DEPARTMENT OF DEFENSE

GENERAL SERVICES ADMINISTRATION

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

48 CFR Parts 42 and 52

Federal Acquisition Regulation (FAR); Hazardous Materials

AGENCIES: Department of Defense (DoD), General Services Administration (GSA), and National Aeronautics and Space Administration (NASA).

ACTION: Proposed rule.

SUMMARY: The Civilian Agency Acquisition Council and the Defense Acquisition Regulatory Council are considering a change to FAR 42.302(a)(39) and the clause at 52.223–3 to remove the implication that Contract Administration Services were responsible for administering statutory and regulatory requirements for hazardous materials.

DATE: Comments should be submitted to the FAR Secretariat at the address shown below on or before May 1, 1989, to be considered in the formulation of a final rule.

ADDRESS: Interested parties should submit written comments to:
General Services Administration, FAR Secretariat (VRS), 18th & F Streets, NW., Room 4041, Washington, DC 20405.

Please cite FAR Case 89–15 in all correspondence related to this issue.

FOR FURTHER INFORMATION CONTACT: Margaret A. Willis, FAR Secretariat, Room 4041, GS Building, Washington, DC 20405, (202) 523–4755.

SUPPLEMENTARY INFORMATION:

A. Regulatory Flexibility Act

The proposed rule does not appear to have a significant impact on a substantial number of small entities and analysis of the proposed revision indicates that it is not a "significant revision" as defined in FAR 1.501, i.e., it does not alter the substantive meaning of any coverage in the FAR having a significant cost or administrative impact on contractors or offerors, or have significant effect beyond the internal operating procedures of the issuing agencies.

Accordingly, and consistent with section 1212 of Pub. L. 98–525 and section 302 of Pub. L. 98–577 pertaining to publication of proposed regulations (as implemented in FAR Subpart 1.5, Agency and Public Participation) solicitation of agency and public views on the proposed revision is not required. Since such solicitation is not required, the Regulatory Flexibility Act (5 U.S.C. 601, et seq.) does not apply.

B. Paperwork Reduction Act

The Paperwork Reduction Act does not apply because the proposed changes do not impose recordkeeping information collection requirements or collection of information from offerors, contractors, or members of the public which require the approval of OMB under 44 U.S.C. 3501, et seq.

List of Subjects in 48 CFR Parts 42 and 52

Government procurement.

Dated: February 14, 1989.

Harry S. Rosinski,

Acting Director, Office of Federal Acquisition and Regulatory Policy.

Therefore, it is proposed that 48 CFR Parts 42 and 52 be amended as set forth below:

1. The authority citation for 48 CFR Parts 42 and 52 continues to read as follows:

Authority: 40 U.S.C. 486(c); 10 U.S.C. Chapter 137; and 42 U.S.C. 2473(c).

PART 42—CONTRACT ADMINISTRATION

2. Section 42.302 is amended by revising paragraph (a)(39) to read as follows:

42.302 Contract administration functions

(a) * * *

(39) Ensure contractor compliance with contractual safety requirements.

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PART 52—SOLICITATION PROVISIONS AND CONTRACT CLAUSES

3. Section 52.223–3 is amended by revising paragraph (d) of the clause to read as follows:

52.223–3 Hazardous Material Identification and Material Safety Data.

* * * * *

(d) Nothing contained in this clause shall relieve the Contractor from complying with applicable Federal, state, and local laws, codes, ordinances, and regulations (including the obtaining of licenses and permits) in connection with hazardous material.

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[FR Doc. 89–4490 Filed 2–27–89; 8:45 am]

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federal register

Tuesday
February 28, 1989

Part V

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 341

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 341

[Docket No. 76N-052E]

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

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) expectorant drug products are generally recognized as safe and effective and not misbranded. (Expectorants are drugs taken orally to promote or facilitate the removal of secretions from the respiratory airways.) FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on expectorant drug products that have come to the agency's attention. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: February 28, 1990.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

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

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products is being issued in the following segments: anticholinergics and expectorants, bronchodilators, antitussives, nasal decongestants, antihistamines, and combinations. The first segment, the tentative final monograph for anticholinergic drug products and expectorant drug products, was published in the **Federal Register** of July 9, 1982 (47 FR 30002). Interested persons were invited to file by September 7, 1982, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by November 8, 1982. New data could have been submitted until July 11, 1983, and comments on the new data until September 9, 1983. Final agency action occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC expectorant drug products.

In a notice published in the **Federal Register** of August 27, 1982 (47 FR 37934), the agency advised that it had extended the period for comments, objections, or requests for oral hearing for OTC anticholinergic drug products and expectorant drug products. The notice allowed the period for comments, objections, or requests for oral hearing to be extended to November 8, 1982.

The agency's final rule, in the form of a final monograph, for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products is also being published in segments. Final agency action on expectorant drug products occurs with the publication of this document, which establishes §§ 341.3(d), 341.18, and 341.78 and adds professional labeling information in § 341.90(d) for OTC expectorant drug products in Part 341 (21 CFR Part 341). Combination drug products containing expectorant drugs are addressed in the tentative final monograph on combination cough-cold drug products which was published in the **Federal Register** of August 12, 1988 (53 FR 30522). The agency's final action on OTC anticholinergic drug products was published in the **Federal Register** of November 8, 1985 (50 FR 46582).

In the preamble to the agency's proposed rule on OTC expectorant drug products (47 FR 30002), the agency stated that no expectorant active ingredients had been found to be generally recognized as safe and effective and not misbranded, but that Category I labeling was being proposed in that document in the event that data were submitted that resulted in the upgrading of any ingredient to monograph status in the final rule. In this final rule, one expectorant ingredient, guaifenesin, is included in the monograph.

The Advisory Review Panel on OTC Oral Cavity Drug Products (Oral Cavity Panel) reviewed safety and effectiveness data on four expectorant ingredients (potassium iodide, ammonium chloride, tolu balsam, and horehound), but did not classify any expectorants in Category I in its report published in the **Federal Register** of May 25, 1982 (47 FR 22920). In the tentative final monograph for OTC oral health care anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, and demulcent drug products, published in the **Federal Register** of Janaury 27, 1988 (53 FR 2436 at 2448), the agency referred the data on these four expectorant ingredients to the rulemaking for OTC expectorant drug products because the ingredients had been reviewed earlier and more extensively by the Cough-Cold Panel and because no new data were submitted to the agency in support of the effectiveness of any expectorant for oral health care use. In this final rule, based on a lack of safety and/or effectiveness data, the agency concludes that the four expectorant ingredients (potassium iodide, ammonium chloride, tolu balsam, and horehound) considered by the Oral Cavity Panel are nonmonograph ingredients.

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

at the final monograph stage, but is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

As discussed in the proposed regulation for OTC expectorant drug products (47 FR 30003), the agency advises that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the Federal Reigster. Therefore, on or after February 28, 1990, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Any OTC expectorant drug product that is subject to the monograph, whether formulated as a single ingredient or a combination drug product, must meet the requirements of this final rule upon its effective date. Further, any OTC drug product subject to this monograph that is repackaged or relabled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In response to the proposed rule on OTC expectorant drug products, five drug manufacturers, two drug manufacturer associations, one health professional, and one health care professional society submitted comments on expectorants. There was one request for a hearing. Copies of the comments and the hearing request received are on public display in the Dockets Management Branch. Any additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

In proceeding with this final monograph, the agency has considered all comments, new data, the request for an oral hearing, and the changes in the procedural regulations. A summary of the comments and FDA's responses to them follows. A discussion of the new data and the request for an oral hearing are contained in those responses.

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

I. The Agency's Conclusions on the Comments

A. General Comments on Expectorant Drug Products

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

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the Federal Register of May 11, 1972 (37 FR 9464) and in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the Federal Register of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. (See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F. 2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).)

2. One comment disagreed with the agency's statement that "no expectorant active ingredients have been determined to be generally recognized as safe and effective and not misbranded" (47 FR 30002). Arguing that the evidence to support the safety and effectiveness of these ingredients may not be conclusive, the comment stated that most of these drugs are not unsafe when used as directed by the manufacturers. The drugs may be effective in a "significant proportion of patients," the comment maintained, and it would be desirable to examine the physiologic and pharmacologic effects of these drugs to determine whether larger than recommended doses do have measurable beneficial or harmful effects in patients who claim that "standard" doses produce subjective benefits. The comment added that there is evidence that larger than recommended doses of expectorants cause nausea or emesis, and there is a pharmacologic basis for believing that subemetic doses can improve respiratory tract mucus clearance.

The comment pointed out that the Panel recognized that the available data showed conflicting results regarding the effectiveness of guaifenesin and that the experts disagreed on the appropriate dosage for OTC use of this ingredient (47 FR 30006). According to the comment, if tests on guaifenesin show that the ingredient has emetic quality, it could be assumed that other commonly used expectorants may have similar qualities because the emetic quality is common to most oral expectorants. Because there is an ongoing test on guaifenesin, the comment emphasized the need to avoid a final "commitment" regarding the effectiveness of oral expectorants.

The agency's statement that "no expectorant active ingredients have been determined to be generally recognized as safe and effective and not misbranded" was a tentative conclusion based on a lack of adequate studies at that time to support the use of these drugs for their claimed effects. The agency agrees with the Panel that although many of the expectorants on the market with long usage are generally safe, most lack evidence of effectiveness (41 FR 38355). It is believed that many of the drugs that are claimed to have expectorant activity act reflexly by irritating the gastric mucosa, which in turn stimulates the respiratory tract secretions (Ref. 1). Saline expectorants, ammonium salts, citrates, iodides, antimony and potassium tartrate, ipecac expectorants, creosotes, and guaiacols are included in this group of drugs. Some experimental evidence suggests that these substances do increase respiratory tract secretions, but the data are sparse and unconvincing. Except for data on guaifenesin, no new test data were submitted on any of these ingredients following publication of the tentative final monograph. Thus, at present, adequate data do not exist to support general recognition of any of these other OTC ingredients as effective expectorants.

Gauifenesin was classified by the Panel in Category III for further study as an expectorant active ingredient. After reviewing new effectiveness data, FDA determined that the data supported the effectiveness of guaifenesin as an expectorant; therefore, guaifenesin is included in this final monograph as an expectorant (see comment 5 below).

Manufacturers may test nonmonograph expectorant ingredients to determine whether the Panel's recommended doses or even larger

doses are effective. If the larger than recommended doses are not within a known safety range, additional safety studies will be needed. Any clinical testing of nonmonograph ingredients should be conducted under the provisions of a Notice of Claimed Investigational Exemption for a New Drug (IND) (Form FDA–1571) (OMB Approval No. 0910–0014), as set forth in 31 CFR 312.1.

Reference

(1) Swinyard, E.A., "Respiratory Drugs," *in* "Remington's Pharmaceutical Sciences," 17th Ed., Mack Publishing Co., Easton, PA, p. 867, 1985.

3. In response to the agency's request for definitions of the term "expectorant" in lay language (47 FR 30004), one comment suggested that "expectorant" be defined as "a drug taken by mouth which loosens abnormal secretions in the lung and thereby enables sputum to be coughed up more easily." The comment added that, in defining an expectorant drug, it should be recognized that expectorant drugs are those which are usually given by mouth whereas those that are taken by inhalation may be "mucolytics," "surfactants," and "bronchorrheics." It pointed out that in other countries, oral expectorant drugs include "bronchomucotropics" and "mucoregulators," and some "mucolytics" may be given by mouth as well as by inhalation.

By inviting public comment on definitions for "expectorant," the agency acknowledged the difficulty in defining this word in lay terms. However, the agency concludes that the definition offered by the comment for the term "expectorant" is not clearer or more appropriate than that proposed by the agency in § 341.3 (47 FR 30009), although one of the comment's suggestions is being adopted.

At this time, only an oral expectorant (guaifenesin) is included in the monograph. Therefore, the agency agrees that it is appropriate to include in the definition that expectorants are for oral use. The comment's suggested phrase "a drug taken by mouth" has been paraphrased to read "a drug taken orally." Since no expectorants for inhalation use are included in the monograph, it is not necessary to separate expectorant drugs into "mucolytics," "surfactants," and "bronchorrheics" as suggested by the comment. The phrase "abnormal secretions in the lung" may be misleading because other areas of the respiratory tract, in addition to the lungs, may also be the site of mucus secretions. The use of the word "abnormal" might also unduly alarm consumers. Therefore, § 341.3 of this final monograph contains the following definition of expectorant: "a drug taken orally to promote or facilitate the removal of secretions from the respiratory airways."

B. Comments on Specific OTC Expectorant Active Ingredients

4. One comment stated that it is not clear why beechwood creosote is classified as an antitussive and a nasal decongestant because current evidence suggests that it acts only as an expectorant. The comment did not submit any additional information.

The comment's statement was in reference to the agency's discussion at 47 FR 30006 that beechwood creosote was classified in Category III by the Panel as an expectorant, antitussive, and nasal decongestant. The Panel reviewed several submissions on combination products containing beechwood creosote, for which nasal decongestant and cough relief claims were made (Ref. 1). The Panel also reviewed one reference that reported some increases of respiratory tract fluid in animals given high doses of beechwood creosote, indicating a possible usefulness as an expectorant (Ref. 2). Although beechwood creosote was found safe for antitussive, nasal decongestant, and expectorant use, the Panel found the data insufficient to demonstrate effectiveness for any of these uses. Accordingly, the Panel placed beechwood creosote in Category III for antitussive, nasal decongestant, and expectorant use and recommended additional studies to upgrade the ingredient to Category I.

In the tentative final monographs on OTC antitussive drug products (48 FR 48576 at 48590) and nasal decongestant drug products (50 FR 2220 at 2235), the agency agreed with the Panel's Category III classification of beechwood creosote. No new data have been submitted to the agency to demonstrate the effectiveness of beechwood creosote as an expectorant; therefore, the ingredient is not included in this final monograph for OTC expectorant drug products.

References

(1) OTC Volumes 040208, 040235, and 040289.

(2) Stevens, M. E., et al., "On the Expectorant Action of Creosote and the Guaiacols," *Canadian Medical Association Journal*, 48:124–127, 1943.

5. One comment submitted a study to support the reclassification of guaifenesin as an expectorant from Category III to Category I (Ref. 1). The comment requested an oral hearing with respect to the omission of guaifenesin as a Category I expectorant in the tentative final monograph on grounds that the data submitted and the drug's record of safe and effective use for over 50 years establish guaifenesin as a generally recognized safe and effective expectorant. The comment also requested an oral hearing on the ground that the record is devoid of any evidence which would support a finding that guaifenesin containing products labeled for use as an expectorant are misbranded.

In the tentative final monograph for OTC expectorant drug products (47 FR 30002 at 30005), the agency tentatively adopted the Panel's Category III classification of guaifenesin, because of insufficient effectiveness data, and stated that one additional well-designed, double-blind study in which subjective evaluations are correlated with objective measurements would be needed to upgrade guaifenesin from Category III to Category I. A study was submitted to satisfy this requirement.

The agency has reviewed the study and concludes that the study and the data previously evaluated by the Panel are adequate to support the reclassification of guaifenesin as an expectorant from Category III to Category I. This randomized, double-blind, placebo-controlled study was conducted in a domiciled population of 40 patients with chronic bronchitis accompanied by productive cough. The purpose of the study was to equate subjective improvement and evaluations of difficulty in raising sputum with objective measurements of expectorant action, i.e., an increase in sputum volume and a decrease in sputum viscosity. The results showed that over the first 4 to 6 days there was an initial increase in the volume of sputum produced by the patients who received guaifenesin, followed by a reduction. The total sputum volume for the 15-day study period was not significantly different between placebo and guaifenesin patients; however, the sputum volume produced by the guaifenesin patients at day 15 was approximately one-third the sputum volume produced by the placebo patients. This was accompanied by changes in the appearance and viscosity of the sputum and an improvement in the subjective assessment of the difficulty in raising sputum. Four patients receiving guaifenesin experienced a complete clearing of sputum production. Placebo patients showed a gradual reduction in sputum volume, but changes in sputum character and subjective assessment

were much less pronounced. No patient in the placebo group had clearing of symptoms or clearing of sputum.

Statistical analysis of the data showed that the mean percentage of total sputum volume expectorated by day 7 was significantly greater for patients taking guaifenesin than placebo (69.3 percent versus 53.7 percent, $p < 0.001$). The mean number of days to expectoration of 75 percent of the total sputum volume was significantly lower on guaifenesin than on placebo (8.40 versus 10.65 days, $p < 0.001$). For sputum viscosity and difficulty of raising sputum, mean values on day 15 and mean total severity scores were significantly lower in the guaifenesin group than in the placebo group ($p < 0.001$). Scatterplots suggested a fairly strong correlation between sputum parameters and subjective symptom evaluations. The agency concludes that the data provide clinical evidence of the expectorant action of guaifenesin. Therefore, guaifenesin is being included as an expectorant ingredient in the final monograph for OTC expectorant drug products.

The study was conducted using a 10-milliliter dose of 190 milligrams (mg) guaifenesin three times a day. Although this dosage is in the lower range of the Panel's recommended dose, the agency believes that, based on all of the data in the administrative record, the Panel's recommended dosage should be used in the final monograph (§ 341.78(d)) as follows: "Adults and children 12 years of age and over: oral dosage is 200 to 400 milligrams every 4 hours not to exceed 2,400 milligrams in 24 hours. Children 6 to under 12 years of age: oral dosage is 100 to 200 miligrams every 4 hours not to exceed 1,200 milligrams in 24 hours. Children 2 to under 6 years of age: oral dosage is 50 to 100 milligrams every 4 hours not to exceed 600 milligrams in 24 hours. Children under 2 years of age: consult a doctor."

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

Because guaifenesin has been reclassified from Category III to monograph status, the agency concludes that the comment's request for a hearing is moot.

References

(1) Comment No. LET077, Docket No. 76N–052C, Dockets Management Branch.

(2) Letter from W.E. Gilbertson, FDA, to R. E. Keenan, A. H. Robins Co., coded ANS002, Docket No. 76N–052C, Dockets Management Branch.

6. Three comments requested that the indications for expectorants (guaifenesin) be expanded to include a cough reduction claim. One comment stated that expectorants help ease cough by relieving the bronchial passageways of bothersome mucus, by relieving irritated membranes in the respiratory passageways, and by stimulating the flow of respiratory tract secretions, which allows ciliary motion and coughing to move the loosened material through the pharnyx more easily. The comment added that recognition of these facts is well-documented and cited the Panel's report (41 FR 38355), several published and unpublished studies (Refs. 1 through 6), and other standard reference textbooks (Refs. 7 and 8) in support of its statements.

Another comment stated that expectorants should specifically be indicated for relief of a dry, nonproductive cough because these terms are more meaningful to consumers. The comment explained that consumers will be better able to identify that they need an expectorant if terms such as "dry, hacking or irritating cough," or "upper chest cough" are used in the labeling. The third comment stated that cough relief is generally recognized as an end benefit of the use of an expectorant and agreed with and cited most of the information that was discussed by the first comment (Refs. 1 through 5, 9, and 10). In addition, this comment submitted a new study on the effect of guaifenesin on cough induced by citric acid aerosol challenge (Ref. 11). The comment requested that the phrase "to help relieve cough" be added at the end of each of the indications for use provided under (1) and (2) of proposed § 341.78(b) of the tentative final monograph for expectorant drug products.

The agency has reviewed the submitted data and concludes that the data are insufficient to support a specific cough reduction (antitussive) claim for guaifenesin (Refs. 1 through 11). Connell et al. (Ref. 2) studied the effect of guaifenesin in 20 patients with cough associated with acute bronchitis, bronchitis with asthma, and chronic pulmonary fibrosis, and in 12 patients with chronic pulmonary tuberculosis. A few patients reported no subjective improvement, but the majority of patients noted that expectoration was easier and freer, and that useless, irritating cough was diminished, with the most striking results in patients with acute bronchitis with dry, irritating cough. The agency does not consider this uncontrolled study adequate to demonstrate that guaifenesin reduces cough. Few details of the study were provided, and all evaluations were subjective and undocumented.

In phase I of their study, Stevens et al. (Ref. 3) studied the effect of guaifenesin on the respiratory tract fluid of cats and rabbits; in phase II they compared the antitussive effect of guaifenesin in tablet form with placebo tablets in humans. The patient population consisted of medical students who were asked to record as accurately as possible the number of coughs per day whenever the student had a cold. The investigators concluded that guaifenesin had a sedative effect upon cough, probably, in view of the phase I animal experiments, due to an increased output of respiratory tract fluid. The agency finds that this study was not well-controlled, is sparsely detailed, and lacks objective measurement of cough.

Hayes et al. (Ref. 4) conducted a two-phase study on the effectiveness of guaifenesin as a expectorant. Each phase was open labeled and involved 50 subjects with stable cough due to chronic disease (pulmonary tuberculosis, bronchiectasis, or bronchitis). The effect of the drug on sputum tenaciousness, frequency of cough, and overall severity of cough was subjectively evaluated. The authors reported that in phase I, guaifenesin was credited with reducing the number of coughs in 54 percent of the testing periods (not a 54-percent reduction). In phase II, the frequency of cough was reduced in 59 percent of the testing periods. The agency finds this study unacceptable because only subjective assessments were made and results were reported as changes observed in 150 "periods" of assessment without futher information with respect to what constituted a period; therefore, no comparability for measurement could be established. It also is not clear whether the product studied contained an oral sympathomimetic ingredient (desoxyephedrine hydrochloride) in addition to guaifenesin. Additionally, phase I of the study was uncontrolled, and in phase II the vehicle was given during the washout periods. The agency notes that Cass et al. (Ref. 9), discussed below, indicated that the vehicle was shown to have activity. Thus, the only baseline for phase II of the Hayes study was pretreatment.

Schwartz et al. (Ref. 5) tested the relative merits of potassium iodide and a product containing a combination of guaifenesin and desoxyephedrine hydrochloride on cough and pulmonary function in asthmatic patients. The study is inadequate because details are lacking concerning the measurement of efficacy parameters and because the guaifenesin product contained an additional ingredient.

Three unpublished studies (Protocols 06, 08, and 14) and other information cited by one comment had previously been submitted to the agency to establish the effectiveness of guaifenesin as an expectorant (Ref. 6). The agency concluded that the studies were not sufficient to demonstrate the effectiveness of guaifenesin (Ref. 12). Cough frequency was assessed in the studies, but was measured subjectively; not objective cough-counting techniques were used. Thus, these studies are unacceptable to demonstrate a cough reduction claim.

The standard references cited by the comment did not contain any data to demonstrate a cough reduction claim for guaifenesin (Refs. 7 and 8).

Cass et al. (Ref. 9) measured the effectiveness of three antitussives in patients with cough due to chronic respiratory disease. The drugs used were terpin hydrate, ammonium chloride, an aromatic syrup (placebo), and a product containing a combination of 100 mg of guaifenesin and 1 mg of desoxyephedrine hydrochloride. The placebo served as the vehicle for all test preparations. This was a double-blind study with no washout between regimens. Subjective scores were determined on side effects, effects on cough, effects on sputum volume and tenaciousness, taste preference, and overall efficacy. The physician's and technican's assessments of efficacy were also subjectively scored. The study reports that all regimens reduced cough, but that only the aromatic syrup and the product containing guaifenesin and desoxyephedrine hydrochloride reached statistical significance, which "is not marked." For overall efficacy, the product containing guaifenesin and desoxyephedrine hydrochloride was recorded as the only preparation for which statistical significance was achieved. The agency finds this study unacceptable because the selection criteria do not adequately control variables, and this negates the value of the study. Additionally, the guaifenesin preparation contained desoxyephedrine hydrochloride, and the effect of this ingredient is not explained or evaluated. Moreover, the fact that 20 percent of the patients were discharged before the study was completed suggests that the inclusion criterion of cough did not ensure comparability.

Packman (Ref. 11) compared the antitussive effect of guaifenesin (100 and 200 mg) versus aqueous placebo on artificially induced cough in the 3 hours following administration. This was a single-blind, crossover study in which 37 subjects received one of the three treatments on three separate occasions at 7-day intervals. Subjects were challenged with citric acid aerosol at 30 minutes, 1 hour, 2 hours, and 3 hours after dosing. Baseline cough counts were required to be in the range of 10 to 15 coughs. Coughs were recorded on a coded pneumotach recording. The sponsor concluded that, when compared with baseline, both 100 mg and 200 mg guaifenesin demonstrated significantly greater reduction in cough counts than placebo at all post-treatment timepoints.

Although this study noted the superiority of single doses of guaifenesin over a placebo control in reducing the number of coughs occurring in healthy subjects after artificial induction of cough with citric acid, the agency has reservations about the use of citric acid aerosol induced cough studies for cough claims for expectorants. As discussed in the tentative final monograph for OTC antitussive drug products (48 FR 48583), the agency does not consider induced cough studies alone as adequate to demonstrate the antitussive effectiveness of an ingredient. Likewise, induced cough studies are not adequate alone to demonstrate a cough reduction claim for expectorants. Moreover, in view of the recent study by Kuhn et al. (Ref. 13), discussed below, that failed to show any difference in cough between placebo and guaifenesin in patients with cough due to natural disease, the value of induced cough studies is questionable. Therefore, the agency concludes that the Packman study is unacceptable to demonstrate a cough relief claim. Studies to support the efficacy of guaifenesin in relieving cough must be conducted in patients with cough due to naturally occurring disease.

The agency also notes that the results of the Packman study (Ref. 11) are inconsistent with previously reported results from the same investigator under similar conditions. In an earlier study, Packman et al. (Ref. 14) found that guaifenesin was no better than placebo in reducing cough, although it appeared to enhance the combination of dextromethorphan and phenylpropanolamine.

In addition, a recent study by Kuhn et al. (Ref. 13) failed to show that guaifenesin is effective in suppressing cough in patients with cough due to natural disease. Kuhn's study suggests that artificial induction of cough may not be an appropriate method for studying expectorants. The investigators studied the efficacy of guaifenesin in reducing cough frequency in young adults with acute upper respiratory disease of less than 48 hours duration with cough. Evaluations were made by using an objective cough-counting system and a questionnaire. Guaifenesin and its syrup vehicle were administered to 42 patients in this double-blind study for a 36-hour treatment period. A total of 2,400 mg (30 milliliters every 6 hours) of guaifenesin was administered. The protocol was similar to that suggested by the Panel (41 FR 38312 at 38369). In essence, simultaneously recorded subjective responses determined by questionnaire were compared with the cough counts obtained from a tape recording over a 60-hour period. Differences in sputum volume (a decrease in 88 percent in the treatment group and 62 percent in the placebo group) and decrease in viscosity (96 percent versus 54 percent in treatment and placebo groups, respectively) were demonstrated in the questionnaires of both groups when compared with baseline. However, the cough tape showed no differences in median cough frequency between the groups. Moreover, the tape demonstrated a diurnal pattern, which was present both before and after treatment and which was not reflected in the subjective cough frequency estimates obtained from the questionnaires.

In conclusion, none of the studies dealing with naturally occurring cough are acceptable for a cough reduction claim for guaifenesin because none of them used objective cough counting techniques (Refs. 2 through 6 and 9). The Panel emphasized objective cough counting as a requirement for any claim for amelioration of cough (41 FR 38355 and 38369), and the agency concurs. Moreover, the agency does not consider induced-cough studies alone as adequate to demonstrate a cough reduction claim. The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (address above) (Refs. 15 and 16).

Based on the discussion above, the agency is not including in the expectorant final monograph a specific cough reduction (antitussive) claim for expectorants. However, submitted data demonstrate that guaifenesin loosens and thins sputum and bronchial secretions and makes expectoration easier. In the the Vercelli study (see comment 5 above), over the first 4 to 6 days, patients who received guaifenesin produced a greater increase in sputum volume than did placebo patients. The mean percentage of total sputum volume expectorated by day 7 was significantly greater for guaifenesin patients than for placebo patients (69.3 percent vs 53.7 percent, $p < 0.001$). Sputum became less viscous in patients who received

guaifenesin. Expectoration of secretions appeared to be easier in the guaifenesin-treated group than in the placebo group. The agency concludes that the results of the Vercelli study demonstrate that guaifenesin facilitates expectoration of retained secretions by increasing sputum volume and making sputum less viscous.

Terms such as "productive" and "nonproductive" cough are commonly used in the labeling of OTC cough-cold drug products. A productive cough produces phlegm (sputum), while a nonproductive cough is dry and often irritative. The agency notes that the Cough-Cold Panel stated that expectorants are agents that are used to promote or facilitate the evacuation of secretions from the bronchial airways to provide for the temporary relief of coughs due to minor throat and bronchial irritation as may occur with upper respiratory infection. This may be accomplished by reducing the thickness of these secretions or by augmenting the formation of a more fluid secretion. The secretions (sputum or phlegm) expectorated consists in part of respiratory tract fluids together with a varying mixture of saliva and postnasal secretions (41 FR 38355).

The Cough-Cold Panel also stated in its report that expectorants reduce the thickness of secretions or augment the formation of a more fluid secretion (41 FR 38355). By facilitating the evacuation of secretions from the bronchial airway, local irritants are removed. While such an effect may indirectly serve to diminish the tendency to cough, the mechanism of this indirect action is quite different from that of an antitussive which is specifically designed to inhibit or suppress cough. Any claim relating to the reduction of cough must be supported by objective cough counting studies. Expectorants would be expected to have their major usefulness in the irritative nonproductive cough as well as those coughs productive of scanty amounts of thick, sticky secretions (41 FR 38355).

Based on the above discussion, the agency believes that the phrase "helps loosen phlegm (sputum) and thin bronchial secretions to make coughs more productive" is an appropriate alternative labeling statement. However, any labeling suggesting that an expectorant is a "cough suppressant (antitussive)," "helps you cough less," "helps relieve cough," "helps ease cough" or is "for cough" or is a "cough formula" without the type of clarifying statements mentioned above would be inappropriate. Thus, because expectorants loosen and thin sputum and bronchial secretions, and coughing enhances the removal of such secretions from the respiratory passageways, the agency is revising the indications for expectorants in § 341.78(b) as follows: "Helps loosen phlegm (sputum) and thin bronchial secretions to" (select one or more of the following: "rid the bronchial passageways of bothersome mucus," "drain bronchial tubes," and "make coughs more productive").

References

(1) Comment No. C00197, Docket No. 76N–052C, Dockets Management Branch.

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(3) Stevens, M. E., et al., "On the Expectorant Action of Creosote and the Guaiacols," *Canadian Medical Association Journal*, 48:124–127, 1943.

(4) Hayes, E. W., et al., "A Clinical Evaluation of the Effectiveness of Robitussin in Chronic Cough," *Diseases of the Chest*, 30:441–448, 1956.

(5) Schwartz, E., et al., "The Use of Antitussives in the Management of Bronchial Asthma," *American Practitioner and Digest of Treatment*, 2:585–588, 1956.

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

(7) Modell, W., "Drugs of Choice 1980–1981," C. V. Mosby Co., St. Louis, p. 461, 1980.

(8) "AMA Drug Evaluations," 4th Ed., American Medical Association, New York, p. 469, 1980.

(9) Cass, L. J., et al., "Comparative Clinical Effectiveness of Cough Medication," *American Practitioner and Digest of Treatment*, 2:844–851, 1951.

(10) Comment No. C00190, Docket No. 76N—052C, Dockets Management Branch.

(11) Packman, E. W., "Miscellaneous Colds Products, CRD No. 81–39," draft of unpublished study, Comment No. C00190, Docket No. 76N–052C, Dockets Management Branch.

(12) Letter from W. E. Gilbertson, FDA, to F. A. Clark, A. H. Robins Co., coded ANS, Docket No. 76N–0052, Dockets Management Branch.

(13) Kuhn, J. J., et al., "Antitussive Effect of Guaifenesin in Young Adults with Natural Colds," *Chest*, 82:713–718, 1982.

(14) Packman E. W., et al., "The Utility of Artificially Induced Cough as a Clinical Model for Evaluating Antitussive Drug Combinations. Part I: Liquid and Solid Formulations of Systemic Drugs," *Current Therapeutic Research*, 21:855–866, 1977.

(15) Letter from W. E. Gilbertson, FDA, to G. F. Hoffnagle, Richardson-Vicks, Inc., coded LET085, Docket No. 76N–052C, Dockets Management Branch.

(16) Letter from W. E. Gilbertson, FDA, to A. W. Mercill, The Proprietary Association, coded LET086/ANS, Docket No. 76N–052C, Dockets Management Branch.

7. One comment requested that the labeling of guaifenesin as an OTC expectorant be expanded to include labeling for health professionals (but not for the general public) as follows: "For the treatment of bronchitis, asthma, and chronic obstructive pulmonary disease when these conditions are complicated by thickened and/or impacted mucus." The comment stated that both the agency and the Cough-Cold Panel recommended that clinical trials to document the efficacy of guaifenesin be conducted in patients suffering from these conditions. The comment further stated that guaifenesin has been demonstrated to increase sputum volume and decrease sputum viscosity, and these factors enhance the expectoration of viscous bronchial secretions and thus aid in the treatment of these respiratory conditions. The comment (Ref. 1) submitted 25 references (Refs. 2 through 26) in support of its professional labeling claim.

The agency has reviewed the data submitted by the comment and concludes that the proposed labeling indication is not substantiated for the reasons described below. However, based upon the Vercelli study that supported the reclassification of guaifenesin as an expectorant from Category III to Category I (Ref. 27), the agency concludes that the following professional labeling claim, which is different from that proposed by the comment, is acceptable for guaifenesin: "Helps loosen phlegm and thin bronchial secretions in patients with stable chronic bronchitis."

Of the 25 references submitted by the comment, only 8 are concerned with the efficacy of guaifenesin as a single ingredient (Refs. 2, 3, 6, 9, 17, 21, 22, and 26), while 2 used a product containing an oral sympathomimetic ingredient (1 mg desoxyephedrine hydrochloride) and guaifenesin (Refs. 5 and 19). Most of these studies contain deficiencies which are sufficiently significant to preclude using the data in support of the comment's proposed professional labeling claim (Refs. 2, 3, 5, 17, 19, 21, and 22), while several of these studies provide some subjective support for a professional labeling claim (Refs. 6, 9, and 26). These latter three studies plus the Vercelli study (Ref. 27) provide sufficient support for the agency's professional labeling claim for guaifenesin noted above. The other 15 studies involved combination products, usually containing one bronchodilator, or a variety of other drugs, so that the effect of guaifenesin could not be adequately addressed (Refs. 4, 7, 8, 10 through 16, 18, 20, and 23 through 25).

The agency has the following comments on the studies in which guaifenesin was studied as a single

ingredient: Ackerman (Ref. 2) studied the use of antibiotics versus guaifenesin; however, he did not evaluate the expectorant or antitussive activity of guaifenesin. Blanchard et al. (Ref. 3) did a retrospective analysis of the investigators' subjective assessment of the efficacy of guaifenesin. Diagnostic criteria were not met; and there was no random assignment, no comparability of groups, and no controls. Chodosh (Ref. 6) studied the efficacy and mechanism of action of guaifenesin in chronic bronchitic patients. Evaluations included clinical assessment, pulmonary function tests, and sputum cytology (physical and chemical properties). Chodosh reported that statistical analysis revealed "general clinical improvement" with guaifenesin compared to placebo and sputum was more easily raised above the improvement noted with water alone. Although objective measures of test results were not provided, the study suggests that guaifenesin is efficacious in patients with bronchitis and that certain laboratory determinations can be correlated with clinical assessment of the drug. Hayes et al. (Ref. 9) subjectively evaluated the effectiveness of guaifenesin in reducing sputum tenaciousness in patients with pulmonary tuberculosis, bronchiectasis, or bronchitis, in a 2-phase study. A total of 150 observations were made for the patients studied. The investigators reported that guaifenesin was effective in loosening secretions in 80 percent of the 150 testing periods in phase I and in 75 percent of the testing periods in phase II.

The multi-center study by Robinson et al. (Ref. 17) evaluated guaifenesin's effect on both productive and nonproductive cough and the expectoration of sputum. Ease of expectoration was studied in subjects with acute upper respiratory infection (of 12 to 72 hours duration) with both "dry" and "productive" coughs. The study indicated that, based on subjective assessment, guaifenesin facilitated raising of sputum in productive cough but not in non-productive cough. The results obtained for some of these subjects were pooled for analysis; other results were not. Statistical analysis was carried out, but the subjects were classified each day as either improving, no change, or worsening. With the number of variables involved, objective measurement would appear essential for both cough and sputum parameters as noted by the Panel (41 FR 38369).

Stevens et al. (Ref. 19) studied guaifenesin in animals and humans. The details of the study are sparse, and the study appears uncontrolled. Also, the patient population used in the study (medical students with colds) is inappropriate for the proposed professional labeling claim. Thomson et al. (Ref. 22) measured mucociliary clearance from the lung following administration of guaifenesin, but the clinical efficacy of the drug was not demonstrated. Wojcicki et al. (Ref. 26) evaluated four drug regimens in patients with chronic bronchitis, tuberculosis, bronchiectasis, and chronic bronchitis with asthma. The drugs tested were (1) a combination of narcotine (a non-narcotic antitussive) and guaifenesin, (2) narcotine, (3) guaifenesin, and (4) placebo. Ease of expectoration was subjectively measured. The investigators reported that the two regimens with guaifenesin (1 and 3) appeared to facilitate expectoration in 75 percent of the subjects. The agency's more detailed comments and evaluation of these references are on file in the Dockets Management Branch (address above) (Ref. 28).

The Vercelli study was conducted in patients with chronic bronchitis (Ref. 27). The results demonstrated the effectiveness of guaifenesin in helping to loosen and raise sputum. (See comment 5 above.) Based on this objective study (Ref. 27) and the subjective studies which support the use of guaifenesin in helping to raise sputum (Refs. 6, 9, and 26), the agency believes that the comment's suggested labeling claim "For the treatment of bronchitis, asthma, and chronic obstructive pulmonary disease when these conditions are complicated by thickened and/or impacted mucus" should be revised to read as follows: "Help loosen phlegm and bronchial secretions in patients with stable chronic bronchitis." The agency disagrees with the comments' specific suggested claim for the following reasons: (1) The effectiveness of guaifenesin in the symptomatic relief of sputum removal in asthmatics has not been demonstrated. Moreover, in asthma, the narrowing of the bronchi and drying of secretions can result in inspissated material and mucus plugs which further reduce the airway and produce difficult breathing. The appropriate treatment for such a condition is hydration, bronchoscopy with lavage and suctioning combined with anti-inflammatory drugs and bronchodilators. Without such an approach in the treatment of asthmatics, a safety concern exists.

(2) The patient population in the Vercelli study consisted of persons with chronic bronchitis. Because no objective data were generated in a population with the other conditions mentioned by the comment, the agency is limiting the professional labeling claim for guaifenesin to patients with chronic bronchitis.

(3) The study population in the Vercelli study did not have conditions that would be characterized as "complicated by thickened and/or impacted mucus." Sputum characteristics were based on a 4-point scale; a 4 was assigned to a sputum sample which was pus-like, uniformly clumped, and did not move down a glass microscope slide inclined at a 45° angle. A value of 3 was assigned to a pus-like (clump-stringy) sample exhibiting very slow movement. Thickened and/or impacted mucus denotes sputum which is firmly lodged or wedged. The category which would be comparable to thickened and/or impacted would be a 4. The sputum of no patients in either test group was assigned a 4, but more than half of all patients had sputum characterized as a 3. Additionally, the term "complicated" means associated with other diseases, which in reference to the bronchi usually means infection. Infections would be treated with antibiotics. The Vercelli study did not include patients who required the use of antibiotics. Thus, the comment's suggested terms are not in keeping with the patient population that was studied and are not appropriate for a professional labeling claim. The use of the term "stable" in the revised claim eliminates the acute brochitic and the chronic bronchitic patients whose disease may be complicated.

Therefore, the agency is including the indication "Helps loosen phlegm and thin bronchial secretions in patients with stable chronic bronchitis" as a professional labeling claim for guaifenesin in § 341.90(d). This professional labeling claim is only permitted for single ingredients expectorant drug products because no data have been presented to support the use of expectorant combination drug products, e.g., an expectorant and an antitussive, in the chronic bronchitic patient population.

References

(1) Comment No. C00196, Docket No. 76N-052C, Dockets Management Branch.

(2) Ackerman, B., "Treatment of Undifferentiated Respiratory Infections in Infants," *Clinical Pediatrics*, 7:391–395, 1968.

(3) Blanchard, K., et al., "Effective Antitussive Agent in the Treatment of Cough in Childhood," *Journal-Lancet*, 74:443–446, 1954.

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Journal of Respiratory Diseases, 54:78–82, 1973.

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(8) Grover, F.W., "Oxtriphylline Glyceryl Guaiacolate Elixir in Pediatric Asthma: With a Theophylline Review," *Annals of Allergy*, 23:127–147, 1965.

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(12) Levin, S.J., et al., "Theophylline-Glyceryl Guaiacolate Elixir (Quibron) Clinical and Blood Level Studies in Bronchial Asthma in Children," *Annals of Allergy*, 20:315–319, 1962.

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(15) Puls, R.J., "Clinical Study With Oxtriphylline-Glyceryl Guaiacolate Tablets in Chronic Pulmonary Disease: A Double-Blind Crossover Study," *Current Therapeutic Research*, 6:353–356, 1964.

(16) Refinetti, P., et al., "Novahistine in the Treatment of Congestive Processes of the Respiratory Tract," *Current Therapeutic Research*, 30:33–37, 1981.

(17) Robinson, R.E., et al., "Effectiveness of Guaifenesin as an Expectorant: A Cooperative Double-Blind Study," *Current Therapeutic Research*, 22:284–296, 1977.

(18) Schiller, I.W., et al., "Theophylline Glyceryl Guaiacolate (Quibron) in Bronchial Asthma," *Diseases of the Chest*, 42:384–387, 1962.

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(26) Wojciki, J., et al., "The Use of Duopect as an Expectorant-Antitussive Agent," *Archivum Immunologiae Et Therapiae Experimentalis*, 23:135–142, 1975.

(27) Comment No. LET077, Docket No. 76N–052C, Dockets Management Branch.

(28) Letter from W.E. Gilbertson, FDA, to S.L. Mercurio, Norwich Eaton Pharmaceuticals, Inc., coded LET084, Docket No. 76N–052C, Docket Management Branch.

8. One comment stated that the study on which the agency based the reclassification of guaifenesin as an expectorant from Category III to Category I was seriously flawed and thus does not justify the claim that this drug is effective as an expectorant (Ref. 1). The comment maintained that the study contained the following flaws:

(1) The qualifications of the investigator were not included in the date that were received and reviewed by the comment.

(2) The study involved 40 patients with chronic bronchitis who were hospitalized in a pulmonary hospital in Italy. It is unclear whether randomization was adequate in this small group of patients and whether blinding was maintained in view of guaifenesin's distinctive taste.

(3) The study did not use patients similar to the majority of those for whom the drug will be used. The study involved hospitalized patients in Italy with chronic bronchitis, whereas guaifenesin is used in the United States almost exclusively for self-treatment of colds or acute bronchitis.

(4) There were a number of other serious design flaws. For example, the patients received numerous drugs in addition to guaifenesin, including bronchodilators (36 patients), cough suppressants (11 patients), antihistamines (3 patients), antianxiety agents (3 patients), and diuretics. How much of these medications the patients received and whether their use was similar in control and treatment groups were not stated in the study. These drugs could have a substantial effect on sputum volume, viscosity, and cough severity. Other factors that can affect cough and sputum, such as smoking habits and fluid intake, were not measured.

(5) The two groups of 20 patients each (control and treatment) were different even before the drug (or placebo) was given. The group of patients designated to be treated with guaifenesin had a statistically significant greater severity (frequency) of cough and increased difficulty in coughing compared with the placebo group.

(6) Other differences between the guaifenesin and placebo groups cast further doubts on how well the 40 patients were randomized. Four patients in the guaifenesin group, but none in the placebo group, had complete disappearance of their cough by day 13. This condition continued through day 15. If these four patients all had chronic bronchitis, complete disappearance of cough would be an unusual finding.

(7) The study made little use of objective methods. The only "objective" measurements used were sputum volume (which could be changed dramatically by the presence of saliva) and a subjective judgment of the viscosity of sputum based on how it looked on slide. A much more objective method, using a viscosimeter, has been described by Hirsch et al. (Ref. 2) who found guaifenesin was ineffective as an expectorant in patients with chronic bronchitis. Viscosity was not improved with the drug when measured with the viscosimeter.

(8) Many if the improvements that may be attributable to quaifenesin were mainly subjective and did not begin until after 8 to 10 days of treatment. Such benefits would not be very useful to persons with short-term respiratory infections (such as colds) who desire quick relief.

The agency's evaluation of the study referred to by the comment is discussed in comment 5 above. The FDA supports the Category I classification of guaifenesin as an expectorant and has the following responses to the comment's criticisms of the study:

(1) The qualifications of the investigators are included in the guaifenesin submission (Ref. 3). When the study was submitted, the agency reviewed the curriculum vitae of the investigators and found the investigators qualified.

(2) According to the protocol, patients were assigned under double-blind conditions by use of a randomization schedule, which resulted in a well-balanced distribution of patients for age,

sex, sputum volume, and sputum viscosity. The guaifenesin group tended to have more severe symptoms than the placebo group with respect to cough and difficulty of expectoration. A randomization schedule is included in the statistical report section of the submission. The agency believes that the baseline characteristics were comparable for the two groups. With regard to the comment's concern that the study was not blinded due to guaifenesin's distinctive taste, the agency believes that it is not always possible to duplicate the distinct characteristics of a test drug without introducing the possibility of another variable to the test system. Although the placebo may not have had the same bitter aftertaste as guaifenesin, the placebo and treatment regimens both contained the syrup vehicle, but the placebo did not contain guaifenesin. Thus, the agency believes that the study was adequately blinded and controlled.

(3) Expectorants are indicated for the loosening of phlegm and bronchial secretions. The Panel suggested that to evaluate expectorants either patients with chronic bronchitis, pulmonary emphysema, or inactive pulmonary tuberculosis whose condition is relatively stable with no evidence of intercurrent infection that would affect cough or the character of the sputum, or patients with an acute upper respiratory infection, such as acute bronchitis with a dry nonproductive cough, could be used (41 FR 38369).

The agency believes that although either patient population recommended by the Panel can be used to evaluate expectorants, in order to accurately record the effect of these drugs on sputum production and viscosity, it may be more prudent to choose a population with chronic or stable symptoms (such as the chronic bronchitics chosen for this study) rather than a population with short-term symptoms (such as patients with acute upper respiratory infections). Hospitalization of the patients in the study was desirable because it ensured compliance to the protocol, enabled the investigators to maintain a controlled environment, and facilitated the recording of objective measurements.

(4) The comment criticized the use of concomitant drug therapy in the study. Many patients with chronic cough secondary to chronic bronchitis and other diseases may require occasional therapy for their comfort. To discontinue totally such therapy for a 2-week study period may be inappropriate or unethical. The submitted case histories document that cough suppressants, antihistamines, antianxiety drugs, and bronchodilators were used. However, the clinical report states that the use of these medications was minimal, occurring only once or twice per patient during the study. The use of these drugs was equally distributed between placebo and guaifenesin groups, i.e., 5 placebo patients and 6 guaifenesin patients received an antitussive; 1 placebo patient and 2 guaifenesin patients received an antianxiety drug, and 20 placebo patients and 16 guaifenesin patients received a bronchodilator. Fluid intake was permitted with no restrictions unless medical reasons prohibited it. Smoking habits were not mentioned in the study. The agency notes that the use of bronchodilators (the medication used most frequently) and antitussives would more likely have an effect on cough reduction rather than expectoration. Because a cough reduction claim for expectorants has not been demonstrated by objective measures and, therefore, is not permitted, the effect of these drugs on the study results is considered negligible. (See comment 6 above.)

(5) The comment contended that treatment and placebo groups were different initially. Patients with chronic bronchitis were selected, but were required to have additional entrance criteria, i.e., must have had normal temperature and did not require the use of antibiotics or steroids. A 3-day washout period before baseline sputum values were recorded was required. The use of antitussives, mucolytics, and anticholinergics was prohibited. In subjects who required concomitant drugs, the use of these drugs was recorded on a one-time basis.

Subjective evaluations based on a 4-point scale (a rating of 0 to 3) were used to assess the frequency of cough and difficulty in raising sputum. Baseline values for all subjects in both placebo and treatment groups were a rating of either 2 or 3 for both study variables. Because a cough reduction claim for expectorants is not permitted, the comment's objection that the guaifenesin group's frequency of cough and difficulty in coughing was more severe than the placebo group appears moot. There is no objective method for assessing the difficulty of expectoration, but the differences between moderate effort (a rating of 2) and marked effort (a rating of 3) appear to be almost negligible. More importantly, placebo and treatment groups were not different at baseline in the other parameters of volume and viscosity, and it is with these two characteristics that differences in results were in fact recorded.

(6) Disappearance of cough in four patients in the guaifenesin group was a recorded result noted after the study had been in progress. The agency does not consider this occurrence a randomization problem. Although it may be true that it is unusual for a cough to disappear totally in patients with chronic bronchitis, it is not unusual for a cough to disappear for a day or two as recorded in the study (days 13 to 15). The American Thoracic Society's definition of chronic bronchitis notes the presence of a productive cough daily for at least 3 months of the year (Ref. 4). Moreover, as noted in the agency's statistical evaluation of the study, the four guaifenesin patients with no cough symptoms by the 13th or 14th day had no efficacy variables recorded thereafter. In all analyses, the sponsor replaced these missing values by the last available patient observation. This is a conservative approach in that true values for these patients (later during treatment) would probably show a higher degree of improvement than their last evaluation, and results are not substantially changed if these patients are excluded from the analysis. Finally, the relationship of cough and lung mucociliary clearance has been reported to be complementary (Ref. 5). Cough appears to be initiated when mucociliary clearance is ineffective. Guaifenesin has been shown to improve mucociliary clearance and to increase the output of respiratory tract fluid. Therefore, it is possible, although not proven, that, due to improvement in mucociliary clearance, cough decreased or disappeared transiently because it was not needed.

(7) The criticism that the study makes little use of objective methods is valid to a degree; however, because of the difficulty in evaluating the effectiveness of expectorants, both objective and subjective evaluations are used. The variables that were evaluated in the study included sputum volume, sputum characteristics, difficulty of expectoration, and cough severity. Daily sputum volume was objectively measured, a 24-hour collection measured in milliliters was recorded. Sputum characteristics were measured using a 4-point scale that described sputum characteristics and rapidity of flow down a microscope slide tilted at a 45-degree angle. Although this measurement cannot be recorded in terms such as those used to express measurements from a viscosimeter (e.g., pounds per square inch), it is objective. Values were assigned as follows: 4 (puslike, uniformly clumped and no movement down the slide); 3 (clump-

stringy with very slow movement); 2 (dense, stringy, and slow movement down the slide); and 1 (clear and flowed quickly). Additionally, as discussed at a workshop on lung mucociliary clearance, there is a large range of mucus viscosity that is recorded during adequate mucociliary transport, but a narrow range for elasticity. How these two characteristics influence expectoration is unclear, but elasticity appears more important than viscosity (Ref. 5).

There are no objective methods for measuring the difficulty of expectoration; therefore, subjective evaluations must be relied upon. A 4-point scale was also used to assess difficulty of expectoration. The values assigned were: 0 (no difficulty); 1 (with slight effort); 2 (with moderate effort); and 3 (with great effort).

For cough severity, objective methods can be used (i.e., cough counting); however, the study did not use objective methods but simply used a 4-point scale of 0 (absence of symptoms); 1 (intermittent, sporadic cough); 2 (many coughing spells throughout the day); and 3 (continuous coughing). The Panel reviewed the Hirsch study (Ref. 2), referred to by the comment, in which a viscosimeter was used (41 FR 38362). However, the Panel did not recommend that this type of instrument be used to evaluate expectorants.

(8) With respect to the time required for the action of guaifenesin to be documented and whether such benefits would be useful for persons with short-term respiratory symptoms who desire quick relief, the data showed that over the first 4 to 6 days the sputum volume increased in guaifenesin patients and then decreased. The mean percentage of total sputum volume expectorated by day 7 was significantly greater on guaifenesin than on placebo (69.3 percent vs. 53.7 percent, $p<0.001$) and the mean number of days to expectoration of 75 percent of the total sputum volume was significantly lower on guaifenesin than on placebo (8.40 vs. 10.65 days, $p<0.001$). The change in sputum characteristics was accompanied by improvement in subjective measures of raising sputum and of cough severity.

A recent study by Kuhn et al. (Ref. 6) on the effectiveness of guaifenesin on the symptoms of the common cold demonstrated no antitussive effect, but recorded improvement in the treatment group over placebo with respect to changes in sputum, i.e., an increase in volume and ease of expectoration. As set forth in this document, OTC labeling for expectorants does not refer to specific disease entities, but rather that the product is to be used to loosen phlegm (sputum) and thin bronchial secretions. However, the agency is including a professional labeling claim for guaifenesin in this document that allows the use of the drug in individuals with stable chronic bronchitis. (See comment 7 above.) In addition, the Panel noted a study by Thomson et al. (41 FR 38363) that reported that, in bornchitic patients, inhaled radioactive particles were removed more rapidly and within 5 hours after administering guaifenesin than after administering the placebo. This study suggests that the therapeutic action of guaifenesin may occur shortly after administration, but that the effect of the drug on sputum volume requires longer to record objectively.

The agency does not find the guaifenesin study seriously flawed as claimed by the comment. The agency acknowledges that there are conflicting reports in the literature regarding guaifenesin's effectiveness as an expectorant, and much of the controversy deals with determining suitable objective test methods for evaluating expectorants. The Panel recognized the value of using both subjective and objective methodology and recommended that only one additional subjective study be done. The subjective study could also use objective methods, such as sputum volume, sputum viscosity, and character and color of sputum (41 FR 38369).

The agency determined that objective measures of sputum volume and viscosity correlated with subjective evaluations should be performed to established the effectiveness of guaifenesin as an expectorant. The guaifenesin study has fulfilled these requirements, and, on this basis, guaifenesin has been upgraded to monograph status.

References

(1) Comment No. C00199, Docket No. 76–052C, Dockets Management Branch.

(2) Hirsch, S. R., et al., "The Expectorant Effect of Glyceryl Guaiacolate in Patients with Chronic Bronchitis. A Controlled in Vitro and in Vivo Study," *Chest*, 63:9–14, 1973.

(3) Comment No. LET077, Docket No. 76N–052C, Dockets Management Branch.

(4) Harris, H. W., et al., "Chronic Bronchitis, Asthma, and Pulmonary Emphysema," *American Review of Respiratory Diseases*, 85:762, 1962.

(5) Clarke, S. W., et al., "Lung Mucociliary Clearance and the Deposition of Therapeutic Aerosols (General Summary)," *Chest*, 80:921–924, 1981, Supplement.

(6) Kuhn, J. J., et al., "Antitussive Effect of Guaifenesin in Young Adults with Natural Colds," *Chest*, 82:713–718, 1982.

9. One comment maintained that, although the Panel was unable to make a determination that ipecac is effective, ipecac as an emetic agent would, in theory, have marked expectorant action. The comment stated that the expectorant action of ipecac has been demonstrated in animals and, because techniques for evaluating the effectiveness of expectorants in humans are still unsatisfactory, extrapolations from animal studies which correlate with pharmacologic theory should be acceptable. If clinical judgement supports these extrapolations, the comment contended that ipecac and other expectorants can be considered as potentially effective provided they are used in the appropriate dosage, which may be greater then the conventional dosage.

The agency recognizes that some animal studies show that ipecac can increase the flow of respiratory tract fluid (41 FR 38364). However, human studies reviewed by the Panel did not demonstrate ipecac's effectiveness as an expectorant. Although animal studies are very useful in the preliminary stages of drug development to indicate a drug's possible effect in humans, animal studies alone cannot be used to support the effectiveness of a drug in humans. Clinical trials conducted in the target population are needed to assess a drug's effect in humans. The comment submitted no new data to support the effectiveness of ipecac as an expectorant. Ipecac and other nonmonograph expectorant ingredients can be tested in humans to determine whether conventional doses or even larger doses are effective. If larger than recommended doses are not within a known safety range, additional safety studies will be needed. The agency notes that two studies in humans on ipecac (at a dose corresponding to 0.82 mg of total alkaloids of ipecac) have been submitted to the agency and are presently under review. (See comment 10 below.)

10. Two comments disagreed with the agency's tentative conclusion at 47 FR 30007 that the effectiveness of ipecac as an expectorant has not been established. One of the comments stated that its combination liquid drug product, which contains ipecac as well as other ingredients, has been sold for more than 62 years as a "natural" ingredient OTC cough medicine. Two clinical studies that were previously submitted to the agency and hundreds of physician's confidential patient reports have attested to the efficacy of the product, the comment maintained. The comment added that if its small company is

required to change the formula of the product, the company would lose its marketing franchise. The product would then become just another "me too" product with no formula or performance individuality to distinguish it or to help offset a huge, competitive market.

The confidential patient reports, isolated case reports, random experience, and reports lacking details that permit scientific evaluation cannot be regarded as proof of effectiveness, but must be corroborated by clinical studies. The two studies mentioned by one of the comments were discussed in the tentative final monograph (47 FR 30007). The studies were conducted using a combination product containing ipecac, beechwood creosote, cascara, menthol, white pine, wild cherry, and alcohol. The agency concluded that because the ingredients of the combination drug product were not studied individually, it was impossible for the agency to ascertain which ingredients in the product were responsible for any of the effects obtained. Additionally, the studies did not include any objective measurements of sputum volume and sputum viscosity. The agency considers these measurements necessary to establish the effectiveness of an expectorant ingredient.

After the comments were submitted, and while the administrative record was open, the agency approved a proposed protocol for studying ipecac that had been submitted by one of the comments (Refs. 1, 2, and 3). On January 6, 1987, after the administrative record had closed, a citizen petition was filed with the agency submitting two studies on the effectiveness of ipecac as an expectorant (Ref. 4). The studies are presently under review. Therefore, at this time, ipecac is not included in the final monograph for OTC expectorant drug products. However, if the submitted new data establish the effectiveness of ipecac as an expectorant, procedures to amend the monograph will be initiated under 21 CFR 330.10(a)(12). Regulatory policy for products containing nonmonograph ingredients is set forth in the **Federal Register** of May 13, 1980 (see 45 FR 31424 to 31425).

Concerning the economic effects of reformulation cited by the comment, the agency published a notice in the **Federal Register** of February 8, 1983 (48 FR 5806), announcing the availability of an assessment of the economic impacts of the agency concluded that the OTC drug review. In that assessment, the agency concluded that the OTC drug review was not a major rule as defined in Executive Order 12291, but recognized that significantly large impacts might be experienced by some small firms in some years. FDA has a statutory mandate to assure that OTC drug products are safe and effective for their intended use and are properly labeled. The statute does not allow FDA to waive these important public health considerations merely because a product's formula individuality may be lost or because additional costs may be incurred by a manufacturer in order to achieve compliance with a monograph.

References

(1) Comment Nos. RPT003 and SUP001, Docket No. 76N–052C, Dockets Management Branch.

(2) Letters from W.E. Gilbertson, FDA, to H. Jenkins, Creomulsion Co., coded LET080 and LET082, Docket No. 76N–052C, Dockets Management Branch.

(3) Letter from H. Jenkins, Creomulsion Co., to W.E., Gilbertson, FDA, coded LET081, Docket No. 76N–052C, Dockets Management Branch.

(4) Comment No. CP, Docket No. 76N–052C, Dockets Management Branch.

11. One comment stated that it is not clear why ipecac syrup should be limited to children 6 years of age and over and that apparently there is no suggestion that it is more dangerous in children under 6 and over 2.

As dicussed in the tentative final monograph (47 FR 30007), the agency based its evaluation of the use of ipecac syrup in children on the recommendation of a committee of experts in pediatric drug therapy who 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 placed ipecac syrup as an expectorant in Category III for effectiveness and adopted the pediatric committee's recommendation that ipecac syrup not be given to children under 6 years of age except as directed by a doctor.

The comment provided no new information that would lead the agency to alter the Panel's recommendations or its conclusions in the tentative final monograph regarding the OTC use of ipecac syrup in children under 6 years of age. Therefore, ipecac syrup is not included in this final monograph.

C. Comments on OTC Expectorant Labeling

12. One comment noted its continuing position that FDA cannot legally and should not, as a matter of policy, prescribe exclusive lists of terms from which indications for use for OTC drugs must be drawn, thereby prohibiting alternative OTC drug labeling terminology that is truthful, not misleading, and intelligible to the consumer. The comment added that these views were presented to FDA in oral and written testimony in connection with the September 29, 1982 agency hearing on the exclusivity policy.

The comment added that these labeling restrictions prevent the use of words that have been widely understood and commonly used for generations on OTC medications. The comment stated that the industry has long encouraged an agency policy that would allow choice in labeling nonprescription medicines for consumer use and urged the Commissioner to avoid restricting alternative labeling not only in this monograph but also in future proposed rulemakings.

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

13. One comment objected to the agency's limiting the statement of identity of expectorant drug products to only one term, i.e., "expectorant." The comment urged FDA to allow manufacturers alternative ways of expressing the statement of identity in accord with 21 CFR 201.61, which allows the statement of identity to include an accurate statement of the general pharmacological category(ies) of the drug or the principal intended actions(s) of the drug. The comment stated that by using the principal intended actions to describe these products instead of using only their pharmacologic categories, an expectorant could be described as a product "for the loosening of phlegm." The comment added that such a description would have more meaning to laymen and should not be prohibited.

Wherever possible, the agency prefers to use the general pharmacologic category as the statement of identity because information on the principal intended action of the product is provided in the indications section. However, in instances where the pharmacologic category is not appropriate as the statement of identity, the principal intended action is used. For example, the statement of identity for an antihistamine used as a nighttime sleep-aid is "nighttime sleep-aid."

The alternative statement of identity suggested by the comment for expectorant drug products is similar to the indications statements that were proposed for these drugs in § 341.78(b) of the tentative final monograph (47 FR 30009). The agency sees no need to include in the statement of identity for expectorants the same information found in the indications section. However, because the phrase is descriptive of the action of expectorant drug products, it or similar phrases may appear elsewhere in the labeling of an OTC expectorant drug product (but may not appear in any portion of the labeling required by the monograph and may not detract from such required information) provided they meet the provisions of section 502 of the act (21 U.S.C. 352) relating to misbranding. Therefore, the comment's suggestion is not being included in this final monograph.

14. One comment referred to the following warning for expectorants in proposed § 341.78(c)(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." The comment stated that the words "or where cough is accompanied by excessive secretions unless directed by a doctor" are "surplus" and are not needed.

The comment did not provide any data to support its contention that the last portion of the warning is not needed. The agency believes that the words which the comment considers as "surplus" are necessary in the warning statement because these words reinforce the importance of consulting a physician in cases of coughs where a serious disease condition may be present. As the Panel noted, expectorants are used * * * to provide for the temporary relief of coughs due to minor throat and bronchial irritation as may occur with upper respiratory infection (41 FR 38355). The agency notes that a cough frequently accompanies both minor upper respiratory infections and more serious respiratory infections. In minor upper respiratory conditions in which cough is nonproductive or is accompanied by scanty, thick secretions, and lasts for no more than a week, an expectorant can be used by the self-medicating consumer to make the cough more productive by loosening and thinning the bronchial secretions and phlegm. Accordingly, the agency is allowing the following claim for expectorants: "Helps loosen phlegm (sputum) and thin bronchial secretions to" (select one or more of the following: "rid the bronchial passageways of bothersome mucus," "drain bronchial tubes," and "make coughs more productive"). (See comment 6 above.)

The agency is aware that a chronic cough or cough accompanied by excessive secretions may be indicative of a more serious respiratory disease for which a physician should be consulted. Therefore, the warning proposed in § 341.78(c)(2) (redesignated as § 341.78(c)(1) in this document) is being included in this final monograph without the change suggested by the comment. In addition, the agency believes that the term "chronic bronchitis" should also be included in the warning. Patients with chronic bronchitis who have a persistent cough or excessive secretions should seek the advice of a physician before using an expectorant. Additionally, to make the warning clearer to consumers, the agency is substituting the phrase "phlegm (sputum)" for "secretions." Therefore, the agency is revising the warning to read as follows: "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema, or where cough is accompanied by excessive phlegm (sputum) unless directed by a doctor."

15. Three comments disagreed with the agency's proposed substitution of the word "doctor" for "physician" in OTC drug labeling. One comment stated that because "physician" is a term that is recognized by people of all ages and social and economic levels, there is no need for the change, which would be costly and provide no benefit. The comment further contended that physician is a more accurate term, whereas "doctor" is a broad term that could confuse and mislead the lay person into taking advice on medication from persons other than medical doctors, such as optometrists, podiatrists, and chiropractors. The other two comments added that the term "physician" is clearly defined as a person licensed to practice medicine, whereas the term "doctor" is ambiguous and much more general. One of these comments recommended that FDA not eliminate "physician," the more specific term, but allow the option of using either term.

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

16. One comment objected to elimination of the term "Caution(s)" in the labeling of OTC drug products. The comment claimed that a warning precludes use under certain conditions, whereas "caution" does not preclude use, but may often alert the consumer to a potential problem, e.g., "Caution: If irritation develops discontinue use and consult a physician." Thus, the word "warning" is harsher than "caution." The comment stated that a caution may also be used to add emphasis, e.g., "Caution: Use only as directed," or to alert the user to a special need regarding the care of a product, e.g., "Caution: Keep out of direct sunlight;" "Store in refrigerator;" "Replace bottle cap."

The comment argued that it would undoubtedly dilute the impact of essential warning statements if "cautions," which require the consumer to take certain precautions while using the product, were intermingled with "warnings," which signal that the product should not be used at all under specified circumstances. Although both types of statements are usually used to call attention to danger, the distinction

is important, particularly when products contain long lists of warnings. The comment added that because the same phrases may be warnings with regard to one class of products and merely cautions with regard to another, the flexibility of both terms is essential in order to prepare accurate and comprehensible labeling.

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

The agency notes that historically there has not been consistent usage of the signal words "warning" and "caution" in OTC drug labeling. For example, in §§ 369.20 and 369.21 (21 CFR 369.20 and 369.21), which list "warning" and "caution" statements for drugs, the signal words "warning" and "caution" are both used. In some instances, either of these signal words is used to convey the same or similar precautionary information.

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.

D. Comments on Testing

17. One comment stated that because there is a striking lack of data regarding the use of expectorant drugs in children, it is important to have research conducted to clarify the role of these agents in the care of children.

The agency agrees with the comment that there is a lack of data regarding the use of expectorant drugs in children. Because of this lack of data, the Panel consulted a committee of experts on pediatric drug therapy in order to determine pediatric dosages for OTC cough-cold drug ingredients. The Panel and the pediatric committee recommended that pediatric dosages based on age be allowed for those OTC drugs that had a wide margin of safety and for which adequate effectiveness data were available.

The Panel reviewed one study on the effectiveness of guaifenesin as an antitussive in 76 infants and children, 2 months to 16.5 years of age (Ref. 1). The investigators reported no disagreeable side effects, such as nausea, vomiting, and loss of appetite, and concluded that the efficacy of this guaifenesin product in the treatment of cough in children can be attributed to its "expectorant, demulcent, and general antitussive qualities resulting from an increased respiratory tract fluid." The agency concurs that research on other expectorants should be conducted to clarify the role of these ingredients in the care of children.

Reference

(1) Blanchard, K., and R.A. Ford, "Effective Antitussive Agent in the Treatment of Cough in Childhood," *The Journal-Lancet*, 74:443–446, 1954.

18. One comment disagreed with the agency's changes in the Panel's recommended testing requirements for expectorant drugs. The comment stated that the Panel had concluded that because there were no suitable objective methods at that time for evaluating expectorants, the subjective evaluation of the patient must be relied upon for the assessment of the drug's expectorant activity (41 FR 38369). The comment added, however, that in the tentative final monograph, the agency stated, with respect to guaifenesin, that although the Panel required only subjective tests for determining the effectiveness of expectorants, the agency believed that objective measurements of sputum volume and sputum viscosity should be done (47 FR 30005). The comment maintained that although there may be objective methodology to measure guaifenesin's expectorant activity, guaifenesin may or may not be truly representative of expectorant drugs as a class. Therefore, objective methodology to assess other expectorants has not yet been established. Furthermore, different expectorants may produce different effects by which their therapeutic benefits are achieved. Therefore, different objective and subjective criteria may be needed to assess their efficacy. The comment concluded that to be consistent with the Panel's recommendations, the emphasis in studying expectorants should be on clinical benefits, such as relief of discomfort, breathing comfort, and ease of expectoration, all primarily subjective parameters. If objective criteria are feasible and appropriate, they can be added to the subjective criteria, the comment added.

In changing the requirements for testing expectorant drugs, the agency was aware that the Panel stated that there were no suitable objective measures for evaluating the ease in raising secretions when testing expectorants, but that the Panel also stated that "additional help in evaluating effectiveness may be provided by some objective indices such as: the volume and dry weight of sputum collection over a given time (12 to 24 hours); the character and color of the sputum raised; and some measure of its flow properties, such as viscosity of consistency" (41 FR 38369). The Panel recognized that these objective indices would be useful in evaluating the efficacy of expectorants. The agency is requiring objective measurements of sputum volume and viscosity because it believes that if an expectorant works there should be a measurable objective change in sputum volume and sputum viscosity. The objective sputum volume and viscosity tests that were used in the study to support the efficacy of guaifenesin were feasible and appropriate. The volume of sputum collected over a 24-hour period was measured daily, and the sputum viscosity was measured by using a 4-point scale that described sputum characteristics and rapidity of flow down a microscope slide tilted at a 45-degree angle. The study demonstrated the efficacy of guaifenesin and showed that subjective improvement could be correlated with objective measures of expectorant action, i.e., an increase in volume and a decrease in viscosity of sputum. (See comment 5 above.)

With regard to the comment's statement that objective methodology to measure the effectiveness of other expectorant ingredients has not been established, the agency acknowledges that because of the potentially different mechanisms of action of expectorants, it can be expected that there may be different objective and subjective criteria that might be used to demonstrate the efficacy of expectorants. However, regardless of the mechanisms of action, expectorants as a class should help to remove secretions from the respiratory airways by reducing the viscosity of secretions or by increasing the volume, thus making the secretions more fluid. For this reason, the agency believes that the objective measures used in testing guaifenesin should also be used in testing the efficacy of other expectorants.

The methods for studying guaifenesin, which were found acceptable by the agency, do not preclude a

manufacturer's proposing other reasonable objective and subjective methods for studying expectorants. The agency will meet with industry officials at their request to discuss testing protocols for any ingredient or condition that industry wishes to upgrade to monograph status. (See the OTC Drug Review Policy statement, published in the **Federal Register** of September 29, 1981; 46 FR 47740 and clarified April 1, 1983; 48 FR 14050.)

19. One comment objected to the shortening of the time period for testing expectorants from 5 years after publication of the final monograph, as recommended by the Panel, to 12 months after publication of the tentative final monograph, as stated by FDA in the tentative final monograph. The comment stated that this time reduction would pose a hardship on small companies, particularly because an acceptable protocol for determining the effectiveness of expectorants has not been established, the requirements for testing have been expanded, and because a small company cannot afford the immense costs involved in developing experimental methodology. The comment stated that a 5-year period after publication of the final monograph would enable a small company to draw on the experience and expertise of larger companies, which are better able to develop suitable protocols and methodology. Thus a small company could focus its attention and limited resources on the additional clinical trials needed to demonstrate efficacy of its products.

As stated in the tentative final monograph for OTC anticholinergic drug products and expectorant drug products (47 FR 30002), in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979), the court ruled that the marketing of Category III drugs after publication of a final monograph is illegal. Consequently, the agency deleted the provision of the OTC drug procedural regulations that had allowed the OTC marketing of a Category III drug after a final monograph had been established. Thus, the time allowed for the concurrent marketing and testing of Category III expectorants was reduced from 5 years after publication of the final monograph to 12 months after publication of the tentative final monograph.

The agency does not believe that this time reduction is unreasonable. Manufacturers have been aware of the Category III classification of expectorants since the Panel's report was published in September 1976, and have had ample opportunity to discuss testing protocols with the agency and to conduct clinical trials. The agency has emphasized that each manufacturer of a product with a Category III condition need not undertake the necessary testing. Manufacturers have been encouraged to work with other manufacturers and with trade associations in developing protocols and arranging for the necessary studies to establish Category I status.

Regarding the comment's concern that a small company faces an additional burden in trying to develop an acceptable protocol for testing expectorants, an acceptable protocol has now been developed for one expectorant, guaifenesin, and this ingredient has been reclassified to Category I. (See comment 5 above.) The guaifenesin protocol that was developed and approved contains the same principles that the Panel had recommended (41 FR 38369); thus, developing suitable protocols does not necessarily entail immense cost or highly technical procedures. The agency also emphasizes that publication of a final monograph does not preclude a manufacturer's testing an ingredient. After a final monograph has been published, any interested person can petition the Commissioner to amend the monograph to include a particular ingredient or condition. (See 21 CFR 10.30 and 330.10(a)(12).)

II. Summary of Significant Changes From the Proposed Rule

1. Guaifenesin has been reclassified from Category III to Category I and is included in this final monograph as an OTC expectorant. The agency concludes that the Vercelli study (see comment 5 above) demonstrates that guaifenesin, by increasing sputum volume and making sputum less viscous, facilitates expectoration of retained secretions. Because expectorants loosen and thin sputum and bronchial secretions, and coughing enhances the removal of such secretions from the respiratory passageways, the agency is revising the indications for expectorants in § 341.78(b) as follows: "Helps loosen phlegm (sputum) and thin bronchial secretions to" (select one or more of the following: "rid the bronchial passageways of bothersome mucus," "drain bronchial tubes," and "make coughs more productive"). (See comments 5 and 6 above.)

2. Both the Cough-Cold Panel and the Oral Cavity Panel reviewed data on the safety and effectiveness of ingredients used as expectorants in OTC drug products. The Oral Cavity Panel, in its report on OTC oral health care drug products published in the **Federal Register** of May 25, 1982 (47 FR 22760), classified potassium iodide in Category II, and ammonium chloride, tolu balsam, and horehound in Category III as expectorants. The Cough-Cold Panel reviewed twenty expectorants, including the expectorants reviewed by the Oral Cavity Panel, except for horehound.

Following publication of the advance notice of proposed rulemaking for OTC oral health care drug products, the agency received no data or comments in support of the effectiveness of any expectorant for oral health care use. Because the Cough-Cold Panel did an extensive review of expectorant ingredients and no data to support safety and/or effectiveness have been submitted, the agency concludes in this final rule that the expectorants that were considered by the Oral Cavity Panel, i.e., potassium iodide, ammonium chloride, tolu balsam, and horehound, are nonmongraph ingredients.

3. The agency has included the phrase "taken orally" in the definition of expectorant in § 341.3. (See comment 3 above.)

4. The agency has reviewed the labeling proposed in the tentative final monograph and has concluded that the indication proposed in § 341.78(b)(2), "Relieves irritated membranes in the respiratory passageways by preventing dryness through increased mucus flow" is not supported by the data submitted. The Panel proposed this claim as a Category I labeling indication for expectorants (41 FR 38355) and it was also included in the tentative final monograph (47 FR 30009). However, because of a lack of efficacy data at that time, no expectorant ingredients were classified in Category I by the Panel in its report or by the agency in the tentative final monograph.

The agency has reevaluated the Panel's report and the data on expectorants that were submitted to the Panel (41 FR 38355 to 38370) and finds the evidence inadequate to support this particular labeling claim. A review of product labeling submitted to the Panel indicates that some products containing expectorants were labeled with claims such as "for relief of minor throat or bronchial irritation," and "soothes irritated throat membranes"; however, no data supporting these claims were provided (Ref. 1).

Moreover, the data submitted on guaifenesin, the only expectorant ingredient included in this final monograph, did not demonstrate that guaifenesin relieves irritated membranes in the respiratory passageways by preventing dryness through increased mucus flow. The guaifenesin data demonstrate that the

drug increases sputum volume and viscosity (which supports the indications in this final monograph), but no evaluations were done to show that the increase in sputum volume and viscosity relieved irritated membranes in the respiratory passageways. Therefore, in the absence of substantiating data, the labeling proposed in § 341.78(b)(2) is not included in the final monograph. However, the agency recognizes that many cough-cold drug products are formulated with inactive ingredients such as sugar-based syrups and other mucilaginous substances that can provide a soothing effect on the mucosa of the throat. As discussed in the tentative final monograph for OTC oral health care drug products, published in the **Federal Register** of January 27, 1988 (53 FR 2450), terms such as "soothing" may be used to describe the action of a sugar-based syrup or lozenge. Use of this term is not considered as making a demulcent claim because the term describes certain physical and chemical attributes of a drug product and is distinctly separate from labeling indications. Terms that describe product characteristics (e.g., color, odor, flavor, and feel) often appear in consumer labeling as additional product information. Because such claims are not directly related to the safe and effective use of a drug product, the agency considers these claims to be outside the scope of the monograph. Any term that is outside the scope of the monograph may appear in any portion of the labeling not required by the monograph, but such labeling may not detract from the required information. Therefore, the labeling of an OTC expectorant drug product could include truthful terms that describe product characteristics, such as "soothing," provided such terms are placed in an area of the labeling that is outside the required monograph labeling.

Reference

(1) OTC Volumes 040099, 040108, 040163, 040190, 040201, 040219, and 040220.

5. Proposed § 341.78(c)(1) is not included in this final monograph. Proposed § 341.78(c)(1) provided a warning not to give expectorants to children under 2 years of age unless directed by a doctor. Because the directions provided under new § 341.78(d) state clearly that a doctor should be consulted for the use of expectorants in children under 2 years of age, the agency believes that the proposed warning is repetitious and unnecessary. According, proposed § 341.78(c)(2) has been redesignated as § 341.78(c)(1), and proposed § 341.78(c)(3) as § 341.78(c)(2).

6. The agency has modified the warning proposed in § 341.78(c)(2) of the tentative final monograph (redesignated as § 341.78(c)(1)) to include "chronic bronchitis" and has substituted the phrase "phlegm (sputum)" for "secretions." (See comment 14 above.)

7. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulation will give manufacturers the option of using either the word "physician" or the word "doctor." This final monograph provides that option. (See comment 15 above.)

8. In § 341.90(d) the agency is including the following professional labeling claim for guaifenesin as a single ingredient expectorant drug product: "Helps loosen phlegm and thin bronchial secretions in patients with stable chronic bronchitis." (See comment 7 above.)

III. The Agency's Final Conclusions on OTC Expectorant Drug Products

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC expectorant drug products are generally recognized as safe and effective and not misbranded. Specifically, the only monograph ingredient for expectorant use is guaifenesin. All other ingredients for expectorant use that were considered in this rulemaking are considered nonmonograph ingredients, i.e., antimony potassium tartrate, chloroform, iodides (calcium iodide anhydrous, hydriodic acid syrup, iodized lime, potassium iodide), ipecac fluidextract, squill preparations (squill, squill extract), turpentine oil (spirits of turpentine), ammonium chloride, beechwood creosote, benzoin preparations (compound tincture of benzoin, tincture of benzoin), camphor, eucalyptol/eucalyptus oil, horehound, ipecac syrup, menthol/peppermint oil, pine tar preparations (extract white pine compound, pine tar, syrup of pine tar, compound white pine syrup, white pine), potassium guaiacolsulfonate, sodium citrate, terpin hydrate preparations (terpin hydrate, terpin hydrate elixir), and tolu preparations (tolu, tolu balsam, tolu balsam tincture). Any drug product marketed for use as an OTC expectorant drug product that is not in conformance with the monograph (21 CFR Part 341) may be considered a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)) and misbranded under section 502 of the act (21 U.S.C. 352) and may not be marketed for this use unless it is the subject of an approved application. An appropriate citizen petition to amend the monograph may also be submitted under 21 CFR 10.30.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (47 FR 30009). The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this final rule for OTC expectorant drug products, is a major rule.

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

List of Subjects in 21 CFR Part 341

Expectorant drug products, Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

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

1. The authority citation for 21 CFR Part 341 continues to read as follows:

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

2. Section 341.3 is amended by adding new paragraph (d) to read as follows:

§ 341.3 Definitions.

* * * * *

(d) *Expectorant drug.* A drug taken orally to promote or facilitate the removal of secretions from the respiratory airways.

3. Section 341.18 is added to Subpart B to read as follows:

§ 341.18 Expectorant active ingredient.

The active ingredient of the product is guaifenesin when used within the dosage limits established in § 341.78(d).

4. Section 341.78 is added to Subpart C to read as follows:

§ 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 states, under the heading "Indications," the following: "Helps loosen phlegm (sputum) and thin bronchial secretions to" (select one or more of the following: "rid the bronchial passageways of bothersome mucus," "drain bronchial tubes," and "make coughs more productive"). Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

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

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

(2) "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 a fever, rash, or persistent headache, consult a doctor."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions" for products containing guaifenesin identified in § 341.18: Adults and children 12 years of age and over: oral dosage is 200 to 400 milligrams every 4 hours not to exceed 2,400 milligrams in 24 hours. Children 6 to under 12 years of age: oral dosage is 100 to 200 milligrams every 4 hours not to exceed 1,200 milligrams in 24 hours. Children 2 to under 6 years of age: oral dosage is 50 to 100 milligrams every 4 hours not to exceed 600 milligrams in 24 hours. 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.

5. Section 341.90 is amended by adding paragraph (d) to read as follows:

§ 341.90 Professional labeling.

* * * * *

(d) *The following labeling indication may be used for products containing guaifenesin identified in § 341.18 when used as a single ingredient product.* "Helps loosen phlegm and thin bronchial secretions in patients with stable chronic bronchitis."

Dated: November 9, 1988.

Frank E. Young,

Commissioner of Food and Drugs.

[FR Doc. 89–4517 Filed 2–27–89; 8:45 am]

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federal register

Tuesday
February 28, 1989

Part VI

Federal Emergency Management Agency

44 CFR Part 352

Commercial Nuclear Power Plants; Emergency Preparedness Planning; Final Rule

FEDERAL EMERGENCY MANAGEMENT AGENCY

44 CFR Part 352

[Docket No. 352 INT.]

Commercial Nuclear Power Plants; Emergency Preparedness Planning

AGENCY: Federal Emergency Management Agency.

ACTION: Interim rule.

SUMMARY: This rulemaking adopts a new Part in Title 44 CFR Emergency Management and Assistance, Chapter 1, Federal Emergency Management Agency (FEMA), Subchapter E Preparedness. New Part 352 concerns licensee certification and determinations and provisions of Federal assistance for offsite radiological emergency planning and preparedness for commercial nuclear power plants under Executive Order 12657. This part responds to a requirement in section 6(a) of the Order that FEMA issue directives and procedures to implement the Order. This part is intended to ensure that plans and procedures are in place to respond to radiological emergencies at commercial nuclear power plants in operation or under construction. Part 352 consists of two Subparts, A and B. This rulemaking was developed by an FEMA/Nuclear Regulatory Commission (NRC) staff task force.

Subpart A: Certifications and Determinations

This Subpart establishes policies and procedures for submission by a commercial nuclear power plant licensee of a certification for Federal assistance under Executive Order 12657. It contains policies and procedures for FEMA's determination, with respect to a certification. It establishes a framework for providing formal Federal assistance to licensees. It also provides procedures for review and evaluation of the adequacy of licensee offsite radiological emergency planning and preparedness.

Subpart B: Federal Participation

This Subpart establishes policies and procedures for providing Federal support for offsite radiological emergency planning and preparedness in a situation when such support under E.O. 12657 has been requested. It describes the process for providing Federal facilities and resources to a nuclear power plant licensee after an affirmative determination on the licensee certification under Subpart A. It describes response functions which Federal agencies might provide and the process for allocating responsibilities among Federal agencies through the Federal Radiological Preparedness Coordinating Committee (FRPCC) and Regional Assistance Committees (RACs).

DATES: This is an interim rule. It is effective March 30, 1989. However, public comment is requested. These comments should be submitted in writing to the address listed below no later than May 1, 1989. Upon completion of the comment period a review of the docket will be made and as appropriate, amendments to the rule adopted.

FOR FURTHER INFORMATION CONTACT: Craig S. Wingo, Chief, Technological Hazards Division, State and Local Programs and Support Directorate, Washington, DC 20472, (202) 646-3026.

ADDRESS: Written comments should be submitted to Rules Docket Clerk, FEMA, Room 840, 500 C Street, SW., Washington, DC 20472. The Docket is open for inspection and copying, during normal business hours, Monday thru Friday 8:30 am–5:00 pm—holidays excepted.

SUPPLEMENTARY INFORMATION:

Background

An integrated approach to the development of offsite radiological emergency planning, preparedness and response involving licensees and State and local governments, voluntary organizations and the Federal Government is the approach most likely to provide the best protection to the public. To carry out the foregoing, FEMA is engaged in a cooperative effort with licensees and State and local governments and other Federal agencies in the development of State and local plans and preparedness to cope with radiological emergencies at commercial nuclear power facilities. These activities are described in 44 CFR Part 350, "Review and Approval of State and Local Radiological Emergency Plans and Preparedness" and Part 351, "Radiological Emergency Planning and Preparedness," which sets out Federal agency roles and assigns tasks for assisting State and local governments.

In the event of an actual radiological emergency, the Federal Radiological Emergency Response Plan (FRERP) provides for the overall Federal support to State and local governments for all types of radiological incidents including those occurring at nuclear power plants. The FRERP was published in the **Federal Register** on November 8, 1985 (50 CFR Part 46542).

Discussion

On November 18, 1988, the President issued Executive Order 12657 (53 FR 47513) "Federal Emergency Management Agency Assistance in Emergency Preparedness Planning at Commercial Nuclear Power Plants."

The Executive order was issued to ensure that adequate offsite radiological emergency planning and preparedness is in place at commercial nuclear power plants to satisfy the emergency planning requirements of the NRC for the issuance or retention of operating licenses. The order applies to those situations where State and local governments, either individually or together, decline or fail to prepare commercial nuclear power plant radiological emergency preparedness plans that are sufficient to meet NRC licensing requirements or to participate adequately in the preparation, demonstration, testing, exercise or use of such plans.

As required by section 2(b)(2) of Executive Order 12657, "[i]n carrying out any of its responsibilities under this order, FEMA * * * shall take care not to supplant State and local resources. FEMA shall substitute its own resources for those of the State and local governments only to the extent necessary to compensate for the nonparticipation or inadequate participation of those governments, and only as a last resort after appropriate consultation with the Governors and responsible local officials in the affected area regarding State and local participation."

Executive Order 12657 directs FEMA to undertake three basic functions in a "decline or fail" circumstance: (1) To assist the licensee in the development of an emergency response plan; (2) to participate in the testing and other activities designed to ensure that the plan can be effectively implemented in the event of an emergency; and (3) to prepare for and to undertake, if necessary, an operational role in responding to an emergency. An undertaking by FEMA of the first two of those functions is not dependent on a request from State or local government officials. As recognized in this regulation (44 CFR 352.5(c)(2)), the "realism doctrine" assumes that in the event of an actual radiological emergency State and local officials will make their best efforts to protect the public, including requesting Federal assistance if necessary. FEMA's operational function in the event of an emergency is premised on the "realism doctrine."

Upon certification in writing to FEMA by a licensee of non-participation or inadequate participation by State or local governments, the Director of FEMA is authorized to take actions to provide the appropriate Federal assistance.

This regulation supports the amendments made to NRC's rule, 10 CFR 50.47 (c)(1) and 10 CFR Part 50, Appendix E, Section IV.F., effective December 13, 1987, (52 FR 42078) for those situations where State or local governments decline or fail to participate in radiological emergency planning and preparedness.

In connection with nuclear power plant licensing, FEMA has previously entered into a Memorandum of Understanding (MOU) (50 FR 15485, April 18, 1985) with the NRC, under which FEMA will furnish assessments and findings and determinations as to whether or not offsite emergency plans and preparedness are adequate and continue to be capable of implementation (e.g., adequacy and maintenance of procedures, training, resources, staffing levels and qualification and equipment adequacy). These assessments, findings and determinations will be used by the NRC in connection with its own licensing and regulatory responsibilities. FEMA will support these assessments, findings and determinations in the NRC licensing process and related administrative and court proceedings (See 10 CFR Part 50).

FEMA's procedures for processing and making determinations on licensee certification requests under this regulation are described as follows: Upon receipt of a licensee certification, FEMA will evaluate the certification as to whether it meets the criteria of "decline or fail" as used in section 1(a) of Executive Order 12657. Upon an affirmative determination, FEMA will begin providing advice to the licensee. A separate FEMA evaluation will focus on the licensee's request for Federal facilities and resources.

If an affirmative determination is made that Federal facilities and resources are needed, then FEMA will initiate actions to provide these facilities and resources under Subpart B. During this process, FEMA will seek advice from the NRC as to whether or not the licensee has maximally utilized its resources and the extent to which the licensee has complied with 10 CFR 50.47(c)(1).

This regulation also provides the framework for FEMA's review and evaluation of licensee offsite radiological emergency planning and preparedness. Specifically, FEMA will conduct its review and evaluation activities under 44 CFR Part 352 in a manner consistent with 44 CFR Part 350 to the extent those policies and procedures are appropriate and not inconsistent with the intent of Executive Order 12657. Any apparent inconsistencies or incongruities between the "350 process" and the review and evaluation under 44 CFR Part 352 shall be resolved through the FEMA/NRC stering committee within the framework of the NRC/FEMA MOU.

Federal policies and procedures for ensuring that plans and procedures are in place to respond to radiological emergencies at commercial nuclear power plants are covered by several existing documents. In addition to the FEMA and NRC regulations, the NRC/FEMA MOU on planning and preparedness and the FRERP, these documents include: The joint FEMA/NRC "Criteria for Preparation and Evaluation of Radiological Emergency Response Plans and Preparedness in Support of Nuclear Power Plants" [NUREG–0654/FEMA-REP–1, Rev. 1. and Supp. 1] and the NRC/FEMA MOU for incident response. Except for Supplement 1, these documents pertain to situations where State and local governments participate in radiological emergency planning and preparedness. Those policies and procedures pertain to situations in which State and local governments participate adequately in the emergency planning process and have produced response plans which meet NRC licensing requirements. In those instances, Federal agencies provide assistance directly to the State and local governments. Supp. 1 to NUREG–0654 applies to utility plans only.

This regulation identifies a mechanism for consulting with Federal agencies as participants in the proceedings of the FRPCC and the RACs which were established by 44 CFR Part 351. Such consultations address the best way to apply Federal facilities and resources. The functions of the FRPCC and the RACs are expanded to include providing advice to FEMA regarding provision to and use of Federal technical assistance, facilities, and resources by affected licensees.

In the event of an actual radiological emergency, E.O. 12657 requires FEMA to take all steps necessary for ensuring the implementation of plans developed under the order; and to coordinate the actions of other Federal agencies in achieving maximum effectiveness of Federal efforts in responding to the emergency. Planned response functions of Federal agencies are needed to ensure that the Federal government is prepared to assume any and all functions and undertakings necessary to provide adequate protection of the public in cases within the scope of this Executive order. In the event of an actual emergency, FEMA will coordinate with the State and local governmental authorities and undertake offsite response functions as may be needed. FEMA will transfer such functions to State and local governments when they exercise their authority and related response functions.

The Executive order also requires FEMA to assume any necessary command and control function, or to delegate it to another Federal agency, in the event that no competent State and local authority is available to perform such function. Federal planning for this contingency will be accommodated in the next revision of the Federal Radiological Emergency Response Plan.

The Executive order makes provision for FEMA, to the extent permitted by law, to obtain full reimbursement for services performed by FEMA or other Federal agencies pursuant to E.O. 12657 from any affected licensee and from any affected, non-participating or inadequately participating State and local government. The policy and procedures for the reimbursement process will be covered in a separate regulation to be published in the **Federal Register.**

Section 6 of Executive Order 12657 states that FEMA shall issue interim and final directives and procedures implementing the order as expeditiously as is feasible, and in any event, shall issue interim directives and procedures not more than 90 days following the effective date of this order and shall issue final directives and procedures not more than 180 days following the effective date of this order which is November 18, 1988.

In order to meet these deadlines, FEMA is issuing this regulation as an interim rule with a request for public comment instead of issuing a proposed rule with request for comment followed by a final rule. Meeting executive order deadlines is considered good cause for not issuing the rules as a proposed rule with a sixty day comment period. In accordance with 44 CFR 1.4 (c), (e) and (f), such notice and public procedure is omitted as impractical or unnecessary. In lieu of this omission public comment is requested on the interim rule and FEMA will conduct full rulemaking including review and action on the comments to the same extent as if this were a proposed rule.

The assistance described in this Part is not Federal financial assistance described in 44 CFR Part 4 and, thus,

does not require use of the intergovernmental review procedure described therein.

Regulatory Flexibility Certification

In accordance with the Regulatory Flexibility Act of 1980, 5 U.S.C. 605(b), the Director has certified that this rule will not have a significant economic impact upon a substantial number of small entities. The rule places obligations and burdens only on nuclear power plant licensees which are electric utility companies dominant in their service areas. These licensees are not "small entities" as set forth in the Regulatory Flexibility Act and do not meet the small business size standards [set forth in Small Business Administration regulations in 13 CFR Part 121.] A copy of the certification, and attendant material is available for inspection and copying in the Rules Docket.

Environmental Assessment and Finding of No Significant Environmental Impact.

The Director has determined under the National Environmental Policy Act of 1969 and FEMA Regulation 44 CFR Part 10, "Environmental Considerations" that this rule is not a major Federal action significantly affecting the quality of the human environment. Therefore, an environmental impact statement is not required. In support of this finding, an environmental assessment has been prepared which is available for inspection and copying for a fee in the Rules Docket.

Regulatory Analysis

This rule is not a major rule as the term is used in Executive Order 12291 and implementing OMB guidance. It will not have an annual effect on the economy of $100 million or more, will not result in a major increase in costs or prices to consumers, individual industries, Federal, State or local agencies, or geographic regions and will not have a significant adverse impact on competition, employment, investment, productivity, innovation or the ability of United States based enterprises to compete with foreign based enterprises in domestic or export markets.

Paper Work Reduction Act

This rule contains information requirements that are subject to the Paper Work Reduction Act of 1980 (44 U.S.C. 3501 *et seq.*) and the OMB implementing regulation 5 CFR Part 1320. These requirements have been submitted to OMB for approval, and the OMB number is 3067–0201.

Federalism Executive Order

A Federalism assessment under E.O. 12612 has been prepared and a copy is available for inspection and copying for a fee at the Rules Docket.

List of Subjects in 44 CFR Part 352

Nuclear power plants and reactors, radiation protection, Intergovernmental relations and Federal assistance.

Accordingly, Subchapter E Chapter 1, Title 44, Code of Federal Regulations is amended by adding Part 352.

PART 352—FEDERAL EMERGENCY MANAGEMENT AGENCY ASSISTANCE IN EMERGENCY PREPAREDNESS PLANNING AT COMMERCIAL NUCLEAR POWER PLANTS

Subpart A—Certifications and Determinations

Sec.

Subpart B—Federal Participation

Authority: Federal Civil Defense Act of 1950, as amended [50 U.S.C. App. 2251 *et seq.*]; Robert T. Stafford Disaster Relief and Emergency Assistance Act, 42 U.S.C. 5121 *et seq.*; 31 U.S.C. 9701 *et seq.*; Executive order 12657; Executive Order 12148; Executive Order 12127 and Executive Order 12241.

Subpart A—Certifications and Determinations

§ 352.1 Definitions.

As used in this Part, the following terms and concepts are defined:

(a) *Associate Director* means the Associate Director, State and Local Programs and Support, FEMA or designee.

(b) *Director* means the Director, FEMA or designee.

(c) *EPZ* means Emergency Planning Zone.

(d) *FEMA* means the Federal Emergency Management Agency.

(e) *NRC* means the Nuclear Regulatory Commission.

(f) *Regional Director* means the Regional Director of FEMA or designee.

(g) *Local government* means boroughs, cities, counties, municipalities, parishes, towns, townships or other local jurisdictions within the plume and ingestion exposure pathway EPZs that have specific roles in emergency planning and preparedness.

(h) *Decline or fail* means a situation where State or local governments do not participate in preparing offsite emergency plans or have significant planning or preparedness inadequacies and have not demonstrated the commitment or capabilities to correct those inadequacies so as to satisfy NRC licensing requirements.

(i) *Governor* means the Governor of a State or his/her designee.

(j) *Certification* means the written justification by a licensee of the need for Federal compensatory assistance. This certification is required to activate the Federal assistance under this Part.

(k) *Responsible local official* means the highest elected official of an appropriate local government.

(l) *Technical assistance* means services provided by FEMA and other Federal agencies to facilitate offsite radiological emergency planning and preparedness such as: Provision of support for the preparation of offsite radiological emergency response plans and procedures; FEMA coordination of services from other Federal agencies; provision and interpretation of Federal guidance; provision of Federal and contract personnel to offer advice and recommendations for specific aspects of preparedness such as alert and notification and emergency public information.

(m) *Federal facilities and resources* means personnel, property (land, buildings, vehicles, equipment), and operational capabilities controlled by the Federal government related to establishing and maintaining radiological emergency response preparedness.

(n) *Licensee* means the utility which has applied for or has received a license from the NRC to operate a commercial nuclear power plant.

(o) *Reimbursement* means the payment to FEMA/Federal agencies, jointly or severally, by a licensee and State and local governments for assistance and services provided in processing certifications and

implementing Federal compensatory assistance under Part 352.

(p) *Host FEMA Regional Office* means the FEMA Regional Office that has primary jurisdiction by virtue of the nuclear power plant being located within its geographic boundaries.

(q) *Command and control* means making and issuing protective action decisions and directing offsite emergency response resources, agencies, and activities.

§ 352.2 Scope, purpose and applicability.

(a) This Part applies whenever State or local governments, either individually or together, decline or fail to prepare commercial nuclear power plant offsite radiological emergency preparedness plans that are sufficient to satisfy NRC licensing requirements or to participate adequately in the preparation, demonstration, testing, exercise, or use of such plans. In order to request the assistance provided for in this Part, an affected nuclear power plant applicant or licensee shall certify in writing to FEMA that the above situation exists.

(b) The purposes of this Part are as follows: (1) To establish policies and procedures for the submission of a licensee certification for Federal assistance under Executive Order 12657, (2) set forth policies and procedures for FEMA's determination to accept, accept with modification or reject the licensee certification, (3) establish a framework for providing Federal assistance to licensees and (4) provide procedures for the review and evaluation of the adequacy of offsite radiological emergency planning and preparedness. Findings and determinations on offsite planning and preparedness made under this Part are provided to the NRC for its use in the licensing process.

(c) This Part applies only in instances where Executive Order 12657 is used by a licensee and its provisions do not affect the validity of the emergency preparedness developed by the licensee independent of or prior to Executive Order 12657.

§ 352.3 Licensee certification.

(a) A licensee which seeks Federal assistance under this Part shall submit a certification to the host FEMA Regional Director that a decline or fail situation exists. The certification shall be in the form of a letter from the chief executive officer of the licensee. The contents of this letter shall address the provisions set forth in paragraphs (b) and (c) of this Section.

(b) The licensee certification shall delineate why such assistance is needed based on the criteria of decline or fail for the relevant State or local governments.

(c) The licensee certification shall document requests to and responses from the Governor(s) or responsible local official(s) with respect to the efforts taken by the licensee to secure their participation, cooperation, commitment of resources or timely correction of planning and preparedness failures.

(Approved by the Office of Management and Budget under control number 3067–0201)

§ 352.4 FEMA action on licensee certification.

(a) Upon receiving a licensee certification, the host Regional Director shall immediately notify FEMA Headquarters of the licensee certification. Within 10 days, the host Regional Director shall acknowledge in writing the receipt of the certification to the licensee.

(b) Within 15 days of receipt of the certification, the Regional Director shall publish a notice in the **Federal Register** that a certification from the licensee has been received, and that copies are available at the Regional Office for review and copying in accordance with 44 CFR 5.26.

(c) FEMA Headquarters shall notify the NRC of receipt of the certification and shall request advice from the NRC on whether a decline or fail situation exists.

(d) The host FEMA Regional Office shall provide, after consulting with State and responsible local officials, a recommended determination on whether a decline or fail situation exists to the FEMA Associate Director within 20 days of receipt of the licensee certification.

(e) The FEMA Associate Director shall make a final determination on whether a decline or fail situation exists within 30 days of receipt of the licensee certification and shall advise the licensee, NRC, and State and local officials.

§ 352.5 FEMA determination on the commitment of Federal facilities and resources.

(a) A licensee request for Federal facilities and resources shall document the licensee's maximum feasible use of its resources and its efforts to secure the use of State and local government and of volunteer resources.

(b) Upon a licensee request for Federal facilities and resources, FEMA headquarters shall notify NRC and request advice from the NRC as to whether the licensee has made maximum use of its resources and the extent to which the licensee has complied with 10 CFR 50.47(c)(1). The host FEMA Regional Director shall make a recommendation to the FEMA Associate Director on whether the provision of these facilities and resources is warranted. The FEMA Associate Director shall make a final determination as to whether Federal facilities and resources are needed.

(c) In making the determination under paragraph (b) of this Section, FEMA:

(1) Shall work actively with the licensee, and before relying upon any Federal resources, shall make maximum feasible use of the licensee's own resources, which may include agreements with volunteer organizations and other government entities and agencies.

(2) Shall assume that, in the event of an actual radiological emergency or disaster, State and local authorities would contribute their full resources and exercise their authorities in accordance with their duties to protect the public from harm and would act generally in conformity with the licensee's radiological emergency preparedness plan.

(d) The FEMA Associate Director shall make a final determination on the need for and commitment of Federal facilities and resources. The FEMA determination shall be made in consultation with affected Federal agencies and in accordance with 44 CFR 352.21. FEMA shall inform the licensee in writing of the Federal support which will be provided. This information shall identify Federal agencies that are to provide Federal support, the extent and purpose of the support to be provided, the Federal facilities and resources to be committed and the limitations on their use. The provision of the identified Federal support shall be made under the policies and procedures of Subpart B of this Part.

§ 352.6 Review and evaluation.

FEMA shall conduct its activities and make findings under this Part in a manner consistent with 44 CFR Part 350 to the extent that those procedures are appropriate and not inconsistent with the intent and procedures required by E.O. 12657. This order shall take precedence, and any inconsistencies shall be resolved under the procedures in the NRC/FEMA MOU on planning and preparedness.

Subpart B—Federal Participation

§ 352.20 Purpose and scope.

This Subpart establishes policy and procedures for providing support for offsite radiological emergency planning and preparedness in a situation where

Federal support under Executive Order 12657 (E.O. 12657) has been requested. This Subpart:

(a) Describes the process for providing Federal technical assistance to the licensee for developing its offsite emergency response plan after an affirmative determination on the licensee certification under Subpart A (44 CFR 352.4 (d) and (e));

(b) Describes the process for providing Federal facilities and resources to the licensee after a determination under Subpart A (44 CFR 352.5(d)) that Federal resources are required;

(c) Describes the principal response functions which Federal agencies may be called upon to provide;

(d) Describes the process for allocating responsibilities among Federal agencies for planning site-specific emergency response functions; and

(e) Provides for the participation of Federal agencies, including the members of the FRPCC and the RACs.

§ 352.21 Participating Federal agencies.

(a) FEMA may call upon any Federal agency to participate in planning for the use of Federal facilities and resources in the licensee offsite emergency response plan.

(b) FEMA may call upon the following agencies and others as needed, to provide Federal technical assistance and Federal facilities and resources:

(1) Department of Commerce;
(2) Department of Defense;
(3) Department of Energy;
(4) Department of Health and Human Services;
(5) Department of Housing and Urban Development;
(6) Department of the Interior;
(7) Department of Transportation;
(8) Environmental Protection Agency;
(9) Federal Communications Commission;
(10) General Services Administration;
(11) National Communications System;
(12) Nuclerar Regulatory Commission;
(13) United States Department of Agriculture; and
(14) Department of Veterans' Affairs.

(c) FEMA is the Federal agency primarily responsible for coordinating Federal assistance. FEMA may enter into Memorandums of Understanding (MOUs) and other instruments with Federal agencies to provide technical assistance and to arrange for the commitment and utilization of Federal facilities and resources as necessary. FEMA also may use a MOU to delegate to another Federal agency, with the consent of that agency, any of the functions and duties assigned to FEMA. Following OMB review and approval, FEMA will publish such documents in the **Federal Register.**

§ 352.22 Functions of the Federal Radiological Preparedness Coordinating Committee (FRPCC).

Under 44 CFR Part 351, the role of the FRPCC is to assist FEMA in providing policy direction for the program of technical assistance to State and local governments in their radiological emergency planning and preparedness activities. Under this Subpart, the role of the FRPCC is to provide advice to FEMA regarding Federal assistance and Federal facilities and resources for implementing Subparts A and B of this Part. This assistance activity is extended to licensees. The FRPCC will assist FEMA in revising the Federal Radiological Emergency Response Plan (FRERP).

§ 352.23 Functions of a Regional Assistance Committee (RAC).

(a) Under 44 CFR Part 351, the role of a RAC is to assist State and local government officials to develop their radiological emergency plans, to review the plans, and to observe exercises to evaluate the plans. Under Subparts A and B of this Part, these assistance activities are extended to the licensee.

(b) Prior to a determination under Subpart A (44 CFR 352.5(d)) that Federal facilities and resources are needed, the designated RAC for the specific site will assist the licensee, as necessary, in evaluating the need for Federal facilities and resources.

(c) In accomplishing the foregoing, the RAC will use the standards and evaluation criteria in NUREG–0654/FEMA–REP–1, Rev. 1, Supp. 1 [1] or approved alternative approaches, and RAC members shall render such technical assistance as appropriate to their agency mission and expertise.

(d) Following a determination under Subpart A (44 CFR 352.5(d)) that Federal facilities and resources are needed, the RAC will assist FEMA in identifying agencies and specifying the Federal facilities and resources which the agencies are to provide.

§ 352.24 Provision of technical assistance and Federal facilities and resources.

(a) Upon a determination under Subpart A (44 CFR 352.4(e)) that a decline or fail situation exists, FEMA and other Federal agencies will provide technical assistance to the licensee.

(b) The applicable criteria for the use of Federal facilities and resources are set forth in Subpart A (44 CFR 352.5(c) (1) and (2)). Upon a determination under Subpart A (44 CFR 352.5(d)) that Federal resources or facilities will be required, FEMA will consult with the FRPCC, the RAC, the individual Federal agencies, and the licensee, to determine the extent of Federal facilities and resources that the government could provide, and the most effective way to do so. After such consultation, FEMA will specifically request Federal agencies to provide those Federal facilities and resources. The Federal agencies, in turn, will respond to confirm the availability of such facilities and resources and provide estimates of their costs.

(c) FEMA will inform the licensee in writing of the Federal support which will be provided. This information will identify Federal agencies which are to be included in the plan, the extent and purpose of technical assistance to be provided and the Federal facilities and resources to be committed, and the limitations of their use. The information will also describe the requirements for reimbursement to the Federal government for this support.

(d) FEMA will coordinate the Federal effort in implementing the determinations made under Subpart A (44 CFR 352.5(d)) so that each Federal agency maintains the committed technical assistance, facilities and resources after the licensee offsite emergency response plan is completed. FEMA and other Federal agencies will participate in training, exercises, and drills, in support of the licensee offsite emergency response plan.

(e) In carrying out paragraphs (a) through (c) of this Section, FEMA will keep affected State and local governments informed of actions taken.

(Approved by the Office of Management and Budget under control number 3067–0201)

§ 352.25 Limitation on committing Federal facilities and resources for emergency preparedness.

(a) The commitment of Federal facilities and resources will be made through the authority of the affected Federal agencies.

(b) In implementing a determination under Subpart A (44 CFR 352.5(d)), that Federal facilities and resources are necessary for emergency preparedness, FEMA shall take care not to supplant State and local resources. Federal facilities and resources shall be substituted for those of the State and local governments in the licensee offsite emergency response plan only to the extent necessary to compensate for the nonparticipation or inadequate participation of those governments, and

[1] Copy available from FEMA Distribution Center, P.O. Box 70274, Washington, DC 20024.

only as a last resort after consultation with the Governor(s) and responsible local officials in the affected area(s) regarding State and local participation.

(c) All Federal planning activities described in this Subpart will be conducted under the assumption that, in the event of an actual radiological emergency or disaster, State and local authorities would contribute their full resources and exercise their authorities in accordance with their duties to protect the public from harm and would act, generally, in conformity with the licensee's offsite emergency response plan.

§ 352.26 Arrangements for Federal response in the Licensee Offsite Emergency Response Plan.

Federal agencies may be called upon to assist the licensee in developing a licensee offsite emergency response plan in areas such as:

(a) Arrangements for use of Federal facilities and resources for response functions such as:

(1) Prompt notification of the emergency to the public;

(2) Assisting in any necessary evacuation;

(3) Providing reception centers or shelters and related facilities and services for evacuees;

(4) Providing emergency medical services at Federal hospitals; and

(5) Ensuring the creation and maintenance of channels of communication from commercial nuclear power plant licensees to State and local governments and to surrounding members of the public.

(b) Arrangements for transferring response functions to State and local governments during the response in an actual emergency; and (c) Arrangements which may be necessary for FEMA coordination of the response of other Federal agencies.

§ 352.27 Federal role in the emergency response.

In addition to the Federal component of the licensee offsite emergency response plan described in Subpart B (§ 352.26), and after complying with E.O. 12657, section 2(b)(2), which states that FEMA: shall take care not to supplant State and local resources and that FEMA shall substitute its own resources for those of State and local governments only to the extent necessary to compensate for the nonparticipation or inadequate participation of those governments, and only as a last resort after appropriate consultation with the Governors and responsible local officials in the affected area regarding State and local participation, FEMA shall provide for initial Federal response activities, including command and control of the offsite response, as may be needed. Any Federal response role, undertaken pursuant to this section, shall be transferred to State and local governments as soon as feasible after the onset of an actual emergency.

§ 352.28 Reimbursement.

In accordance with Executive Order 12657, section 6(d), and to the extent permitted by law, FEMA will coordinate full reimbursement, either jointly or severally, to the agencies performing services or furnishing resources, from any affected licensee and from any affected non-participating or inadequately participating State or local government.

Dated: February 23, 1989.

Julius W. Becton, Jr.,

Director, FEMA.

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