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Part III

**Department of
Health and Human
Services**

Food and Drug Administration

**21 CFR Parts 310 and 341
Cold, Cough, Allergy, Bronchodilator, and
Antiasthmatic Drug Products for Over-
The-Counter Human Use; Proposed
Amendment of Monograph for OTC
Bronchodilator Drug Products; Proposed
Rule**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310 and 341

[Docket No. 94N-0247]

RIN 0905-AA06

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-The-Counter Human Use; Proposed Amendment of Monograph for OTC Bronchodilator Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the final monograph for over-the-counter (OTC) bronchodilator drug products to remove pressurized metered-dose aerosol container dosage forms for the ingredients epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride. This action is being taken because the OTC marketing of such drug products will require an approved application containing certain information not required by the monograph. The agency is also proposing to amend the regulation that lists nonmonograph active ingredients to add any ingredient(s) in a pressurized metered-dose aerosol container for OTC bronchodilator drug products. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments or objections by May 23, 1995; written comments on the agency's economic impact determination by May 23, 1995. FDA is proposing that any final rule that may issue based on this proposal become effective 30 days after its date of publication in the **Federal Register**.

ADDRESSES: Submit written comments or objections to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5000.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of October 2, 1986 (51 FR 35326), FDA issued a final monograph establishing conditions

under which OTC bronchodilator drug products are generally recognized as safe and effective and not misbranded. Section 341.76(d)(2)(i) (21 CFR 341.76(d)(2)(i)) provides for products containing epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride for use in a pressurized metered-dose aerosol container (hereinafter referred to as an inhaler or MDI).

In the final monograph (51 FR 35326 at 35333, comment 10), the agency responded to a comment that agreed that bronchodilators in a MDI dosage form should be available OTC, but objected to allowing them to enter the marketplace without preclearance by FDA through approval of applications (new drug (NDA) or abbreviated new drug (ANDA)). The comment contended that the complexities of pressurized MDI aerosol dosage forms for inhalation are such that agency preclearance is necessary to assure the safety and effectiveness of these drug products. The comment stated that the proposed rulemaking was deficient because it did not discuss the complexities of the design, control, manufacture, and market use of MDI drug delivery systems and the monograph did not set forth manufacturing standards for MDI delivery systems. The comment suggested that a full application would not be required, but that preclearance of "manufacturing controls information and bioavailability data" by the agency should be required.

Based on the data and other information available when the final monograph for OTC bronchodilator drug products was published, the agency disagreed with the comment, stating its belief that the state of the technology for MDI drug delivery systems was such that bronchodilator drug products in MDI dosage forms could be generally recognized as safe and effective. The agency indicated that it had reviewed data available at that time from its Drug Product Problem Reporting System computerized data base for all bronchodilator drug products in MDI dosage forms. The agency noted that no problems related to metered-dose mechanisms had been reported for these OTC drug products between 1980 and 1984. Therefore, the agency concluded that the technology available to produce reliable MDI mechanisms allowed the agency to generally recognize MDI dosage forms for OTC bronchodilator drug products containing epinephrine preparations as specified in the final monograph.

The agency also pointed out in the final rule (51 FR 35326 at 35334), however, that agency regulations in 21

CFR 2.125(d) state that the use of a chlorofluorocarbon (CFC) as a propellant in a self-pressurized container of a drug product will not result in the drug product being adulterated and/or misbranded provided the drug has an NDA. Therefore, all OTC bronchodilator drug products in MDI's that contain a CFC as a propellant (which include all marketed OTC MDI products containing epinephrine) were marketed only under an approved application. The agency anticipated that MDI products would continue to contain a CFC propellant and that marketing would continue under approved applications containing information on manufacturing controls for the MDI.

Since publication of the final monograph for OTC bronchodilator drug products, several developments have changed the agency's views about pressurized MDI dosage forms. These include: (1) Legislation that requires a phaseout of ozone-depleting substances, including CFC propellants in MDI drug products; (2) the need for safety data on the alternative propellants that will replace CFC's in MDI dosage forms, as well as evidence that the new MDI's deliver the drug effectively; (3) recent publications reporting chemistry, manufacturing, and controls problems resulting from changes to the container and closure system of redesigned MDI dosage forms; (4) the need for safety and effectiveness data for the new drug products as a result of these chemistry, manufacturing, and controls changes; and (5) international workshops and FDA advisory committee discussions focusing on regulatory requirements for modifications to an approved innovator MDI and bioequivalence of generic MDI aerosol products. These issues have caused the agency to reconsider the inclusion of MDI dosage forms in the final monograph for OTC bronchodilator drug products. The agency has determined that an assessment of the safety and effectiveness of each product must be made. The agency's discussion of these issues follows.

II. New Issues That Affect MDI Drug Products

A. Proposed Replacement of CFC Propellants

The Clean Air Act Amendments of 1990, Title VI (Pub. L. 101-549), signed into law on November 15, 1990, requires the phaseout of ozone-depleting substances. The Environmental Protection Agency (EPA) has promulgated regulations implementing the phaseout provisions contained in section 604 of the Clean Air Act

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 asthma 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-CFC-containing 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 double-blind, 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 self-pressurized 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

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

- (1) Sciarra, J. J., and A. J. Cutie, "Aerosols," in Remington's Pharmaceutical Sciences, 18th ed., edited by A. R. Gennaro, Mack Publishing Co., Easton, PA, pp. 1694-1721, 1990.
- (2) Parkkali, L., "Comparison of Two Different Salbutamol Inhalation Aerosols in Release of Bronchial Obstruction," *Current Therapeutic Research*, 33:539-542, 1983.
- (3) Rees, P. J., and T. J. H. Clark, "The Importance of Particle Size in Response to Inhaled Bronchodilators," *European Journal of Respiratory Diseases*, Suppl. 119, 63:73-78, 1982.
- (4) 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.
- (5) Newman, S. P. et al., "The Effect of Changes in Metered Volume and Propellant Vapour Pressure on the Deposition of Pressurized Inhalation Aerosols," *International Journal of Pharmaceutics*, 11:337-344, 1982.
- (6) Dalby, R. N., and P. R. Byron, "Comparison of Output Particle Size Distribution from Pressurized Aerosols Formulated as Solutions or Suspensions," *Pharmaceutical Research*, 5(1):36-39, 1988.
- (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.
- (8) The 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.

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

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 (actuators). Puff-to-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

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.

References

- (1) 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.
- (2) Godin, J., and J. L. Malo, "Acute Bronchoconstriction Caused by Beclovent and Not Vancertil," *Clinical Allergy*, 9:585-589, 1979.
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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 CFC-containing 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-CFC-containing 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-to-puff 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).

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 racementhine 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

products. A statutory phaseout of CFC propellants used in these MDI aerosol products exists, although an exemption for MDI's for the treatment of asthma and COPD exists through 1997. Based on this phaseout, manufacturers may eventually decide or need to reformulate their existing MDI aerosol products with non-CFC-containing propellant systems. The agency considers it essential that any such reformulated products be evaluated and approved by the agency before they are marketed.

Consequently, the agency is proposing to amend § 341.76(d)(2) of the final monograph for OTC bronchodilator drug products to remove § 341.76(d)(2)(i)(a) and (d)(2)(i)(b). The agency proposes amending § 310.545(a)(6) for bronchodilator drug products by adding new paragraph (C) and listing thereunder "any ingredient(s) in a pressurized metered-dose aerosol container." The proposal would also remove § 341.76(e) from the final monograph because that information now appears in § 330.1(i) (21 CFR 330.1(i)) as part of the general labeling policy for OTC drug products.

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and, thus, is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. All currently marketed MDI aerosol drug products are currently the subject of an approved application. This proposed amendment of the monograph will not affect the status of any currently marketed product. As is currently the case for marketed MDI aerosol products, an approved application will be required for any product that is reformulated to contain a non-CFC propellant. Accordingly, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory

Flexibility Act, no further analysis is required.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC bronchodilator MDI aerosol drug products that contain epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride. Comments regarding the impact of this rulemaking on these drug products should be accompanied by appropriate documentation. A period of 75 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined that under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Interested persons may, on or before May 23, 1995, submit written comments or objections to the Dockets Management Branch (address above). Written comments on the agency's economic impact determination may be submitted on or before May 23, 1995. Three copies of all comments or objections are to be submitted, except that individuals may submit one copy. Comments and objections are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by supporting memorandum or brief. Comments and objections may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 341

Labeling, Over-the-counter drugs. Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 310 and 341 be amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512-516, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b-360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354-360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b-263n).

2. Section 310.545 is amended by adding new paragraphs (a)(6)(iv) and (d)(26) and by revising paragraph (d) introductory text to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(6) * * *

(iv) *Bronchodilator drug products.*

(A)—(B) [Reserved]

(C) Approved as of April 10, 1995. Any ingredient(s) in a pressurized metered-dose inhaler container.

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(26) of this section.

* * * * *

(26) April 10, 1995, for products subject to paragraph (a)(6)(iv)(C) of this section.

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTI-ASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

3. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

§ 341.76 [Amended]

4. Section 341.76 is amended by removing paragraphs (d)(2)(i) and (e); by redesignating paragraph (d)(2)(ii) as (d)(2), and revising the paragraph heading to read as follows:

§ 341.76 Labeling of bronchodilator drug products.

* * * * *

(d) * * *

(2) *For products containing epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride identified in § 341.16(d), (e), and (g) for use in a hand-held rubber bulb nebulizer.* * * *

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Dated: February 6, 1995.

William K. Hubbard,

Interim Deputy Commissioner for Policy.

[FR Doc. 95-5825 Filed 3-8-95; 8:45 am]

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