DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 341 and 369

[Docket No. 76N-052B]

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

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) bronchodilator drug products (drug products used in the symptomatic treatment of wheezing and shortness of breath of asthma) are generally recognized as safe and effective and not misbranded. 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 bronchodilator 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: October 2, 1987. For additional information concerning this effective date, see "Paperwork Reduction Act of 1980" appearing in the preamble of this document.

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

SUPPLEMENTARY INFORMATION: In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products, together with the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. 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 second segment, the tentative final monograph for OTC bronchodilator drug products, was published in the **Federal Register** of October 26, 1982 (47 FR 47520). Interested persons were invited to file by December 27, 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 February 23, 1983. New data could have been submitted until October 26, 1983, and comments on the new data until December 26, 1983. Final agency action occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC bronchodilator drug products.

In the **Federal Register** of August 30, 1983 (48 FR 39242), the agency published a notice reopening the administrative record for OTC bronchodilator drug products to accept comments that had been filed with the Dockets Management Branch, FDA, since the date the administrative record officially closed and to include the results of a meeting of FDA's Pulmonary-Allergy Drugs Advisory Committee held on May 13 and 14, 1983. This meeting was held to discuss the issue of OTC marketing of the bronchodilator drug metaproterenol sulfate. The administrative record was also reopened for the filing of additional comments on the OTC marketing of metaproterenol sulfate metered-dose inhaler products. Interested persons were invited to submit comments on the OTC marketing of metaproterenol sulfate on or before October 31, 1983. Data and information received after the administrative record was reopened are on display in the Dockets Management Branch.

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 OTC bronchodilator drug products occurs with the publication of this document, which establishes §§ 341.1, 341.3, 341.16, 341.76, and 341.90 for OTC bronchodilator drug products in new Part 341 (21 CFR Part 341).

The OTC 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 bronchodilator drug products (47 FR 47520), 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 Register.** Therefore, on or after October 2, 1987, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In response to the proposed rule on OTC bronchodilator drug products, 4 drug manufacturers, 275 health professionals, 7 health care professional societies, 1 citizen's group, and 3 private individuals submitted comments. A request for oral hearing before the

Commissioner was also received on one issue. 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 objections, requests for oral hearings, and the changes in the procedural regulations.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notices 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.

I. The Agency's Conclusions on the Comments

A. General Comment on Bronchodilator Drug Products

1. Several comments from health care professionals and one comment from a health care professional society objected to the OTC marketing of any drug product for the treatment of asthma. These comments generally expressed the opinion that self-diagnosis and self-treatment of asthma can lead to serious clinical consequences and that this condition should be treated only under the supervision of a physician. One comment noted "the potential for rebound phenomenon in regard to the bronchospasm with overuse of the [bronchodilator] inhalers" and stated that "with judicial use [of bronchodilators] involving medical care and patient education, this potential is still present, but minimized." One comment contended that if the safety of a drug were the sole requirement for OTC status, many current prescription drugs could qualify. Another comment stated that the asthmatic episode may result in an impairment of respiratory functions ranging from a moderate degree of disability to life-threatening asphyxiation. One comment agreed that OTC bronchodilator drug products should be available to asthmatics who have been diagnosed by a physician.

The Panel reviewed the available data for OTC bronchodilator drug products and was aware of the risks associated with the self-diagnosis and self-treatment of asthma. The Panel concluded that it is reasonable to have bronchodilators available on a nonprescription basis and that, when taken as directed, the drugs are safe for OTC use (41 FR 38320). The Panel recommended that bronchodilator drug products be available OTC with appropriate labeling, and in the tentative final monograph the agency concurred in this recommendation.

Bronchodilator drug products have been available OTC and used extensively for many years. The agency concludes that the benefits of the continued OTC availability of these drug products outweigh the risks mentioned by the comments. OTC availability of bronchodilator drug products provides asthmatics ready access to this essential medication without the need for additional visits to a physician's office or to a hospital emergency room. This availability especially benefits those asthmatics whose attacks are triggered by common environmental factors (e.g., primarily by exertion, anxiety, exposure to cold, etc.) when immediate use may be essential. In addition, physician-diagnosed asthmatics who do not have easy access to medical care will continue to benefit from OTC use.

For many years, asthmatics have safely and effectively used OTC drug products containing ingredients included in this final monograph. However, in order to minimize inappropriate use of these products by consumers who may be tempted to self-diagnose and self-treat asthma, the Panel recommended and the agency is requiring in this final regulation a warning on the products that they should not be used unless a diagnosis of asthma has been made by a doctor. In addition, the agency has added a new warning in this final monograph to limit the use of OTC bronchodilators by asthmatics who have been hospitalized for asthma or who are taking a prescription drug product for asthma. This new warning is intended to alert patients with active, serious asthma that they should not rely solely on an OTC bronchodilator without consulting a physician. (See comment 15 below.)

The agency is requiring in this final monograph appropriate warnings to provide for the proper use of OTC bronchodilators. First, persons with heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland are informed not to use the drug unless directed by a doctor. Second, persons who are taking a prescription drug for high blood pressure or depression are informed not to use the drug without first consulting their doctor. Third, the labeling for each specific active ingredient includes a warning not to continue use of the drug, but to seek medical assistance immediately, if symptoms are not relieved within the time interval specified for that ingredient or if the symptoms become worse. Finally, the labeling also describes side effects that may occur and advises the consumer to consult a doctor if these effects persist or become worse. The agency concludes that this labeling will provide adequate information to asthmatics to provide for the safe and effective use of OTC bronchodilator drug products.

B. Comments on the Switch of Prescription Bronchodilators to OTC Status

2. Numerous comments objected to FDA's decision to initiate a prescription to OTC switch of metaproterenol sulfate in a metered-dose inhaler without prior consultation with experts outside of FDA. The comments stated that the agency's intention to switch metaproterenol sulfate from prescription to OTC use was first announced in the **Federal Register** of October 26, 1982 (47 FR 47524) and contended that the agency should have obtained input in advance from FDA's Pulmonary-Allergy Drugs Advisory Committee and other health professionals directly involved in the management of asthma. According to the comments, if such experts had been consulted, the agency would have obtained a broad spectrum of expert opinion concerning the safety of metaproterenol sulfate for use as an OTC drug. One comment added that, although the switch was announced in the **Federal Register,** few physicians who treat asthma read this publication. One comment also asked for assurance that a similar lapse in the advisory review process not occur in the future.

Although the agency publishes notices in the **Federal Register,** it is concerned, as pointed out by one comment, that physicians may not be aware of the **Federal Register** publications, and therefore cannot provide comment on various drug decisions contained in the **Federal Register.** The agency believes that the dissemination of information published in the **Federal Register** is of the utmost importance. Some of the methods FDA uses to disseminate such information are by the use of press releases, which are provided by FDA to the news media, and the FDA Drug Bulletin, which contains information regarding new drug developments, changes in labeling, etc., and is sent to physicians and other health professionals. In addition, FDA routinely mails information to professional

organizations and societies, which then can be instrumental in disseminating information to their members.

As stated in the tentative final monograph on OTC bronchodilator drug products (47 FR 47524), the proposal to switch metaproterenol in a metered-dose inhaler to OTC status was based on the agency's review of the published literature on metaproterenol sulfate's safe and effective use as a prescription drug and on the 9 years of safe use of the product as demonstrated by a review of adverse reaction experiences reported to the agency. It is true that metaproterenol was not reviewed by the Cough-Cold Panel and, therefore, there was no public announcement that the drug was being considered for OTC use. However, following publication of the tentative final monograph that allowed OTC marketing of metaproterenol, there was a 60-day comment period during which interested persons could comment on the proposed regulation. Eight comments were received during the comment period, but only four concerned metaproterenol; three favored and one opposed OTC status for metaproterenol. After one company began OTC marketing of metaproterenol in January 1983, considerable criticism was voiced by the medical community, particularly allergists and pediatricians. The main concern stressed by the comments opposing OTC use of metaproterenol was the drug's potential for misuse by both adults and children and the lack of sufficient input from the medical-scientific community before metaproterenol was allowed to be marketed OTC.

Because of this controversy, a special meeting of FDA's standing Pulmonary-Allergy Drugs Advisory Committee was convened on May 13 and 14, 1983. The meeting was called in order to provide a public forum for discussion of the marketing status of metaproterenol in a metered-dose inhaler. Formal presentations were made by individuals as well as professional organizations. During the actual Committee deliberations, the complexity of the issue was apparent. In voting to recommend that the FDA rescind its proposal to make metaproterenol an OTC drug, the Committee did not reach a clear consensus but ultimately voted four to three in favor of recommending to FDA that the drug be restricted to prescription status. The Committee also felt that this issue merited further discussion.

In May 1983, the only U.S. manufacturer of metaproterenol sulfate in metered-dose inhalers stopped marketing the drug OTC pending FDA's review of this matter and, on June 3, 1983, the agency published a notice in the **Federal Register** (48 FR 24925) advising that metaproterenol could be marketed only as a prescription drug until a final decision is made by the agency either under this OTC drug review rulemaking or under the established regulations for exempting prescription drugs in 21 CFR 310.200. At this time, the agency advises in this final rule that metaproterenol is a nonmonograph ingredient and may not be marketed as an OTC drug unless it is the subject of an approved application for OTC use or is eventually included at a later date in the final monograph. (See comment 3 below.)

Given the public response to the agency's decision to switch metaproterenol from prescription to OTC use, the agency agrees that in this particular situation it would have been preferable to have involved the Pulmonary-Allergy Drugs Advisory Committee in the decision-making process leading to the OTC marketing of metaproterenol. However, it is important to emphasize that the agency does not believe that all decisions it makes about drugs require the prior involvement of an advisory committee or the use of notice-and-comment rulemaking procedures. This issue was extensively discussed in the proposed rule-related notice in the **Federal Register** of June 3, 1983 (48 FR 24925 to 24928). That notice stated that:

> FDA has been given the statutory responsibility to make a broad range of decisions involving the suitability of drugs for use by the American public. These decisions involve the safety and effectiveness of drugs, their status as a prescription or OTC drug, the indications for their use, and other vital labeling information. In general, these decisions are made without rulemaking. Moreover, although many important decisions affecting drug approval are made with the assistance of advisory committees, many are not. FDA's advisory committees cannot, as a practical matter, be involved in all important decisions affecting drug approval or drug use. Even if they could be, it would be inappropriate for FDA to refrain in all cases from exercising its statutory responsibility to regulate drugs and their uses unless and until an advisory committee approved the agency's intended actions. Congress has given the duty of approving drugs to FDA, not to advisory committees. The agency believes that advisory committees are an important adjunct to its decision-making, but it does not believe that advisory committees should be viewed as an indispensable part of all FDA procedures for regulating drugs. Less than a decade ago, a Congressional subcommittee strongly criticized FDA for relying too often and too heavily on advisory committees in deciding important drug issues. Although FDA believes that that criticism was misplaced given the factual background against which it was made, the subcommittee's underlying point is valid; FDA is responsible for making decisions about drugs, and the agency must therefore exercise restraint in the extent to which it uses advisory committees to improve its decision-making process, making sure that committee advice supplements FDA's expertise without displacing the agency's authority.

Because of the ongoing controversy regarding possible OTC status for beta-adrenergic bronchodilator drug products in metered-dose inhalers, and based on the Advisory Committee's previous recommendation that this issue merited further discussion, the agency held an open public meeting of its Pulmonary-Allergy Drugs Advisory Committee on May 19, 1986 to discuss the possible OTC marketing of current prescription beta adrenergic drug products in metered dose inhalers. The following professional groups opposed switching from prescription to OTC status for these drug products and submitted comments for the Committee's consideration: the American Academy of Allergy and Immunology, the American Thoracic Society, the American Academy of Pediatrics, and the American Society of Hospital Pharmacists (Refs. 1 through 4). The American Academy of Allergists also opposed switching these drugs to OTC status and presented its statement at the Committee's meeting (Ref. 5). A comment from the American Pharmaceutical Association (Ref. 6) supported OTC status for these beta adrenergic drugs in metered-dose inhalers if these drugs are required to be dispensed by pharmacists. At the May 19th meeting, the Committee discussed the role of physicians, drug companies, and pharmacists in providing adequate patient education and the role of asthma patients themselves in gaining adequate information to assure the proper use of inhaled beta adrenergic drug products. The Committee considered the importance of physician monitoring of the use of beta adrenergic metered-dose inhalers by asthmatic patients. The Committee members felt that such monitoring was essential because asthmatic patients represent a broad spectrum of severity of disease, and the Committee expressed the opinion that OTC availability of inhaled beta adrenergic drug products would be detrimental to physician monitoring of the use of these drug products. The Committee commented on recently published data concerning the lack of patient compliance with the physician's directions for use of aerosolized

medications and concluded that insufficient data were available describing the success of physician monitoring of patient compliance in the use of these drugs to evaluate approving OTC availability of current prescription beta adrenergics in metered-dose inhalers. The importance of educational programs to improve patient care was discussed at length and the drug companies that gave presentations to the Committee emphasized their continued commitment to developing such programs whether these drugs remain prescription drugs or become available OTC. The Committee concluded that the available data did not provide support for OTC availability of prescription beta adrenergic drugs in metered-dose inhalers at this time.

References

(1) Comment No. C00005, Docket No. 86N-0063, Dockets Management Branch.

(2) Comment No. C00007, Docket No. 86N-0063, Dockets Management Branch.

(3) Comment No. C00019, Docket No. 86N-0063, Dockets Management Branch.

(4) Comment No. C00018, Docket No. 86N-0063, Dockets Management Branch.

(5) Transcripts of the May 19, 1986, Meeting of the FDA Pulmonary-Allergy Drugs Advisory Committee, Dockets Management Branch.

(6) Comment No. C00002, Docket No. 86N-0063, Dockets Management Branch.

3. Many comments, mostly from health care professionals and health care professional societies, objected to the agency's proposal that metaproterenol sulfate in metered-dose inhalers be switched from prescription to OTC status because of the following major concerns: this drug in the inhaler dosage form has abuse and misuse potential, particularly in teenagers; possible drug interactions between metaproterenol sulfate and theophylline could cause adverse reactions such as arrhythmia and myocardial toxicity; in the 1960's the United Kingdom and Australia experienced deaths that were associated with OTC availability of beta agonists such as metaproterenol sulfate in aerosol dosage forms (Refs. 1 and 2); the physician will lose the ability to closely supervise the care of asthmatic patients and to properly instruct the patient in the use of the inhaler; OTC availability may cause delay in the emergency treatment of a serious life-threatening asthmatic attack because metaproterenol is an effective long-lasting drug; it is inappropriate to "prescribe" via advertising directed towards asthmatics; the proposed OTC warnings regarding fatalities with metaproterenol sulfate inhaler drug products are not comparable to the warnings required for prescription drug products; the potential for the development of patient tolerance of beta agonists with increased use of metaproterenol sulfate due to the OTC status of the drug could result in the eventual lack of drug effect; and there may be a decrease in the effectiveness of inhaled bronchodilators when viral respiratory tract infections, allergic reactions, or other stimuli result in an inflammatory component to airways obstruction.

Several comments urged the agency to require safety studies, particularly in children, prior to the OTC release of metaproterenol sulfate in metered-dose inhalers. Two comments from a health care professional society urged the agency to monitor possible misuse and abuse of metaproterenol sulfate inhalers as well as adverse reactions once this drug is switched to OTC status. A comment from another health care professional society urged the agency to reverse its decision to allow OTC marketing of metaproterenol sulfate in metered-dose inhalers until the medical and scientific community could study further the possibility of switching this drug to OTC status.

However, several comments supported OTC status for metaproterenol sulfate in metered-dose inhalers. These comments expressed confidence in the ability of asthmatics to understand and heed label warnings and directions. One comment contended that maintaining drug products on prescription status does not endow the products with increased safety and argued that OTC status for metaproterenol would provide savings in medical costs. The comment stated that the OTC availability of metaproterenol sulfate in metered-dose inhalers would benefit mild asthmatics, especially those in isolated areas or inner cities where medical care is not easily available, and that the hazards of overuse of the drug are exaggerated. Other comments contended that metaproterenol sulfate in metered-dose inhalers is safer than currently available OTC inhalers.

One comment rebutted several of the concerns raised by comments opposing OTC status for metaproterenol sulfate. The comment submitted statements by experts who argued that there is no factual basis to the claim that OTC sales of metaproterenol sulfate in metered-dose inhalers were associated with asthma deaths in the United Kingdom or Australia (Ref. 3). The comment submitted a review of the pharmacologic literature on metaproterenol, of data collected by the Drug Abuse Warning Network of the National Institute on Drug Abuse, of FDA adverse reaction reports, and of information compiled by the FDA's Poisoning Surveillance and Epidemiology Branch (Ref. 3). Based on its review of the above data, the comment concluded that there is no significant potential for abuse or misuse of metaproterenol sulfate inhalers.

Another comment submitted a "consumer information booklet" designed to enhance the consumers' understanding of asthma, how to control attacks, and how to use medication properly. The booklet describes asthma, several situations that can precipitate an asthma attack, the symptoms of an asthma attack, the steps asthmatics should take when they have an asthma attack, and how to properly use the inhaler containing the medication. The booklet emphasizes the need for the diagnosis of asthma by a physician and the importance of continued supervision of the treatment of asthma by a physician. The booklet also states that "asthma is a serious condition. You should work closely with your doctor and take any needed medications regularly. Call your doctor immediately or go to the hospital if you are unable to control an attack in its early stages." The comment contended that the booklet addresses many of the concerns raised in opposition to the switch of metaproterenol sulfate metered-dose inhalers to OTC status and that "such labeling could be considered a viable approach to alleviating the concerns of the medical community when the issue of metaproterenol sulfate aerosols and OTC status is considered again."

One comment supported OTC status of this drug if it is dispensed in consultation with a pharmacist because patients must be clearly and strongly warned that chronic use of sympathomimetic bronchodilators may lead to a decrease in the effectiveness of these drugs. However, this comment also stated that if provisions for dispensing metaproterenol OTC only in consultation with a pharmacist could not be required under current regulations, it would support OTC status for the drug anyway. Another comment supported OTC status of this drug only if it is dispensed in consultation with a pharmacist. This comment stated that "pharmacy students receive many, many hours of training concerned with drug consultation to patients."

As noted above, on June 3, 1983, the agency clarified the marketing status of metaproterenol sulfate in metered-dose inhalers in a **Federal Register** notice. The agency stated that the drug may not be marketed OTC until a final decision is made by the agency either under the OTC drug review rulemaking or under

the provisions of 21 CFR 310.200. The agency also stated that since the proposal to switch metaproterenol sulfate in metered-dose inhalers to OTC status, "the agency has evaluated the critical comments made in response to the OTC marketing of [this drug] and the data and arguments presented at the May 13, 1983 [Pulmonary-Allergy Drugs], advisory committee meeting. Despite the advisory committee's vote [to return metaproterenol to prescription status], FDA continues to believe that a careful weighing of risks and benefits supports the proposal that metaproterenol sulfate metered-dose inhaler should be made available without a prescription."

In the **Federal Register** of August 30, 1983 (48 FR 39242), the agency reopened the administrative record for OTC bronchodilator drug products to accept additional comments made after the closing of the record on December 27, 1982. The additional comment period ended October 31, 1983. Comments submitted in the additional comment period after the agency reopened the administrative record did not provide any additional data in support of restricting this drug product to prescription status. Although the comment period has closed, the agency continues to receive letters both for and against the OTC status of this drug. Copies of these letters have been included in this docket. As discussed in comment 3 above, the agency received additional comments concerning OTC availability of beta adrenergic drugs, such as metaproterenol, in metered-dose inhalers that are included in Docket No. 86N-0063, Dockets Management Branch, and held an open public meeting of its Pulmonary-Allergy Drugs Advisory Committee to discuss the general issue of OTC marketing of beta-adrenergic bronchodilator drug products in metered-dose inhalers on May 19, 1986.

The agency recognizes that at this time controversy remains in the medical and scientific community concerning the switch of metaproterenol sulfate in metered-dose inhalers to OTC status. This was made evident by the narrow vote of the Pulmonary-Allergy Drugs Advisory Committee in 1983 to retain prescription status and the discussion of the Advisory Committee at its May 19, 1986 meeting. Under the current circumstances, the agency concludes that a metered-dose inhaler which contains metaproterenol sulfate cannot be generally recognized as safe and effective at this time. Therefore, this drug is not being included in this final monograph. However, it should be noted that the present nonmonograph status of the drug would not necessarily preclude FDA approval for OTC marketing under an approved application. A drug that is not generally recognized as safe and effective for OTC use may nonetheless be determined to be safe and effective under 21 U.S.C. 355 following FDA's evaluation of data submitted in support of an application for that purpose. OTC marketing under an application would provide FDA with postmarketing controls, such as adverse reaction reporting, generally not available to drugs covered by an OTC drug monograph.

References

(1) Campbell, A.H., "Mortality from Asthma and Bronchodilator Aerosols," *Medical Journal of Australia*, 1:386–291, 1976.

(2) Inman, W.H.W., and A.M. Adelstein, "Rise and Fall of Asthma Mortality in England and Wales in Relation to Use of Pressurized Aerosols," *Lancet*, 2:279–285, 1969.

(3) Comment C00224, Docket No. 76N–052B, Dockets Management Branch.

(4) Transcripts of the May 13 and 14, 1983, Meeting of the FDA Pulmonary-Allergy Drugs Advisory Committee, identified as TS, Docket No. 76N–052B, Dockets Management Branch.

4. Three comments recommended that the agency consider switching metaproterenol sulfate in oral dosage forms from prescription to OTC status. One comment stated that "oral dosage forms are . . . important in the safe and effective management of bronchial asthma" and would provide alternative therapy to other currently available oral bronchodilators. Another comment contended that oral agents "should be used much more than asthma inhalers" and that oral beta agonists are safer than oral theophylline. This comment stated that "only the oral beta agonists [such as metaproterenol sulfate] should be allowed OTC." The third comment stated that oral metaproterenol sulfate is a more likely candidate for OTC dispensing than the inhaler dosage form of the drug because the oral form has "been studied sufficiently for FDA approval in children aged 6 to 12 years and [the oral form] is free of the inhaler abuse potential."

Oral dosage forms of metaproterenol sulfate have been approved for prescription use as bronchodilators since 1974 (Ref. 1). However, the agency does not believe that metaproterenol sulfate in oral dosage forms can be generally recognized as safe for OTC use. The agency notes that while both the oral and inhaled dosage forms of metaproterenol sulfate have been shown to be effective, the oral dose of 20 milligrams (mg) three to four times a day for a maximum daily dose of 80 mg for metaproterenol sulfate is approximately ten times greater than the inhaled dose of 1 to 3 inhalations containing 0.65 mg metaproterenol sulfate per inhalation, not to exceed 12 inhalations a day for a maximum daily dose of 7.8 mg. In a study comparing oral and aerosol bronchodilators in children 7 to 15 years of age, side effects such as heart discomfort, headache, and dizziness occurred more frequently with the oral dosage form of this drug than with the inhaled form (Ref. 2). In addition, a review of FDA's adverse reaction reporting system for the years 1974 to 1984 (Ref. 3) indicates that adverse reactions are reported more frequently for the oral dosage forms of metaproterenol sulfate than for the inhalation dosage forms of the drug. Specifically, these records indicate (when the only drug involved in the reported adverse reaction was either oral metaproterenol or inhaled metaproterenol) over 100 reactions reported for the oral dosage forms whereas less than 50 reactions were reported for the inhalation dosage forms. Side effects involving the heart such as palpitations, tachycardia, and hypertension accounted for over one-third of the reactions with the oral drug. Such side effects were reported five times more frequently with the oral forms of the drug than with the inhaled dosage form. Almost half of the adverse reactions with oral metaproterenol involved nervous reactions such as tremor, agitation, anxiety, and nervousness, and these reactions were three times more frequent for the oral forms of the drug than for the inhaled form. Chest pain, headache, and abdominal pain were reported for oral metaproterenol, while no reactions of pain were reported for the inhaled drug. In view of this adverse reaction information, the agency has determined that oral dosage forms of metaproterenol sulfate will not be included in this final monograph.

References

(1) Letters from J.R. Crout and M.J. Finkel, FDA, to R. Munies, Boehringer-Ingelheim, Ltd., OTC Volume 04BFM, Docket No. 76N–052B, Dockets Management Branch.

(2) Lee, H.S., "Comparison of Oral and Aerosol Adrenergic Bronchodilators in Asthma," *Journal of Pediatrics*, 99:805–807, 1981.

(3) Department of Health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listing," pertinent pages for the years 1974–1984, OTC Volume 04BFM, Docket No. 76N–052B, Dockets Management Branch.

5. One comment assumed that inhaler bronchodilator drug products that contain either albuterol sulfate or isoetharine mesylate are currently

marketed OTC and requested that these inhalers be removed from OTC status because of contraindications and potentially harmful side effects for some individuals. Another comment (in support of OTC availability of metaproterenol in aerosol dosage forms) urged the agency to consider other beta$_2$ agonists such as albuterol sulfate and terbutaline sulfate in aerosol dosage forms for OTC availability. The comment contended that "these newer drugs have extensive worldwide experience, and dose-response data support a high margin of safety." The comment added that albuterol sulfate and terbutaline sulfate have "greater specificity for beta$_2$ receptors" and a longer duration of action than metaproterenol and thus are more effective and potentially safer than metaproterenol.

The agency clarifies that albuterol, isoetharine, and terbutaline are currently available only by prescription and have never been approved for OTC use in the United States. Additionally, the agency is not aware that any of these drugs has ever been marketed OTC in this country. The Panel did not review any of these drugs as possible switches from prescription to OTC status. At the time of the Panel's deliberations, terbutaline had been approved under an application and was marketed as a prescription drug for a relatively short time in the United States. At that time albuterol was not approved for prescription use. Under the agency's Drug Efficacy Study Implementation program, drug products containing isoetharine were classified as effective bronchodilators (43 FR 30349). However, isoetharine was not considered for OTC status. The agency did not propose to switch any of these drug products to OTC status in the tentative final monograph.

Furthermore, the agency believes that general recognition of the safety of the beta $_2$ agonists albuterol and terbutaline for OTC use does not exist at this time as a result of the controversy in the medical and scientific community concerning the safety of the beta $_2$ agonist metaproterenol sulfate for OTC use. (See comment 3 above.) Therefore, albuterol and terbutaline will not be included in this final rule. However, the agency may consider changing the status of these drugs at a later time under the new drug procedures or 21 CFR 310.200.

With respect to the request to remove albuterol and isoetharine mesylate from OTC status, these drugs remain prescription drug products. Therefore, the comment's request is moot.

6. Several comments from health care professionals and one comment from a health care professional society assumed that the ingredient isoproterenol is currently marketed as an OTC bronchodilator and objected to OTC status for this ingredient. The comments stated that isoproterenol is an extremely dangerous medication. Some of the comments noted that this ingredient is overused and abused. The comments requested that isoproterenol be removed from the OTC marketplace.

The agency notes that isoproterenol has never been approved for OTC status nor has it been marketed OTC in the United States to the agency's knowledge. The agency has not proposed that isoproterenol be switched from prescription to OTC status. Therefore, this drug remains a prescription drug and the comments' request to remove isoproterenol from the OTC marketplace is moot.

7. One comment stated that theophylline for use as a bronchodilator should be restricted to prescription status only.

The agency agrees with the comment. Although the Panel classified theophylline preparations as safe and effective for OTC use as bronchodilators and recommended that theophylline be available OTC as a single ingredient at specified dosages (41 FR 38373 to 38374), the agency mentioned in the preamble of the advance notice of proposed rulemaking (41 FR 38313) that the Panel's decision might be subject to modification in the tentative final monograph. Following publication of the Panel's report in the **Federal Register**, the agency received additional information regarding theophylline which suggested that the safe and effective use of the drug requires careful dosage titration based on theophylline serum concentrations. The agency discussed this additional information in a notice published in the **Federal Register** of December 10, 1976 (41 FR 54032) announcing that it disagreed with the Panel's recommendation regarding OTC use of theophylline, and that theophylline should not be made available as a single ingredient in OTC drug products. This decision limited the use of theophylline as a single ingredient to prescription products only.

In the tentative final monograph for OTC bronchodilator drug products, the agency reaffirmed its dissent from the Panel's recommendations to switch theophylline as a single ingredient from prescription to OTC status, and placed theophylline in Category II for OTC use as a single ingredient (47 FR 47521). Following publication of the tentative final monograph, no comments or data were submitted in support of changing the agency's Category II decision concerning theophylline as a single ingredient. Therefore, theophylline is considered a nonmonograph ingredient and is not included in this final monograph.

The agency notes that combination drug products that contain theophylline will be discussed in the tentative final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products in a future issue of the **Federal Register**. Therefore, such combinations will not be discussed in this document.

C. Comments on Specific OTC Bronchodilator Active Ingredients

8. Three comments objected to the continued OTC availability of asthma medications containing ephedrine. One comment mentioned serious cardiac side effects associated with ephedrine and asked that FDA reconsider its position. Another comment mentioned the death of a youngster who was not receiving regular medical care and developed severe asthma which he tried to self-treat with ephedrine. The third comment speculated that, if asked, a majority of the membership of the American Academy of Allergy and Immunology would oppose the OTC availability of ephedrine.

The Cough-Cold Panel thoroughly evaluated ephedrine as an OTC bronchodilator drug product. The Panel was aware of serious side effects such as rapid heart beat and elevated blood pressure associated with the use of ephedrine. However, the Panel cited two studies in which 25 mg ephedrine (adult OTC dosage is 12.5 to 25 mg every 4 hours) was demonstrated to have little or no effect on the heart beat or blood pressure of adult asthmatics (41 FR 38370). Other side effects associated with the use of ephedrine include tenseness, nervousness, tremor, sleeplessness, loss of appetite, nausea, and difficulty in urination in older males who may have an enlarged prostate gland. However, the Panel concluded from the data available to it that ephedrine preparations are safe and effective bronchodilator drug products for OTC use in physician-diagnosed mild cases of asthma when labeled as it recommended (41 FR 38370 to 38371).

The agency agrees with the Panel and believes that the labeling proposed in the tentative final monograph in § 341.76(c) (1) through (6), and as expanded in this final monograph (see comment 1 above), adequately advises consumers not to use this drug without

consulting a physician, not to use the drug if they have certain medical conditions, and to consult a doctor when the drug does not provide relief within a specific time interval or causes side effects that persist.

The comment did not provide any details about the death of the youngster who developed severe asthma which he tried to self-treat with ephedrine. The agency points out that OTC bronchodilator drug products containing ephedrine are not labeled for use in children under 12 years of age. The directions in § 341.76(d)(1) advise that for children under 12 years a doctor should be consulted. The agency has provided a dosage schedule for children under 12 years in § 341.90, the professional labeling section of the monograph, to inform physicians of the appropriate dosages to use.

The agency concludes that with appropriate labeling ephedrine can be safely and effectively used as an OTC bronchodilator drug product and is including this drug in the final monograph.

9. A number of physicians submitted comments objecting to the continued OTC availability of epinephrine as a bronchodilator drug product; some stated that epinephrine metered-dose inhalers should be removed from the market because they are a significant threat to the public health. Some of the comments stated that the OTC marketing of metaproterenol is a safer alternative and preferable to the OTC marketing of epinephrine. One comment from the American Academy of Allergy and Immunology cited epinephrine as an extremely hazardous medication and urged FDA to undertake a vigorous campaign to remove it from the OTC market once metaproterenol is approved. Several comments contended that asthmatic patients rely too heavily upon inhalers that often contain epinephrine and over-medicate themselves in the mistaken belief that if the regular dose fails to achieve the desired results, a more frequent dose will work. This approach to medication causes tolerance and dependency and often causes a patient with serious asthma to delay seeking professional treatment until it is too late. One comment pointed out that some patients tend to use inhalers as frequently as every 10 minutes to obtain further relief. Another comment maintained that patients over-medicate to the point of tachyphylaxis, i.e, decreasing response following consecutive doses at short intervals.

Several comments mentioned that serious side effects, even death, can result from the overuse of epinephrine. One comment stated that the death rate from asthma reached epidemic proportions in the United Kingdom some years ago until it was correlated with the sale of epinephrine nebulizers. The comment also maintained that epinephrine causes rebound congestion in the bronchial airways identical to the rebound congestion caused by epinephrine on the nasal mucosa. In addition, the comment voiced concern that epinephrine affects both alpha and beta receptors causing a rise in blood pressure, increased cardiac rate, and cardiac irritability. Some comments mentioned personal experiences with significant and troublesome side effects that required emergency room treatment and that were caused by the unsupervised and excessive use of epinephrine inhalers.

Three comments expressed a favorable view of OTC epinephrine inhalers. Two comments noted that there are few, if any, adverse reaction reports involving epinephrine abuse and/or overdose in the literature, adding that the paucity of adverse reaction reports is probably a result of epinephrine's weak potency as an aerosol bronchodilator. Although epinephrine may relieve cases of simple asthma, patients with more severe symptoms do not get relief and therefore are likely to seek appropriate medical care promptly. Another comment maintained that because currently available OTC bronchodilator inhalers are of sufficient potency and of an appropriately short acting nature, consumers can be trusted to use these inhalers safely.

The agency notes that similar comments were submitted following publication of the Panel's report in the **Federal Register** of September 9, 1976 (41 FR 38312). In its report, the Panel thoroughly reviewed the available literature and evaluated the risks associated with the OTC use of epinephrine (41 FR 38371 to 38372). At that time, the Panel recognized that although the wide use of epinephrine aerosols for the temporary relief of bronchospasms has been attended by few and mild side effects, a patient with a severe and worsening obstructive pulmonary disease may obtain temporary relief from an epinephrine inhaler and thus feel a false sense of security. As a result, the patient may delay seeking professional attention until the disease has reached life-threatening severity. The Panel, nevertheless, believed that the hazards associated with epinephrine use were avoidable by using low concentrations of epinephrine and by requiring proper labeling. The Panel also stated that because epinephrine stimulates both alpha and beta receptors, it would be expected to have a local constrictor effect on blood vessels in the lungs which would limit systemic absorption and toxicity of the drug (41 FR 38371 to 38372).

The Panel was fully 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 with the use of epinephrine inhalation products. As pointed out by the agency in the tentative final monograph, the Panel concluded that these data and these risks are adequately defined for epinephrine inhalation products in the labeling and do not outweigh the benefits to be derived from the OTC use of these products (47 FR 47522).

Because a number of comments to the Panel's report disagreed with the Panel's recommendation to allow the OTC marketing of epinephrine to continue, the agency, in its tentative final monograph on OTC bronchodilator drug products published in the **Federal Register** of October 26, 1982 (47 FR 47520), reevaluated the risks associated with the OTC availability of epinephrine. The agency concluded that epinephrine, epinephrine bitartrate, and epinephrine hydrochloride (racemic) (since renamed racepinephrine hydrochloride) in pressurized metered-dose inhalation aerosol dosage forms can be generally recognized as safe and effective for OTC use 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 mg epinephrine per inhalation not more often than every 3 hours. The agency concluded that the proposed dose provides an adequate margin of safety for the OTC marketing of epinephrine or equivalent in a metered-dose aerosol inhalation dosage form.

The agency finds that none of the comments submitted to the tentative final monograph provide additional data that could persuade the agency to limit epinephrine inhalation products to prescription use only. The Panel and the agency acknowledge that asthma requires professional diagnosis and management and concludes that a warning statement not to use the product unless a diagnosis of asthma has been made by a physician is adequate.

Regarding the comment on the relationship between the use of the drug and a rise in the death rate from asthma in the United Kingdom several years ago, the Panel reviewed and discussed this matter in its report (41 FR 38371 to

38372). The Panel and the agency note that the question arose because of an increase in the number of deaths among those using a chemically related drug, isoproterenol. Reports of an increase in deaths from isoproterenol had their origin in England. Epinephrine aerosol had been marketed for many years before its safety was seriously questioned by the incidence of side effects and deaths in England. The Panel stated that the preparation used in England had a concentration of isoproterenol five times greater than that used in Sweden, Australia, and the United States where no such increase in deaths had been noted. It was inferred that the high concentration of isoproterenol accounted for the increase in deaths. Deaths decreased when a lower concentration of isoproterenol was used.

The agency notes that the labeling proposed in the tentative final monograph and as expanded in this final monograph (see comment 1 above) adequately warns the consumer against initial self-diagnosis of asthma and against abuse and excessive use of bronchodilator drug products. The agency shares the concern voiced by the comments regarding the possibly serious consequences that could develop from the excessive use of epinephrine drug products. Therefore, the agency is requiring that the first sentence of the warning in § 341.76(c)(6)(i) and the warning contained in § 341.76(c)(6)(ii) appear on the label of the marketed product in boldface type. (See comment 11 below.)

Based on the Panel's recommendations and an OTC marketing history of many years under approved applications, the agency concludes that, with this expanded and revised labeling of the drug product, the continued OTC availability of epinephrine benefits the consumer and is not a safety hazard. Therefore, in this final monograph, the agency is including epinephrine, epinephrine bitartrate, and racepinephrine as bronchodilator active ingredients.

Regarding the comments' remarks concerning the OTC marketing of metaproterenol sulfate as a safe and preferable alternative to epinephrine, the agency notes that because many specialists in the field have serious reservations about the OTC availability of metaproterenol sulfate, it is not being given monograph status at this time. (See comment 3 above.)

D. Comments on Dosages for OTC Bronchodilators

10. One comment agreed that bronchodilators in metered-dose inhaler dosage forms should be available OTC. However, the comment objected to allowing drug products with such dosage delivery systems to enter the marketplace without FDA preclearance through approval of applications. The comment contended that the complexities of pressurized metered-dose aerosol dosage forms for inhalation are such that agency preclearance is necessary to assure the safety and effectiveness of these drug products. The comment stated that the proposed rulemaking is deficient because it does not discuss the complexities of the design, control, manufacture, and market use of metered-dose inhalation dosage delivery systems, nor does the tentative final monograph set forth manufacturing standards for metered-dose inhaler delivery systems.

The comment noted that some of the factors that influence the safety, effectiveness, and bioavailability of aerosolized bronchodilator drugs are the geometric pattern and propulsive force of the aerosol spray, the maintenance of a proper seal for the metering valve container closure, the maintenance of a constant accurate dose from the first dose delivered to the last dose delivered from a container, inactive ingredients in the products such as propellents, and the size of the aerosolized droplets containing the drug (the droplets must be of an appropriate size to ensure that they reach the desired site in the lungs).

The comment noted that the agency considers timed-release dosage forms to be new drugs under 21 CFR 200.31 and claims that metered-dose inhalation drug delivery systems are of a comparable complexity as timed-release dosage forms. The comment contended that, if FDA considers timed-release dosage forms new drugs, metered-dose inhalation dosage forms should also be new drugs and suggested that they be handled under the provisions of 21 CFR 330.11 as "NDA deviations" from OTC drug monographs. The comment explained that a full new drug application (NDA) would not be required, but that preclearance of "manufacturing controls information and bioavailability data" by the agency would be required. The comment argued that such a preclearance process is necessary to assure that metered-dose inhalation dosage forms are safe and effective. The comment included a copy of an oral presentation concerning "dosage reproducibility of inhalation metering aerosol drug dose delivery systems" (Ref. 1) in support of the position that the complexity of these dosage forms requires preclearance under NDA's. The comment noted that FDA has required preclearance of products marketed in this dosage form as new drugs for many years and questioned the sudden change in policy and what protection the agency was providing consumers to ensure that these drug products would be formulated as safe and effective. The comment requested a public hearing before the Commissioner if FDA does not require in the final monograph premarket approval of these products through a NDA.

For the reasons discussed below, the agency disagrees with the comment and believes that the state of the technology for metered-dose inhalation drug delivery systems is such that bronchodilator drug products in metered-dose inhalers in dosage ranges specified in the monograph can be generally recognized as safe and effective. As with all OTC drug products covered by monographs, it is the responsibility of the manufacturer to ensure that the products meet the standards set forth in the appropriate drug monograph and that the product design provides an appropriate effective dose. The agency believes that requirements in the Current Good Manufacturing Practice regulations (21 CFR Part 211) adequately address the control of the quality of drug product containers, components, and the drug product itself and that specific requirements for metered-dose inhalation drug delivery systems in the monograph are unnecessary. Specifically, § 211.160 states that:

(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(1) Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. . . .

In addition, § 211.165 states that:

(a) For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. . . .

* * * * *

(d) Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical

quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.

(e) The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. . . .

In addition, by regulation (21 CFR 330.1(e)), a product may contain only suitable inactive ingredients which are safe and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity.

The agency has reviewed data from its Drug Product Problem Reporting System computerized data base for all bronchodilator drug products in metered-dose inhaler dosage forms including prescription drug products as well as OTC drug products (Ref. 2). A total of 27 product problems have been reported for metered-dose inhalers marketed OTC between 1973 and 1984. Over 17 million units of metered-dose inhalers containing epinephrine have been marketed after 1980. No problems related to the metered-dose mechanisms have been reported for these OTC drug products since 1980. During the period 1982 through 1984, 71 product problems possibly related to the metered-dose mechanism or the product closure have been reported for prescription metered-dose inhalers. Approximately twenty of these reports concern leaking of the product around the closure or the seal of the product. Five complaints concerned clogging of the inhaler even though the patient had cleaned the inhaler properly. Defective mouthpieces were reported several times. Two complaints stated that the product sprayed continuously after releasing the mechanism used to deliver a dose, another complaint stated that the inhaler sprayed too much, a few complained that the product did not aerosolize properly, and one complained that the dose was too strong. Several reports stated that the inhaler would not spray at all, while one report stated that the inhaler would not spray at first and then when it did spray there was no drug effect. Another complaint contended that the inhaler did not work because the propellant had leaked. Approximately twenty reports complained that the inhaler either did not work after only part of the medication had been delivered or that the product delivered fewer doses than the labeling indicated it should deliver. Several of these reports questioned whether the inhaler was giving the proper dose. In four cases, the reports complained that the dose was too low or the product had low potency. One report stated that the inhaler worked intermittently and another report stated that the product "backfires" after it is half used. One report complained that the propellant or other ingredient was bad, another report said that the product was defective, and a third report stated that the actuator did not work.

The agency believes that the relatively small number of product problems reported since 1982 for prescription drug products in metered-dose inhalers and the lack of any such reports related to the metered-dose mechanism for OTC inhalers indicates that the current state of the technology available to produce reliable metered-dose inhaler mechanisms allows the agency to generally recognize metered-dose inhaler dosage forms for OTC bronchodilators containing epinephrine preparations as specified in the monograph. The agency therefore believes that the concerns raised by the comment are adequately addressed under the Current Good Manufacturing Practice regulations (21 CFR Part 211) and that requiring application approval for such drug products is no longer necessary unless the product contains a chlorofluorocarbon as a propellant.

Agency regulations in 21 CFR 2.125(d) state that the use of a chlorofluorocarbon as a propellant in a self-pressurized container of a drug product will not result in the drug product being adulterated and/or misbranded provided the drug has an approved NDA. Therefore, OTC bronchodilator drug products in metered-dose inhalers that contain a chlorofluorocarbon as a propellant may be marketed only under an approved NDA.

The agency notes that the Panel recommended that 1 to 3 inhalations of a 1-percent solution of epinephrine be generally recognized as safe and effective as an OTC bronchodilator and the agency concurred in the tentative final monograph (47 FR 47522). Such solutions are used in hand-held rubber bulb nebulizers for oral inhalation in much the same manner as metered-dose inhalers are used. The precise dose of epinephrine delivered with a hand-held rubber bulb nebulizer is variable and the reproducibility of factors such as the pattern of the spray and the size of the aerosolized droplets are also variable. In addition, the agency has provided a three-fold dosage range, i.e., a range of 0.16 to 0.5 mg, for epinephrine in metered-dose inhalers of one to two inhalations containing the equivalent of 0.16 to 0.25 mg of epinephrine per inhalation.

In view of the general recognition and current use of 1 percent epinephrine in hand-held rubber bulb nebulizers with their recognized variables, the lack of significant reports of problems with currently marketed bronchodilator drug products in metered-dose inhalers, and the requirements of 21 CFR Part 211 and 21 CFR 330.1(e), the agency disagrees with the comment that preclearance of bronchodilators such as epinephrine in metered-dose inhalers is necessary or that specific manufacturing standards for metered-dose inhalers be included in the monograph for OTC bronchodilator drug products. Because concerns regarding variability and reproducibility of precise doses of epinephrine are not critical to the general recognition of this drug as safe and effective for use in inhalation dosage forms, the Commissioner concludes that a hearing on this issue is not warranted.

References

(1) Comment No. C00002, Docket No. 76N–052B, Dockets Management Branch.

(2) Department of Health and Human Services, Food and Drug Administration, "Drug Product Problem Reporting System: Products Searched for: All Aerosols for Inhalation," pertinent pages for the years 1971–1984, OTC Volume 04BFM, Docket No. 76N–052B, Dockets Management Branch.

11. Several comments were received from physicians expressing views that inhaled bronchodilators should not be available as OTC drug products. The comments expressed concern over the potential for overuse and abuse of metered-dose aerosols for asthmatic patients. One comment was concerned about the "problem patient who has free access to inhaled bronchodilators and uses more and more of the medication with less and less beneficial effect and more and more side effect." Another comment stated that "past problems (morbidity and mortality) seem to be related to repeated use of inhaled medications thus delaying more vigorous treatment. What safeguards are being initiated to lessen rather than increase this problem?" The comments felt strongly that these kinds of medications should be available by prescription only, to ensure satisfactory monitoring of patient response to prevent unnecessary tragedies. One comment suggested that more investigative research should be conducted "into the overuse and/or poor treatment results" from any OTC aerosolized bronchodilators when used as the sole treatment for bronchospasm. Another comment agreed with the agency's decision that OTC medication

should be available to asthmatics and noted that there is considerable evidence documenting the effectiveness of therapeutic sprays and aerosols in a wide variety of allergic and respiratory disorders including asthma.

The agency responded in the tentative final monograph to similar comments which disagreed with the Panel's recommendation to allow the OTC marketing of epinephrine inhalation products for the treatment of asthma. Those comments recommended that the FDA require these products to be dispensed only by prescription (47 FR 47522). The comments expressed similar objections to the self-treatment of asthma with OTC inhalation drug products, specifically products containing epinephrine. As the agency stated in the tentative final monograph, the Panel was well aware of the abuse potential and the possible adverse effects that may occur with the use of inhalation products, but felt the risks involved do not outweigh the benefits to be derived from the OTC use of these products. (See comment 1 above.)

The agency concurred with the Panel's recommendation that asthma requires a professional diagnosis and recommended the following warning for all bronchodilators in § 341.76(c)(1) of the tentative final monograph: "Do not take this product unless a diagnosis of asthma has been made by a doctor." The agency recognizes that once a diagnosis of asthma has been made, physicians may prescribe medication in oral dosage forms and recommend the use of an aerosol bronchodilator as needed, depending upon the patient's condition. The agency acknowledges that inhaled OTC bronchodilators are not necessarily appropriate for use as the sole treatment for bronchospasm and that the use of other dosage forms in conjunction with them may be indicated. Decisions regarding the appropriate dosage forms for a particular patient should be made by the patient and the physician. However, it is reasonable to have bronchodilator aerosols available OTC so that relief may be obtained quickly when necessary without the need to obtain a physician's prescription.

The agency believes that the warning statements and the directions for use required on the label adequately inform a consumer about the dangers of overusing an aerosol bronchodilator. For instance, § 341.76(c)(6)(i) of this final monograph states: "Do not use this product more frequently or at higher doses than recommended unless directed by a doctor. Excessive use may cause nervousness and rapid heart beat, and, possibly, adverse effects on the heart." The agency has added the words "more frequently" to the first sentence of this warning and slightly revised the statement for clarity. The agency has also determined that the first sentence of this warning shall be required to appear in bold print to further emphasize to consumers not to overuse this type of product. The directions instruct the consumer to start with one inhalation, then to wait at least 1 minute. If not relieved, to use once more and not to use again for at least 3 hours. The agency emphasizes that, unless directed by a physician, the use of OTC inhaled bronchodilators is not recommended for use by patients who have been diagnosed as having severe asthma. As an added safeguard, the agency is including in this final monograph an additional warning statement that alerts patients who have active, serious asthma, i.e., have been hospitalized for asthma or who are taking any prescription drug for asthma, against using any OTC bronchodilators unless directed to do so by a physician. (See comment 15 below.)

E. Comments on OTC Bronchodilator Labeling

12. One comment requested that the final monograph for OTC bronchodilator drug products be modified to clarify which isomer of epinephrine is to be used as a standard in determining equivalency to epinephrine base. The comment stated that the biological activity of racemic epinephrine either as epinephrine base or as epinephrine hydrochloride (racemic) (since renamed racepinephrine hydrochloride) has approximately one-half the biological activity of *l*-epinephrine. The comment cited two references to substantiate the different biological activities of the isomers of epinephrine (Refs. 1 and 2). The comment suggested that, because of the difference in biological activity between the *d* and *l* forms of epinephrine, proposed § 341.76(d)(2)(ii) should be revised to clarify that the concentration of epinephrine for use in a hand-held rubber bulb nebulizer is equivalent to 1 percent *l*-epinephrine base.

Section 502(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(e)) requires that a drug's label bears the "established name" of the drug. It is the agency's policy to use as established names those names designated in official compendia such as the United States Pharmacopeia (USP). When the tentative final monograph for OTC bronchodilator drug products was published on October 26, 1982, epinephrine was the official USP XX nomenclature for *l*-epinephrine (Ref. 3); it remains the official name for *l*-epinephrine in USP XXI (Ref. 4). The agency acknowledges the varying biological activity of the different isomers of epinephrine, but because the term "epinephrine" is the official USP terminology, it is intended to convey the same meaning as "*l*-epinephrine." Similarly, both "epinephrine" and "*l*-epinephrine" convey the same meaning as "epinephrine base." Therefore, the agency is revising the term "epinephrine base" in § 341.76(d) of the tentative final monograph to read "epinephrine" in this final monograph.

References

(1) Weiner, N., "Norepinephrine, Epinephrine, and the Sympathomimetic Amines" *in* "The Pharmacological Basis of Therapeutics," 6th Ed., Macmillan Publishing Co., New York, p. 144, 1980.

(2) Patil, P.N., J.B. La Pidus, and A. Tye, "Steric Aspects of Adrenergic Drugs," *Journal of Pharmaceutical Sciences*, 59:1205–1234, 1970.

(3) "The United States Pharmacopeia XX—The National Formulary XV," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 278–282, 1980.

(4) "The United States Pharmacopeia XXI—The National Formulary XVI," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 374–375, 1985.

13. One comment contended that the labeling indications in the tentative final monograph for metaproterenol sulfate in a metered-dose inhaler for OTC use are unnecessarily restrictive because they do not specifically include emphysema and bronchitis as conditions that can be relieved by the drug. The comment stated that the two conditions are contained in the approved prescription drug labeling for metaproterenol sulfate and that published clinical data and extensive clinical experience also support the safety and efficacy of metaproterenol sulfate for OTC use by persons with emphysema or bronchitis. The comment requested that the indications be revised to include emphysema and bronchitis as follows: "For temporary relief of shortness of breath, tightness of chest, and wheezing due to bronchial asthma, emphysema, or bronchitis." Likewise, the comment requested that the warnings for metaproterenol sulfate be revised to include the two conditions as follows: "Do not take this product unless a diagnosis of asthma, emphysema, or bronchitis has been made by a doctor."

The agency advises that the latest FDA approved labeling for metaproterenol sulfate in a metered-dose inhaler indicates the drug for use "as a bronchodilator for bronchial

asthma and for reversible bronchospasm which may occur in association with bronchitis and emphysema" (Ref. 1). The prescription drug labeling does not recommend the generalized use of metaproterenol sulfate in all cases of bronchitis and emphysema as implied by the comment. However, because metaproterenol sulfate is not included as a monograph condition in this final rule, the comment's labeling request is moot (see comment 3 above).

Reference

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

14. Many comments objecting to OTC status for metaproterenol sulfate in metered-dose inhalers stated that this drug is inappropriate for use in children under 12 years of age. Some of the comments contended that OTC status for this drug product would make the drug widely available for use in the under 12 age group even though it is not labeled for use in this age group. The comments stated that existing data are inadequate to demonstrate the safety of the drug in children under 12 years of age and that the drug has not been approved by FDA for use in this age group. Several comments stated that OTC availability of this drug product will increase abuse and misuse by children under 12 years of age. Some comments further stated that because parents cannot accurately diagnose the severity of a child's asthma attack, they would inappropriately attempt to treat a severe attack with metaproterenol sulfate inhalers, and this could result in serious consequences such as adverse reactions, delayed medical care, or even death.

One comment, posing a counter argument, noted that metaproterenol sulfate metered-dose inhalers are not labeled for use in children under 12 years of age, and stated that "there is no evidence in the available literature or any other reason to suggest that metaproterenol [metered-dose inhaler] would pose serious risks for this age group if it were made available OTC with appropriate warnings against use by children under the age of 12." The comment pointed out that, although this drug product is not approved by FDA for use in children under 12 years of age, it "is in fact widely used in younger patients without serious adverse results." The comment further stated that "the American Academy of Pediatrics, Section on Allergy and Immunology, recently recommended oral metaproterenol for infants and toddlers, and metaproterenol [metered-dose inhaler] for acute pediatric episodes in a dosage of two to three inhalations." The comment noted that oral dosage forms of metaproterenol sulfate are approved by FDA for use in children under 12 years of age and that metaproterenol metered-dose inhalers are approved for use in children under 12 years of age in the United Kingdom. The comment compared the OTC availability of metaproterenol sulfate in metered-dose inhalers, labeled with directions to consult a physician for use in children under 12 years of age, with similar OTC labeling for codeine and diphenhydramine antitussive drug products that direct the parent to consult a physician for use in children under 6 years of age. The comment pointed out that FDA dealt with the safety problems of using these drugs in younger children through appropriate labeling, and argued that such labeling would be equally effective in assuring the safe OTC use of metaproterenol inhalers.

The comment stated further that it is committed to performing additional pediatric studies, in an effort to increase scientific knowledge of the drug and to confirm the safety of the drug "in the unlikely event that a child under 12, or his parent, ignored prominent label warnings and purchased the drug for the child's use." The comment added that the research effort is not intended to secure a pediatric indication for OTC use.

In the tentative final monograph, the agency cited one study concerning the use of metaproterenol sulfate in metered-dose inhalers in children (Ref. 1). In that double-blind crossover study in a group of 10 children between the ages of 7 and 14 years, the pulse rate of each child was recorded for 60 minutes following the administration of 1.5 mg metaproterenol sulfate as an aerosol. No significant increase in pulse rates was found. Also, the authors did not note any adverse effects from this treatment. In addition, the agency is aware that this drug is widely used in children under 12 years of age as a prescription drug product. However, the labeling for the use of metaproterenol sulfate in metered-dose inhalers, as proposed in the tentative final monograph, did not include directions for use in children under 12 years of age. Instead, the labeling directed the parent to consult a physician before using the drug in this age group. The directions, warnings, and drug interaction statements for many OTC drug products instruct the consumer to seek the supervision of a physician or other health care professional under specified circumstances, particularly when using the drug in young children. The agency believes that such labeling is adequate to provide for the safe and effective use of OTC bronchodilator drug products.

Because metaproterenol sulfate in metered-dose inhalers is used widely in children under 12 years of age, the agency acknowledges and commends the commitment of one drug manufacturer to perform studies of the drug in this age group. However, because metaproterenol sulfate is not included in this final monograph, the agency will not address further the safety of this drug in children under 12 years of age in this document. (See comment 3 above.)

Reference

(1) 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.

15. One comment supporting OTC status for metaproterenol sulfate in metered-dose inhalers suggested that all OTC bronchodilators in aerosol dosage forms be labeled with additional warnings against their use (1) if the person has been hospitalized within the past several years for asthma, or (2) if the person is presently taking steroids for asthma. The comment suggested these additional warnings to ensure that patients with active, serious asthma do not purchase and rely on OTC bronchodilators without consulting a physician. The comment requested that FDA modify the tentative final monograph to include these additional warnings.

The agency agrees with the comment that patients with active, serious asthma should not rely on aerosol bronchodilator drug products unless directed by a physician, and that such patients need medical supervision by a physician. FDA's Pulmonary-Allergy Drugs Advisory Committee discussed its concerns about the use of OTC bronchodilator drug products by severe asthmatics at its meeting on May 13 and 14, 1983, concerning OTC status for metaproterenol sulfate (Ref. 1). The Advisory Committee indicated and the agency agrees that a medical history of hospitalization for asthma within the past several years and/or current use of prescription drug products such as steroids are indications that a patient may have serious active asthma (Ref. 1). The Advisory Committee believed that the use of OTC metaproterenol metered-dose inhalers should be restricted to adults who are not receiving concomitant medication, have not been

hospitalized previously for asthma, and have never received steroids for asthma. Although the Advisory Committee only discussed metaproterenol metered-dose inhalers, the agency believes that the Committee's concerns are applicable to the use of any OTC bronchodilator, whether an aerosol or other dosage form, and that additional warnings are warranted under the circumstances above.

The agency believes that the comment's suggested phrase, "hospitalized within the past several years," would be helpful to describe "active, serious" asthma. However, as the Advisory Committee discussed, people who have previously been hospitalized for asthma should not use metaproterenol metered-dose inhalers unless directed by a doctor. The agency agrees that if a person has been hospitalized for asthma there is a presumption that the condition is serious. Under these circumstances, no OTC bronchodilator drug should be used unless directed by a doctor.

In addition, the agency agrees with the comment and with the Advisory Committee that people with active, serious asthma who are taking steroids prescribed by a doctor for this condition should not use OTC bronchodilators without first consulting the doctor. The agency also believes, in view of the Advisory Committee's concerns regarding concomitant asthma medication, that patients should not take any OTC bronchodilator drug product without consulting a doctor if they are also taking a prescription drug product for asthma. Therefore, the agency is adding to the final rule the following warning for all OTC bronchodilator drug products: "Do not use this product if you have ever been hospitalized for asthma or if you are taking any prescription drug for asthma unless directed by a doctor." The agency believes that this warning statement will better alert these patients not to use the product unless directed to do so by a doctor.

Reference

(1) Transcripts of the May 13 and 14, 1983, meeting of the FDA Pulmonary-Allergy Drugs Advisory Committee, identified as TS, Docket No. 76N-052B, Dockets Management Branch.

16. One comment questioned the agency's decision to propose professional labeling in § 341.90 of the tentative final monograph. The comment suggested that this proposal establishes a new category of OTC drug products in which only the adult dose is provided and the directions for the product state that a doctor be consulted for children under 12 years of age. Thus, information about the dosage for children under 12 years may appear in the labeling of the product provided to health professionals but not to the general public. The comment agreed with the intent of the proposal, i.e., that these products are not suitable for medically unsupervised use in children; however, the comment questioned the mechanism proposed. The comment stated that "If professional labeling refers to package inserts," it is hard to envision companies preparing separate labeling for professional samples. The comment added that the wording is permissive, not mandatory, and that it is possible that dosing information for children may not be provided at all. The comment was also concerned about the possible publication of the information in publications that are available to the general public in bookstores.

The comment asked the agency to consider the following questions: "(1) Is it in anyone's interest to try to restrict information about dosage, knowing that while the regulation may be enforced, the information will still be disseminated? Does the ability to avoid the intent of the regulation promote disrespect for regulation in general? (2) Does restricting information about dosage for the general public interfere with the availability of the information to the physician?"

The comment proposed the following labeling for these drug products: "Dosage for children under 12 must be determined by your doctor. The dosage will usually be within the following ranges." The above labeling would be followed by the dosage ranges for the individual age groups. The comment felt that this would provide the correct information and warnings, allow a user's check on the doctor's instructions, and provide a written reminder of the oral directions received from the physician.

The agency defines professional labeling as information that is provided to health care professionals only and not to the general public. There are often situations in which the use of OTC drug products requires the supervision of a physician, such as the use of ephedrine preparations in asthmatic children under 12 years of age. In these situations, professional labeling provides information to the physician concerning such things as dosages or other indications for the OTC drug product. This information is generally not found in the labeling or package inserts made available to consumers or in publications such as the Physician's Desk Reference (PDR) for Nonprescription Drugs. Information in professional labeling is made available to health care professionals through literature and samples provided by representatives of the drug companies, through advertisements in professional journals, and by publication in professional books such as the PDR discussing prescription drugs. Because these are the principal methods for disseminating the information, the agency does not believe that limiting the information about dosage that is available to the general public interferes with the availability of this information to physicians.

As the comment pointed out, some professional books and journals may be obtained by consumers who then will have access to information in professional labeling. The agency cannot prevent consumers from obtaining such information. However, the agency can require sufficient information on the label of the drug product for the safe and effective use of the product on an OTC basis. For example, the agency believes that the dosage regimen for ephedrine for asthmatic children under 12 years of age requires medical supervision by a physician. Therefore, this information should be provided to physicians and is not intended to be included in the labeling provided to the consumer. The required OTC labeling directs parents who wish to give the drug to asthmatic children under 12 years to consult their physicians for information on how to give the drug. The agency believes that the regulations concerning the dosage information for ephedrine are in the best interest of the patient and does not believe that they encourage consumers to try to circumvent the intent of regulations or that they promote disrespect for regulation in general.

The agency disagrees with the comment's proposed labeling that would state that the dosage for children under 12 years of age must be determined by a doctor, followed by a dosage range for the individual age groups. Consumers may not consult a doctor concerning dosage requirements for children under 12 years if such information is provided on the label. Therefore, the agency is retaining in this final monograph, § 341.90 *Professional labeling*, which provides to health care professionals (but not to the general public) recommended dosage ranges for ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride for children under 12 years of age.

II. Summary of Significant Changes From the Proposed Rule

1. The name "Epinephrine hydrochloride (racemic)," proposed in § 341.16(f) of the tentative final monograph, was not an official or a compendial name for this drug. A compendial monograph for racepinephrine hydrochloride became official on January 1, 1986 (Ref. 1). Therefore, the name "Racepinephrine hydrochloride" is used in this final monograph for this ingredient. In addition, because the term "epinephrine" is the official terminology for the term "epinephrine base," this term has been revised to read "epinephrine" in § 341.76(d) in the monograph. (See comment 12 above.)

Reference

(1) "The United States Pharmacopeia XXI—The National Formulary XVI, Supplement 3," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 2031–2032, 1985.

2. The agency believes that metaproterenol sulfate in metered-dose inhalers cannot be generally recognized as safe and effective as an OTC bronchodilator at this time and has not included this drug in the final monograph. (See comment 3 above.)

3. The agency is not including proposed § 341.76(b)(2), *Other allowable statements,* in this final monograph but is incorporating the statements proposed in that section of the tentative final monograph in the indications section in this final monograph.

4. The agency has added a warning to § 341.76(c) against use, unless directed by a doctor, of OTC bronchodilators in asthmatics who have been hospitalized for asthma or who are taking prescription drugs for asthma. This warning helps ensure that patients with active, serious asthma do not use OTC bronchodilators except under the supervision of a physician. (See comment 15 above.)

5. To further emphasize that asthmatics should not overuse epinephrine in aerosol dosage forms, the agency has modified, for clarity, the warning in § 341.76(c)(6)(i) and is requiring that the first sentence of this warning appear on the label of the product in boldface type. This warning instructs the asthmatic not to use higher doses than recommended nor to use the product more frequently than recommended. In addition, the warning explains the possible consequences of excessive use of the product. (See comment 11 above.)

6. Because of concern that possibly serious consequences could develop from the excessive use of epinephrine drug products, the agency is also requiring that the warning in § 341.76(c)(6)(ii) appear on the label of the marketed product in boldface type. This warning instructs the asthmatic to discontinue use of the product, and to seek medical assistance if relief is not obtained in 20 minutes or if symptoms become worse. (See comment 9 above.)

7. The agency has substituted the word "use" for the word "take" in the warning statements for clarity and consistency. The word "use" is more appropriate for inhalation drug products and is also appropriate for oral dosage forms.

8. The agency has moved the portion of § 369.20 Epinephrine Inhalation 1:100 (not for injection) that warns against use of the product if it is brown in color or contains a precipitate, with minor modifications for clarity, to the bronchodilator monograph as § 341.76(c)(6)(iii). This warning is needed to ensure that an ineffective product is not used.

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

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC bronchodilator drug products are generally recognized as safe and effective and not misbranded. Specifically, the following ingredients are included in this final rule for OTC bronchodilator use: ephedrine, ephedrine hydrochloride, ephedrine sulfate, epinephrine, epinephrine bitartrate, racephedrine hydrochloride, and racepinephrine hydrochloride. All other ingredients for OTC bronchodilator use are considered nonmonograph ingredients. These include by example, but not by way of limitation, those ingredients previously considered by the Panel or the agency in the course of this rulemaking, e.g., belladonna alkaloids, euphorbia pilulifera, metaproterenol sulfate, methoxyphenamine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate, and single-ingredient theophylline preparations (theophylline, anhydrous; aminophylline; theophylline calcium salicylate; theophylline sodium glycinate). Any drug marketed for use as an OTC bronchodilator drug product that is not in conformance with the monograph (21 CFR Part 341) will be considered a new drug within the meaning of section 201(p) of the act (21 U.S.C. 321(p)) and misbranded under section 502(a) of the act (21 U.S.C. 352(a)) and may not be marketed for this use unless it is the subject of an approved NDA.

In the **Federal Register** of April 22, 1985 (50 FR 15810) the agency proposed to change its "exclusivity" policy for the labeling of OTC drug products that has existed during the course of the OTC drug review. Under that policy, the agency had maintained that the terms used in an OTC drug product's labeling were limited to those terms included in a final OTC drug monograph.

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing the exclusivity policy and establishing three alternatives for stating the indications for use in OTC drug labeling. Under the final rule, 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 required OTC drug labeling other than indications for use (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under an OTC drug monograph.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (47 FR 47520). 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 bronchodilator 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 bronchodilator 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.

Paperwork Reduction Act of 1980

In accordance with the Paperwork Reduction Act of 1980 (44 U.S.C. Chapter 35), the collection of information requirements of § 341.76(d)(2)(i)(*b*) in these regulations will be submitted for approval to the Office of Management and Budget (OMB). These requirements will not be effective until FDA obtains OMB approval. FDA will publish a notice concerning OMB approval of these requirements in the **Federal Register** prior to April 2, 1986.

The agency is removing portions of § 369.20 applicable to epinephrine in inhalation dosage forms and to oral ephedrine preparations because these portions of that regulation are superceded by the requirements of the bronchodilator final monograph (Part 341). The items being removed include the entries for "Ephedrine Preparations (oral)" and "Epinephrine Inhalation 1:100 (not for injection)" under § 369.20. As noted above, the agency has moved the portion of § 369.20 Epinephrine Inhalation 1:100 (not for injection) that warns against use of the product if it is brown in color or contains a precipitate, with minor modifications for clarity, to the bronchodilator monograph.

List of Subjects

21 CFR Part 341

Labeling, Over-the-counter drugs.

21 CFR Part 369

Labeling, Medical Devices, 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:

1. By adding new Part 341, to read as follows:

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

Subpart A—General Provisions

Subpart B—Active Ingredients

Subpart C—Labeling

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 5.11.

Subpart A—General Provisions

§ 341.1 Scope.

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

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

§ 341.3 Definitions.

As used in this part:

(a) *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.

(b) [Reserved]

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 ingredient:

(a) Ephedrine.

(b) Ephedrine hydrochloride.

(c) Ephedrine sulfate.

(d) Epinephrine.

(e) Epinephrine bitartrate.

(f) Racephedrine hydrochloride.

(g) Racepinephrine hydrochloride.

Subpart C—Labeling

§ 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.* The labeling of the product states, under the heading "Indications," the phrase listed in paragraph (b)(1) of this section. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed below, may also be used, as provided in § 330.1(c)(2), subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) "For temporary relief of shortness of breath, tightness of chest, and wheezing due to bronchial asthma."

(2) In addition to the required information identified in paragraph (b)(1) of this section, the labeling of the product may contain one or more of the following statements:

(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 use this product unless a diagnosis of asthma has been made by a doctor."

(2) "Do not use 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) "Do not use this product if you have ever been hospitalized for asthma or if you are taking any prescription drug for asthma unless directed by a doctor."

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

(5) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, or racephedrine hydrochloride identified in § 341.16 (a), (b), (c), and (f).* (i) "Do not continue to use 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."

(6) *For products containing epinephrine, epinephrine bitartrate, or racepinephrine hydrochloride identified in § 341.16 (d), (e), and (g).* (i) "Do not use this product more frequently or at higher doses than recommended unless directed by a doctor. [first sentence in boldface type] Excessive use may cause nervousness and rapid heart beat, and, possibly, adverse effects on the heart."

(ii) "Do not continue to use this product, but seek medical assistance immediately if symptoms are not relieved within 20 minutes or become worse." [sentence in boldface type]

(iii) *For products intended for use in a hand-held rubber bulb nebulizer.* "Do not use this product if it is brown in color or cloudy."

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

(*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. 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.

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

§ 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 (f).* 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].

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

2. The authority citation for 21 CFR Part 369 continues to read as follows:

Authority: Secs. 502, 503, 506, 507, 701, 52 Stat. 1050–1052 as amended, 55 Stat. 851, 59 Stat. 463 as amended, 52 Stat. 1055–1056 as amended (21 U.S.C. 352, 353, 356, 357, 371); 21 CFR 5.11.

§ 369.20 [Amended]

3. In Subpart B, § 369.20 *Drugs; recommended warning and caution statements* is amended by removing the entries for "Ephedrine Preparations (Oral)" and "Epinephrine Inhalation 1:100 (nor for injection)."

Dated: September 10, 1986.

Frank E. Young,

Commissioner of Food and Drugs.

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