Adams et al. (Ref. 4) indicated that, unlike most dosage forms, inactive ingredients in MDI aerosol formulations and the container and closure system are important contributors to the safety and effectiveness and, thus, to the therapeutic equivalence of these products. The agency is aware that different pharmacodynamic effects in aerosolized drugs have been hypothesized to occur due to differential deposition of drugs in various segments of the respiratory tract, resulting in different absorption characteristics. Such differences between test and reference products could arise from differences in characteristics of the suspension formulation or in the performance characteristics of the delivery devices (valve and actuator) used in the products.

FDA's Division of Bioequivalence (the Division), in the Office of Generic Drugs, has developed interim guidance that recommends methods to generic applicants to document in vivo bioequivalence of albuterol MDI aerosols and recommends a safety evaluation study as part of the documentation of in vivo bioequivalence (Ref. 5). The Division advises that the methods presented therein are not rigid and are not considered by the Division to be the sole methods of documenting bioequivalence. However, because limited experience exists in the application of these methods to the determination of bioequivalence of different albuterol MDI aerosol drug products, the report encouraged sponsors to assess the general applicability and reliability of the methods recommended.

In response to this interim guidance, one comment (Ref. 6) requested that the agency withdraw the guidance because it would permit a generic version of albuterol MDI aerosol to be released for marketing without long-term safety studies. The comment referred to data presented by another MDI aerosol manufacturer during the September 14 and 15, 1993, Committee meeting (Ref. 3). The comment explained that clinical comparison of two nearly identical MDI aerosol products produced similar pharmacodynamic responses, but exhibited significant differences in safety profiles (changes in serum potassium and glucose, finger tremor, and heart rate). Because of safety concerns, the MDI aerosol manufacturer withdrew its request for agency approval of its product. The comment pointed out that the manufacturer's data presented at the meeting demonstrate that even minor changes in drug

delivery may affect patient safety. The comment added that different valves and new suppliers of drug substances and excipients used in MDI aerosol products may lead to patients being exposed to new valve extractives and to new impurities. The comment emphasized that although some minor changes may be evident in single-dose studies, longer-term clinical trials are needed to assess the full side effect liability of changed products (i.e., new excipients or component design alterations) for regular or intermittent administration.

Wong and Hargreave (Ref. 7) discuss the need for premarket approval and subsequent bioequivalence requirements for reformulated and generic MDI aerosol products. The authors state that there is a need to demonstrate clinical bioequivalence and relative potency of MDI aerosols before marketing generic versions, new types of delivery devices, and new products of the same class of drug. The authors explain that certain characteristics of the inhaled aerosols are known to influence effectiveness, e.g., particle size, coalescence of droplets and evaporation of propellants, rate of delivery, concentration of the drug during nebulization, plume geometry, and the constituents (i.e., drug, propellants, and surfactants). Other factors, such as the valve assembly, rubber seals, and actuator mouthpiece in a pressurized MDI, can also influence drug availability and, therefore, need consideration and regulation to ensure adequate drug deposition in the lungs. The authors point out that although several in vitro tests and in vivo radioaerosol studies can be used to predict or measure the deposition of inhaled particles in the airway, none of these studies can yet be relied on to ensure clinical bioequivalence. The authors conclude that both in vitro and in vivo testing of clinical effect should be required to establish the bioequivalence of generic MDI aerosols.

As part of the required premarket approval process, the agency is continuing to review methodology for in vitro and in vivo bioequivalence testing for reformulated and generic MDI aerosol products. The agency has also sponsored pharmacodynamic studies to help develop that methodology. The agency agrees with the conclusion in the CEC's report that changes in propellants should be considered major changes in pressurized MDI aerosol products and that extensive premarket testing is required prior to market approval of MDI aerosols reformulated with non-CFC propellants. The agency also agrees with the Committee's recommendation

that in vivo bioequivalence documentation should be provided for generic suspension MDI aerosol products for oral inhalation.

References

(1) Report of the Commission of the European Communities' Committee for Proprietary Medicinal Products, "Matters Relating to the Replacement of CFCs in Medicinal Products," December 15, 1993, in OTC Vol. 04BFMA3.

(2) Drug Information Association, "MDI's in the New Millennium: Workshop on Regulatory Issues of Efficacy, Safety, and Quality with Metered Dose Inhalers (MDI's) Drug Dosage Forms-October 18 and 19, 1993," in OTC Vol. 04BFMA3.

(3) Transcripts of the FDA Generic Drugs Advisory Committee Meeting with Pulmonary-Allergy Drugs Advisory Committee Representation, September 14–15, 1993, identified as TS, Docket No. 94N–0247, Dockets Management Branch.

(4) Adams, W. P. et al., "Regulatory Aspects of Modifications to Innovator Bronchodilator Metered Dose Inhalers and Development of Generic Substitutes," *Journal* of Aerosol Medicine, 7:119–134, 1994.

(5) FDA Division of Bioequivalence, Office of Generic Drugs, "Interim Guidance for Documentation of In Vivo Bioequivalence of Albuterol Inhalation Aerosols (Metered Dose Inhalers)," January 27, 1994, in OTC Vol. 04BFMA3.

(6) Petition from Glaxo Inc., to FDA, April 6, 1994, in OTC Vol. 04BFMA3.

(7) Wong, B. J. O., and F. E. Hargreave, "Bioequivalence of Metered-Dose Inhaled Medications," *Journal of Allergy and Clinical Immunology*, 92(3):373-379, 1993.

III. Summary of Agency's Proposed Changes

The agency is proposing that all MDI aerosol dosage forms must have premarket approval to ensure their safety and effectiveness. This proposal is based on a reconsideration of the nature of these products, potential future reformulations to include new propellants, and the recommendations of the agency's Committee (discussed above).

This proposed amendment removes the ingredients epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride in pressurized MDI aerosol dosage forms from the final monograph for OTC bronchodilator drug products. It does not affect the monograph status of these ingredients when used in a hand-held rubber bulb nebulizer. Such products will remain in the final monograph for OTC bronchodilator drug products.

All currently marketed OTC pressurized MDI aerosol drug products are the subject of approved applications. The agency has explained in this document why it concludes that agency approval remains essential for these