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Draft Guidance on Naloxone Hydrochloride

August 2024

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Active Ingredient:	Naloxone hydrochloride
Dosage Form:	Spray, metered
Route:	Nasal
Strength:	3 mg/spray
Prescribing Information:	Over-the-counter (OTC)
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 (T) product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard (RS) product that may significantly affect the local or systemic availability of the active ingredient. For example, the T product can be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the RS product 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 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

[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.

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
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.[3]

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

1. Type of study: Fasting
   Design: Single-dose, two-way crossover
   Strength: 3 mg/spray
   Dose: 3 mg, administered as one spray in one nostril
   Subjects: Healthy males and non-pregnant, non-lactating females

   Analyte to measure: Naloxone in plasma

   Bioequivalence based on: Naloxone

   The 90% confidence intervals of the following pharmacokinetic parameters should meet the acceptable limits of [80.00 - 125.00]: Log-transformed AUC_{0-t}, AUC_{0-inf}, and $C_{max.}$ In addition, prospective applicants should submit partial AUC of early time points as supportive data to assess the onset of naloxone effect. Prospective applicants should collect sufficient quantifiable pharmacokinetic samples to allow a comparison of exposure to naloxone between the T product and the RS product within the initial 4 minutes, first 10 minutes, and 10-30 minutes after administration.

Additional information:

Device:
The reference listed drug (RLD) is presented as two single-use nasal spray devices. The nasal spray device is the device constituent part.

[3] Recommendations for testing at various lifestages are not relevant for this product given it is a single-use configuration.

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

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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.