

Draft Guidance on Fentanyl Citrate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Fentanyl Citrate

Form/Route: Spray, Metered/Nasal

I. In Vitro option:

If the test product is qualitatively (Q_1) and quantitatively (Q_2) the same as the reference product, then bioequivalence may be documented by an in vitro approach in lieu of an in vivo approach. Equivalent in vitro performance of the test product to the reference product should be established for both strengths (100 mcg/spray and 400 mcg/spray). The current FDA recommendations for documenting bioequivalence of nasally-administered products via in vitro testing may be found in the draft guidance “Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action”. The guidance is available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070111.pdf>, under Biopharmaceutics Draft (April 2003). As specified in the guidance, in vitro bioequivalence of the higher strength should be characterized by the full set of tests. If bioequivalence of the higher strength is acceptable, then abbreviated in vitro testing is recommended to document bioequivalence of the lower strength test product to the lower strength reference product.

II. In Vivo option:

If the test product is **not** qualitatively (Q_1) and quantitatively (Q_2) the same as the reference product, the following study is recommended to document bioequivalence of the test product to the reference product:

Recommended studies: 1 study

Type of study: BE Study with Pharmacokinetic (PK) Endpoints

Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: EQ 0.4 mg (400 mcg) base/spray x 1 spray (dose: EQ 0.4 mg base)

Subjects: Healthy males and nonpregnant females, general population, aged 18 to 50 years

Additional comments:

1. Exclude subjects who have received any opioid or monoamine oxidase (MAO) inhibitor within 14 days of dosing.

2. 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. Please 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 (400 mcg) base administered to a healthy volunteer who had not received any opioid within 14 days of dosing.
3. 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.
4. 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.
5. Per 21 CFR 314.94(a)(9)(v), a generic fentanyl citrate nasal solution product may include different inactive ingredients provided that the 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.
6. While comparative in vitro studies are not required, in vitro studies outlined in the 2002 Guidance for Industry, *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070575.pdf>) should be submitted for Chemistry, Manufacturing, and Controls evaluation.

Analytes to measure (in appropriate biological fluid): Fentanyl in plasma (PK study only)

Bioequivalence based on (90% CI): Fentanyl in plasma (PK study only)

Waiver request of in vivo testing: EQ 0.1 mg (100 mcg) base/spray based on (i) acceptable bioequivalence study on the EQ 0.4 mg (400 mcg) base/spray strength and (ii) proportional similarity of the formulations across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in vivo testing.

Dissolution test method and sampling times: Not applicable