

## Draft Guidance on Nicotine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Dosage Form; Route:** Film, extended release; transdermal

**Recommended Studies:** Three studies

1. Type of study: Bioequivalence study with pharmacokinetic endpoints  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 21 mg/24 hr  
Subjects: Males and non-pregnant, non-lactating females, smokers  
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*.
  - Unless otherwise justified, the nicotine 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 product, and worn for 24 hours. Applicants should randomize subjects to receive either the test or reference 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 pharmacokinetics 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 pharmacokinetic study. The applicant should prespecify their inclusion criteria for the statistical analysis of pharmacokinetic endpoints and perform their primary pharmacokinetic analysis on the per protocol population, however, pharmacokinetic samples should be collected and analyzed from all subjects at all sampling times regardless of the adhesion scores of the TDS and regardless of the inclusion criteria for the statistical analysis of pharmacokinetic endpoints. 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 pharmacokinetic bioequivalence study.

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

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

**Waiver request of in vivo testing:** The 7 mg/24 hr and 14 mg/24 hr strengths of the TDS may be considered for a waiver of in vivo bioequivalence testing based on (i) an acceptable bioequivalence study with the 21 mg/24 hr strength TDS, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) 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 21 mg/24 hr strength of the test product are the same as the corresponding ratios for the active surface areas of each strength of the reference product compared to the 21 mg/24 hr strength of the reference 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 reference products. 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: 21 mg/24 hr

Subjects: Males and non-pregnant, non-lactating females, smokers

Additional comments:

- The applicant may elect to evaluate the pharmacokinetic bioequivalence (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 bioequivalence, 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 pharmacokinetic bioequivalence and adhesion.

3. Type of study: Skin irritation and sensitization study

Design: Randomized, evaluator-blinded, within-subject repeat in vivo

Strength: 7 mg/24 hours

Subjects: Males and non-pregnant, non-lactating females, smokers

Additional comments:

- All test articles (i.e., one 7 mg/24 hr test product<sup>1</sup>, one 7 mg/24 hr reference product, optional vehicle TDS<sup>2</sup> and optional negative control<sup>3</sup>) should be applied simultaneously to each subject at different positions on an application site recommended for dosing in the approved labeling for the reference product.
- Sequential TDS applications should be made to the same application site every 24 hours, for a total of 21 consecutive days. The TDS applied on Day 21 should be removed on Day 22.
- 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.

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#### **Additional comments relating to all studies:**

In addition to the recommendations in the general guidances referenced above, and the product specific recommendations related to the individual studies, the following product specific recommendations should be considered.

- Exclusion Criteria (the applicant may add additional criteria): Subject who currently has any of the following conditions:
  - a. Thrombophlebitis, thromboembolic disorders
  - b. A history of deep vein thrombophlebitis or thromboembolic disorders
  - c. Cerebrovascular or coronary artery disease (current or history)
  - d. Valvular heart disease with complications
  - e. Severe hypertension
  - f. Diabetes with vascular involvement
  - g. Headaches with focal neurological symptoms
  - h. Major surgery with prolonged immobilization

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<sup>1</sup> The test product evaluated should be the actual TDS to be marketed.

<sup>2</sup> The optional 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.

<sup>3</sup> An example of the optional negative control treatment is an occlusion type device with normal saline applied on a polyester pad under the cover or within the device chamber.