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