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Draft Guidance on Epinephrine

December 2025

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Active Ingredient:	Epinephrine
Dosage Form:	Spray
Route:	Nasal
Strengths:	1 mg/spray, 2 mg/spray
Recommended Studies:	Two options: (1) Five in vitro bioequivalence studies or (2) one in vivo bioequivalence study with pharmacokinetic endpoints.

I. Option 1: Five in vitro bioequivalence studies

To demonstrate bioequivalence by this option, the test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard (RS) that may significantly affect the local or systemic availability of the active ingredient. For example, the test product can be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the RS to satisfy no difference in inactive ingredients.

FDA recommends that prospective applicants conduct the following in vitro bioequivalence studies on samples from each of three or more batches of the test product and three or more batches of the RS, with no fewer than 10 units from each batch. FDA recommends that three

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RS.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ± 5% of those used in the RS.

primary stability batches be also used to demonstrate in vitro bioequivalence.[3] The three batches of the test 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 test 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

Additional comments: Refer to the most recent version of the FDA product-specific guidance on *Fluticasone Propionate Nasal Metered Spray* (NDA 020121)[a] 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.[4]

II. Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-way crossover
   Strength: 2 mg/spray
   Dose: 2 mg, administered as one spray in one nostril
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: (a) Subjects should adhere to the reference listed drug (RLD) product labeling for administration. (b) The analytical method should have sufficient sensitivity to adequately quantify the concentration of epinephrine in plasma. (c) Since epinephrine is an endogenous substance, the plasma concentrations of epinephrine should be corrected for baseline endogenous levels by subtracting the mean pre-dose baseline value (average of at least three pre-dose values, e.g., -1, -0.5, and 0 hours). Any negative values obtained from baseline correction at time 0 hour should be designated as zero (0). Both baseline corrected and baseline uncorrected data should be submitted in the application. (d) Ensure an adequate washout period between treatments (e.g., 12 days or more).

   Analyte to measure: Epinephrine in plasma

[3] If bioequivalence of the 2 mg/spray strength is acceptable, then drug in small particles/droplets and plume geometry bioequivalence tests may not be needed for the 1 mg/spray strength provided the 1 mg/spray product is manufactured without changing the actuator and metering valve or pump (other than diptube, due to different volumes of product or other factors) used in the 2 mg/spray product. With the exception of the reduced testing, the Agency recommends the same protocols and the acceptance criteria used to establish bioequivalence of the 2 mg/spray product be used for the 1 mg/spray product.

[4] Specific recommendations for in vitro bioequivalence testing at various lifestages are not relevant for this product given it is a single-use configuration.

Bioequivalence based on (90% CI): Baseline-corrected AUC and C_{max} for epinephrine. The 90% confidence intervals for the geometric mean T/R ratios of the baseline-corrected AUC and C_{max} should fall within the limits of 80.00%-125.00%. In addition, prospective applicants should submit partial AUC of early time points as supportive data to assess the onset of epinephrine effect. Prospective applicants should collect sufficient quantifiable pharmacokinetic samples to allow a comparison of exposure to epinephrine between the test product and the RS within the first 10 minutes ($AUC_{0\text{-}10min}$) and 30 minutes ($AUC_{0\text{-}30min}$) after administration.

Waiver request of in vivo testing: 1 mg/spray strength based on (i) acceptable bioequivalence study on the 2 mg/spray strength, (ii) proportional similarity of the formulations across both strengths,[5] (iii) formulation Q1 and Q2 sameness with the RS with respect to the inactive ingredient n-dodecyl beta-D-maltoside,[6] and (iv) same device across strengths.

Additional information:

Device:
The RLD is presented as two single-use nasal spray devices. The nasal spray device 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 device when designing the test device including:

- Single-use, single-dose format
- No priming

User interface assessment:
An abbreviated new drug application 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*.[b]

[5] Formulation proportionality of the proposed test product may be established through either numerical proportionality of the inactive ingredients across both strengths or identical inactive ingredient composition maintained across both strengths.
[6] If there is Q1 and/or Q2 difference in the absorption enhancer between the test product and RS, FDA encourages applicants to discuss their proposal for submitting a waiver request of in vivo testing via the pre-ANDA meeting pathway. For additional information, refer to the most recent version of the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.[b]

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[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
[b] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.