

## **Draft Guidance on Fentanyl**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

**Active Ingredient:** Fentanyl

**Dosage Form; Route:** Spray; sublingual

**Recommended Study:** One study

Type of study: Bioequivalence (BE) study with pharmacokinetic endpoints

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

Strength: 0.4 mg/spray x 1 spray (dose: 0.4 mg)

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

Additional comments:

- 1) Subjects are instructed not to inhale sprayed droplets and not to swallow for at least five minutes after the dose is administered.
- 2) Exclude subjects who have received any opioid or monoamine oxidase inhibitor within 14 days of dosing.
- 3) Exclude subjects with mucositis.
- 4) Use an opioid antagonist, such as naltrexone hydrochloride oral tablet, 50 mg, 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 sublingual spray 0.4 mg/spray×1 spray administered to a healthy volunteer who has not received any opioid within 14 days of dosing.
- 5) 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 should be in place for assessing and treating ventilatory depression, and personnel qualified to treat ventilatory emergencies should be immediately available.
- 6) All subjects should adhere to the pertinent safety issues in the risk evaluation and mitigation strategy (REMS) guidelines for transmucosal immediate-release fentanyl products and to the warnings in the approved labeling for fentanyl sublingual spray.

- 7) Per 21 CFR 314.94(a)(9)(v), a generic fentanyl sublingual spray 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 different inactive ingredients, the firm should provide supportive information that difference of inactive ingredients does not cause local irritation.
  - 8) BE studies should include a plan for systematic evaluation (both subjective and by physical examination) of local irritation/toxicity.
  - 9) Comparative in vitro studies (such as spray actuation content, spray content uniformity, particle size distribution, etc.) between test and reference products for BE purposes are not recommended.
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**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/spray, 0.2 mg/spray, 0.6 mg/spray, 0.8 mg/spray, 1.2 mg/spray and 1.6 mg/spray based on (i) acceptable BE study on the 0.4 mg/spray strength and (ii) proportional similarity of the formulations across all strengths

**Dissolution test method and sampling times:** Not applicable