DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 341

[Docket No. 76N-052B]

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

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) bronchodilator drug products (drug products used in the symptomatic treatment of the wheezing and shortness of breath of asthma) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal deals only with bronchodilator drug products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by December 27, 1982. New data by October 26, 1983. Comments on the new data by December 26, 1983. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Comments on the agency's economic impact determination by February 23, 1983.

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

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, National Center for Drugs and Biologics (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

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

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

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

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

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

In response to the advance notice of proposed rulemaking, 4 manufacturers, 2 manufacturers' associations, 1 consumer, 39 health care professionals, and 19 health care professional societies submitted comments on bronchodilator drug products. Copies of the comments received are also on public display in the Dockets Managment Branch.

This tentative final monograph would amend Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations in Part 341 (as set forth in the tentative final monograph on anticholinergic drug products and expectorant drug products that was published in the **Federal Register** of July 9, 1982 (47 FR 30002)) in Subpart A, by adding in § 341.3, new paragraph (c); by adding Subpart B, consisting at this time of § 341.16; and in Subpart C, by adding new §§ 341.76 and 341.90. This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC bronchodilator drug products, as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established.

Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph (46 FR 47738).

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register**. In some advance notices of proposed rulemaking previously published in the OTC drug review, the agency suggested an earlier effective date. However, as explained in the tentative final monograph for OTC anticholinergic drug products and expectorant drug products (published in the **Federal Register** of July 9, 1982; 47 FR 30002), the agency has concluded that, generally, it is more reasonable to have a final monograph be effective 12 months after the date of its publication in the **Federal Register**. This period of time should enable manufacturers to reformulate, relabel or take other steps to comply with a new monograph with a minimum disruption of the marketplace thereby reducing economic loss and ensuring that consumers have continued access to safer and effective drug products.

On or after the effective date of the monograph, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce. Further, any OTC drug products subject to this monograph that are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

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

I. The Agency's Tentative Conclusions on the Comments

1. Many comments, mostly from health care professionals, objected to the Panel's recommendation that theophylline be available OTC. The comments raised two major concerns: appropriate dosages are difficult to determine, and the potential risk of toxicity is great. Several other comments supported the Panel's placement of theophylline in Category I, citing the savings in time and money to patients who would no longer have to visit a physician to obtain a prescription and nothing that adverse reactions tend to be minor while benefits in relief of wheezing and labored breathing tend to be significant.

Several comments objected to the term "excessive use" in the warning against the use of theophylline in children under 12 years of age in § 341.76(b)(4)(v). Another comment objected to the Panel's recommendations concerning the theophylline tablet dissolution testing in § 341.45. One comment pointed out that unpublished information has been generated indicating that measurements of whole-blood theophylline levels are almost as high as measurements of serum theophylline levels. A manufacturer of timed-release products commented that in view of the Panel's conclusion that small doses of theophylline at more frequent time intervals are desirable, timed-release dosage forms of theophylline may be preferable to immediate-release dosage forms.

In the **Federal Register** of December 10, 1976 (41 FR 54032), the agency announced that it did not agree with the Panel's recommendation that theophylline be classified in Category I and be made available for OTC use as a single ingredient. At that time, the agency stated that additional information, which was not available during the Panel's deliberations, indicated that the Panel's recommended therapeutic dose may be toxic to some individuals and suggested that the safe and effective use of theophylline requires careful dosage titration based on theophylline serum concentrations. The December 10, 1976 notice included a summary of the information on which the agency's decision was based. None of the comments in favor of the OTC availability of theophylline contained data from studies in support of a change in the agency's decision to place theophylline as a single ingredient in Category II. The advantages of OTC availability of theophylline cited by these comments, e.g., savings in time and money when a prescription is not required to obtain theophylline, do not outweigh the potential risk of toxicity. The agency therefore reaffirms its December 10, 1976 decision at this time and tentatively concludes that theophylline should not be available as a single ingredient in OTC drug products. Accordingly, §§ 341.16(d), 341.45, 341.76(b)(4), and 341.90(k) have been deleted from the monograph. Specific responses to the comments concerning the warning against the use of the drug in children under 12 years of age, dissolution testing of theophylline preparations, whole-blood and serum levels of theophylline, and timed-release dosage forms are obviated at this time by the agency's decision to place theophylline as a single ingredient in Category II.

The agency is reviewing the use of theophylline as an ingredient in OTC combination drug products and will address such combinations in a future **Federal Register** publication of the tentative final monograph for cold, cough, allergy, bronchodilator, and antiasthmatic combination products. Should the agency determine that theophylline-containing combinations are generally recognized as safe and effective, the above-mentioned sections, modified to apply to theophylline-containing combinations only, will be incorporated into the monograph at that time. The agency will also respond to specific comments concerning the warning against the use of theophylline in children under 12 years of age, dissolution testing of theophylline preparations, whole-blood and serum levels of theophylline, and timed-release dosage forms at that time should theophylline-containing combinations be included in the monograph.

2. One comment requested clarification of the phrase "pressurized preparation," as used by the Panel in stating its conclusions on the dosage of epinephrine-containing products (41 FR 38372), and asked whether the phrase

refers to an aerosol preparation, to a hand-held nebulizer preparation, or to both.

FDA has approved a number of epinephrine-containing aerosol products for OTC marketing through the NDA procedure. These products are marketed in containers pressurized with propellants, which dispense metered doses of the drug for oral inhalation in the form of an areosolized spray. There are other epinephrine-containing solutions on the OTC market that are to be used with hand-held nebulizers. Based upon a review of the Panel's report and minutes of the Panel meetings, the agency concludes that the Panel intended the phrase "pressurized preparation" to apply only to aerosol preparations.

3. A number of comments disagreed with the Panel's recommendation to allow the OTC marketing of epinephrine inhalation products for the treatment of asthma and recommended that the agency require these products to be dispensed only by prescription. The comments generally expressed the opinion that the self-diagnosis and self-treatment of asthma with aerosolized epinephrine can lead to serious clinical consequences. The comments argued that asthmatic patients have a propensity for abusing propellant devices and that this abuse could produce a psychological dependence and result in the administration of toxic doses of epinephrine. The comments also argued that there is a possibility of fatal reactions in asthmatics with cardiac disease who self-medicate with these products. The comments noted that the agency had proposed in the **Federal Register** of April 15, 1972 to limit epinephrine inhalation products to prescription use and stated that the agency should not have suspended that action.

The Panel reviewed the available data for epinephrine products, including the references cited in the agency's proposal of April 15, 1972. The Panel, therefore, was aware of the risks associated with the self-diagnosis and self-treatment of asthma, as well as the abuse potential and the possible adverse effects that may occur with the use of epinephrine inhalation products. However, the Panel concluded from these data that these risks are adequately defined for epinephrine inhalation products in § 341.76(b)(3) and do not outweigh the benefits to be derived from the OTC use of these products.

The comments provided no additional data that persuade the agency to limit epinephrine inhalation products to prescription use only. The Panel acknowledged that asthma requires professional diagnosis and management and recommended a warning in § 341.76(b)(1) for all bronchodilators, "*Caution:* Do not take this product unless a diagnosis of asthma has been made by a physician." The Panel believed, and the agency concurs, that once the diagnosis of asthma has been made by a physician it is reasonable to have bronchodilators available OTC so that in mild cases relief may be obtained quickly without the delays of obtaining a physician's prescription.

The agency believes that epinephrine, epinephrine bitartrate, and epinephrine hydrochloride (racemic) can be generally recognized as safe and effective when used in an aqueous solution equivalent to 1 percent epinephrine in a hand-held rubber bulb nebulizer at a dosage for adults and children 4 years of age and older of 1 to 3 inhalations not more often than every 3 hours.

Based on the Panel's recommendations and an OTC marketing history of many years under approved NDAs (Ref. 1), the agency also believes that epinephrine, epinephrine bitartrate, and epinephrine hydrochloride (racemic) in pressurized metered-dose inhalation aerosol dosage forms can be generally recognized as safe and effective at a dosage for adults and children 4 years of age and older of 1 to 2 inhalations of a metered dose equivalent to 0.16 to 0.25 milligram (mg) epinephrine per inhalation not more often than every 3 hours. The agency believes that requiring a metered-dose range for pressurized aerosol dosage forms in addition to the Panel's recommended dosage provides additional assurance that the product can be used safely on an OTC basis.

In a study by Kjellman, Tollig, and Wettrel (Ref. 2) comparing racemic epinephrine and salbutamol, 10 asthmatic children ranging from 7 to 16 years of age inhaled 2 doses of 0.9 milligram per kilogram bodyweight (a dose of 18 mg for a 20–kilogram (44-pound) child) racemic epinephrine 150 minutes apart. Blood pressure and heart rate were measured during and after the dosing period. No significant changes were found in the heart rate or the diastolic pressure. A small but significant increase was found in the mean systolic pressure (+7 millimeters of mercury) 5 minutes after the inhalation of epinephrine. There was no significant change in systolic pressure at 30 minutes and 150 minutes after inhalation of epinephrine. The dose given showed only a mild effect in blood pressure measurements even though it was more than 36 times greater than the highest dose (0.50 mg epinephrine in two inhalations) proposed by the agency for metered-dose aerosols. The agency believes that the proposed dose provides an adequate margin of safety for the OTC marketing of epinephrine or the equivalent in a metered-dose aerosol inhalation dosage form.

The agency proposes the following labeling directions for epinephrine, epinephrine bitartrate, and epinephrine hydrochloride (racemic) in pressurized metered-dose inhalation aerosol dosage forms based on the Panel's recommendations and the currently approved NDA labeling for these products (Ref. 1):

(i) *For use in a pressurized metered-dose aerosol container.* Each inhalation contains the equivalent of 0.16 to 0.25 milligram of epinephrine base.

(*a*) Inhalation dosage for adults and children 4 years of age and older: start with one inhalation, then wait at least 1 minute. If not relieved, use once more. Do not use again for at least 3 hours. The use of this product by children should be supervised by an adult. Children under 4 years of age: consult a doctor.

(*b*) The labeling must include directions for the proper use of the inhaler and for the proper care and cleaning of the mouthpiece. The directions must be clear, direct, and provide the consumer with sufficient information for the safe and effective use of the product.

References

(1) Copy of FDA-approved labeling including dosages from NDA 10–374, NDA 16–126, and NDA 16–803, OTC Volume 04BTFM, Docket No. 76N–052B, Dockets Management Branch.

(2) Kjellman, B., H. Tollig, and G. Wettrell, "Inhalation of Racemic Epinephrine in Children with Asthma," *Allergy*, 35:605–610, 1980.

4. Several comments objected to the Category I classification of methoxyphenamine hydrochloride and recommended that this ingredient be available only by prescription. The comments argued that methoxyphenamine is a weak bronchodilator, that there are better bronchodilators on the market, and that because it is an adrenergic compound it possesses the potential to cause adverse cardiovascular effects. One of the comments also expressed the opinion that methoxyphenamine should not be allowed OTC because asthma should be diagnosed and managed by health professionals and marketing the drug OTC would not be in the best interest of the public.

Besides the Panel's evaluation, methoxyphenamine hydrochloride was

also reviewed by the National Academy of Sciences—National Research Council (NAS/NRC) Drug Efficacy Study Group for several indications including its use as a bronchodilator. Based on the report of the NAS/NRC Drug Efficacy Study Group, FDA, in a notice published in the **Federal Register** of April 26, 1972 (37 FR 8405), concluded that methoxyphenamine was possibly effective as a bronchodilator. No new data to support the effectiveness of methoxyphenamine were submitted in response to the April 26, 1972 **Federal Register** notice. Therefore, the agency published a notice of opportunity for hearing in the **Federal Register** of August 21, 1973 (38 FR 22501) reclassifying methoxyphenamine from possibly effective to lacking substantial evidence of effectiveness. No response was filed following the August 21, 1973 notice of opportunity for hearing. Therefore, in a notice of withdrawal of approval published in the **Federal Register** of January 16, 1981 (46 FR 3983), FDA withdrew approval of NDA 6–550 for methoxyphenamine hydrochloride and extended the notice to "any drug product that is identical, related, or similar to" the drug product containing methoxyphenamine hydrochloride.

The data reviewed by the NAS/NRC Drug Efficacy Group and the Panel concerning the effectiveness of methoxyphenamine hydrochloride were the same with the exception of a study by Roy, Seabury, and Johns (Ref. 1) which was reviewed by the Panel but not by the NAS/NRC Drug Efficacy Study Group. The agency has reviewed this study and concludes that it is inadequate to demonstrate the effectiveness of methoxyphenamine hydrochloride. The subjects studied included patients with mild hypertrophic emphysema as well as bronchial asthma. The authors did not specify which results were obtained in patients with bronchial asthma alone. Thus, the data cannot be analyzed with respect to the effectiveness of methoxyphenamine hydrochloride in the OTC target population, i.e., patients with mild bronchial asthma.

Therefore, the agency has reclassified methoxyphenamine hydrochloride in Category II in this tentative final monograph.

Reference

(1) Roy, E. C., J. H. Seabury, and L. E. Johns, Jr., "Spirometric Evaluation of Orthoxine in Bronchial Asthma," *Journal of Allergy*, 20:364–368, 1949.

5. One comment objected to the placement of belladonna alkaloids used as bronchodilators in Category II. The comment claimed that inhaled smoke from burning a stramonium belladonna preparation in cigarette or powder form provides asthmatic patients with relief of bronchial spasms. The comment maintained that marketing experience for over 100 years, submitted effectiveness studies, and a low incidence of reported intoxications should justify the ingredient's placement in Category I or at least Category III to allow for additional testing.

The agency disagrees with the comment. FDA affirms the Panel's determination that the effectiveness studies that were conducted were not sufficient to establish general recognition of effectiveness for belladonna alkaloids as a bronchodilator. FDA also agrees with the Panel that potential toxicity problems represent a negative benefit-to-risk ratio in that the psychotomimetic (producing manifestations resembling those of a psychosis, e.g., visual hallucinations, distortion of perception, and schizophrenia-like behavior) properties and potentially excessive anticholinergic effects of these drugs are undesirable characteristics for an OTC drug product. The agency believes that there is insufficient evidence to indicate that further testing would support Category I status for these drugs and concurs with the Panel's Category II classification.

6. One comment objected to the Panel's recommendation of a double-blind crossover protocol for testing Category III bronchodilators. The comment maintained that a crossover or parallel study would be appropriate, depending on the specific ingredient to be tested, and that the manufacturer should be allowed to choose which protocol to use.

In the preamble to the agency's proposed rule revising the OTC procedural regulations (45 FR 31422), the agency advised that tentative final and final monographs will no longer contain recommended guidelines for testing Category III ingredients. Interested persons may submit data and information to demonstrate the safety or effectiveness of any bronchodilator ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47770). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submissions of test data and other information. Thus the agency will not address this comment at this time, but will be glad to discuss the design of studies for specific bronchodilator drugs with manufacturers who may conduct such studies.

7. One comment suggested that the Panel's recommended drug interaction precaution for bronchodilator drug products should be deleted. This proposed precaution is "Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor." The comment argued that terms such as "antihypertensive," "antidepressant," and "monoamine oxidase inhibitor" are highly technical; that only a small percentage of the population is likely to understand this warning; and that including such a warning in the labeling of an OTC drug is contrary to the well-established principle that unnecessary or confusing precautions tend to dilute the significance of all instructions in the labeling and, hence, should be avoided.

The agency agrees with the comment that the Panel's proposed drug interaction precaution may not be readily understood by all consumers. However, it considers a warning of this type necessary to alert consumers because antihypertensive and antidepressant drugs are widely prescribed. To simplify this precautionary statement the agency is proposing to substitute the term "high blood pressure" for the term "antihypertensive" and the term "depression" for "antidepressant." The agency also believes that the words "monoamine oxidase inhibitor" would be confusing to consumers and need not be included in the precautionary statement to convey the intended message. Accordingly, the drug interaction precaution has been revised and will read as follows: "*Drug interaction precaution:* Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor."

8. One comment stated that the Panel used an inappropriate standard in categorizing some Category II claims, and that the Panel rejected claims such as "relieves gasping of air," "free breathing restored," and "breathes a sigh of relief" because the claims were made in emotional terms. The comment argued that there is no statute that bans emotional claims on the labeling of OTC drugs and urged FDA to reject all recommendations of the Panel based on an "improper standard."

The agency agrees with the Panel that these claims are inappropriate for OTC labeling and should remain in Category II. The Panel's purpose in reviewing

labeling claims was to eliminate false, vague, confusing, and misleading claims. The agency believes that the above claims should be in Category II because they do not specifically indicate the pharmacologic effect of a drug and are exaggerated. Such overstatements and exaggerations tend to create a false image of a drug and are unclear and potentially misleading.

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

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

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and has proposed the recategorization of two bronchodilator active ingredients. In addition, the agency proposes to place metaproterenol sulfate in a metered-dose inhalation aerosol dosage form in Category I. For the convenience of the reader, the following table is included as a summary of the categorization of bronchodilator active ingredients by the Panel and the proposed classification by the agency.

Bronchodilator active ingredients	Panel	Agency
Belladonna alkaloids	II	II
Ephedrine	I	I
Ephedrine hydrochloride		
Ephedrine sulfate		
Racephedrine hydrochloride		
Epinephrine	I	I
Epinephrine bitartrate		
Epinephrine hydrochloride (racemic)		
Euphorbia pilulifera	III	III
Metaproterenol sulfate	[1]	I
Methoxphenamine hydrochloride	I	II
Pseudoephedrine hydrochloride	II	II
Pseudoephedrine sulfate		
Theophylline (anhydrous)	I	II
Aminophylline		
Theophylline calcium salicylate		
Theophylline sodium glycinate		

[1] Not reviewed.

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for bronchodilator drug products (41 FR 38329 and 38376). The agency is offering these guidelines as the Panel's recommendations without adopting them or making any formal comment on them. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any bronchodilator ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the Federal Register of September 29, 1981 (46 FR 47740). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

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

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

1. The agency has classified in Category I epinephrine, epinephrine bitartrate, and epinephrine hydrochloride (racemic) in an aqueous solution equivalent to 1 percent epinephrine when used in a hand-held rubber bulb nebulizer. The agency has also proposed a dose for epinephrine, epinephrine bitartrate, and epinephrine hydrochloride (racemic) in a pressurized metered-dose inhalation aerosol dosage form of 1 to 2 inhalations of the equivalent of 0.16 to 0.25 mg epinephrine not more often than every 3 hours for adults and children 4 years of age and older. (See comment 3 above.)

2. The agency has reviewed the literature concerning the safety and effectiveness of metaproterenol sulfate as a bronchodilator in the form of a pressurized metered-dose inhalation aerosol and believes that it can be generally recognized as safe and effective for OTC use. Metaproterenol sulfate has been marketed under an approved NDA for 9 years as a prescription drug product in a pressurized metered-dose inhalation aerosol dosage form that contains 0.65 mg per inhalation with an adult dosage of 1 to 3 inhalations not more often than every 3 hours (Ref. 1).

The agency has reviewed studies by Emirgil, Dwyer, and Sobol (Ref. 2); Rodgers and Bickerman (Ref. 3); Chester et al. (Ref. 4); Roth, Watson, and Novey (Ref. 5); Shim and Williams (Refs. 6 and 7); Blackhall, Macartney, and O'Donnell (Ref. 8); and Chervinsky and Belinkoff (Ref. 9) concerning the safety and effectiveness of metaproterenol sulfate in a pressurized metered-dose inhalation aerosol dosage form. Several of these studies evaluated products that are marketed under the approved NDA (Refs. 2, 3, 4, 7, 8, and 9), and all but one (Ref. 3) were double-blinded. All of the studies were performed in asthmatic patients, although one study (Ref. 3) also included patients with chronic bronchitis and patients with emphysema and chronic bronchitis, and another study (Ref. 9) also included patients with chronic bronchitis. A crossover design was used in all of the studies. Seven of the studies evaluated inhaled doses of metaproterenol sulfate within the dosage range of 0.65 to 1.95 mg (Refs. 2 through 6, 8, and 9). The eighth study evaluated an inhaled dose of 3.25 mg metaproterenol sulfate (Ref. 7). All of the studies demonstrated an immediate bronchodilator effect after metaproterenol sulfate inhalation. Those studies that measured bronchodilation beyond 3 hours after dosing showed a 3- to 6-hour duration of action (Refs. 2 through 6 and 9).

Five of the studies detected no significant change in blood pressure measurements following inhalation of metaproterenol sulfate (Refs. 2, 3, 5, 7, and 9), and six of the studies detected no significant change in the pulse rate (Refs. 2, 3, 5, 7, 8, and 9). In one study, a patient gagged once on a dose of metaproterenol (Ref. 9). This was not a serious reaction and the patient was able to continue the dosage schedule without further problems. Seven of the studies did not detect any adverse reactions to inhaled metaproterenol sulfate (Refs. 2 through 8). However, a review of FDA adverse reaction reports since 1973 indicates that adverse reactions such as dizziness, nervousness, dry mouth, rapid heart beat, palpitations, and allergic reactions have been reported in cases where inhaled metaproterenol sulfate was the only drug given. In these cases, overdose was not indicated, other circumstances were not indicated as a cause of the reaction, and enough information was available to indicate a possible cause-and-effect relationship between the use of inhaled metaproterenol sulfate and the reaction.

Based on the safe and effective use of metaproterenol sulfate in a pressurized metered-dose inhalation aerosol dosage form under an approved NDA for 9 years, on a review of the literature, and on a review of FDA adverse reaction reports, the agency believes that metaproterenol sulfate can be generally recognized as safe and effective. The agency is therefore proposing that metaproterenol sulfate be Category I as an OTC bronchodilator in a pressurized metered-dose inhalation aerosol that contains 0.65 mg per inhalation with an adult dosage of 1 to 3 inhalations not more often than every 3 hours. The labeling directions and warnings are based on the current NDA approved labeling (Ref. 10).

References

(1) Letter from J. R. Crout, M.D., FDA, to Boehringer Ingleheim Ltd., OTC Volume 04BTFM, Docket No. 76N–052B, Dockets Management Branch.

(2) Emirgil, C., K. Dwyer, and B. J. Sobol, "A Comparison of the Duration of Action and the Cardiovascular Effects of Metaproterenol and Isoetharine-Phenylephrine Combination," *Current Therapeutic Research*, 19:371–378, 1976.

(3) Rodgers, J. M., and H. A. Bickerman, "An Evaluation of the Duration of Bronchodilator Activity of Bronkometer® and Metaprel® in Patients with Reversible Bronchospasm," *Current Therapeutic Research*, 28:147–153, 1980.

(4) Chester, E. H., et al., "Bronchodilating Effect of Terbutaline Aerosol," *Clinical Pharmacology and Therapeutics*, 23:630–634, 1978.

(5) Roth, M. J., A. F. Wilson, H. S. Novey, "A Comparative Study of the Aerosolized Bronchodilators, Isoproterenol, Metaproterenol and Terbutaline in Asthma," *Annals of Allergy*, 38:16–21, 1977.

(6) Shim, C., and M. H. Williams, Jr., "Comparison of Oral Aminophylline and Aerosol Metaproterenol in Asthma," *The American Journal of Medicine*, 71:452–455, 1981.

(7) Shim, C., and M. H. Williams Jr., "Bronchial Response to Oral Versus Aerosol," Metaproterenal in Asthma *Annals of Internal Medicine*, 93:428–431, 1980.

(8) Blackhall, M. I., B. Macartney, and S. R. O'Donnell, "The Acute Effects of the Administration of Rimiterol Aerosol in Asthmatic Children," *British Journal of Clinical Pharmacology*, 6:59–62, 1978.

(9) Chervinsky, P., and S. Belinkoff, "Comparison of Metaproterenol and Isoproterenol Aerosols: Spirometric Evaluation after Two Months' Therapy," *Annals of Allergy*, 27:611–616, 1969.

(10) Copy of FDA-approved labeling from NDA 16–402, OTC Volume 04BTFM, Docket No. 76N–052B, Dockets Management Branch.

3. The agency has deleted § 341.16(c) and the reference to § 341.16(c) in § 341.76(b)(2) of the Panel's recommended monograph. These sections provided dosages and warnings for methoxyphenamine hydrochloride. The agency has reclassified methoxyphenamine hydrochloride in Category II. (See comment 4 above.)

4. The agency has deleted §§ 341.16(d), 341.45, 341.76(b)(4), and 341.90(k) of the Panel's recommended monograph. These sections provided dosages, testing guidelines, warnings, and professional labeling for single ingredient theophylline products. In the **Federal Register** of December 10, 1976 (41 FR 54032), the agency announced that it disagreed with the Panel's Category I classification of single ingredient theophylline products. At that time, the agency determined that because it is essential to have a physician titrate theophylline dosages, based on individual patient measurements of theophylline serum levels, theophylline should not be available OTC as a single ingredient product. The agency reaffairms that position and classifies theophylline, as a single ingredient, in Category II. (See comment 1 above.)

5. The agency has added to § 341.76 a "Statement of identity" paragraph and a "Directions" paragraph to conform with the format of other recently published advance notices of proposed rulemaking and tentative final monographs. Inclusion of new paragraphs has necessitated a redesignation of § 341.76(a) to § 341.76(b) and § 341.76(b) to § 341.76(c). The agency is also redesignating Subpart D as Subpart C and placing the labeling sections of the monograph in Subpart C.

6. The Panel recommended five indications for bronchodilator drug products in § 341.76(a)(2) as follows:

(i) "For temporary relief of bronchial asthma."

(ii) "For symptomatic control of bronchial asthma."

(iii) "Provides temporary relief from acute symptoms of bronchial asthma."

(iv) "Relaxes tense bronchial muscles to ease breathing for asthma patients."

(v) "For temporary relief of wheezing (attacks and distress) of bronchial asthma."

The agency is concerned that none of these indications alone would provide the consumer who is suffering from bronchial asthma with a clear understanding of the relief that an OTC bronchidilator can be expected to provide. Believing that it is important for the consumer to know what to expect of a medication, the agency has developed the following indication, which is included in the tentative final monograph in § 341.76(b)(1): "For temporary relief of shortness of breath, tightness of chest, and wheezing due to bronchial asthma." This indication is being proposed for all OTC bronchodilator drug products.

Portions of the indications recommended by the Panel have been combined and revised by the agency into statements that may be included in labeling at the manufacturer's option. These statements appear in § 341.76(b)(2) in this tentative final monograph under the heading "Other Allowable Statements" as follows:

(i) "For the" (select one of the following: "temporary relief" or "symptomatic control") "of bronchial asthma."

(ii) "Eases breathing for asthma patients" (which may be followed "by reducing spasms of bronchial muscles").

The agency believes that these statements, as revised, contain information in addition to the indication that could be helpful to consumers. The statements are not required but may appear in bronchodilator drug product labeling provided they are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information. The agency welcomes comment on these labeling changes.

7. In § 341.76(b) (1), (2) (i), and (3) (ii) the Panel recommended use of the signal word "Caution" in a section of the labeling where the heading *"Warnings"* is also recommended. The agency notes that historically there has not been a consistent usage of the signal words "warning" and "caution" in OTC drug labeling. For example, in §§ 369.20 and 369.21 (21CFR 369.20 and 369.21), which list "warning" and "caution" statements for drugs, the signal words "warning" and "caution" are both used. In some instances either of these signal words is used to convey the same or similar precautionary information.

FDA has considered which of these signal words would be most likely to attract consumers' attention to that information describing conditions under which the drug product should not be used or its use should be discontinued. The agency concludes that the signal word "warning" is more likely to flag potential dangers so that consumers will read the information being conveyed. Therefore, FDA has determined that the signal word "warning," rather than the word "caution," will be used routinely in OTC drug labeling that is intended to alert consumers to potential safety problems. Accordingly, the signal word "Caution" has been deleted from this tentative final monograph. Also, § 341.76(b) (1), (2)(i), and (3)(ii) have been redesignated § 341.76(c) (1), (4)(i), and (5)(ii), respectively.

8. In several of the warnings and directions in its monograph, the Panel recommended the use of the word "physician". The agency is substituting the word "doctor" for "physician" in the warnings and directions in all OTC drug monographs because it believes that the word "doctor" is more commonly used and better understood by consumers. If the word "doctor" is adopted in the final monograph, the agency will use this language in other final monographs and other applicable OTC drug regulations and will propose amendments to those regulations accordingly. Public comment on this proposed change in labeling language is invited.

9. The Panel recommended the following warning (in § 341.76(b)(2)(ii))

regarding possible side effects of ephedrine-containing bronchodilator drug products: "Nervousness, tremor, sleeplessness, nausea and loss of appetite may occur." The agency believes that consumers should be advised that these reactions to ephedrine may occur in some persons, and that the labeling should include a warning to consult a doctor if these reactions persist or become worse. The agency has therefore revised this warning, which appears in § 341.76(c)(4)(ii) in the tentative final monograph. In addition, because the potential of ephedrine to cause these side effects may be increased at higher than recommended OTC doses, the agency is adding the following sentence to the directions in § 341.76(d)(1) for use of ephedrine-containing products: "Do not exceed recommended dose unless directed by a doctor."

10. The agency has revised the Panel's recommended drug interaction precaution for ephedrine containing and epinephrine containing drug products to read as follows: *"Drug interaction precaution:* Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor." The agency concludes that terms such as "antihypertensive," "antidepressant," and "monoamine oxidase inhibitor," which were previously used in this warning, may not be readily understood by all consumers. However, because antihypertensive and antidepressant drugs are widely prescribed, the agency believes it is necessary to have a warning on bronchodilators to alert consumers to avoid taking antihypertensive or antidepressant drugs simultaneously in order to avoid any adverse reactions. (See comment 7 above.) This precaution appears in § 341.76(c)(3) of the tentative final monography.

11. The agency has deleted § 341.76 (b)(2)(v) and (b)(3)(vi) of the Panel's recommended monograph. These sections provided warnings against using ephedrine preparations in children under 12 years of age and using epinephrine inhalation preparations in children under 4 years of age. The directions provided in new § 341.76(d) state clearly that a doctor should be consulted for the use of ephedrine preparations in children under 12 years of age and the use of epinephrine inhalation preparations in children under 4 years of age. The agency believes that these warnings are therefore repetitious and unnecessary.

12. The agency has moved the Panel's recommended warning in § 341.76(b)(2)(iii) and has included it in new § 341.76(c)(2). The warning states: "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." Although the Panel recommended this warning only for oral ephedrine preparations, a similar warning is included in the currently approved NDA labeling for epinephrine preparations and metaproterenol sulfate in metered-dose inhalation aerosol dosage forms. The agency is therefore proposing that this warning be required for oral ephedrine preparations and for epinephrine preparations and metaproterenol sulfate in metered-dose inhalation aerosol dosage forms.

13. The agency has moved part of the Panel's recommended warning in § 341.76(b)(3)(v) and has included it as part of the warning in new § 341.76(c)(4)(i). The warning previously stated: "Keep this product out the reach of children and adolescents because unsupervised access may cause abuse or possible adverse effects on the heart of excessively used." The agency believes that such a warning may encourage rather than discourage abuse. The agency has, therefore, modified the warning in § 341.76(c)(5)(i) to emphasize the possible adverse effects of overdosage and has deleted any reference to possible abuse of the drug product by children and adolescents. In addition, the agency has added the statement "The use of this product by children should be supervised by an adult" in the directions paragraph (§ 341.76(d)(2)) for epinephrine drug products to prevent possible overdosage in this age group.

The agency proposes to revoke the existing warnings for oral ephedrine preparations and epinephrine in an inhalation dosage form in § 369.20 at the time that this monograph becomes effective.

The agency has examined the economic consequences of this proposed rulemaking and has determined that it does not require either a Regulatory Impact Analysis, as specified in Executive Order 12291, or a Regulatory Flexibility Analysis, as defined in the Regulatory Flexibility Act (Public Law 96–354). Specifically, it would switch metaproterenol sulfate in a metered-dose inhalation aerosol dosage form from prescription to OTC marketing status and would require reformulation of product containing methoxyphenamine hydrochloride as a single active ingredient by placing this drug in Category II. However, methoxyphenamine hydrochloride had already been effectively removed from the marketplace by the agency's withdrawal of an approved NDA. (See the **Federal Register** of January 16, 1981; 46 FR 3983.) This proposal also reaffirms the agency's dissent from the Panel's recommendation to switch theophylline as a single ingredient from prescription to OTC status (see the **Federal Register** of December 10, 1976; 41 FR 54032), but because this dissent prevented the switch from being implemented, the OTC market will not be affected, nor will continued OTC availability of combination drug products containing theophylline be affected. Some relabeling will be required, but can be accomplished with minimal cost. Therefore, the agency concludes that the proposed rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that the proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities, as defined in the Regulatory Flexibility Act.

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

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

Management Branch, Food and Drug Administration.

List of Subjects in 21 CFR Part 341

OTC drugs: Anticholinergics, Expectorants, Bronchodilators.

PART 341—[AMENDED]

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982)), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 341 (as set forth in the tentative final monograph that was published in the Federal Register of July 9, 1982 (47 FR 30002)) to read as follows:

1. In Subpart A, § 341.3 is amended by adding new paragraph (c), to read as follows:

§ 341.3 Definitions.

* * * * *

(c) *Bronchodilator drug.* A drug used to overcome spasms that cause narrowing of the bronchial air tubes, such as in the symptomatic treatment of the wheezing and shortness of breath of asthma.

2. By adding Subpart B, consisting at this time of § 341.16, to read as follows:

Subpart B—Active Ingredients

§ 341.16 Bronchodilator active ingredients.

The active ingredients of the product consist of any of the following when used within the dosage limits established for each ingredients:

(a) Ephedrine.
(b) Ephedrine hydrochloride.
(c) Ephedrine sulfate.
(d) Epinephrine.
(e) Epinephrine bitartrate.
(f) Epinephrine hydrochloride (racemic).
(g) Metaproterenol sulfate.
(h) Racephedrine hydrochloride.

3. In Subpart C, new §§ 341.76 and 341.90 are added, to read as follows:

§ 341.76 Labeling of bronchodilator drug products.

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

(b) *Indications.* (1) The labeling of the product contains the following statement under the heading "Indications": "For temporary relief of shortness of breath, tightness of chest, and wheezing due to bronchial asthma."

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

(i) "For the" (select one of the following: "temporary relief" or "symptomatic control") "of bronchial asthma."

(ii) "Eases breathing for asthma patients" (which may be followed by: "by reducing spasms of bronchial muscles").

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

(1) "Do not take this product unless a diagnosis of asthma has been made by a doctor."

(2) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(3) *"Drug Interaction Precaution.* Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor."

(4) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, or racephedrine hydrochloride identified in § 341.16(a), (b), (c), and (h).* (i) "Do not continue to take this product, but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse."

(ii) "Some users of this product may experience nervousness, tremor, sleeplessness, nausea, and loss of appetite. If these symptoms persist or become worse, consult your doctor."

(5) *For products containing epinephrine, epinephrine bitartrate, epinephrine hydrochloride (racemic), or metaproterenol sulfate identified in § 341.16(d), (e), (f), and (g).* (i) "Do not take this product at higher than recommended doses unless directed by a doctor. Excessive use may cause nervousness and rapid heart beat, and, possibly, adverse effects on the heart."

(ii) "Do not continue to take this product, but seek medical assistance immediately if symptoms are not relieved within 20 minutes or become worse."

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

(1) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, or racephedrine hydrochloride identified in § 341.16(a), (b), (c), and (h).* Adults: oral dosage is 12.5 to 25 milligrams every 4 hours, not to exceed 150 milligrams in 24 hours, or as directed by a doctor. Do not exceed recommended dose unless directed by a doctor. Children under 12 years of age: consult a doctor.

(2) *For product containing epinephrine, epinephrine bitartrate, and epinephrine hydrochloride (racemic) identified in § 341.16(d), (e), and (f)*—(i) *For use in a pressurized metered-dose aerosol container.* Each inhalation contains the equivalent of 0.16 to 0.25 milligram of epinephrine base.

(a) Inhalation dosage for adults and children 4 years of age and older: start with one inhalation, then wait at least 1 minute. If not relieved, use once more. Do not use again for at least 3 hours. The use of this product by children should be supervised by an adult. Children under 4 years of age: consult a doctor.

(b) The labeling must include directions for the proper use of the inhaler and for the proper care and cleaning of the mouthpiece. The directions must be clear, direct, and provide the consumer with sufficient information for the safe and effective use of the product.

(ii) *For use in a hand-held rubber bulb nebulizer.* The ingredient is used in an aqueous solution at a concentration equivalent to 1 percent epinephrine base. Inhalation dosage for adults and children 4 years of age and older: 1 to 3 inhalations not more often than every 3 hours. The use of this product by children should be supervised by an adult. Children under 4 years of age: consult a doctor.

(3) *For products containing metaproterenol sulfate identified in § 341.16(g) in a pressurized metered-dose aerosol container.* Each inhalation contains 0.65 milligram metaproterenol sulfate.

(i) Inhalation dosage for adults: start with one inhalation, then wait 2 minutes. If not relieved, inhalation can be repeated, then wait another 2 minutes. If still not relieved, inhalation can be repeated one more time. Do not use again for at least 3 hours. Do not use more than 12 inhalations in 24 hours unless directed by a doctor. Children under 12 years of age: consult a doctor.

(ii) The labeling must include directions for the proper use of the inhaler and for the proper care and cleaning of the mouthpiece. The directions must be clear, direct, and provide the consumer with sufficient information for the safe and effective use of the product.

§ 341.90 Professional labeling.

The labeling of the product provided to health professionals (but not to the general public) may contain the following additional dosage information for products containing the active ingredients identified below:

(a) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, or racephedrine hydrochloride identified in § 341.16 (a), (b), (c), and (h):* Children 6 to under 12 years of age: oral dosage is 6.25 to 12.5 milligrams every 4 hours, not to exceed 75 milligrams in 24 hours. Children 2 to under 6 years of age: oral dosage is 0.3 to 0.5 milligram per kilogram of body weight every 4 hours, not to exceed 2 milligrams per kilogram of body weight in 24 hours.

(b) [Reserved]

Interested persons may, on or before December 27, 1982, submit to the Dockets Management Branch (HFA–305,), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before February 23, 1983. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before October 26, 1983, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before December 26, 1983. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305) (address above). Received data and comments may also be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on December 26, 1983. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register** unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: July 20, 1982.

Mark Novitch,

Acting Commissioner of Food and Drugs.

Dated: September 27, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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