# DEPARTMENT OF HEALTH AND HUMAN SERVICES

# Food and Drug Administration

## 21 CFR Parts 310 and 341

[Docket No. 94N-0247]

RIN 0905-AA06

## Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-The-Counter Human Use; Proposed Amendment of Monograph for OTC Bronchodilator Drug Products

**AGENCY:** Food and Drug Administration, HHS.

#### **ACTION:** Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the final monograph for over-thecounter (OTC) bronchodilator drug products to remove pressurized metered-dose aerosol container dosage forms for the ingredients epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride. This action is being taken because the OTC marketing of such drug products will require an approved application containing certain information not required by the monograph. The agency is also proposing to amend the regulation that lists nonmonograph active ingredients to add any ingredient(s) in a pressurized metereddose aerosol container for OTC bronchodilator drug products. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

**DATES:** Written comments or objections by May 23, 1995; written comments on the agency's economic impact determination by May 23, 1995. FDA is proposing that any final rule that may issue based on this proposal become effective 30 days after its date of publication in the **Federal Register**. **ADDRESSES:** Submit written comments or objections to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

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 October 2, 1986 (51 FR 35326), FDA issued a final monograph establishing conditions

under which OTC bronchodilator drug products are generally recognized as safe and effective and not misbranded. Section 341.76(d)(2)(i) (21 CFR 341.76(d)(2)(i)) provides for products containing epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride for use in a pressurized metered-dose aerosol container (hereinafter referred to as an inhaler or MDI).

In the final monograph (51 FR 35326 at 35333, comment 10), the agency responded to a comment that agreed that bronchodilators in a MDI dosage form should be available OTC, but objected to allowing them to enter the marketplace without preclearance by FDA through approval of applications (new drug (NDA) or abbreviated new drug (ANDA)). The comment contended that the complexities of pressurized MDI 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 was deficient because it did not discuss the complexities of the design, control, manufacture, and market use of MDI drug delivery systems and the monograph did not set forth manufacturing standards for MDI delivery systems. The comment suggested that a full application would not be required, but that preclearance of "manufacturing controls information and bioavailability data" by the agency should be required.

Based on the data and other information available when the final monograph for OTC bronchodilator drug products was published, the agency disagreed with the comment, stating its belief that the state of the technology for MDI drug delivery systems was such that bronchodilator drug products in MDI dosage forms could be generally recognized as safe and effective. The agency indicated that it had reviewed data available at that time from its Drug Product Problem Reporting System computerized data base for all bronchodilator drug products in MDI dosage forms. The agency noted that no problems related to metered-dose mechanisms had been reported for these OTC drug products between 1980 and 1984. Therefore, the agency concluded that the technology available to produce reliable MDI mechanisms allowed the agency to generally recognize MDI dosage forms for OTC bronchodilator drug products containing epinephrine preparations as specified in the final monograph.

The agency also pointed out in the final rule (51 FR 35326 at 35334), however, that agency regulations in 21

CFR 2.125(d) state that the use of a chlorofluorocarbon (CFC) 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 NDA. Therefore, all OTC bronchodilator drug products in MDI's that contain a CFC as a propellant (which include all marketed OTC MDI products containing epinephrine) were marketed only under an approved application. The agency anticipated that MDI products would continue to contain a CFC propellant and that marketing would continue under approved applications containing information on manufacturing controls for the MDI.

Since publication of the final monograph for OTC bronchodilator drug products, several developments have changed the agency's views about pressurized MDI dosage forms. These include: (1) Legislation that requires a phaseout of ozone-depleting substances, including CFC propellants in MDI drug products; (2) the need for safety data on the alternative propellants that will replace CFC's in MDI dosage forms, as well as evidence that the new MDI's deliver the drug effectively; (3) recent publications reporting chemistry, manufacturing, and controls problems resulting from changes to the container and closure system of redesigned MDI dosage forms; (4) the need for safety and effectiveness data for the new drug products as a result of these chemistry, manufacturing, and controls changes; and (5) international workshops and FDA advisory committee discussions focusing on regulatory requirements for modifications to an approved innovator MDI and bioequivalence of generic MDI aerosol products. These issues have caused the agency to reconsider the inclusion of MDI dosage forms in the final monograph for OTC bronchodilator drug products. The agency has determined that an assessment of the safety and effectiveness of each product must be made. The agency's discussion of these issues follows.

# II. New Issues That Affect MDI Drug Products

## A. Proposed Replacement of CFC Propellants

The Clean Air Act Amendments of 1990, Title VI (Pub. L. 101–549), signed into law on November 15, 1990, requires the phaseout of ozone-depleting substances. The Environmental Protection Agency (EPA) has promulgated regulations implementing the phaseout provisions contained in section 604 of the Clean Air Act