

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310 and 341

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PDM

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the tentative final monograph (TFM) for over-the-counter (OTC) cough-cold combination drug products to remove the combination of an oral bronchodilator (products containing ephedrine or its salts) and an expectorant, and to reclassify this combination drug product as Category II (not generally recognized as safe and effective for OTC use). FDA is also proposing to classify the combination of an oral bronchodilator and an oral nasal decongestant as Category II. FDA is issuing this notice of proposed rulemaking after considering data and information on the appropriateness of these combination drug products to treat mild asthma. Elsewhere in this issue of the **Federal Register**, FDA is proposing to amend the final monograph (FM) for OTC bronchodilator drug products to require additional labeling for all ingredients included in the FM. These proposed rules are part of FDA's ongoing review of OTC drug products.

DATES: Submit written or electronic comments on the proposed monograph amendment and on FDA's economic impact determination by [*insert date 120 days after date of publication in the Federal Register*]. See section IX of this document for the proposed effective date of any final rule that may publish based on this proposal.

ADDRESSES: You may submit comments, identified by Docket No. 1976N-0052G by any of the following methods:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow instructions for submitting comments on the agency Web site.
- E-mail: *fdadockets@oc.fda.gov*. Include Docket No. 1976N-0052G in the subject line of your e-mail message.
- FAX: 301-827-6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions]:
Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the agency name and Docket No. 1976N-0052G. All comments received will be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For detailed instructions on submitting comments and additional information on the rulemaking process, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and/

or the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Cazemiro R. Martin or Gerald M. Rachanow, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2222.

SUPPLEMENTARY INFORMATION:

I. Background

A. Advance Notice of Proposed Rulemaking (ANPRM)

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 ANPRM to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic (cough-cold) drug products, together with the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. The Panel recommended that the combination of an oral bronchodilator and an expectorant be Category I (generally recognized as safe and effective), provided the product is labeled only for cough associated with asthma (41 FR 38312 at 38326). The Panel did not provide any additional discussion of this combination. The Panel placed the combination of an oral bronchodilator with either an analgesic-antipyretic, anticholinergic, antihistamine, or antitussive (when the product is labeled only for cough associated with asthma) ingredient in Category II (not generally recognized as safe and/or effective) (41 FR 38312 at 38326).

B. TFM

FDA concurred with the Panel in the cough-cold combinations TFM (53 FR 30522 at 30556, August 12, 1988). FDA also classified the combination of caffeine and ephedrine or pseudoephedrine in Category II (53 FR 30522 at 30557). No comments on these specific combinations were submitted in response to the TFM.

C. FM

In the **Federal Register** of October 2, 1986 (51 FR 35326), FDA issued a FM for OTC bronchodilator drug products. The oral active ingredients included in the bronchodilator monograph are ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride (§ 341.16(a), (b), (c), and (f) (21 CFR 341.16(a), (b), (c), and (f))). The OTC bronchodilator FM also includes epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride (§ 341.16(d), (e), and (g)) as active ingredients administered by “inhalation.” Because this proposed rule addresses only oral bronchodilator ingredients, it does not apply to epinephrine and its salts.

D. Proposal to Remove Ephedrine From the Bronchodilator FM

In the **Federal Register** of July 27, 1995 (60 FR 38643), FDA published a proposed rule to amend the FM for OTC bronchodilator drug products to remove the ingredients ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride and to classify those ingredients as Category II. In that proposal, FDA did not discuss the rationale of an ephedrine-guaifenesin combination product because the removal of ephedrine ingredients from the monograph would have eliminated such combination products from the market. After FDA published its 1995 proposed rule, the Drug Enforcement Administration (DEA) issued new requirements restricting the sale of

ephedrine, its salts, optical isomers, and salts of optical isomers. DEA allows continued, but restricted sales of these ephedrine drug products. In response to the changes in DEA's requirements and comments received on FDA's 1995 proposal, FDA has reconsidered its proposed action and intends to allow continued OTC marketing of single ingredient ephedrine bronchodilator drug products. Elsewhere in this issue of the **Federal Register**, FDA is proposing to amend the FM for OTC bronchodilator drug products to require additional labeling for all ingredients included in the FM.

E. Bronchodilator Combination Drug Products

In the **Federal Register** of September 27, 2001 (66 FR 49276), FDA issued a final rule establishing that cough-cold combination drug products containing any oral OTC bronchodilator active ingredient in combination with any analgesic(s) or analgesic-antipyretic(s), anticholinergic, antihistamine, oral antitussive, or stimulant active ingredient are not generally recognized as safe and effective and are misbranded for OTC use. In the **Federal Register** of December 23, 2002 (67 FR 78158), FDA issued a final rule for OTC cough-cold combination drug products. That final rule did not address the combination of an oral bronchodilator and an expectorant or the combination of an oral bronchodilator and an oral nasal decongestant. Neither combination had been previously classified. FDA indicated that these two combination products would be addressed in a future issue of the **Federal Register**. FDA is addressing these combination products in this document.

The only expectorant ingredient in the OTC cough-cold drug products monograph is guaifenesin (§ 341.18 (21 CFR 341.18)). Therefore, the only currently marketed OTC bronchodilator combination drug products contain an ephedrine component and guaifenesin.

II. FDA's Concerns About Ephedrine-Guaifenesin Combination Products

A. Asthma and Its Treatment

Asthma is a chronic lung disease caused by inflammation of the airways, resulting in episodes of airway narrowing and obstruction. Common symptoms of asthma can include wheezing, shortness of breath, tightness of the chest, difficulty breathing after exercise, and coughing. This cough is not usually productive. People with asthma generally do not require therapy with an expectorant, because increased sputum production and expectoration are not important features of asthma (Ref. 1).

The National Heart, Lung, and Blood Institute (NHLBI)/The World Health Organization (WHO) Global Initiative for Asthma (Ref. 2), the NHLBI'S National Asthma Education Prevention Program (Ref. 3), and the American Academy of Allergy Asthma and Immunology (Ref. 4), recommend pharmacological intervention to treat asthma. These organizations based this recommendation on the understanding that airway obstruction in asthma consists of bronchial smooth muscle spasm and variable degrees of airway inflammation. This inflammation is characterized by edema, mucous secretion, and the influx of a variety of inflammatory cells causing recurrent episodes of wheezing, shortness of breath, chest tightness, and coughing in susceptible individuals.

These organizations recommend pharmacological intervention with what they term as "controller" and "reliever" medications (Refs. 2, 3, and 4). Medications used to "control" asthma include what are commonly called "anti-inflammatory" agents (e.g., inhaled corticosteroids, antileukotrienes, cromones) and long-acting bronchodilators used daily on a long-term basis to lessen the severity of persistent asthma symptoms and signs. Medications used

to relieve acute symptoms of asthma include the short-acting bronchodilators (primarily inhaled). None of the controller or reliever medications in these asthma guidelines include expectorants.

B. Monograph Uses of Ephedrine and Guaifenesin

Ephedrine is a sympathomimetic drug currently labeled as a bronchodilator for OTC use. The current OTC indication is “For temporary relief of shortness of breath, tightness of chest, and wheezing due to bronchial asthma” (§ 341.76(b)(1) (21 CFR 341.76(b)(1))). The labeling of the product may also state one or both of the following uses in § 341.76(b)(2):

(i) “For the” (select one of the following: “temporary relief” or “symptomatic control”) “of bronchial asthma”, and (ii) “Eases breathing for asthma patients” (which may be followed by: “by reducing spasms of bronchial muscles”).

Guaifenesin is the only expectorant active ingredient included in the cough-cold monograph (§ 341.18). It is labeled for OTC use to “help loosen phlegm (mucus) and thin bronchial secretions to” (select one or more of the following: “rid the bronchial passageways of bothersome mucus,” “drain bronchial tubes,” and “make coughs more productive”) (§ 341.78(b) (21 CFR 341.78(b))).

In the FM for OTC expectorant drug products (54 FR 8494 at 8500, February 28, 1989), FDA stated that the effectiveness of guaifenesin in the symptomatic relief of sputum removal in asthmatics had not been demonstrated. Guaifenesin at the usual recommended dose is of doubtful value for asthma and the clinical data to support its efficacy is conflicting (Refs. 5 and 6). Moreover, in asthma, the drying of secretions along with the narrowing of the airways could potentially result in inspissated (thickened or dried) material and mucus plugs. This could then further increase airway obstruction

and lead to further breathing difficulties. FDA pointed out that appropriate treatment for the condition of inspissated secretions is hydration, bronchoscopy with lavage and suctioning combined with anti-inflammatory drugs, and bronchodilators. FDA noted that without such an approach in the treatment of asthmatics, a safety concern may exist for the use of guaifenesin in asthma.

When FDA made these statements in the expectorant section of the cough-cold drug products rulemaking in 1989, it did not change its proposed Category I categorization of a combination of an oral bronchodilator active ingredient and an expectorant active ingredient in the August 12, 1988, cough-cold combinations TFM (53 FR 30522 at 30561). Likewise, FDA did not revise its categorization of this combination in the August 12, 1988, cough-cold combinations TFM when it published its proposal in 1995 to remove ephedrine from the OTC bronchodilator FM. The removal of ephedrine ingredients from the monograph would have eliminated such combination products from the market. FDA also did not discuss this combination in the December 23, 2002, final rule for OTC cough-cold combination drug products because a decision on the status of ephedrine as an OTC bronchodilator was still pending at that time. FDA discusses the rationale and the benefits/risks of ephedrine-guaifenesin combination drug products in this document (see section II.D of this document).

C. OTC Drug Monograph Combination Policy

The policy for combination products included in OTC drug monographs in § 330.10(a)(4)(iv) states:

An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient

makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

D. Rationale and Benefit/Risk of Ephedrine-Guaifenesin Combination Products

Combination products containing ephedrine and guaifenesin can include in their labeling the indications in §§ 341.76(b) and 341.78(b) (see section II.B of this document). For example, the indications section for these combination products could read as follows:

For temporary relief of shortness of breath, tightness of chest, and wheezing due to bronchial asthma. Eases breathing for asthma patients by reducing spasms of bronchial muscles. Helps loosen phlegm (mucus) and thins bronchial secretions to rid the bronchial passageways of bothersome mucus, drain bronchial tubes, and make cough more productive.

Based on the pathogenesis of asthma, FDA considers the role of expectorants inappropriate in the routine pharmacological management of this disease. There is little evidence in the clinical literature to support the use of expectorants in asthma (Refs. 5 and 6). The use of expectorants in the treatment of asthma is also inconsistent with current asthma management guidelines (Refs. 2 through 5).

The Panel's recommendation of monograph status for the combination of an oral bronchodilator and an expectorant was made in the early 1970's. In 1995, the American Thoracic Society (ATS) discussed chronic obstructive pulmonary disease (COPD) and asthma (Ref. 9). ATS stated that in the past, asthma was generally included under the broad classification of COPD.

According to ATS, patients with unremitting asthma are classified as having COPD, while patients with asthma whose airflow obstruction is completely reversible are not considered to have COPD. ATS stated that the pharmacotherapy of COPD is similar to that of asthma. ATS indicates that the goals of therapy for COPD are to induce bronchodilation, decrease the inflammatory reaction, and facilitate expectoration. In discussing drugs affecting mucus, ATS mentioned a study of organic iodide and stated that the values of other agents have not been clearly demonstrated. Expectorants are not included in ATS's recommended pharmacologic therapy for the management of mild or mild-to-moderate COPD (Ref. 9).

FDA no longer considers the combination of an oral bronchodilator (i.e., ephedrine) and an expectorant (i.e., guaifenesin) as providing rational concurrent therapy for a significant proportion of the asthma population for whom self-treatment with OTC drugs may be appropriate (i.e., people with mild asthma). FDA also no longer believes that each active ingredient in the combination makes a contribution to the claimed effect. Asthma patients with severe asthma exacerbations and status asthmaticus may develop mucus plugging in small airways causing severe airflow limitation. Current management in these situations often requires mechanical ventilation, bronchoscopy, and/or mucolytic therapy (Refs. 7 and 8), but not the use of an expectorant. Coughing that may accompany asthma is generally treated with the use of bronchodilators (inhaled and occasionally oral) and not with an expectorant, because increased sputum production is not usually problematic in mild asthma (Ref. 1). Use of an oral bronchodilator in combination with an expectorant is not part of the recommended pharmacological management of asthma (Refs. 2, 3, and 4). FDA believes a health care provider should make

the determination whether an expectorant is needed and, in those minority of cases where it may be, then prescribe an expectorant or recommend an appropriate OTC drug product. OTC bronchodilator drug products are required to have the following warning in their labeling: “Do not use this product unless a diagnosis of asthma has been made by a doctor” (§ 341.76(c)(1)). If a health care provider determines that an oral bronchodilator and an expectorant are both needed, any small proportion of people with asthma who would use both ingredients can obtain both drug products separately.

E. DEA Restrictions on OTC Ephedrine Drug Products

FDA believes that most people who currently self-treat for mild asthma purchase and use the combination ephedrine-guaifenesin drug product primarily because it is more readily available than OTC single-ingredient ephedrine drug products. As discussed elsewhere in this issue of the **Federal Register**, DEA regulations place restrictions on the sale of single-entity OTC ephedrine drug products. These restrictions include:

- Stocking the product behind the counter where only employees have access (21 CFR 1309.71(a)(2));
- Requiring a record of the purchaser’s name and address, the quantity of drug product purchased, and the method of transaction (21 CFR 1310.06); and
- Seeing two forms of identification and obtaining a signature of the purchaser prior to completing the sale (21 CFR 1310.07(d)).

In contrast, the DEA restrictions on the sale of combination ephedrine drug products are not as stringent. Most importantly, DEA regulations currently do not require that OTC combination ephedrine drug products be stocked behind the counter (62 FR 52294, October 7, 1997). In addition, retail distributors of

combination ephedrine drug products are not required to do the following: (1) Register with the DEA (§ 1309.21 (21 CFR 1309.21)) or (2) make or keep records for certain sales (§ 1310.03 (21 CFR 1310.03)), such as:

- Sales limited to combination ephedrine drug products;
- Sales that do not exceed a single transaction amount of 24 grams of ephedrine;
- Sales that are limited almost exclusively for personal use, either directly to walk-in customers or in face-to-face transactions by direct sales; and
- Sales that are to an individual for legitimate medical use.

See 21 CFR 1300.02(b)(29) and §§ 1309.21 and 1310.03 for DEA regulations applicable to single-entity ephedrine drug products.

III. FDA's Tentative Conclusion and Proposal

A. Bronchodilator and Expectorant Combination Drug Products

FDA no longer considers ephedrine combination drug products as generally recognized as safe and effective for continued OTC availability. Based on the pathogenesis of asthma and the recommendations from various groups involved in the management of asthma (Refs. 2, 3, and 4), FDA tentatively concludes that there is currently no role for expectorants in the pharmacological management of this chronic lung disease for a significant proportion of people with mild asthma.

FDA has tentatively determined that OTC combination products containing an oral bronchodilator and an expectorant should no longer be available because they do not meet the standards for safe and effective OTC drug products. These combination products are not rational therapy for the treatment of mild asthma because the expectorant component does not contribute to the relief of the condition (see section II.D of this document) for

a significant portion of the population. Additionally, this combination is inconsistent with the combination requirements set forth in § 330.10(a)(4)(iv) because the expectorant ingredient does not make a contribution to the claimed effects. Therefore, in this proposed rule, FDA is proposing to reclassify the combination of any single oral bronchodilator active ingredient and any single expectorant active ingredient (currently listed in § 341.85(l) (21 CFR 341.85(l)) of the TFM, 53 FR 30522 at 30561) from Category I to Category II.

B. Bronchodilator and Oral Nasal Decongestant Combination Drug Products

During the rulemaking for OTC cough-cold drug products, no data or comments were submitted on the combination of an oral bronchodilator and an oral nasal decongestant active ingredient. This combination was not discussed by the Panel in its report or by FDA in the TFM or FM. FDA does not believe that this specific combination drug product is marketed OTC at this time. If such a product were marketed, the uses for this combination containing ephedrine and a nasal decongestant are found in § 341.76(b) and 21 CFR 341.80(b). Thus, the labeling would include the bronchodilator claims discussed in section II.B of this document and the claim “temporarily relieves nasal congestion.” FDA does not have data showing that people who need relief of the symptoms of mild asthma (wheezing, tightness of chest, and shortness of breath) concurrently need relief of nasal congestion. FDA has not received any information that indicates this combination provides rationale concurrent therapy for a significant proportion of an asthmatic target population. Therefore, FDA considers this combination not to be generally recognized as safe and effective for OTC use. FDA is proposing to classify the combination of an oral bronchodilator (products containing ephedrine or its salts) and any oral nasal decongestant as Category II.

IV. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure by state, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million in any one year (adjusted annually for inflation).

FDA believes that this proposed rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. In addition, the proposed rule is not a significant regulatory action as defined by the Executive order.

FDA is not required to prepare a statement of costs and benefits under the Unfunded Mandates Reform Act because this proposed rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation. The current inflation adjusted statutory threshold is about \$110 million.

The purpose of this proposed rule is to reclassify the combination of any single oral bronchodilator active ingredient and any single expectorant active ingredient (currently listed in § 341.85(l) of the TFM, 53 FR 30522 at 30561) from Category I to Category II (nonmonograph). Single entity oral bronchodilator and expectorant drug products will remain available OTC for consumer use at this time. This proposed rule also places the combination of an oral bronchodilator and an oral nasal decongestant in Category II. FDA does not believe this combination is currently marketed; therefore, there should be no economic impact on manufacturers.

The potential benefits of this action include better self-treatment of the symptoms of mild asthma. Most people with mild asthma do not need an expectorant to control their symptoms. Nevertheless, FDA believes that some people with asthma continue to purchase the combination ephedrine-guaifenesin products affected by this rule mainly because they are more readily accessible than the single ingredient ephedrine products, which are subject to more DEA restrictions. People with mild asthma would continue to have access to single ingredient ephedrine products and could easily purchase an OTC expectorant. Although this action may pose some minor inconvenience to people with asthma who currently use the combination products, they will still be able to purchase single-ingredient ephedrine products from outlets that are in compliance with DEA single-ingredient ephedrine requirements.

All of the currently marketed OTC ephedrine combination drug products known to FDA are combined with guaifenesin. After the effective date of any final rule based on this proposal, manufacturers will have the choice of either stopping the introduction of their combination product into interstate commerce or reformulating their combination product(s) to a single-ingredient

ephedrine product and complying with DEA requirements for selling these products. FDA's Drug Listing System (DLS) identifies 14 manufacturers and 8 distributors/repackers of 36 combination ephedrine hydrochloride and guaifenesin drug products. Other standard reference books (e.g., American Drug Index and Red Book) identify additional ephedrine combination drug products, and FDA is aware that products containing monograph labeling marketed via magazines and catalogues may not be included in the DLS database. Therefore, FDA estimates that there are about 25 manufacturers and distributors/repackers of approximately 50 products that would be affected by the proposed rule. In many cases, manufacturers would bear the costs of stopping the introduction of their products into interstate commerce or the reformulation and subsequent relabeling of the affected products.

The cost to reformulate a drug product varies greatly depending on the nature of the product and manufacturing process, and the size of the firm. No manufacturer would have to change its product dosage form to comply with this rule. However, some manufacturers may have to revalidate (e.g., product, process and/or new supplier), conduct stability tests, and change master production records in order to ensure compliance with good manufacturing practice (21 CFR parts 210 and 211). FDA estimates that the cost of reformulation would range from \$100,000 to \$500,000 per product. However, many of these manufacturers already produce a single-ingredient ephedrine product. Moreover, others had previously produced a single-ingredient product before switching to the combined ephedrine-guaifenesin product and may, therefore, need only revalidate. Thus, FDA does not know how many products manufacturers will choose to fully reformulate. If 20 products were reformulated, and using the midpoint of the estimated cost to reformulate of

\$300,000, the cost to all manufacturers of reformulation would be approximately \$6 million (20 products x \$300,000 per product). FDA believes that because some manufacturers currently marketing ephedrine combination drug products also market single-ingredient ephedrine products, the reformulation costs associated with this proposed rule may be lower. However, those manufacturers who market only the ephedrine combination drug product would incur the full costs to reformulate, if they so choose, to a single-ingredient ephedrine drug product.

The cost to relabel OTC drug products also varies depending on the type of packaging, the outlet type, and the extent of the necessary labeling changes. FDA estimates that the cost of relabeling would generally be between \$2,000 and \$3,000 per product. Assuming a high-cost scenario, and that all 50 estimated products would be relabeled, the total labeling cost would be approximately \$150,000 (50 products x \$3,000 per product).

Based on Small Business Administration size standards, approximately 75 percent of the 14 domestic manufacturers of the affected products are small entities (e.g., fewer than 750 employees), as are most of the 8 distributors/repackers. FDA cannot assess the economic impact on all of these entities because sales data for products sold through all markets are not available. Based on IMS Health data, the two largest selling brands (produced by two different manufacturers and representing three individual products) of oral tablets containing a combination of ephedrine-guaifenesin active ingredients had sales of approximately \$4.257 million in 2001 (Ref. 10). This figure represents the sales of products affected by this proposed rule in pharmacies, chain drug stores, mass merchandisers, food stores with pharmacies, and proprietary stores (defined as stores under 10,000 square feet of floor space

that sell OTC drug products, but do not have a pharmacy). These sales accounted for about 0.06 percent of the total sales (approximately \$7,715.703 million) of all respiratory therapy drugs (USC 28000, Respiratory Therapy) reported by IMS Health in 2001 (Ref. 11). FDA has no information on the sales volume of the affected combination products in other outlet types, e.g., convenience stores, magazine ads, and gas stations.

FDA expects that the industry will experience little overall reduction in sales for the labeled use of ephedrine bronchodilator drug products, because those consumers using the combination product can switch to single ingredient products. FDA anticipates that the manufacturers of the two largest selling brands of oral tablets containing a combination of ephedrine-guaifenesin active ingredients will reformulate these products to single-ingredient ephedrine drug products. If reformulation does not occur upon issuance of a final rule, these manufacturers will incur lost sales of approximately \$4 to \$5 million annually. FDA cannot calculate the magnitude of lost sales for other companies that market these combination drug products because IMS data do not include specific sales information for products marketed by those companies. FDA believes that the sales of the combination ephedrine-guaifenesin bronchodilator drug products do not make up a large proportion of the total revenues of most of these firms. Consumers will still be able to purchase single-ingredient ephedrine bronchodilator drug products. Accordingly, an increase in sales may occur for current manufacturers of single-ingredient products and manufacturers who reformulate combination products to single-ingredient products.

FDA considered but rejected two alternatives for the proposed rule: (1) Additional labeling and (2) leaving the combination ephedrine-guaifenesin

drug products on the OTC market. FDA does not believe that additional labeling would ensure proper use of this combination product because FDA no longer considers it to be a rational concurrent therapy and because FDA believes that both active ingredients do not make a contribution to the claimed effect. Current treatment guidelines for mild asthma do not recommend the use of an expectorant. FDA believes that a doctor should make a case-by-case determination whether a person with mild asthma needs an expectorant drug product, and in those rare instances should prescribe or recommend an appropriate product. For the same reasons, FDA has tentatively concluded that it would be inappropriate to leave ephedrine-guaifenesin combination drug products in the OTC drug marketplace. FDA proposes that manufacturers be required to stop introducing their combination product into interstate commerce, or to implement any required reformulation and labeling changes to a single-ingredient product within 180 days after any final rule based on this proposal is published.

There is one other federal rule—DEA regulations controlling the distribution of OTC ephedrine drug products—that is related to, but does not conflict with, this proposed rule. Manufacturers and other marketers of OTC ephedrine drug products must register with DEA (§ 1309.21) and meet other DEA requirements.

With regard to the Regulatory Flexibility Act, FDA does not believe that the proposed rule will have a significant economic impact on a substantial number of small entities. However, there is uncertainty concerning both the number of affected entities and products. This analysis of impacts, together with other relevant sections of this document, serves as FDA's initial regulatory flexibility analysis. FDA specifically requests detailed industry comment

regarding both the number of small entities and products affected, as well as any potentially significant impact of this rule on small entities.

V. Paperwork Reduction Act of 1995

FDA notes that this proposed rulemaking does not contain any labeling requirements. However, if a company chooses to reformulate its combination product(s) to a single-ingredient product, relabeling would be necessary. Those labeling requirements are found in the existing monograph for OTC bronchodilator drug products in § 341.76. (See proposed changes to that monograph elsewhere in this issue of the **Federal Register**.)

VI. Environmental Impact

FDA has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, FDA has tentatively concluded that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VIII. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit

a single copy of electronic comments or three paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

IX. Proposed Effective Date

FDA is proposing that any final rule that may issue based on this proposal be effective 180 days after its date of publication in the **Federal Register**.

X. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) under Docket No. 1976N-0052G and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Woolcock, A. J., "Asthma," *Textbook of Respiratory Medicine*, 2nd ed., W. B. Saunders Co., Philadelphia, PA, 2:1245-1319, 1994.
2. "Global Strategy for Asthma Management and Prevention. NHLBI/WHO Workshop Report," *National Institutes of Health Publication*, no. 95-3659, January 1995.
3. "Guidelines for the Diagnosis and Management of Asthma. National Asthma Education and Prevention Program (NAEPP) Expert Panel Report," *National Institutes of Health Publication*, Update on Selected Topics 2002, pp. 115-116, 2002.
4. "Pediatric Asthma/Promoting Best Practice. Guide for Managing Asthma in Children," *American Academy of Allergy, Asthma, and Immunology (AAAAI)*, 1999.
5. American Academy of Allergy, Asthma, and Immunology. Practice Parameters for the Diagnosis and Treatment of Asthma, *Journal of Allergy and Clinical Immunology*, 96(5 Part 2):S707-S870, 1995.

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7. Lemanski, R. F., and W. W. Busse, *Journal of the American Medical Association*, 278:1855–1873, 1997.

8. Henke, C. et al., "Combined Bronchoscopy And Mucolytic Therapy For Patients With Severe Refractory Status Asthmaticus On Mechanical Ventilation: A Case Report And Review Of The Literature," *Critical Care Medicine*, 22(2):1880–1883, 1994.

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10. *IMS Health, Retail & Provider Perspective*, Year 2001, Data Extracted December 2002.)(Proprietary data used by FDA with the permission of IMS Health.)

11. *IMS Health, Retail & Provider Perspective*, 2:449, January-December 2001. (Proprietary data used by FDA with the permission of IMS Health.)

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 341

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 310 and 341 (as proposed in the **Federal Register** of August 12, 1988 (53 FR 30522)) be amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

2. Section 310.545 is amended by adding paragraphs (a)(6)(iv)(E) and (d)(27) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(6) * * *

(iv) * * *

(E) *Approved as of* [date 180 days after date of publication in the **Federal Register**]. Any oral bronchodilator active ingredient (e.g., ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride, or any other ephedrine salt) in combination with any expectorant active ingredient (listed in § 341.18 of this chapter) or in combination with any oral nasal decongestant active ingredient (listed in § 341.20 of this chapter).

* * * * *

(d) * * *

(27) [Date 180 days after date of publication in the **Federal Register**], for products subject to paragraph (a)(6)(iv)(E) of this section.

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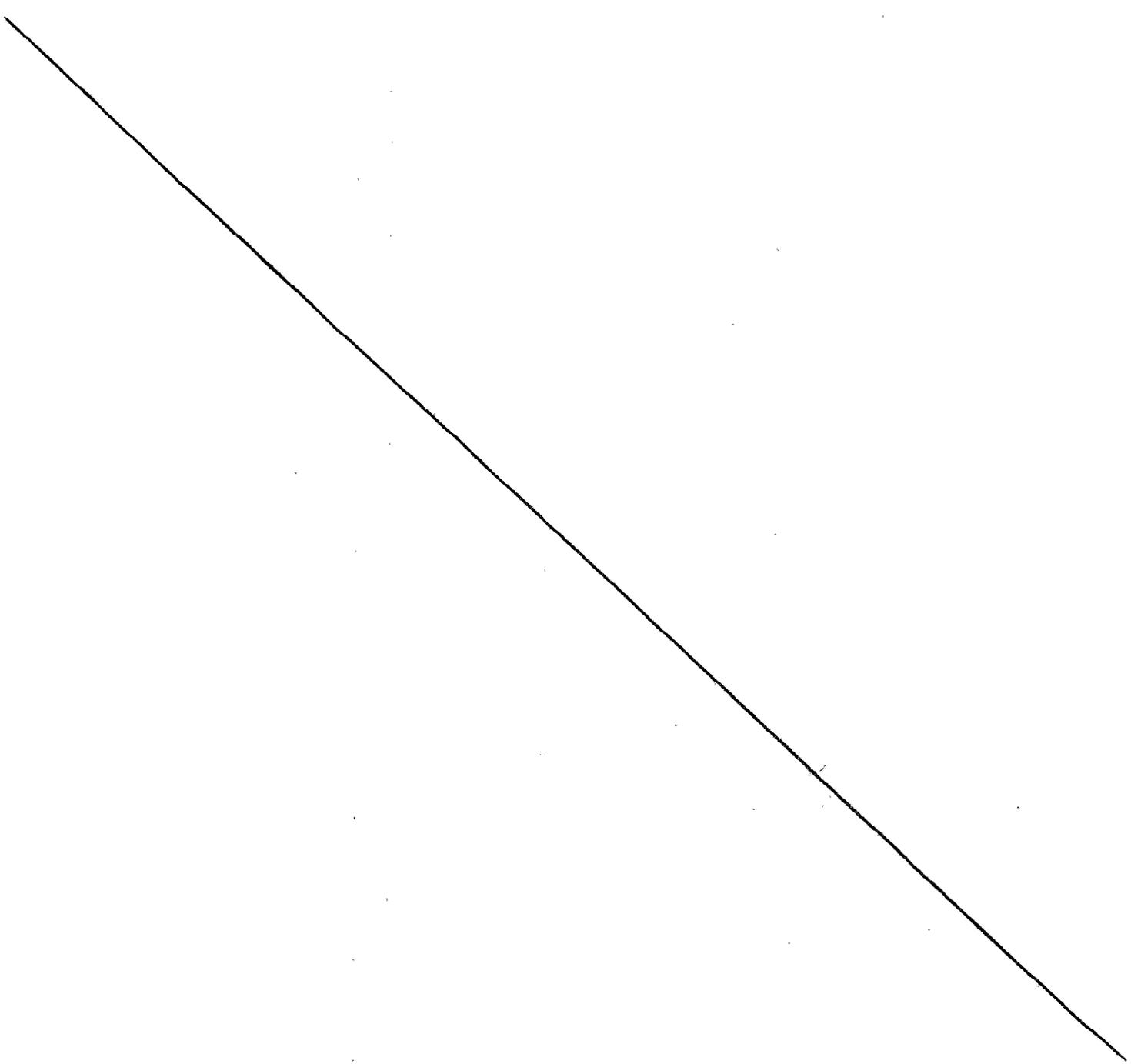
PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTI-ASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

3. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

§ 341.40 [Amended]

4. Proposed § 341.40 is amended by removing paragraph (l) and redesignating paragraphs (m) through (bb) as paragraphs (l) through (aa) respectively.



Dated: 6/30/05
June 30, 2005.



Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. 05-????? Filed ??-??-05; 8:45 am]

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