Contains Nonbinding Recommendations

Draft Guidance on Ciclesonide

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Active ingredient: Ciclesonide

Form/Route: Aerosol, Metered/Nasal

Recommended studies: In vitro studies

In vitro studies are recommended to establish bioequivalence (BE) for Ciclesonide Nasal Aerosol, a locally acting nasal solution product, on the conditions that

- the formulation of the test product (T) is qualitatively (Q1) and quantitatively (Q2) the same as the reference product (R);
- the container closure system of T is comparable to R;
- T has a dose counter.

The recommended in vitro BE studies described below should be conducted using at least 3 batches each of T and R products with no fewer than 10 units of each batch.

(1). Single Actuation Content (SAC) through Container Life

Design: The SAC through container life should be based on a single actuation to determine the delivered (emitted or ex-actuator) drug mass from primed units at the beginning (B), middle (M) and end (E) lifestages of the product. The term B lifestage, M lifestage, and E lifestage indicate the first actuation(s) following the labeled number of priming actuations, the actuation(s) corresponding to 50 percent of the labeled number of full medication doses, and the actuation(s) corresponding to the label claim number of full medication doses, respectively. A suitable apparatus or the USP <601> apparatus A may be used to collect the delivered drug mass following a single actuation. The delivered drug mass should be expressed both as the actual amount and as a percentage of label claim.

Equivalence based on: Delivered drug mass per single actuation using population bioequivalence (PBE) analysis.

(2). Droplet Size Distribution by Laser Diffraction

Design: Droplet size distribution should be determined using laser diffraction or other appropriately validated methodology at the B and E lifestages of the

product. Laser diffraction instrumentation provides plots of obscuration (optical concentration) or percent transmission (%T) and droplet size distribution (D_{10}, D_{50}, D_{90}) over the entire life of a single spray. Information on instrument setup and operation conditions should be submitted to the Agency. The instrument should be operated within the manufacturer's recommended obscuration or percent T range to avoid or minimize multiple scattering (due to high droplet concentration). Droplet size distribution should be characterized at the fully developed phase of a single actuation at two distances from the nose piece tip that eliminate or minimize beam steering resulting from refractive index effects due to evaporation of propellant, if possible. Mean D_{10}, D_{50}, D_{90} values for a given bottle or canister should be computed from the mean of up to three consecutive sprays from that unit at each lifestage. Span $((D_{90} - D_{10})/D_{50})$ can be computed from these data.

Equivalence based on: D_{50} and span using PBE analysis.

(3). Aerodynamic Particle Size Distribution (APSD) by Cascade Impactor (CI)

Design: An induction port in one liter or other appropriate size fitted with a multistage cascade impactor (CI), either USP Apparatus 1 or Apparatus 6 for metered-dose inhalers, or other appropriate apparatus may be used to determine APSD using a validated assay. Information on instrument setup and operation conditions should be submitted to the Agency. The APSD determination of each unit should be performed at the B lifestage of the product and operated at the standard 28.3 liter per minute configuration with the minimum number of actuations justified by the sensitivity of the assay. Deposition data on each deposition site including the valve stem, actuator, nosepiece adaptor, induction port, induction port adaptor, and each impactor stage plus the filter, should be reported in mass unit for profile analysis. Mass balance accountability should be reported based on sum of all deposition sites. The total mass of drug collected on all stages and accessories is recommended to be within 85-115% of label claim for the emitted dose on a per actuation basis.

Equivalence based on: Deposition profile comparison.

(4). Spray Pattern

Design: The spray pattern may be evaluated by non-impaction (laser light sheet and high-speed digital camera), impaction (thin-layer chromatography plate impaction), or other suitable method. The spray pattern test should be performed at two different distances (the plume area is stable within the range of 3 to 6 cm) from the nose piece tip at the B lifestage of the product based on a single actuation.

Equivalence based on: Ovality ratio (ratio of longest diameter to shortest diameter, D_{max}/D_{min}) and area within the perimeter of the true shape (not within the fitted geometric shape) for automated analysis, or ovality ratio and D_{max} for manual analysis using PBE analysis. The spray shape should be compared qualitatively.

(5). Plume Geometry

Design: The plume geometry may be evaluated by high-speed photography, a laser light sheet and high speed digital camera, or other suitable method. Plume geometry tests should be performed at the B lifestage of the product based on a single actuation. Plume angle and plume width should be reported at a single delay time while the fully developed phase of the plume is still in contact with the nasal actuator nose piece tip.

Equivalence based on: Plume angle and plume width. The plume angle should be based on the conical region of the plume extending from a vertex that occurs at or near the nose piece tip. The plume width should be measured at a distance equal to the greater of the two distances selected for characterization of the spray pattern. The ratio of the geometric mean of the three batches of T to that of the three batches of R, based on log transformed data, should fall within 90 – 111% for plume angle and plume width.

(6). Priming and Repriming

Design: T should be primed by wasting the same or smaller number of actuations as required for R to deliver the labeled ex-actuator dose/amount. The priming test should be performed at the B lifestage of the product. The repriming test should be performed following storage for the specified period of non-use after initial use and/or other conditions (e.g., dropping), if the R product labeling provides such repriming information. Priming and repriming tests should be based on the emitted dose (ex-actuator) of a single actuation immediately following the specified number of priming (B lifestage) or repriming actuations in the labeling. The priming and repriming data should be provided following storage in multiple orientations (e.g., valve down or upright positions).

Equivalence based on: The geometric mean emitted dose per single actuation of the three batches of T falls within 95 – 105% of label claim.

Waiver request of in-vivo testing: Not applicable
