*Contains Nonbinding Recommendations*

**Draft Guidance on Oxybutynin**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**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: 3.9 mg/24 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*.

   - Unless otherwise justified, the oxybutynin 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 96 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):** Oxybutynin in plasma (achiral assay)

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

**Waiver request of in vivo testing:** Not applicable

**Dissolution test method and sampling times:** Comparative dissolution testing should be conducted on 12 dosage units each, 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/.

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2. Type of study: Adhesion study
Design: Single-dose, two-treatment, two period crossover in vivo
Strength: 3.9 mg/24 hr
Subjects: Males and non-pregnant, non-lactating females, general population
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.

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3. Type of study: Skin irritation and sensitization study
Design: Randomized, evaluator-blinded, within-subject repeat in vivo
Strength: 3.9 mg/24 hr (Dose: One-half of a 3.9 mg/24 hr TDS)
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments:
   - All test articles (i.e., one half of the 3.9 mg/24 hr test product[1], one half of the 3.9 mg/24 hr reference product, optional vehicle TDS,[2] and optional negative control[3]) should be applied simultaneously to each subject at different positions on an

[1] The test product evaluated should be the actual TDS to be marketed.
[2] 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.
[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.

application site recommended for dosing in the approved labeling of the reference product.

- Sequential TDS applications should be made to the same application site every 72 to 96 hours, for a total of 21 consecutive days. The final TDS should be removed on Day 22.

- There is insufficient information to determine whether it is safe to simultaneously apply two whole, active, 3.9 mg/24 hr oxybutynin TDS on the same subject during a 21-day skin irritation and sensitization study. Since the reference TDS has a matrix design that can be safely cut in half, one half of the reference TDS can be used for these studies. If the test TDS also has a design that can be safely cut to a smaller size, it should also be cut in half, and one half of the test TDS may be applied simultaneously with one half of a reference TDS (to separate skin sites). It would not be acceptable to manufacture a separate batch of the test TDS in order to use a smaller TDS in this study. If the test TDS has a design that cannot be safely cut to a smaller size, and/or if a prospective applicant proposes study design different than what is recommended above, the prospective applicant may submit a pre-abbreviated new drug application (pre-ANDA) meeting request to discuss the proposed approach.

- 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):
  a. Medical history of urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma; or being at risk for these conditions

- Provide a listing of the prescription and over-the-counter drug products that are contraindicated during the study, such as:
  a. Anticholinergic drugs other than test and reference products

- Subjects should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergic agents such as oxybutynin are used in a hot environment.

- Subjects should be advised that anticholinergic agents such as oxybutynin may produce drowsiness (somnolence) or blurred vision, and to exercise caution in decisions to engage in potentially dangerous activities until they have determined its

effects. Subjects should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

- Subjects should be informed of the possible adverse events that may occur with the use of oxybutynin TDS (i.e., application site pruritis, dry mouth, constipation, application site erythema, diarrhea, dysuria, application site vesicles).