Active Ingredient: Talc

Dosage Form; Route: Aerosol, intrapleural

Strength: 4000 mg/spray

Recommended Studies: In vitro studies

FDA recommends the following in vitro studies to establish Bioequivalence (BE) of the Test (T) and Reference (R) intrapleural aerosol products containing talc.

In Vitro Studies

FDA recommends that applicants conduct the following in vitro studies for the T and R products.\(^1\) Use at least three batches each of the T and R products, with no fewer than 10 units from each batch. FDA recommends that three primary stability batches be used to demonstrate in vitro BE, if appropriate. The three batches of T product should be manufactured from, at minimum, three different batches of drug substance(s), excipient(s), and container/closure system.

1. **Type of study: Delivered Amount**

   **Design:** The delivered amount test should be performed using a similar method described in U.S. Pharmacopoeia (USP) <603> for containers fitted with continuous valve delivery, or another appropriate method may be used to determine the delivered amount using a validated assay.

   **Additional comments:** The selected method should specifically measure delivered amount of talc and not delivered amount of the total formulation; USP <603> Delivered Amount method should be adapted accordingly.

   **Equivalence based on:** Population Bioequivalence (PBE) analysis of delivered amount of talc. Please refer to the product-specific recommendation for Budesonide Inhalation Suspension for additional information regarding PBE.\(^2\)

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1 If the R product is available with more than one size of delivery nozzle, the in vitro BE tests should be conducted using the delivery nozzle with the longest length, provided the internal diameters of the other delivery nozzles are the same as that of the longest delivery nozzle.

2. **Type of study**: Delivery Rate  
   The delivered amount test should be performed using a similar method described in USP <603> for containers fitted with continuous valve delivery, or another appropriate method may be used to determine the delivery rate using a validated assay.  
   Additional comments: The selected method should specifically measure the delivery rate of talc, and not the delivery rate of formulation; USP <603> Delivery Rate method should be adapted accordingly.  

**Equivalence based on**: PBE analysis of delivery rate of talc.

3. **Type of study**: Spray pattern  
   **Design**: The spray pattern test should be performed at two different distances from the delivery nozzle orifice. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm from the R delivery nozzle. Impaction (thin-layer chromatography plate impaction), non-impaction (laser light sheet technology), or other suitable method may be used to determine the spray pattern.  
   **Additional comments**: Spray pattern should be measured quantitatively in terms of ovality ratio and area within the perimeter of the true shape (to include a high proportion, e.g., 95% of the total pattern) for the automated analysis or ovality ratio and D\text{max} for the manual analysis. Ovality ratio is defined as the ratio of D\text{max} to D\text{min}. D\text{max} and D\text{min} are the longest and shortest diameters, respectively, that pass through the center of mass or the center of gravity, as appropriate.  

**Equivalence based on**: At two selected distances, (i) qualitative comparison of spray shape, and (ii) PBE analysis of ovality ratio and area within the perimeter of the true shape or ovality ratio and D\text{max}.

4. **Type of study**: Plume geometry  
   **Design**: The timed-sequence sound-triggered flash photography method, laser light sheet technology, or other suitable method may be used to determine the plume geometry at the appropriate post-actuation delay time.  
   **Additional comments**: Plume geometry measurements should be reported at a single delay time while the fully developed plume is still in contact with the delivery nozzle. Plume geometry should be measured quantitatively in terms of plume angle and width. The plume angle is based on the conical region of the plume extending from a vertex that occurs at or near the delivery nozzle. The plume width is measured at a distance equal to the greater of the two distances selected for characterization of the spray pattern.  

**Equivalence based on**: Ratio of the geometric mean of the three batches of T to that of the three batches of R (based on log transformed data) for plume angle and width, which should fall within 90 - 111%.

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3 The distance between the delivery nozzle orifice and point of spray pattern measurement should be the same for T and R.
Additional Information

Formulation:

FDA recommends that the T formulation be qualitatively (Q1)\(^4\) and quantitatively (Q2)\(^5\) the same as the R product.

Device:

Applicants should refer to the FDA Guidance for Industry entitled, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017), which provides the Agency’s current thinking on the identification and assessment of any differences in the design of the user interface for a proposed generic drug-device combination product when compared to its RLD.

FDA recommends that applicants consider the following characteristics of the R product in designing the T product:

- External operating principles and external critical design attributes of the R product
- Continuous delivery valve
- Size and shape of the R product
- Dimensions of the delivery nozzle(s)

In addition, studies should be conducted to support the functionality, accuracy, and robustness of the proposed T product.

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\(^4\) Q1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.

\(^5\) Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.