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Draft Guidance on Naloxone Hydrochloride

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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 naloxone hydrochloride.

Active Ingredient:	Naloxone hydrochloride
Dosage Form; Route:	Spray; nasal
Strength:	8 mg/spray
Recommended Studies:	Two options: (1) in vitro bioequivalence studies or (2) one in vivo bioequivalence study with pharmacokinetic endpoints

FDA recommends the following in vitro or in vivo studies to establish bioequivalence of the test (T) and reference (R) nasal sprays containing naloxone hydrochloride.

I. Option 1: In vitro bioequivalence studies

If the T product formulation is qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the R product formulation, and the nasal spray device (e.g., the pump and actuator design) of the T is appropriate for approval in an ANDA, bioequivalence of the T naloxone hydrochloride nasal spray product to the R naloxone hydrochloride nasal spray product can be established solely by in vitro performance tests in lieu of a pharmacokinetic bioequivalence study. 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
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 product-specific guidance on *Fluticasone Propionate Nasal Spray Metered* (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

If the T formulation is not Q1 and Q2 the same as the R formulation and the nasal spray device (e.g., pump and actuator design) of the T product is appropriate for an ANDA, the following pharmacokinetic study is recommended to establish bioequivalence between the T and R product:

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: 8 mg/spray
   Dose: 8 mg naloxone (8 mg/spray x 1 spray in 1 nostril)
   Subjects: Adult males and non-pregnant females, general population

[1] Q1 (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.
[2] 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.
[3] Specific recommendations for in vitro bioequivalence testing at various life stages are not relevant for this product, given it is a single-use configuration.

Additional comments: The following pharmacokinetic parameters will be evaluated: Log-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}. 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 R product within the initial 4 minutes, first 10 minutes, and 10-30 minutes after administration.

Analyte to measure: Naloxone in plasma

Equivalence based on: AUC and Cmax for naloxone. The 90% confidence interval for the geometric mean T/R ratios of Cmax and AUC should fall within the limits of 80.00 – 125.00%.

Additional information:

Device:
The reference listed drug (RLD) product is presented in a single-dose nasal spray bottle that is the device constituent.

FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD device when designing the test device. In addition, test device design should take into consideration the following characteristics of the RLD device:

- Single unit-dose design
- Metered spray
- No priming

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*.[b]

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