

particles of Teflon (3.2 μm mass median aerodynamic diameter) were incorporated into canisters formulated with two different metered volume sizes (25 and 50 microliters) and with two different propellant vapor pressures. The study indicated that the majority of the dose from a pressurized MDI aerosol is deposited in the oropharynx and that only a small amount reaches the lungs. Increasing the metered volume had no effect on the quantity of aerosol deposited in the lungs, but produced a significantly more central pattern of deposition within the bronchial tree. An increase in vapor pressure, however, resulted in a significant increase in whole lung deposition and a significant reduction in extrathoracic deposition. The authors concluded that changes in formulation alter the deposition pattern of MDI aerosols and, consequently, might bring about changes in clinical effectiveness.

In addition to vapor pressure and velocity characteristics of the propellant, the surfactant and cosolvent in a solution product are other important formulation considerations. Surfactants lubricate the MDI canister valve and prevent aggregation of the individual drug particles. Surfactants also influence droplet evaporation, particle size, and overall hydrophobicity (degree of insolubility in water) of the particles reaching the respiratory passageways and pulmonary fluids (Ref. 1). Variations in the rate of evaporation of propellants and the cosolvent, if present, may lead to a particle size distribution containing a higher or lower proportion of fine particles (Ref. 6), which could have a significant impact on the safety and effectiveness of the new drug product.

A considerable and variable amount of drug is deposited in the oral cavity and thus is swallowed and subject to absorption from the gastrointestinal tract (Ref. 7). The agency is concerned with the possibility that new non-CFC propellants in an MDI product may interact with a cosolvent or other components (e.g., surfactants, valve components, or antioxidants) to produce an irritant or potentially hazardous formulation, or a less effective formulation, when applied to the respiratory system. The agency concludes that additional data will be necessary to demonstrate that inhalation and ingestion of new formulations will not result in local tissue irritation effects or other undesirable consequences, such as loss of effectiveness or local retention, resulting from inappropriate drug deposition characteristics. These additional data will include information on the absorption, distribution, and

retention characteristics of new propellant systems in man following inhalation. This information needs to include an assessment of the likely systemic burden of the propellant. Therefore, the agency considers premarket approval to be essential for any MDI aerosol drug products that combine a known active ingredient with a new propellant system or new valve.

References

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C. Chemistry, Manufacturing, and Controls Concerns

The agency believes that careful consideration must be given to the interactions that can occur between the drug substance, the container and closure system, and the excipients of a MDI aerosol product. Unlike dosage forms composed only of excipients and drug, a MDI consists of the container, the valve, the actuator (mouthpiece), and the formulation. These components collectively constitute the drug product that delivers the drug substance in the desired form to the biological target. Variability in the performance of a MDI may result from the physical characteristics of the drug substance, formulation differences, valve and

actuator design, and the adequacy of control parameters, specifications, and test methods for each component and the drug product. Design modifications of the MDI may result in significant alterations of the dose delivered to the lung. Changes in the source or the composition of any component of the MDI drug product may introduce unknown contaminants (Ref. 1). Impurities (extractables) may occur when the propellant comes in contact with the plastic or rubber components of the MDI canister.

The agency is concerned about the possible association of impurities and extractables with paradoxical bronchospasm as well as with more general toxicity. In one study (Ref. 2), a 24-year-old asthmatic patient who had reported acute wheezing immediately after using an aerosol of beclomethasone dipropionate was challenged with several aerosols. The subject experienced immediate bronchoconstriction after two puffs of an aerosol containing beclomethasone dipropionate and also after inhalation of the vehicle (all the components of the aerosol less the beclomethasone). When the patient was challenged with a different brand of beclomethasone aerosol, however, no bronchospasm occurred. Because the contents of the two beclomethasone aerosols were similar, the authors concluded that rubber or plastic derivative(s) present in the metering valve may have been responsible for the bronchospasm. The authors noted that the manufacturers of the beclomethasone aerosols had confirmed that their internal metering valves were different. The authors also pointed out that the conclusion drawn in a similar study (Ref. 3) suggested that the substance(s) responsible for the reaction might be derived either from the metering valve or the aluminum can.

Most MDI aerosol canisters are made of aluminum. Aluminum is essentially inert, but will react with certain solvents and other chemicals (Ref. 4). Although aluminum can be used without an internal organic coating for certain aerosol formulations (especially those which contain only active ingredient and propellant), many MDI aluminum canisters are internally coated with epon- or epoxy-type resin for added resistance to formulation interaction. The agency is concerned about what interactions might occur between the aluminum canister and the epon- or epoxy-type resin coating and new non-CFC propellants that may eventually be used in these products.

The formulation, actuator, and valve determine the performance of a pressurized MDI aerosol (Ref. 4). The