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Draft Guidance on Fentanyl Citrate

August 2024

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Fentanyl citrate
Dosage Form:	Spray, metered
Route:	Nasal
Strengths:	EQ 0.1 mg Base, EQ 0.3 mg Base, EQ 0.4 mg Base
Recommended Studies:	Two options: (1) Six in vitro bioequivalence studies, or (2) one in vivo bioequivalence study with pharmacokinetic endpoints

I. Option 1: Six 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.[3] FDA recommends that

[1] Q1 (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the RS 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 RS product.
[3] If bioequivalence of the EQ 0.4 mg Base strength is acceptable, then the following bioequivalence tests may not be needed for the EQ 0.1 mg Base and EQ 0.3 mg Base strengths provided both of these strengths of the drug product are manufactured without changing the actuator and metering valve or pump (other than dip tube, due to different

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

Additional Comments: Refer to the most recent version of the product-specific guidance for *Fluticasone Propionate Nasal Metered Spray* (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.

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

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 0.4 mg Base
   Dose: EQ 0.4 mg Base, administered as one spray in one nostril
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments:
   a. Exclude subjects who have received any opioid or monoamine oxidase (MAO) inhibitor within 14 days of dosing.
   b. An opioid antagonist, such as naltrexone hydrochloride oral tablet, 50 mg, should be used to minimize opioid-related adverse events. The opioid antagonist should be administered well in advance of dosing, in order to achieve adequate blockade of opioid receptors. Consult with a physician who is an expert in the administration of opioids for the appropriate dose and regimen of an opioid antagonist for a single dose of fentanyl citrate nasal metered spray, EQ 0.4 mg Base administered to a healthy volunteer who had not received any opioid within 14 days of dosing.
   c. A clear plan for continuous respiratory monitoring from the time of dosing past the time of expected peak effect of the drug (i.e. at least 3 hours from dosing) should be included. Standard operating procedures (SOPs) should be in place for assessing and treating ventilatory depression, and personnel qualified to treat ventilatory emergencies should be immediately available.

volumes of product or other factors) used in the EQ 0.4 mg Base product: droplet size distribution by laser diffraction conducted at the end lifestage, drug in small particles/droplets, and plume geometry. With the exception of the reduced testing, the Agency recommends the same protocols and the acceptance criteria used to establish bioequivalence of the EQ 0.4 mg Base product be used for the EQ 0.1 mg Base and EQ 0.3 mg Base products.

d. All subjects should adhere to the pertinent safety issues in the Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) guidelines for Transmucosal Immediate-Release Fentanyl (TIRF) Products and to the warnings in the approved labeling for fentanyl citrate nasal metered spray.
e. Per 21 CFR 314.94(a)(9)(v), a generic fentanyl citrate nasal solution product may include different inactive ingredients provided that the prospective applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product. In addition, due to concerns of local irritation caused by inactive ingredients change, the firm should provide supportive information that difference of inactive ingredients does not cause local irritation.
f. While in vitro bioequivalence studies are not required for this option, in vitro studies outlined in the most recent version of the FDA guidance for industry on *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*[b] should be submitted for Chemistry, Manufacturing, and Controls evaluation.

Analyte to measure: Fentanyl in plasma

Bioequivalence based on: AUC and C_{max} for fentanyl. The 90% confidence interval for the geometric mean T/R ratios of C_{max} and AUC should fall within the limits of 80.00% – 125.00%.

Waiver request of in vivo testing: EQ 0.1 mg base/spray and EQ 0.3 mg base/spray based on (i) acceptable bioequivalence study on the EQ 0.4 mg base/spray strength and (ii) proportional similarity of the formulations across all strengths.

Additional information:

Device:
The reference listed drug (RLD) is presented in a multi-use nasal spray device. 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 T device including:

- Multi-use
- Metered dose
- Dose counter
- Child-resistant container
- One carbon-lined pouch with adhesive seal per device

User interface assessment:
An abbreviated new drug application (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 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.