CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

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DIVISION OF BIOEQUIVALENCE

Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)*

INTRODUCTION

This Guidance describes the three in vitro tests required in support of the in vivo evaluation of the test product. The minimum size of lots undergoing in vivo and in vitro testing is also specified. These data are to be submitted to the Division of Bioequivalence. An additional set of in vitro testing requirements for the finished product release and stability program is available from the Division of Generic Drugs.

The recommended study design for demonstration of in vivo product bioequivalence is described in the Division of Bioequivalence "Guidance for In Vivo Bioequivalence Studies of Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)," revised February 9, 1989.

MINIMUM LOT SIZE

The in vivo bioequivalence study should be conducted on test product from a production lot or a lot manufactured under production conditions. In order to evaluate the uniformity of the production process, the entire volume of suspension must be packaged (canisters filled) and further, these packaged samples should be randomly selected for use in the bioequivalence study and the in vitro tests. The minimum number of filled canisters of the final product is 5,000 units. The batch record should accompany both the in vivo and the in vitro data submissions. It should be filed in the manufacturing and controls section of the application, as well as in the bioequivalence portion of the application.

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*This statement is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgment of the Division of Bioequivalence at this time. This statement, however, does not necessarily represent the formal position of the Center for Drug Evaluation and Research/the Food and Drug Administration and does not bind or otherwise obligate the Center/the Agency to the views expressed.

IN VITRO TESTS

The following tests are intended to characterize in part the in vitro performance of the test product relative to that of the innovator product(s). For tests described in this Guidance, the assembled canister and actuator units must be in the inverted position. The canisters should be primed prior to conducting the tests. The same canisters of test and reference products do not need to be utilized for each of the three in vitro tests. The lot numbers of the test and reference drug products used in these in vitro tests must be identical to those used in the in vivo bioequivalence study.

1. PARTICLE SIZE DELIVERED FROM THE ACTUATOR (MOUTHPIECE)

Several particle sizing methodologies have been reviewed (1). Of these, the most commonly used methods for pharmaceutical aerosol products are the cascade impactor, the optical microscope and other methods (e.g., the light scattering laser). Particle size distributions from the mouthpiece should be determined using at least two different methods since apparent particle size distributions may differ depending upon the particle sizing technique.

A. Cascade Impactor

The cascade impactor[1] provides an assessment of particle size distribution within the approximate aerodynamic diameter range of 0.5 - 32 microns. The following variables may be determined:

1. the total mass of drug released from the inhalation aerosol,
2. the quantity of drug collected at each location of the cascade impactor device,
3. the mass median aerodynamic diameter [MMAD; the diameter above and below which lies 50% of the mass of the particles (1)] and
4. the geometric standard deviation [GSD (2,3)].

The cascade impactor system should consist of a glass sampling chamber, the cascade impactor (with a minimum of six stages), a vacuum pump and a flow-meter. The glass chamber, custom made to specification, is required to allow the spray to atomize prior to entry into the impactor. Standard dimensions and shapes of the glass chamber have not been established, resulting in a variety of designs (see, for example, 4-7). The volume of the glass chamber should be not less than 0.5 liters and the length of the unobstructed path between the actuator orifice and the far side of glass chamber should be not less than 13 cm. This distance should be sufficient that no coalescence occurs in the chamber. The airflow rate through the chamber should permit collection of particles within the approximate MMAD of 0.5 - 32 microns; the associated airflow rate should be about 10 - 15 liters per minute. The specific chamber dimensions and shape and the airflow rate

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[1]Equipment is available commercially.

through the chamber should be described. Based upon the particular airflow rate, aerodynamic equivalent particle diameters[2] should be tabulated for each of the six or more impactor stages.

General procedures for using the cascade impactor are described in the Appendix.

B. Optical Microscope

The Pharmacopeial Forum states that most particles should be under 5 microns in diameter; only a minimum number should be over 10 microns (8). For Metaproterenol Sulfate Inhalation Aerosol, the USP procedure for particle size determination (9) should be followed, with the exception that the number and percentage of particles less than or equal to 5 microns and less than or equal to 10 microns should be reported for a representative field of view. The number and size of all individual crystalline particles (not agglomerates) more than 10 microns should also be reported. Particle sizes should be determined by the length measured along the longest axis. This procedure should be performed for three test and three reference canisters. For Albuterol Inhalation Aerosol, a similar procedure should be followed.

Instead of using a manual microscope, the firm may prefer to quantitate particle size with an automatic image analyzer (10).

For the aerosolized spray, the firm should submit quality control specifications for the percentage of particles less than or equal to 5 microns and less than or equal to 10 microns. In addition, a specification for an upper particle size limit below which 100% of particles exist should be submitted.

C. Other Methods

Comparative particle size distribution data determined using other methods will be considered, provided that the technical details such as the particle size range and reproducibility are acceptable. A complete description of instrument and experimental variables should be submitted.

For example, the firm may provide particle size distributions based upon the light scattering laser.[3] MMAD and GSD for particle size distributions based upon volume (mass) should be determined for actuations near the beginning, middle and end of the product's labeled number of actuations for three test, three reference and three placebo test canisters (nine determinations each for test, reference and placebo test products). The placebo test product must be identical in all regards to the 'active' test product except for the absence of drug. Particle size distributions should be determined at three different distances measured from the actuator orifice to the laser beam and/or three different delay times measured from spray initiation or detection. In addition to measurements based on mass, the firm should also submit particle size distribution data based on count (number).

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[2]50% cutoff diameters; the diameters of spherical particles of unit density for which 50% will impact on a given slide and 50% will pass onto a succeeding stage (7).

[3]Instruments are available commercially.

2. SPRAY PATTERN AND PLUME GEOMETRY

The spray pattern and plume geometry are used to characterize the performance of the valve and actuator. Various procedures and equipment have been described for evaluation of spray pattern and plume geometry (11,12,13 and references therein). A complete description of the experimental details employed should be submitted.

The spray pattern should be determined by impingement of the spray on a TLC (thin-layer chromatography) plate. Since the observed spray pattern may vary with the distance from the actuator orifice to the TLC plate, a spray pattern profile should be determined at each of three distances within the range of 2.5 - 7.5 cm. The spray pattern should be visualized by a method specific for the drug (propellants and other excipients should not be visualized). The spray patterns at each of the three distances should be consistent both within and between test product canisters and should resemble those of the reference product. Comparative spray pattern profiles should be submitted.

Plume geometry [side view(s) of the plume] data for test and reference products are optional, but submission is encouraged.

3. POTENCY

Potency is defined as the average amount of drug delivered per spray. For this Guidance, potency is based upon the total amount of drug delivered to the Unit Spray Sampling Apparatus by the number of sprays constituting a usual single dose, i.e., two or three sprays (see below). Average weight loss data (as described below) should also be submitted.

A. Metaproterenol Sulfate

The usual single dose of Metaproterenol Sulfate Inhalation Aerosol is two or three sprays. Using the Unit Spray Sampling Apparatus (14) and the described collection and assay procedures (9), the potency based upon three sprays near the beginning, middle and end of the product's labeled number of actuations should be reported. In the case of the 300 inhalation canister, potency should be based upon three sprays at Stations 11-13, three sprays at Stations 150-152 and three sprays at Stations 298-300. Prior to and after each group of three sprays, the canister is weighed. The average weight loss per spray is calculated for each group of three sprays. Potency and weight loss data determined near the beginning, middle and end of the product's labeled number of actuations should be tabulated for ten test and ten reference canisters.

Upper and lower limits for the mean amount of drug delivered per spray and for the amount of drug delivered per spray from individual sets of three sprays should be established based upon test product data. These limits should be expressed as the percent of labeled amount of drug delivered from the mouthpiece per spray and submitted as quality control specifications.

B. Albuterol

The usual single dose for Albuterol Inhalation Aerosol is two sprays. Data and specifications similar to that requested for Metaproterenol Sulfate Inhalation Aerosol should be submitted, based upon two sprays per dose. In the case of the 200 inhalation canister, potency should be based upon two sprays at Stations 11-12, two sprays at Stations 100-101 and two sprays at Stations 199-200.

Appendix - GENERAL PROCEDURES FOR A CASCADE IMPACTOR EMPLOYING GLASS COLLECTING SLIDES[4]

1. The number of actuations required for a single experiment will depend upon the drug entity and the analytical technique employed and should be determined prior to the study. The quantity of drug deposited on each slide must be sufficient for reliable assay, but not so much as to cause slippage to subsequent stages, which would bias the results. In general, no slide surface should be more than 2/3 covered (visual observation). To minimize analytical difficulties, adhesives on the slides should be avoided. The time period between actuations should be constant and the canister should be shaken between each actuation. Following the final actuation, the airflow should be maintained for a time adequate to collect all particles.

2. The amount of drug deposited at each location should be determined by chemical assay. The amounts of drug deposited at each of the following locations should be reported:

a. on actuator
b. on sampling/atomizing chamber
c. on sampling plate #1 plus wall #1
d. on sampling plate #2 plus wall #2
e. repeat (d) for each successive plate plus wall of stages #3,4,5 and 6
f. on filter and/or final collection port

3. Considering the total mass of drug on all sampling plates plus walls and filter as 100%, the firm should tabulate the cumulative percentage of drug less than the stated diameter versus the aerodynamic particle diameters. A log normal distribution curve should be prepared and the MMAD and GSD should be reported (2).

4. Particle size distributions should be determined three times on each of three canisters of the test product (nine determinations). Determinations should be made near the beginning, middle and end of the product's labeled number of actuations. Thus, for a 200 inhalation product in which 15 actuations are required per experiment, the firm should prime the can with 10 actuations, place a new (drug-free) actuator on the can and actuate 15 times (Stations 11-25) into the cascade impactor. The particle size distribution is determined for this experiment. To confirm that 15 complete actuations were discharged, the difference in canister weight before actuation 11 and after actuation 25 should be reported.

In a second experiment on the same canister, the canister is discharged 50 times and a new actuator placed on the canister. The particle size distribution of the drug from Stations 76-90 is then determined. In a third experiment, the particle size distribution of the drug from Stations 186-200

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[4]The procedures described may not apply to certain types of cascade impactors. In such a case, any applicable procedures should be followed and applicable tests should be performed.

is determined. The weight of the material actuated into the cascade impactor as a result of these experiments should also be reported. This procedure is performed on three test product and three reference product canisters.

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