preclearance under existing NDA's, currently marketed OTC MDI drug products are not in question. However, the agency would have great concerns about the safety and effectiveness of new OTC drug products entering the marketplace without agency preclearance, for the reasons discussed in this document. The agency would have still greater concerns if new non-CFC-containing propellants were to be used in new products without agency evaluation of the reformulated products.

The agency noted in the final monograph for OTC bronchodilator drug products (51 FR 35326 at 35334) that the use of a CFC-containing self-pressurized container of a drug product will not result in the drug product being adulterated and/or misbranded provided the drug has an approved NDA. OTC MDI bronchodilator drug products that contain a CFC-containing propellant may therefore be marketed only under an approved NDA. Similarly, based on the intended phaseout of CFC-containing propellants in MDI aerosol dosage forms, the agency now concludes that it is essential that any MDI aerosol reformulation (including use of a new propellant) or component design alterations require premarket approval under an approved NDA to ensure the safety and effectiveness of the bronchodilator drug product.

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D. International Workshops and FDA Advisory Committee Discussions

Both the agency and the international community recognize the need to significantly reduce the production and consumption of substances which deplete the ozone layer. One class of substances currently under discussion are CFC's, which are highly resistant to biotic and abiotic decomposition and. therefore, pass undecomposed from the atmosphere to the stratosphere. Because of the deleterious effect of CFC's on the ozone layer, international consensus is that products containing CFC propellants, including MDI's, must be phased out or reformulated with a suitable non-CFC-containing propellant.

Several international workshops and agency advisory committee discussions have taken place to identify the regulatory requirements necessary to determine the safety and effectiveness of reformulated MDI bronchodilator drug products. On December 15, 1993, the Commission of the European Communities (CEC) issued a guideline report (Ref. 1) that identifies quality, safety, and effectiveness considerations to be addressed by companies in submissions in support of replacements for CFC propellants in an already authorized medicinal product. The report specifies the following major clinical requirements: (1) Ensure safety and effectiveness of the reformulated product, and (2) demonstrate that the change in formulation due to a change in excipients has no adverse effect on the benefit/risk ratio to users in comparison with the existing CFCcontaining product.

The report stated that clinically validated studies, including pharmacodynamic, pharmacokinetic, and in vivo and/or in vitro deposition studies, can be used to determine the effectiveness of the reformulated MDI product. Data on the absorption, distribution, and retention of the new propellant(s) in adults and children under 12 years of age following inhalation are needed to assess the likely systemic burden of the propellant(s) (e.g., heart rate, serum potassium, and assessment of paradoxical bronchospasm). The report cautioned that any change in excipients (including propellants) might result in changes in drug deposition patterns within the lung and might affect absorption and systemic safety. The

guideline emphasizes that monitoring the introduction of new non-CFCcontaining products is necessary in order to identify rare or unexpected adverse effects.

The Drug Information Association held a workshop on October 18 and 19, 1993 (Ref. 2) to discuss the regulatory and data requirements needed to reassure the clinical community and patients that reformulated MDI aerosol products are safe and effective. The workshop summarized the chemistry and manufacturing concerns of the CEC and other regulatory health organizations regarding the safety and effectiveness of reformulated MDI aerosol products. Participants discussed how small changes in MDI aerosol product formulation or component design can significantly affect the safety and effectiveness of a bronchodilator aerosol drug product. Careful consideration was given to bioequivalence issues involving puff-topuff variability, unit spray content, storage conditions, new propellants, particle size, and extractables and impurities profiles. The workshop's conclusions agreed with the international approach to premarket approval of pressurized MDI bronchodilator drug products. These conclusions would apply to both prescription and OTC drug products.

On September 14 and 15, 1993, the agency's Generic Drugs Advisory Committee with representation from the Pulmonary-Allergy Drugs Advisory Committee (hereinafter referred to as the Committee) met to discuss the agency's current policy concerning the documentation of bioequivalence for suspension and solution MDI aerosol products (Ref. 3). The Committee stated that premarket approval is essential to ensure the identity, strength, quality, and purity of generic MDI aerosol products. In addition to the in vitro data required for a new or reformulated existing MDI aerosol under an approved NDA, the Committee recommended in vivo bioequivalence documentation for generic suspension MDI aerosol products for oral inhalation. The Committee also recommended the following bioequivalence testing guidelines for MDI oral inhalation solution products: (1) If excipients are essentially the same, in vitro studies only would be acceptable with the same device, and (2) whether the excipients are or are not essentially the same, in vivo and in vitro studies are required with different devices. Furthermore, the Committee concluded that products with excipients that are not essentially the same may need additional studies (e.g., for safety) (Ref. 3).