

Draft Guidance on Fentanyl Citrate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Buccal, Sublingual Tablet/Oral

Recommended study: 1 study

1. Type of study: Fasting
Design: Single-dose, two-way crossover in-vivo
Strength: 0.4 mg
Subjects: Healthy males and nonpregnant females, general population
Additional Comments:
 1. It is recommended that the subjects should receive naltrexone well in advance of dosing in order to achieve adequate blockade of opioid receptors prior to the administration of fentanyl.
 2. In addition, for safety, elderly subjects and subjects who have received opioids or monoamine oxidase (MAO) inhibitors within 14 days of the dosing should be excluded from bioequivalence studies.
 3. A naltrexone blockade should be used to remove the risk of any opioid-related adverse events. Naltrexone should be administered well in advance of dosing to achieve adequate blockade of opioid receptors. The most common approach is to administer 50 mg of naltrexone at the following times: (1) 12 hours prior to dosing; (2) at the time of study drug dosing; and (3) 12 hours after the last dose of study drug.
 4. 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.
 5. Bioequivalence studies should include a plan for systematic evaluation (both subjective and by physical examination) of local irritation/toxicity.
 6. The bioequivalence study may be performed using either the buccal or sublingual route of administration. The same one route should be used for all subjects in both periods.

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

Bioequivalence based on (90% CI): Fentanyl

Waiver request of in-vivo testing: 0.1 mg, 0.2 mg, 0.6 mg, and 0.8 mg (base equivalent) based on (i) acceptable bioequivalence study on the 0.4 mg strength, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Dissolution test method and sampling times:

Please note that **Dissolution Method Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.