DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 76N–052G]

RIN 0905–AA06

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Combination Bronchodilator Drug Products Containing Theophylline

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that cough-cold combination drug products containing theophylline are not generally recognized as safe and effective and are misbranded for over-the-counter (OTC) use. 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 OTC cough-cold combination drug products containing theophylline that have come to the agency's attention. Also, this final rule lists in a regulation all OTC bronchodilator ingredients that have been found to be not generally recognized as safe and effective and are misbranded. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: January 29, 1996.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5000.

SUPPLEMENTARY INFORMATION:

I. Background

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 (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. The Panel recommended that theophylline as a single ingredient be Category I (generally recognized as safe and effective) (41 FR 38312 at 38373 and 38374). The Panel also recommended that combinations containing an oral sympathomimetic bronchodilator (e.g., ephedrine hydrochloride) and an oral bronchodilator (theophylline) be Category I (41 FR 38312 at 38326). 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, after deletion of a small amount of trade secret information, were placed on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

In the **Federal Register** of December 10, 1976 (41 FR 54032 at 54033), the agency announced that it did not agree with the Panel's recommendation that theophylline be classified in Category I and be made available for OTC use as a single ingredient because additional information, not available during the Panel's deliberations, indicated that the Panel's recommended therapeutic dose for theophylline may be toxic to some individuals. The new information suggested that the safe and effective use of theophylline requires careful dosage titration based on theophylline serum concentrations. The agency reaffirmed its decision to restrict single-ingredient theophylline preparations to prescription use only in the tentative final monograph for OTC bronchodilator drug products (47 FR 47520 at 47521, October 26, 1982). In the final monograph for OTC bronchodilator drug products (51 FR 35326 at 35331, October 2, 1986), the agency stated that it would address theophylline combinations in the tentative final monograph for OTC cough-cold combination drug products, in a future issue of the **Federal Register**.

In the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30544 to 30546, August 12, 1988), combination drug products containing theophylline and ephedrine were reclassified from Category I to Category II (not generally recognized as safe and/or effective). Additionally, the agency classified in Category II any OTC combination drug product that contains theophylline. Interested persons were invited to submit written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs (the Commissioner) and on the agency's economic impact determination for the proposal by December 12, 1988. New data could have been submitted by August 14, 1989, and comments on the new data by October 12, 1989.

In response to the OTC cough-cold combination drug products tentative final monograph, two manufacturers submitted comments and data on theophylline combination drug products, and two physicians submitted a case study related to a theophylline-ephedrine-phenobarbital combination product. Another comment reported injuries it considered to be caused by theophylline toxicity. Although that comment was submitted after the administrative record had closed, the agency considered it important and has addressed it in this final rule. Copies of the comments are on public display in the Dockets Management Branch (address above).

In this final rule, the agency is declaring OTC cough-cold combination drug products containing theophylline to be new drugs under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)), for which an application or abbreviated application (hereinafter called application) approved under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 is required for marketing. In the absence of an approved application, products containing drugs for this use also would be misbranded under section 502 of the act (21 U.S.C. 352). In this final rule, the agency is amending part 310 (21 CFR part 310) (nonmonograph conditions) by adding to § 310.545(a)(6) new paragraph (iv) to include any cough-cold combination drug products containing theophylline.

In the advance notice of proposed rulemaking for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products (41 FR 38312), the agency stated that the conditions for products excluded from the monograph (Category II) should be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the **Federal Register**, regardless of whether further testing is undertaken to justify their future use. The agency also stated that conditions included in the monograph (Category I) should be effective 30 days after the date of publication of the final monograph in the **Federal Register**. In the tentative final monograph for OTC cough-cold combination drug products, the agency extended this 30-day period to 12 months in order to provide a reasonable

period of time for relabeling and reformulation of products covered by the monograph (53 FR 30522 at 30523).

In the case of OTC combination bronchodilator drug products containing theophylline, the agency has determined that no combination is generally recognized as safe and effective for this use. Accordingly, the agency is not establishing any monograph conditions for these combination drug products. Thus, there is no need for a 12-month period for relabeling and reformulation of these products. As stated in the advance notice of proposed rulemaking, these conditions should be eliminated from OTC drug products effective 6 months after the date of publication of this final rule. Therefore, on or after January 29, 1996, no OTC cough-cold combination drug products containing theophylline may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved application. Any such OTC drug product in interstate commerce after the effective date of this final rule that is not in compliance with the regulation is subject to regulatory action. Manufacturers are urged to comply voluntarily with this final rule at the earliest possible date.

In the final rule for OTC bronchodilator drug products (51 FR 35326 at 35338), the agency listed a number of nonmonograph bronchodilator ingredients. At that time, § 310.545 had not been established. Thus, none of these nonmonograph bronchodilator ingredients are listed in that regulation.

Accordingly, at this time, the agency is also listing in § 310.545(a)(6)(iv) all of the nonmonograph bronchodilator active ingredients discussed in that final rule. The effective date of nonmonograph status for these ingredients, which did not apply to combinations containing theophylline, was October 2, 1987. The date of nonmonograph status of combinations containing theophylline will be January 29, 1996.

II. The Agency's Conclusions on the Comments

1. One comment requested that the agency ban theophylline in OTC drug products. The comment mentioned the growing body of medical literature highly critical of theophylline's safety record. The comment contended that theophylline can be a dangerous drug and its use should be tailored (by a physician) to the individual patient. The comment mentioned 26 incidents of theophylline-caused injuries, most of which involved young asthma patients who sustained brain damage from seizures or died as a result of using theophylline. The comment emphasized the need for greater understanding of the use of theophylline, especially when used by children or anyone suffering from fever or a viral infection, such as the flu.

Another comment reported a case involving a 6-year-old child who had been admitted to the hospital with a diagnosis of complex febrile seizures (Ref. 1). Because such febrile seizures often do not reoccur, the child was not placed on anticonvulsant medication, but was observed over time. Several months later, when the child was readmitted with gastroenteritis presumably of viral etiology, the physician discovered that the child had been taking an OTC drug product containing 130 milligrams (mg) theophylline, 24 mg ephedrine, and 8 mg phenobarbital twice daily for asthma prophylaxis. The comment indicated that the presence of phenobarbital in this product could have affected the patient's clinical course and/or recognition of reoccurring seizures. The comment urged the agency to remove this type of combination product from the OTC marketplace.

The agency agrees with the comments that theophylline-containing combination drug products should no longer be available OTC. In the OTC cough-cold combination tentative final monograph (53 FR 30522 at 30544 to 30546), the agency stated its awareness of the increase in adverse effects associated with the use of theophylline and ephedrine combination drug products. Moreover, the agency concluded that whether theophylline is administered as a single ingredient or in combination with other drugs, it is essential that a physician titrate theophylline dosage based on individual patient measurements of theophylline serum levels. Thus, the agency classified any OTC combination drug product containing theophylline as Category II (not generally recognized as safe and/or effective) and reaffirmed its position that theophylline should be administered under professional supervision.

More recent data also support the conclusion that theophylline is not safe for OTC use. These include:

(1) Twenty-six incidents of theophylline-caused injury between 1980 and 1991 (involving mostly young asthma patients), including 6 deaths (likely causally related), 15 cases of brain damage (not otherwise defined), 4 seizures and/or coma, and 1 rapid heartbeat (Ref. 2); (2) FDA adverse reaction reports for the years 1969 to March, 1994 (Ref. 3); and (3) the American Association of Poison Control Centers National Data Collection System (Refs. 4 through 7).

The agency's adverse reaction reporting system (Ref. 3) includes 116 adverse reactions associated with theophylline-containing combination drug products. Twenty-two of these reactions were serious: 4 resulted in death; 15 resulted in hospitalization; and 3 were disabling. These reports include both prescription and OTC use of theophylline combination drug products. Adverse reaction reports involving single ingredient theophylline drug products include 2,175 cases. Of these, 782 were serious, 111 resulted in death, 5 others were considered life-threatening, 4 required medical intervention to prevent impairment, 698 resulted in hospitalization, and 27 were disabling (Ref. 3).

The annual reports of the American Association of Poison Control Centers for the years 1990 to 1993 (Refs. 4 through 7) concerning theophylline exposures state the following: (1) In 1990, there were 6,527 theophylline exposures resulting in 36 deaths, 93 major (severe) outcomes, 622 moderate outcomes, and 2,039 minor outcomes; (2) in 1991, there were 6,744 theophylline exposures resulting in 38 deaths, 138 major outcomes, 619 moderate outcomes, and 2,101 minor outcomes; (3) in 1992, there were 5,735 theophylline exposures resulting in 35 deaths, 113 major outcomes, 596 moderate outcomes, and 1,343 minor outcomes; and (4) in 1993, there were 4,473 theophylline exposures resulting in 27 deaths, 120 major outcomes, 782 moderate outcomes, and 1,026 minor outcomes. The agency notes that these reports do not differentiate theophylline exposure as resulting from prescription or OTC drug products; nor do the reports differentiate exposure as resulting from drug products containing theophylline as a single ingredient or in combination with another active ingredient.

Tsiu et al. (Ref. 8) reported 1,570 published cases of theophylline-induced toxicities from 1973 through 1988, which included 198 seizures, 525 cardiovascular complications, and 63 deaths. The study indicates that many patients suffered serious and frequently fatal side effects, despite receiving ''standard'' prescription doses of theophylline. This type of reporting emphasizes the narrow therapeutic index of theophylline and the need to determine individual dose titration levels.

Sessler (Ref. 9) examined the clinical and pharmacokinetic characteristics of

5,557 theophylline-related toxicity reports from two hospitals over a 2-year period. Ten percent of the reported cases had serum theophylline concentrations above the therapeutic range, while 2 percent of these cases reported serum theophylline concentrations greater than 30 micrograms per milliliter (µg/mL). Of the 116 cases having serum theophylline concentrations greater than 30 µg/mL, 12 percent were due to acute overdose and 88 percent due to chronic overmedication. Sessler stated that cases of theophylline-induced toxicity are relatively common in hospital emergency departments, result primarily from patient and physician dosing errors, and cause a broad range of toxic manifestations of varying severity. Sessler indicated that the most common single cause of toxicity is inappropriate drug administration by the patient, i.e., additional doses administered for the relief of bronchospasm and/or dyspnea (difficulty in breathing).

In a recent prospective study (Ref. 10), Shannon evaluated major theophylline toxicity of 249 subjects with acute theophylline intoxication: 119 subjects with acute intoxication who were not receiving theophylline therapy, 92 subjects with chronic intoxication due to overmedication, and 38 subjects who ere acutely intoxicated while on theophylline therapy. The study pointed out that chronic overmedication is responsible for the high rate of morbidity and mortality in elderly subjects with theophylline intoxication. Shannon concluded that the data support the admonition that theophylline should be used cautiously, if at all, in elderly patients, and that close patient monitoring is necessary.

The data discussed above demonstrate an incidence of theophylline-related, life-threatening events and deaths, and a narrow therapeutic window for the safe use of theophylline. Accordingly, the agency concludes that theophylline should be administered under professional supervision and not be available OTC. Therefore, all OTC cough-cold combination drug products containing theophylline are considered nonmonograph.

References

(1) Comment No. C211, Docket No. 76N–052G, Dockets Management Branch.

(2) Letter from M. Maher, Association of Trial Lawyers of America, to J. S. Benson, FDA, dated October 25, 1990, in OTC Vol. 04THFM, Docket No. 76N–052G, Dockets Management Branch.

(3) Department of Health and Human Services, Food and Drug Administration, ''Spontaneous Reporting System, Line Listing of Adverse Reports: Theophylline Adverse Drug Event Profile,'' January 1969 to March 1994, in OTC Vol. 04THFM, Docket No. 76N–052G, Dockets Management Branch.

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(7) Litovitz, T.L. et al., ''1993 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System,'' The American Journal of Emergency Medicine, 12:580, 1994.

(8) Tsiu, S.J. et al., ''Theophylline Toxicity: Update,'' Annals of Allergy, 64:241–257, 1990.

(9) Sessler, C.N., ''Theophylline Toxicity: Clinical Features of 116 Consecutive Cases,'' The American Journal of Medicine, 88:567–576, 1990.

(10) Shannon, M., ''Predictors of Major Toxicity after Theophylline Overdose,'' Annals of Internal Medicine, 119:1161–1167, 1993.

2. Two comments disagreed with the agency's Category II classification of any OTC cough-cold combination drug product containing theophylline (53 FR 30544 at 30546). One comment stated that OTC combination bronchodilator drug products containing theophylline and ephedrine provide the same benefit to asthmatics as either single active ingredient when used for temporary relief of symptoms associated with episodic asthma. The comment asserted that low dose theophylline and ephedrine combinations have an extensive marketing history and a record of safe and effective use. The comment submitted two clinical studies (Refs. 1 and 2) in support of the therapeutic benefit of both theophylline and ephedrine and the additive effect(s) when both ingredients are taken in combination in fixed dosage. The comment contended that the two clinical studies confirm the following: (1) Low dose theophylline in combination products is therapeutically effective; (2) addition of low dose theophylline enhances the effectiveness of ephedrine; and (3) significant clinical benefit is achieved from using the combination product. The comment concluded that these studies provide substantial evidence to adequately support a final determination by the agency that low dose theophylline in combination with ephedrine is generally recognized as safe and effective as an OTC combination bronchodilator drug product.

The second comment stated that adequate and well-controlled clinical studies and 50 years of successful OTC use in the management of reversible bronchospastic disorder have demonstrated the safety and effectiveness of its OTC combination bronchodilator drug product containing 130 mg theophylline, 24 mg ephedrine, and 8 mg phenobarbital. In support of the additive effects and benefits from combining theophylline with ephedrine, the comment submitted data, literature reviews, and affidavits from several health care providers (Refs. 3 through 50). The comment stated that the data presented show that the combination drug product containing theophylline and ephedrine is a rational drug combination by virtue of the synergistic effects of the two bronchodilators, and that the reduction in the dosage of each component reduces the risk of toxicity from either ingredient. The comment added that such combination drug products provide mild to moderate chronic and stable asthmatic individuals with safe and effective medication that is convenient and cost-effective.

The agency has reviewed the submitted data and information, considered other pertinent information, and determined that the existing data do not support the safety and effectiveness of OTC combination drug products containing theophylline and ephedrine. The agency notes that on July 20 and 21, 1981, the FDA Pulmonary-Allergy Drugs Advisory Committee (the Committee) met and concluded that there was insufficient evidence to demonstrate the additive effect for combination drug products containing theophylline and ephedrine (Ref. 51). The Committee met again on November 4, 1982, and stated that it did not favor the continued OTC or prescription marketing of theophylline and ephedrine fixed combination drug products (Ref. 52). In the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30545 to 30546), the agency agreed with the Committee that: (1) Insufficient evidence exists to support the use of theophylline and ephedrine in combination; (2) ephedrine adds little benefit to the theophylline and ephedrine combination when theophylline is given in a dosage titrated for the individual patient; (3) individual dosage titration for theophylline is needed; and (4) an increase in adverse effects has been associated with the use of theophylline and ephedrine combination drug products.

The additional data submitted by the comments do not change the agency's position. One unpublished study (WM–339) (Ref. 1) addressed the therapeutic benefit of a combination containing 130 mg theophylline and 24 mg ephedrine. This randomized, double-blind, placebo-controlled, four-way crossover study compared the bronchodilator effects of single doses of theophylline, ephedrine, theophylline with ephedrine, and placebo in 30 subjects with reversible bronchospasm. According to the comment, the study demonstrates that ephedrine is an effective single ingredient bronchodilator and that combination drug treatment with theophylline plus ephedrine is significantly more effective than treatment with either single ingredient in providing relief from reversible airway obstruction attributable to bronchial asthma.

The agency finds that study WM–339 (Ref. 1) does not provide substantial evidence that both ingredients in the combination drug product make a contribution to the claimed effects. According to the authors, effectiveness of the two single ingredient products (130 mg theophylline and 24 mg ephedrine), the combination product (both theophylline and ephedrine), and placebo (inert tablet) was compared using the following endpoints: (1) Results of spirometric measurements of forced expiratory volume in 1 second (FEV_1) and the peak expiratory flow rate, (2) subjective evaluations of test subjects, and (3) incidence of therapeutic failure. The authors concluded that the combination therapy was superior to both placebo and to the single ingredients for spirometric measurements at several time points and for subjective patient global responses. Although significantly fewer failure rates were reported for the combination treatment group than for the placebo group, there was no significant difference in treatment failures between either individual ingredient and the combination product.

Flaws in the design and analysis of this study preclude substantiation of the authors' conclusions. First, the agency does not consider a single-dose, crossover study sufficient to establish effectiveness of both components of this fixed combination that would be used for multiple doses in a dynamic illness. Treatment-by-sequence effects, possible carryover effects, and dynamic changes in the subject's baseline disease over time could not be assessed because individual subject information was not provided.

Second, the agency considers inappropriate the method utilized to specify and analyze all effectiveness data recorded for treatment failures. Treatment failures were defined by inability to record at least one FEV_1 measurement with a minimum 15 percent improvement during the first 2 hours, and dropouts after the first 2 hours of observation. The planned analysis specified proper handling of treatment failure dropouts. However, 88 percent (15 of 17) of the subjects with at least a single treatment failure at the 2-hour observation point were allowed to finish the same 6-hour study period and were included in the evaluation of effectiveness. Some of these subjects may have received the allowed 2-hour rescue medication generating ''improved'' data for observation points between 2 and 6 hours, which cannot be attributed to the assigned study drug.

Finally, beta-agonist aerosol rescue medication was allowed by the study protocol at the single 2-hour observation point. This caused effectiveness results to be compromised by inclusion of further data in the analysis of effectiveness whether or not use of the rescue medication was considered a treatment failure.

The agency discussed the Sims et al. study (Ref. 2), submitted by one comment, in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30544). During two phases in that study, several combination products, including one containing 130 mg theophylline and 25 mg ephedrine, were compared to single doses of theophylline and ephedrine in 10 adults with mild but continuously symptomatic asthma and in 10 nonsmoking healthy adults. Reported results were that: (1) A single dose of 130 mg theophylline combined with 25 mg ephedrine produced a bronchodilator effect in subjects with mild to moderate asthma; (2) the theophylline and ephedrine combination caused more side effects (i.e., tremor, nervousness, nausea) than either ingredient alone; and (3) one theopylline and ephedrine combination was more effective than either drug alone, but there was no improvement in bronchodilator effectiveness for another combination despite higher theophylline blood levels achieved after 2 weeks of multiple dosing with a combination product containing theophylline, ephedrine, and phenobarbital. To explain the observed lack of improved lung function after multiple dosing with higher theophylline blood levels, the authors suggested the development of tolerance to theophylline, ephedrine, or both. The agency considers this two-phase study insufficient to support the claim that the combination of theophylline and ephedrine is more effective than either single active ingredient alone for the treatment of mild, continuously symptomatic asthma. The agency concludes that this study does not provide sufficient data to support the use of OTC combination drug products containing theophylline and ephedrine.

The agency has also reviewed the other studies (Refs. 3 through 50) and determined that the data do not substantiate the safe and effective use of OTC combination drug products containing theophylline. References 3 through 6 were previously addressed in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30544). Reference 7 reported superior effects of a combination of two drugs (theophylline and ephedrine) over single ingredient products (theophylline or ephedrine) in ameliorating exercise-induced bronchospasm. However, a three ingredient combination drug product (theophylline, ephedrine, and hydroxyzine hydrochloride) was used in these studies. Further, the side effects (drowsiness, tremors, nausea, insomnia, and palpitations) made the theophylline-ephedrine combination product unacceptable to almost one-half of the subjects in the study.

References 8 and 9 suggested that combinations are more effective than their individual components in controlling induced bronchospasm and modifying both early asthmatic response and late asthmatic response. However, two other reports (Refs. 49 and 50) indicated that oral theophylline has no effect on airway hyperresponsiveness even at dose levels greater than the fixed dose (780 mg per day) currently available OTC.

Reference 10 noted that in some studies additive effects of the combination drug product containing theophylline are recorded and in other studies they are not. Reference 11 was a double-blind, placebo-controlled, randomized cross-over study of a combination of three ingredients (theophylline, ephedrine, and hydroxyzine), another combination of three ingredients (theophylline, ephedrine, and phenobarbital), and a single ingredient product containing ephedrine. The authors reported that both combinations were more effective than ephedrine alone, but the study did not include a single ingredient product containing theophylline. Therefore, the study was unable to evaluate the contribution of ephedrine.

References 12 and 13 indicated that the prescription drugs metaproterenol

(Ref. 12) and terbutaline (Ref. 13) produced additive effects when given with theophylline. However, these data concerning additive effects of prescription drugs are irrelevant to OTC use of ephedrine. Reference 14 involved a comparison of a three ingredient combination drug product containing 130 mg theophylline, 24 mg ephedrine, and 8 mg phenobarbital to a single ingredient product containing 300 mg theophylline, given four times a day. The investigators recorded similar pulmonary function responses for the two products. However, it is difficult to assess these results because the two products contained different amounts of theophylline. The appropriate study to establish effectiveness would have been to compare the combination product to a single ingredient product containing the same amount of theophylline.

None of the other reports (Refs. 15 through 48) contains information to demonstrate safety and effectiveness. References 15 through 26 provided general information only. References 27 through 31 do not contain any clinical trials, and references 32 through 48 involved the comment's sustained action formulation. Some of these studies employed either a placebo control (Ref. 33) or a beta-agonist control other than ephedrine (Refs. 35 through 38). Two other studies (Refs. 32 and 34) compare the safety and effectiveness of a theophylline-containing sustained action dosage form and a theophylline-containing immediate release dosage form. References 39 through 48 lack study controls and are some of the early 1976 trials in Europe that dealt with a variety of disease entities.

The affidavits contained statements from several health care providers that the combination therapy of 130 mg theophylline and 24 mg ephedrine in fixed doses provides safe and effective therapy for the treatment of mild asthma. However, none of the affidavits included any new scientific data to support the safety and effectiveness of any OTC combination drug product containing theophylline and ephedrine.

The agency concludes that the submitted data do not support any combination bronchodilator drug products containing theophylline as safe and effective for OTC use, particularly with regard to effectiveness at steady state. Substantial evidence has not been provided to demonstrate that each ingredient in the combination of theophylline and ephedrine makes a contribution to the claimed effects as noted in § 330.10(a)(4)(iv) (21 CFR 300.10(a)(4)(iv)). Accordingly, in this final rule, combination bronchodilator drug products containing theophylline are not generally recognized as safe and effective and are considered misbranded for OTC use.

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III. Analysis of Impacts

An analysis of the cost and benefits of this regulation, conducted under Executive Order 12291, was discussed in the tentative final monograph of August 12, 1988 (53 FR 30522). No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (53 FR 30522 at 30560), and the substance of that analysis has not changed. Executive Order 12291 has been superseded by Executive Order 12866.

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). 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). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and, thus, is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The agency concludes that there is no basis for the continued marketing of any OTC combination cough-cold drug products containing theophylline with claims or directions for use as a bronchodilator and/or antiasthmatic drug product. In the interim, manufacturers may be able to reformulate to single ingredient ephedrine drug products. However, elsewhere in this issue of the **Federal Register**, the agency is proposing to remove the ingredients ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride from the bronchodilator final monograph and to require premarket approval for any OTC drug product containing these ingredients. If that proposal is finalized, manufacturers will not be able to market any OTC bronchodilator drug products containing theophylline or ephedrine without obtaining an approved application.

Early finalization of the nonmonograph status of OTC cough-cold combination drug products containing theophylline will benefit consumers by early removal from the marketplace of drug products for which safety and effectiveness have not been established. This will result in a direct economic savings to consumers. Bronchodilator drug products containing epinephrine will continue to be available for consumers to use on an OTC basis to treat bronchial asthma. Based on the information above, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

The agency has determined under 21 CFR 25.24(c)(6) 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.

At the time that the final monograph for OTC bronchodilator drug products was published in the **Federal Register** of October 2, 1986 (51 FR 35326), the agency had not established § 310.545, which lists certain active ingredients that are not generally recognized as safe and effective for certain OTC drug uses. Therefore, bronchodilator ingredients that were found to be nonmonograph in 1986 are not currently included in § 310.545. In this final rule, the agency is listing in new § 310.545(a)(6)(iv) all nonmonograph bronchodilator ingredients. New § 310.545(a)(6)(iv)(A) includes the following ingredients: Aminophylline, belladonna alkaloids, euphorbia pilulifera, metaproterenol sulfate, methoxyphenamine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate, and theophylline preparations (theophylline, anhydrous; theophylline calcium salicylate; theophylline sodium glycinate). New § 310.545(a)(6)(iv)(B) includes any combination drug product containing theophylline (e.g., theophylline and ephedrine, or theophylline and ephedrine and phenobarbital). The agency is also amending § 310.545(d) to add new paragraphs (d)(19) and (d)(20) to list the effective dates for the ingredients in new § 310.545(a)(6)(iv)(A) and (a)(6)(iv)(B), respectively.

List of Subjects in 21 CFR Part 310

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 is amended as follows:

PART 310—NEW DRUGS

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

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. Section 310.545 is amended by adding new paragraphs (a)(6)(iv), (d)(19), and (d)(20) to read as follows:

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

(a) * * *

(6) * * *

(iv) *Bronchodilator drug products*—

(A) *Approved as of October 2, 1987.*

Aminophylline
Belladonna alkaloids
Euphorbia pilulifera
Metaproterenol sulfate
Methoxyphenamine hydrochloride
Pseudoephedrine hydrochloride
Pseudoephedrine sulfate
Theophylline, anhydrous
Theophylline calcium salicylate
Theophylline sodium glycinate

(B) Approved as of January 29, 1996. Any combination drug product containing theophylline (e.g., theophylline and ephedrine, or theophylline and ephedrine and phenobarbital).

* * * * *

(d) * * *

(19) October 2, 1987, for products subject to paragraph (a)(6)(iv)(A) of this section.

(20) January 29, 1996, for products subject to paragraph (a)(6)(iv)(B) of this section.

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Dated: July 5, 1995.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

[FR Doc. 95–18449 Filed 7–26–95; 8:45 am]

BILLING CODE 4160–01–P