

Draft Guidance on Beclomethasone Dipropionate Monohydrate

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This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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This is a new draft product-specific guidance for industry on generic beclomethasone dipropionate monohydrate.

Active Ingredient: Beclomethasone dipropionate monohydrate

Dosage Form; Route: Spray, metered; nasal

Strength: EQ 0.042 mg diprop/spray

Recommended Studies: In vitro and in vivo studies

The FDA recommends the following in vitro and in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) nasal sprays containing beclomethasone dipropionate monohydrate.

In Vitro BE Studies

FDA recommends that prospective applicants conduct the following in vitro BE 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 BE. 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 the final drug constituent formulation intended to be marketed. The following in vitro BE tests are recommended:

1. Single actuation content
2. Droplet size distribution by laser diffraction
3. Drug in small particles/droplets
4. Spray pattern
5. Plume geometry
6. Prime and repriming

Additional Comments: Refer to the draft product-specific guidance on *Fluticasone Propionate, Nasal, Spray; Metered* for recommendations on design and equivalence criteria for the aforementioned in vitro BE studies, and general recommendations on the conduct of the in vitro BE studies and data submission.

Pharmacokinetic (PK) BE Study

1. Type of study: Fasting
Design: Single-dose, two-way crossover
Strength: EQ 0.042 mg diprop/spray
Dose: Minimum number of sprays that is sufficient to characterize a PK profile by using a sensitive analytical method.
Subjects: Adult males and non-pregnant, non-lactating females, general population
Additional comments: See below:
 - a. Follow the reference listed drug (RLD) labeling for the method of drug administration
 - b. The analytical method should have sufficient sensitivity to adequately quantify the concentration of beclomethasone 17-monopropionate in plasma
 - c. A Bio-IND is required prior to conduct of the PK study if the dose exceeds the maximum labeled single-dose

Analytes to measure: Beclomethasone dipropionate and beclomethasone 17-monopropionate (active metabolite) in plasma

Equivalence based on: AUC and C_{max} for beclomethasone 17-monopropionate. 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%.

Comparative Clinical Endpoint BE Study

The following BE study with a clinical endpoint is recommended.

The recommendations provided here supersede information provided in the FDA draft guidance for industry on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*. These recommendations are specific to this product and may not be appropriate for comparative clinical endpoint BE studies of any other product, including any other dosage form or strength of beclomethasone dipropionate monohydrate.

1. Type of study: BE Study with Clinical Endpoint
Design: Randomized, double-blind, three-arm, placebo-controlled, parallel group
Strength: EQ 0.042 mg diprop/spray
Dose: EQ 0.168 mg diprop, administered as one spray in each nostril twice a day
Subjects: Adult males and non-pregnant, non-lactating females with seasonal allergic rhinitis
Additional comments: Specific recommendations are provided below

Additional comments regarding the comparative clinical endpoint BE study

1. The FDA recommends conducting a BE study with clinical endpoint in the treatment of seasonal allergic rhinitis 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 one spray in each nostril twice daily for 7 days. All subjects who qualify after the placebo run-in period are to be randomized to receive the test product, RLD, or placebo (vehicle) control during the treatment period, administered as one spray in each nostril twice 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 seasonal allergic rhinitis (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 a 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, with the exception of 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. Use of any prohibited medications and treatments (e.g., systemic or intranasal decongestants, anti-allergy therapy as antihistamines, leukotriene antagonists and corticosteroid therapy) 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].
 - l. Planned travel outside the study area from the time of enrollment to completion of the study.
 - m. Known hypersensitivity to beclomethasone dipropionate, or to similar drug, or to any of the study medications or inactive ingredients.
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) and immunosuppressive therapy.
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 7 scores from the placebo run-in period. The final 7 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. The FDA recommends that each of the test and reference batches used in the clinical endpoint BE study be at least one of the three batches used for the in vitro and in vivo PK BE studies.
14. The 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 draft product-specific guidance on *Adapalene; Benzoyl Peroxide, Gel; Topical, 0.3%; 2.5%* for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.¹
16. Study data should be submitted in a standardized format. Refer to the study data standards published at www.fda.gov.²

¹ Product-Specific Guidances for Generic Drug Development available at www.fda.gov.

Alternate approach to the comparative clinical endpoint BE study

A comparative clinical endpoint BE study is recommended for T beclomethasone dipropionate monohydrate nasal spray product because of an inability to adequately characterize drug particle size distribution (PSD) in aerosols and sprays using commonly used analytical methods. Drug PSD in suspension formulations has the potential to influence the rate and extent of drug availability to nasal sites of action and to systemic circulation. If drug PSD in the T and R products can be accurately measured using a validated analytical method such as morphology-directed Raman spectroscopy or any other advanced methodology, prospective applicants may submit comparative particle size distribution data as part of their drug characterization within their ANDA application. In such case, comprehensive method validation data should be submitted to demonstrate the adequacy of the selected method in identifying and measuring the size of the drug particles without any interference from the excipient particles that are also suspended in the formulation. An orthogonal method may be required if the selected methodology is not sensitive to measure particles beyond a certain size range. Equivalence between T and R drug PSD should be based on PBE analysis on D₅₀ and SPAN.

Additional Information

Formulation:

The FDA recommends that the T formulation be qualitatively (Q1)³ and quantitatively (Q2)⁴ the same as the R formulation.

Device:

This product is a drug-device combination product. Refer to 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*. An ANDA for a proposed generic drug-device combination product should include complete comparative analyses.

The FDA recommends that prospective 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
- Size and shape of the R product
- Number of doses in the R product

Unique Agency Identifier: PSG_019389

² Study Data Standards for Submission to CDER and CBER available at www.fda.gov.

³ Q1 (qualitative sameness) means that the T formulation uses the same inactive ingredient(s) as the R formulation.

⁴ Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T formulation are within $\pm 5\%$ of those used in the R formulation.