

*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

## **Draft Guidance on Budesonide**

**August 2023**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

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<b>Active Ingredient:</b>	Budesonide
<b>Dosage Form:</b>	Spray, metered
<b>Route:</b>	Nasal
<b>Strength:</b>	0.032 mg/spray
<b>Recommended Studies:</b>	Two options: (1) eight in vitro bioequivalence studies, or (2) six in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

FDA recommends the following in vitro or in vitro and in vivo studies to establish bioequivalence of test (T) and reference (R) nasal spray products containing budesonide. The recommendations provided here supersede information provided in the most recent version of the FDA draft guidance for industry on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*.<sup>a</sup>

### **I. Option 1: Eight in vitro bioequivalence studies**

To be eligible for this recommended option to demonstrate bioequivalence, the T and R product formulations should be qualitatively (Q1)<sup>1</sup> and quantitatively (Q2)<sup>2</sup> the same, and the nasal spray device (e.g., pump and actuator design) of the T product is appropriate for an abbreviated new drug application (ANDA).

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<sup>1</sup> Q1 (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.

<sup>2</sup> Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T product are within ± 5% of those used in the R product.

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 R 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. The following in vitro bioequivalence tests are recommended:

1. Single actuation content (SAC)
2. Droplet size distribution by laser diffraction
3. Drug in small particles/droplets
4. Spray pattern
5. Plume geometry
6. Priming and repriming
7. Drug particle size distribution
8. Dissolution

Additional comments: Refer to the most recent version of the FDA product-specific guidance on *Fluticasone Propionate Nasal Metered Spray* (NDA 020121)<sup>b</sup> for recommendations on design and equivalence criteria for the aforementioned in vitro bioequivalence studies, and general recommendations on the conduct of the in vitro bioequivalence studies and data submission.

## **II. Option 2: Six in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study**

If the T product formulation is not Q1 and Q2 the same as the R product formulation and the nasal spray device (e.g., pump and actuator design) of the T product is appropriate for an ANDA, then in vitro bioequivalence studies #1 through #6 (as described in Option 1), and the following in vivo studies are recommended to establish bioequivalence between the T and R products:

### **One in vivo bioequivalence study with pharmacokinetic endpoints:**

1. Type of study: Fasting  
Design: Single-dose, two-way crossover  
Strength: 0.032 mg/spray  
Dose: 0.256 mg, administered as four sprays in each nostril  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments: (1) Follow the reference listed drug (RLD) labeling for the method of drug administration; (2) The analytical method should have sufficient sensitivity to adequately quantify the concentration of budesonide in plasma.

**Analyte to measure:** Budesonide in plasma

**Equivalence based on:** AUC and  $C_{\max}$  for budesonide. The 90% confidence intervals for the geometric mean T/R ratios of AUC and  $C_{\max}$  should fall within the limits of 80.00% - 125.00%.

**One comparative clinical endpoint bioequivalence study:**

These recommendations are specific to this product and may not be appropriate for comparative clinical endpoint bioequivalence studies of any other product, including any other dosage form or strength of budesonide.

1. Type of study: Comparative clinical endpoint bioequivalence study  
Design: Randomized, double-blind, three-arm, placebo-controlled, parallel group  
Strength: 0.032 mg/spray  
Dose: 0.128 mg once daily, administered as two sprays in each nostril  
Subjects: Adult males and non-pregnant, non-lactating females with seasonal allergic rhinitis (SAR)  
Additional comments: Specific recommendations are provided below.

**Additional comments regarding the comparative clinical endpoint bioequivalence study:**

1. FDA recommends conducting a single comparative clinical endpoint bioequivalence study in the treatment of SAR consisting of 2 periods: a 7-day, single-blinded, placebo run-in period (Study Days -7 to -1) to establish a baseline and to identify placebo responders, followed by a 14-day treatment period (Study Days 1 to 14). Prime each product as per the RLD labeling prior to initial dosing. During the placebo run-in period, all subjects are to receive the placebo vehicle administered as two sprays in each nostril once daily for 7 days. All subjects who qualify after the placebo run-in period are to be randomized to receive the T product, R product, or placebo (vehicle) control during the treatment period, administered as two sprays in each nostril once daily for 14 days. The primary endpoint is the difference in the mean change in reflective total nasal symptom scores from baseline through the treatment period.
2. A multi-center study is recommended to avoid potential investigator bias.
3. A double dummy design is not recommended for study blinding due to a concern that the doubled fluid volume may result in washing the drug from its nasal deposition sites, potentially resulting in an altered safety and efficacy profile.
4. Inclusion criteria (the prospective applicant may add additional criteria):
  - a. Males and non-pregnant, non-lactating females, 18 years of age and older. For female subjects of childbearing potential: agreement to practice an approved method of birth control
  - b. History of SAR
  - c. A positive test for relevant specific allergens (e.g., allergen skin test)

- d. Demonstration of significant symptoms during screening and randomization visits, measured by reflective total nasal symptom score (rTNSS) of, for example, at least 6 at the time of enrollment (see items 7 and 8)
5. Exclusion criteria (the prospective applicant may add additional criteria):
  - a. Pregnant or lactating or planning to become pregnant during the study period
  - b. Asthma, except for mild intermittent asthma
  - c. Active or quiescent tuberculous infections of the respiratory tract; untreated local or systemic fungal, bacterial, viral, or parasitic infections
  - d. Presence of glaucoma, cataracts, ocular herpes simplex, conjunctivitis, or other eye infection
  - e. Presence of any nasal mucosal erosion, nasal septal ulcers, or septum perforation on focused nasal examination at screening or randomization
  - f. Recent nasal sinus surgery or nasal trauma
  - g. Other nasal disease(s) likely to affect deposition of intranasal medication, such as acute or chronic sinusitis, rhinitis medicamentosa, nasal polyps, or nasal septal abnormalities
  - h. Presence or history of any clinically significant condition that, in the opinion of the investigator, would compromise the safety of the subject or the conduct of the study
  - i. Respiratory tract infection requiring antibiotic within 4 weeks prior to screening
  - j. Use of any investigational drug within 30 days prior to screening
  - k. Initiation of immunotherapy or its dose escalation for 1 month prior to screening and during the study (it is acceptable if subjects are on a stable regimen for at least 30 days prior to screening and they should maintain the same dose during the study)
  - l. Use of any prohibited medications and treatments (e.g., systemic or intranasal decongestants, anti-allergy therapy as antihistamines, leukotriene antagonists, corticosteroid therapy, and potent cytochrome P450 3A4 inhibitors such as ketoconazole) prior to screening [the prospective applicant should provide a list of medications and treatments, with justification/rationale provided for duration of the washout period prior to screening]
  - m. Planned travel outside the study area from the time of enrollment to completion of the study
  - n. Known hypersensitivity to budesonide, similar drugs, or to any of the components of the study medications
6. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as systemic or intranasal decongestants, anti-allergy therapy as antihistamines, leukotriene antagonists, corticosteroid therapy (parenteral, intranasal, oral, inhaled, or potent topical), anti-IgE antibodies (e.g., omalizumab), immunosuppressive therapy, and potent cytochrome P450 3A4 inhibitors such as ketoconazole.
7. Subjects should self-score their symptoms twice daily (AM and PM, 12 hours apart at the same times daily) throughout the 7-day placebo run-in period and the 14-day randomized

treatment period. Scoring should be made immediately prior to each dose (and 12 hours after the AM dose for once-daily dosing), to reflect the previous 12 hours (*reflective* scores) and how the subject is feeling at the time of evaluation, i.e., at the end of dosing interval (*instantaneous* scores). Each of the following symptoms should be scored using the following scale:

- a. Symptoms: Runny nose, sneezing, nasal itching, and congestion.
- b. Scoring Scale: The following is an example of an acceptable scale. Each score should be objectively defined.

**Table 1. Sample Scoring Scale**

Score	Description
0	absent (no symptom evident)
1	mild (symptom clearly present, but minimal awareness; easily tolerated)
2	moderate (definite awareness of symptom that is bothersome but tolerable)
3	severe (symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

8. Total nasal symptom score (TNSS) is the sum of each individual symptom rating for runny nose, sneezing, nasal itching, and congestion.
9. Baseline mean rTNSS is the mean of the final seven scores from the placebo run-in period. The final seven scores from the placebo run-in period consist of the AM and PM scores on Days -3, -2, and -1 and the AM score (prior to drug dosing) on Day 1 of the 14-day randomized treatment period.
10. Placebo responders should be excluded from the study to increase the ability to show a significant difference between active and placebo treatments, and to increase sensitivity to detect potential differences between active products.
11. Treatment mean rTNSS is the average of 27 scores from the randomized treatment period. The 27 scores consist of the PM score on Day 1 and the AM and PM scores on Days 2 to 14.
12. The recommended primary endpoint is the change from the baseline mean rTNSS to the treatment mean rTNSS, expressed in absolute units rather than percent change from baseline.
13. FDA recommends that each of the T and R batches used in the comparative clinical endpoint bioequivalence study be at least one of the three batches used for the in vitro bioequivalence studies and the in vivo bioequivalence study with pharmacokinetic endpoints.
14. FDA recommends using a statistical model for the endpoint data that takes into account baseline values. If the study was conducted at multiple clinical centers, the center should also be considered in the data analysis.

15. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)<sup>b</sup> for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.
16. Refer to the Study Data Standards Resources website <https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>.

### **Bioequivalence for other configurations:**

If multiple configurations of the T products are developed with different fill weight (i.e., 120 and/or 60 actuations), the bioequivalence studies outlined in Option 1 and 2 above should be conducted with the configuration containing the highest number of labeled actuations.

Bioequivalence for configurations with a lower number of labeled actuations will be based on (i) acceptable bioequivalence studies on the configuration with the highest number of labeled actuations, (ii) same formulation composition across all configurations, and (iii) same container and closure components critical to the product performance across all configurations.

### **Additional information:**

Device:

The RLD is presented in a bottle with a nasal pump and actuator. The pump with actuator is 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 when designing the T device including:

- Metered, multi-dose format
- Same 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*.<sup>a</sup>

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<sup>a</sup> For the most recent version of a guidance, check the FDA guidance website at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

<sup>b</sup> For the most recent version of the product-specific guidance, check the FDA product-specific guidance website at: <https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>.