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Draft Guidance on Fluticasone Propionate

May 2025

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Active Ingredient: Fluticasone propionate

Dosage Form: Spray, metered

Route: Nasal

Strength: 0.093 mg

Recommended Studies: Seven in vitro bioequivalence studies

FDA recommends the following in vitro studies to establish bioequivalence of test (T) and reference standard (RS) metered nasal spray products containing fluticasone propionate. The specific recommendations provided here for fluticasone propionate spray, metered supersede information provided in the most recent version of the FDA draft guidance for industry on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*.[a]

FDA recommends that prospective applicants conduct the following in vitro bioequivalence studies on samples from each of three or more batches of the T product and three or more batches of the RS product, with no fewer than 10 units from each batch. FDA recommends that three primary stability batches be also used to demonstrate in vitro bioequivalence. The three batches of the T product should be manufactured from, at minimum, three different batches of the drug substance, three different batches of critical excipients, and three different batches of the device components (e.g., pump and actuator) proposed for the final device configuration of the commercial product. The T product should consist of the final device constituent part and final drug constituent formulation intended to be marketed.

For comparative in vitro studies, T and RS products should be studied under the same instrumental conditions. Actuation should be conducted in a manner that removes potential

operator bias, either by employing automatic actuation or by employing blinded procedures when manual actuation is used, where feasible. The analyst performing the post-actuation evaluations of the collected data should be blinded to the identity of the samples. Method validation should be performed using RS product, and the lot number(s) used for the validation should be provided. The following in vitro bioequivalence tests are recommended:

1. Type of study: Single Actuation Content (SAC)
   Design: The SAC test should be performed at the beginning (B) and end (E) lifestages of the product.[1] An appropriate apparatus may be used to determine the SAC using a validated assay. The number of actuations per determination should be one.

   Equivalence based on: The SAC comparison of the T and RS products is based on the population bioequivalence (PBE). Refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929)[b] for additional information regarding PBE analysis procedures.

2. Type of study: Droplet Size Distribution by Laser Diffraction
   Design: Droplet size distribution should be determined using laser diffraction or an appropriately validated alternate methodology. Droplet size distribution should be measured for the fully developed phase only at the B and E lifestages using two compressed air flow rates within a range of 50 L/min to 80 L/min through the mouthpiece separated by 20 L/min or more. The volume of air drawn through the delivery system should be 4 L. It is recommended that the studies be performed at two distances within a range of 2 to 7 cm from the tip of the nosepiece with the two distances separated by 3 cm or more.[2]

   Additional Comments: Single spray droplet size distribution and span should be reported based on volume (mass). Mean D_{10}, D_{50}, D_{90} values for a given unit can be computed from the mean of up to three consecutive sprays from that unit at each lifestage. Span can be computed as $((D_{90} - D_{10})/D_{50})$. To assess precision, the data of each spray should also be reported.

   Equivalence based on: PBE of D_{50} and span at two selected distances.

3. Type of study: Spray Pattern
   Design: The spray pattern test should be performed at the B lifestage of the product using two compressed air flow rates within a range of 50 L/min to 80 L/min through the mouthpiece separated by 20 L/min or more and at two different distances from the nosepiece. The volume of air drawn through the delivery system should be 4 L. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm from the RS nosepiece tip. Impaction (thin-layer chromatography plate impaction), non-

[1] Based on the labeled number of actuations, the terms B lifestage, M lifestage, and E lifestage represent the first actuation(s) following the priming, the actuation(s) corresponding to 50 percent of the labeled number of actuations(s), and actuation(s) corresponding to the labeled number of actuations, respectively.
[2] The distance between the nosepiece tip and the laser beam should be the same for both T and RS products.

impaction (laser light sheet and high-speed digital camera), 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 (to include a high proportion, e.g., 95 %, of the total pattern) of the true shape for the automated analysis, or ovality ratio and D_{max} for the manual analysis. Ovality ratio is defined as the ratio of D_{max} to D_{min}. D_{max} and D_{min} are the longest and shortest diameters, respectively, that pass through the center of mass or the center of gravity, as appropriate. The number of sprays per spray pattern should preferably be one.

Equivalence based on: At two selected distances, (i) qualitative comparison of spray shape, and (ii) PBE analysis of ovality ratio and area for automated analysis, or ovality ratio and D_{max} for manual analysis.

4. Type of study: Plume Geometry
Design: The plume geometry test should be performed at B lifestage of the product using two compressed air flow rates within a range of 50 L/min to 80 L/min through the mouthpiece separated by 20 L/min or more. The volume of air drawn through the delivery system should be 4 L. The time-sequenced, sound-triggered flash photography method, laser light sheet technology, and high-speed digital camera, 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 nosepiece tip. Plume geometry should be measured quantitatively in terms of plume angle and width of one side view. The plume angle is based on the conical region of the plume extending from a vertex that occurs at or near the nosepiece tip. 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 RS (based on log-transformed data) for both plume angle and width, which should fall within 90-111% of plume angle and plume width.

5. Type of study: Priming and Repriming
Design: Priming and repriming tests should be based on the emitted dose of a single actuation immediately following the specified number of priming or repriming actuations specified in the reference listed drug (RLD) product labeling. 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 RLD product labeling provides such repriming information.

Additional comments: For BE evaluation, the priming and repriming tests should be based on products stored in the valve-upright position, with the exception of a nasal spray for which the RLD labeling recommends storage in the valve-down position. The priming data can be based on the SAC data at the B lifestage. Repriming would be similarly established based on a single actuation following the specified number of repriming actuations in the RLD product labeling.

Equivalence based on: PBE analysis of the emitted dose of a single actuation immediately following the specified number of priming or repriming actuations specified in the RLD product labeling.

6. Type of study: Drug Particle Size Distribution
Design: The emitted drug particle size distribution (PSD) should be determined using an optimized and validated analytical method (e.g., morphologically-directed Raman spectroscopy). The emitted drug PSD should be measured at the B lifestage of the product.

Additional comments: Samples for drug PSD measurement should be prepared to ensure that the drug is in its suspended state post-actuation. The sample preparation method and selected particle sizing methodology should be adequately optimized and validated to demonstrate the adequacy of the selected method in accurately and reliably identifying and measuring the size of the drug particles without any interference from the excipient particles that are also suspended in the formulation. Drug PSD and span should be reported. An orthogonal method may be required if the selected methodology is not sensitive to measure particles beyond a certain size range.

Equivalence based on: PBE analysis on D50 and span.

7. Type of study: Dissolution
Design: Dissolution tests are recommended to be performed at the B lifestage of the product. An appropriate apparatus (e.g., USP <711> Apparatus 2, USP <724> Apparatus 5, or Transwell system) may be used to determine dissolution measurements using a sufficiently developed and validated method to support its sensitivity in detecting differences in performance between the T and RS products.

Additional comments: Information should be provided to explain the selection of dissolution method parameters such as equipment, product dose amount, media, media volume, stirring/agitation rate, sampling times, etc. The submitted study method information should detail each parameter value and its sensitivity and reproducibility. Dissolution tests should be performed on samples with sufficiently similar drug mass for T and RS products. Dissolution measurements should be reported in mass units and as percent drug dissolved.

Equivalence based on: Comparative analysis of dissolution profiles should be established using an appropriate statistical method (e.g., model independent approach using similarity factor (f_2)). For more information on calculation of f_2 factor, refer to the most recent version of the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.[a]

In vitro bioequivalence data submission recommendations:

Refer to the to the most recent version of the FDA product-specific guidance on *Fluticasone Propionate Metered Nasal Spray* (NDA 020121),[b] which provides recommendations on the in vitro bioequivalence data submission recommendations.

Additional information:

Formulation:
To demonstrate bioequivalence, the T product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the RS product that may significantly affect the local or systemic availability of the active ingredient. For example, the test product can be qualitatively (Q1)[3] and quantitatively (Q2)[4] the same as the RS product to satisfy no difference in inactive ingredients.

Device:
The RLD is presented in a bottle with a nasal pump, actuator, and mouthpiece. The nasal pump, actuator, and mouthpiece are the device constituent part.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the T device including:

- Metered, multi-dose format
- Flexible mouthpiece
- Dose delivery is pump actuated and breath assisted
- Number of doses

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

[3] Q1 (Qualitative sameness) means that the T formulation uses the same inactive ingredient(s) as the reference standard (RS) formulation.
[4] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T formulation are within ± 5% of those used in the RS formulation.

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[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[b] For the most recent version of the product-specific guidance, check the FDA product-specific guidance web page at: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.