. 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 July 11, 1983 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 September 9, 1983. 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 September 9, 1983. 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: April 16, 1982.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: June 7, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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