*Contains Nonbinding Recommendations*

**Draft Guidance on Fentanyl**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:** Film, extended release; transdermal

**Recommended Studies:** Three studies

1. Type of study: Bioequivalence (BE) study with pharmacokinetic (PK) endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 25 mcg/hr
   Subjects: Males and non-pregnant, non-lactating females, general population

   Additional comments:

   - In this document, this dosage form is referred to as a transdermal delivery system (TDS) and includes products that may be described elsewhere or known as *patches* or *extended release films*.
   - A naltrexone blockade should be used to reduce the risk of 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.
   - Unless otherwise justified, the fentanyl TDS should be applied to the same anatomical site on all subjects, selected from among those recommended for dosing in the approved labeling for the reference listed drug (RLD) product, and worn for 72 hours. Applicants should randomize subjects to receive either the test or RLD product in a given study period. When possible, the TDS administered in the second study period should be applied to the same anatomical site as in the first study period, but on the contralateral side of the body.
   - Contact of the TDS with the skin is essential for the in vivo performance of the TDS, and the PK may be altered when a TDS loses its adherence to the skin. Therefore, the adhesion of each TDS should be monitored and recorded throughout the PK study. The PK samples should be collected and analyzed from all subjects at all sampling times regardless of the adhesion scores of the TDS. Provisions should be included in the study protocol to ensure that deliberate actions with the intent to re-apply a detached area of the TDS, to apply pressure to the TDS, or to reinforce TDS adhesion with the skin (e.g., overlays) are avoided throughout the study.

- The applicant should follow FDA's current thinking in the guidance "Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA" for the design and conduct of the PK BE study.

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

**Bioequivalence based on (90% CI):** Fentanyl

**Waiver request of in vivo testing:** The 12.5 mcg/hr, 37.5 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr strength of the TDS may be considered for a waiver of in vivo BE testing based on (1) an acceptable BE study with the 25 mcg/hr strength, (2) acceptable in vitro dissolution testing of all strengths, and (3) proportional similarity of the TDS formulation across all strengths.

NOTE: The proportional similarity of the TDS formulation across all strengths means i) that the amounts of active and inactive ingredients per unit of active surface area are identical for the different strengths of the test product, and ii) that the ratios of the active surface areas of each strength of the test product compared to the 25 mcg/hr strength of the test product are the same as the corresponding ratios for the active surface areas of each strength of the RLD product compared to the 25 mcg/hr strength of the RLD product.

**Dissolution test method and sampling times:** Comparative dissolution testing should be conducted on 12 dosage units each, of all strengths of the test and RLD product. Information on a dissolution method for this drug product can be found on the FDA Dissolution Methods web site, accessible at: http://www.accessdata.fda.gov/scripts/cder/dissolution/.

---

2. Type of study: Adhesion study
Design: Single-dose, two-treatment, two-period, crossover in vivo
Strength: 25 mcg/hr
Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- See comments above for use of naltrexone blockade to reduce the risk of any opioid related adverse events during the study.
- The applicant may elect to evaluate the PK BE (study 1) and the adhesion (study 2) in a single study with a combined purpose, or in independent studies. In either case, the studies should be adequately powered to evaluate the BE, and independently, the comparative assessment of adhesion.
- The applicant should follow FDA's current thinking in the guidance "Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs" for the

design and conduct of the independent adhesion study or the combined study to evaluate both PK BE and adhesion.

---

3. Type of study: Skin irritation and sensitization study
Design: Randomized, evaluator-blinded, within-subject, repeat in vivo
Strength: Vehicle TDS and positive control equivalent to the size of 25 mcg/hr or higher strength (TDS containing active pharmaceutical ingredient should not be used in this study due to safety concerns)
Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- All test articles (i.e., vehicle TDS[1], positive control of low irritancy[2] and optional negative control[3]) should be applied simultaneously to each subject at different positions on an application site recommended in the approved RLD/RS labeling.
- Sequential TDS applications should be made to the same application site every 3 days for a total of 21 consecutive days.
- The applicant should follow FDA's current thinking in the guidance "Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs" for the design and conduct of the skin irritation and sensitization study.

---

[1] The vehicle TDS should contain all of the inactive ingredients in the test product and be identical to the test product in every manner except for the absence of the active ingredient.
[2] Safety concerns preclude the use of comparative studies with the test and RLD products, therefore, the test product can be evaluated by testing a vehicle TDS versus a positive control TDS that produces mild irritation (e.g., ≤ 0.1% sodium lauryl sulfate).
[3] An example of the optional negative control treatment is an occlusive cover or device with normal saline applied on a polyester pad under the cover or within the device chamber.