Amendments of 1990 (58 FR 65018, December 10, 1993). Ozone-depleting substances covered by the Clean Air Act Amendments of 1990 include CFC's and hydrochlorofluorocarbons. The international community has agreed to adjust the phaseout schedule for CFC's to reduced levels of production and consumption (production plus imports minus exports) of 25 percent of baseline level in 1994 and 1995, with a complete phaseout by 1996 (58 FR 65018 at 65020). Existing supplies of previously manufactured products will continue to be marketed until supplies are exhausted. All pressurized MDI antiasthma drugs (both the OTC products containing epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride and numerous antiasthma drugs available by prescription only) contain CFC's as the propellant. A procedure has been established for obtaining essential-use exemptions of ozone-depleting substances used in medical products from this production phaseout. Because there are no currently approved inhalation products that can fully substitute for drugs in MDI's used to treat the symptoms of asthma and chronic obstructive pulmonary disease (COPD) (Ref. 1), FDA and EPA have supported essential use exemptions (Refs. 2 and 3).

In the **Federal Register** of October 18, 1994 (59 FR 52544 at 52546), EPA announced that the Montreal Protocol Technology and Economic Assessment Panel had recommended that essential use exemptions for 1996 and 1997 be granted for CFC's used in MDI's. At an October 1994 meeting, the Parties to the Montreal Protocol on Substitutes that Deplete the Ozone Layer reviewed these recommendations and granted essential use exemptions for 1996 and 1997 for MDI's for the treatment of asthama and COPD (Ref. 4).

Beginning in the late 1980's, the pharmaceutical and other industries began searching for appropriate CFC alternatives. Currently two compounds, HFC-134a and HFC-227ea, are being investigated as alternative propellants to replace CFC's in MDI's. Reformulation of currently approved MDI drug products with these new propellants will require toxicological and clinical studies to establish the safety and efficacy of the new drug products. The agency intends to require sponsors to submit NDA's for these new drug products. These NDA's must be approved before the new products can be marketed.

References

(1) Letter from M. R. Taylor, FDA, to M. H. Shapiro, EPA, December 21, 1993, in OTC Vol. 04BFMA3.

(2) Petition from Sterling Winthrop, Inc., to EPA, August 20, 1993, in OTC Vol. 04BFMA3.

(3) "Metered Dose Inhalers: A Special Case," International Pharmaceutical Aerosol Consortium, July 19, 1993, page 31 and Appendix A, page 1, in OTC Vol. 04BFMA3.

(4) Report of the 6th Meeting of the Parties to the Montreal Protocol on Substances that Deplete the Ozone Layer, October 6–7, 1994, in OTC Vol. 04BFMA3.

B. Safety and Effectiveness Data for Alternative Propellants

MDI's offer a convenient way to administer aerosolized bronchodilator drugs for the treatment of asthma and COPD. Response to drugs administered by inhalation is prompt, often very specific with minimal side effects, and faster in onset than responses to drugs given orally (Ref. 1). With most drugs, MDI response approaches the rapidity of intravenous therapy. Drugs that normally are decomposed in the gastrointestinal tract can be administered safely by inhalation. The MDI dosage form makes inhalation therapy simple, convenient, and more acceptable than atomizers and nebulizers, which are bulky and require cleaning.

Bronchodilator drugs in pressurized MDI aerosols are widely available. Many formulations contain a drug either suspended or dissolved in CFC propellants at high pressure in a small canister. In addition to supplying the necessary force to expel the product, the propellant blend also acts as a vehicle and diluent. Thus, the propellant has much to do with determining the characteristics of the product as it leaves the container. Desirable vapor pressures, stability, and reactivity of CFC propellants are of prime importance in the formulation and manufacture of MDI aerosols. From a solubility standpoint, CFC's are miscible with most nonpolar solvents over a wide range of temperature and are capable of dissolving many substances (Ref. 1). The CFC propellants used in MDI's are not miscible with water. A cosolvent, typically ethanol, must be included in present formulations to increase the solubility of polar drug molecules.

As noted above, manufacturers may need to reformulate their MDI aerosols to replace the CFC propellants with suitable alternatives. The agency is concerned that the use of new excipients, including non-CFCcontaining propellants, could change the distribution characteristics of the drug in the airways, produce a pharmacologic interaction, or enhance toxicity of the active drug substances. Reformulation of pressurized MDI aerosols containing non-CFC-containing propellants might also result in changes in drug deposition patterns within the lung. These changes might alter pulmonary absorption, potentially resulting in changes in safety and/or therapeutic effectiveness of the bronchodilator.

Propellants can affect the therapeutic effectiveness of bronchodilators. A 1983 study (Ref. 2) measured the effects of two different albuterol (salbutamol) MDI products containing the same amount of drug per inhalation. In this doubleblind, crossover study, 46 subjects with stable asthma were challenged with methacholine to produce a moderate bronchial obstruction. Following the methacholine challenge, the subjects were randomized into two groups. Each group received two inhalations from one of two different brands of albuterol MDI aerosol preparations. The peak expiratory flow (PEF) was measured three times in 10 minutes after the inhalation of the drug product. The test was repeated after 3 days to 1 month by giving the subjects the test aerosol that they had not received in the first test. PEF values were determined in the same manner as described for the initial inhalation test product. The data indicated that one preparation relieved bronchial obstruction more effectively than the other preparation. The author suggested that, because both MDI aerosols contained the same drug, the significant difference of the relaxing effect on the bronchial obstruction with these aerosols in the same subject may be due to the properties of the vehicle (propellant).

Currently, MDI aerosols are selfpressurized with CFC propellants that provide a fixed volume of propellant and drug each time the canister valve is pressed. A fixed amount of drug is aerosolized by the pressure of the propellant into small droplets that evaporate to produce smaller respirable particles. These droplets should be between 2 to 5 microns (µm) for maximum delivery of drug to the respiratory tract and to minimize deposition in the oropharynx (Ref. 3).

Propellant vapor pressure, which affects both the droplet size and the velocity at which the particle leaves the MDI device, is important in determining drug deposition in the lung (Ref. 4). Newman et al. (Ref. 5) measured the effects of changes in metered volume and propellant vapor pressure on deposition in the lungs of a pressurized MDI aerosol in 10 subjects with obstructive airway disease. Radiolabeled