metering valve must accurately deliver a measured amount of product and should be reproducible not only for each dose delivered from the same package but from package to package. An integral part of the MDI valve is the metering chamber that is responsible for the delivery of the desired amount of drug. MDI valves function by filling the metering chamber with product, sealing off this chamber from the remaining formulation in the canister when the valve stem is partially depressed, and then releasing the contents of the chamber through the valve stem upon further depression (actuation) (Ref. 5). The valves should retain their prime charge over fairly long periods of time (Ref. 4). However, it is possible for material in the chamber to return slowly to the main body of product. The degree to which this can occur varies with the construction of the valve and the length of time between uses (actuations). Puffto-puff dosage variability due to inadequate valve priming may lead to therapeutic failure and a subsequent asthma attack requiring emergency room and hospital treatment.

One study (Ref. 6) compared the relative bronchodilator effectiveness of two puffs from two different albuterol MDI aerosols containing the same concentration of active ingredient. The study was a randomized, single-blind, crossover clinical trial involving 17 adults with intermittent or mild chronic asthma. Initially, each subject received two puffs of the generic albuterol MDI and two puffs of the brand name albuterol MDI drug product on two occasions at least 3 days apart. The test dose was the first two puffs out of each canister; neither inhaler was primed. Pulmonary function was measured before each test dose and at frequent intervals over an 8-hour period after drug inhalation. Results of this portion of the study indicated that the bronchodilator response was greater with the generic MDI than with the brand name MDI product.

The study was repeated with both MDI products primed prior to the test dose (i.e., two puffs were first discharged into a wastebasket) in 11 subjects willing to return for further testing. Retest data indicated that there was no significant difference in bronchodilation between the two primed inhalers. The results suggested that failure to prime the MDI canister could alter the therapeutic response. The authors explained that variations in valve and actuator design or factory quality control procedures could account for the difference in therapeutic effectiveness of the two products. They added that modifications in valve

design or storage position may account for the loss of valve prime and, thus, be responsible for puff-to-puff dosage variability. On the basis of this study, the authors stated that MDI manufacturers must conduct in vitro studies to determine the frequency of valve priming required for their product, the effect storage position has on valve priming, and the uniformity of drug content of each of several puffs after priming.

Accurate assessment of drug deposition profiles, both the quantity of drug reaching the respiratory airways and its depth of penetration, is critically important in evaluating the bioavailability of MDI aerosol products (Ref. 4). The aim of the MDI drug product is to deliver the maximum amount of drug to the respiratory tract and minimize deposition in the oropharynx (Ref. 7). The portion of the drug product that is ultimately deposited at the desired biological target consists of a mixture of micronized or solubilized active drug substance in a residue matrix of oily excipient material and/or low volatile propellant and/or solvent (Ref. 1). A particle size range less than 5 µm is generally considered more effective than larger particles in producing bronchodilatation (Ref. 8). MDI formulations currently available consist of drugs suspended in CFC propellants or drugs dissolved in propellants containing a significant proportion of less volatile solvents. Particle size distribution from MDI's containing drugs dissolved or suspended in propellant/cosolvent mixtures is governed by the physical characteristics of the valve and the actuator, the concentration of nonvolatile components in the mixture, the initial droplet size (which depends on such factors as actuator design, spray characteristics, and physicochemical characteristics of the solution being sprayed), and the volatile propellant evaporation rate (Ref. 7). The agency is concerned how new non-CFC propellants will affect particle size and particle size distribution.

The effectiveness of two albuterol MDI aerosol products (brands A and B) was compared in a double-blind study involving 31 asthmatics (Ref. 9). Each subject received sequential treatment (0.2 mg albuterol/dose) on two successive days (day 1, inhalation sequence A then B; day 2, inhalation sequence B then A). Results of this study indicated that all subjects had a significantly greater bronchodilation response to the B MDI product than to the A MDI product. Further, in the sequence A-B, the B MDI always produced further bronchodilation while in the sequence B-A sequence, there was no further bronchodilation response to the A MDI. The study indicated that 0.2 mg of B was as effective as 0.4 mg of A. The study showed that two different albuterol inhalers containing the same active ingredients in the same dose can differ significantly in therapeutic effectiveness. The author suggested that the bioavailability of albuterol MDI's may differ from brand to brand because of differences in aerosol particle size or distribution, concentration, and/or the physicochemical characteristics of the propellant.

Factors influencing the ultimate deposition of stable small inhalation particles include the formulation of the products, design of components (specifically the valves or actuators), administrative skills and techniques of the product user, and the anatomical and physiological status of the respiratory system (Ref. 4). Besides the previously mentioned effects of propellant vapor pressure and the metered volume of propellants on drug deposition in the lungs, the selection of the appropriate surfactant (required in pressurized suspension MDI aerosols) and its concentration are important considerations in MDI aerosol drug formulations. As discussed above, surfactants influence droplet evaporation, particle size, and overall hydrophobicity of the particles reaching the respiratory passageways and pulmonary fluids (Ref. 4).

Particle size distribution is also influenced by the MDI component design. Changes in component design, including the actuator and adapter, have been shown to alter the particle size distribution and consequently the penetration and deposition of the active ingredient in the lung. The agency is aware that a variation of particle size distribution up to 40 percent could result from altering the actuation type, valve dimensions, distance from actuator, and other device component variables (Ref. 4). Because the valve and actuator of an approved MDI product may be proprietary to the innovator firm, and therefore unavailable to other drug manufacturers, use of a different valve or actuator for products containing active ingredients currently included in the monograph for OTC bronchodilator drug products may require data to support safety and effectiveness.

Given the complexity of the MDI formulations and the interdependence of each of the MDI components, the agency believes that pressurized MDI aerosol drug products must be carefully evaluated for safety and therapeutic effectiveness. Based on agency