

Draft Guidance on Testosterone

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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: 4 mg/24 hr
Subjects: Testosterone-deficient (hypogonadal) males who are otherwise healthy and between the ages of 18 and 65 years

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*.
- Due to the risk of teratogenicity associated with testosterone, the study should not be conducted in women.
- Unless otherwise justified, the testosterone 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): Testosterone in serum.

Baseline testosterone levels should be measured at -12 and 0 hours before dosing. The mean of the pre-dose testosterone levels should be used for the baseline adjustment of the post-dose levels. Baseline concentrations should be determined for each dosing period, and baseline corrections should be period specific. If a negative plasma concentration value results after baseline correction, this should be set to 0 prior to calculating the baseline-corrected AUC. The baseline corrected and uncorrected data, as well as the statistical analyses, should be submitted to the Agency.

Bioequivalence based on (90% CI): Testosterone, using baseline corrected data.

Waiver request of in vivo testing: The 2 mg/24 hr strength of the TDS may be considered for a waiver of in vivo bioequivalence testing based on (i) an acceptable bioequivalence study with the 4 mg/24 hr strength TDS, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the TDS formulation across both strengths.

NOTE: The proportional similarity of the TDS formulation across both 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 4 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 4 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 both 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: 4 mg/24 hr

Subjects: Testosterone-deficient (hypogonadal) males who are otherwise healthy, and between the ages of 18 and 65 years

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: 2 mg/24 hr
Subjects: Testosterone-deficient (hypogonadal) male who are otherwise healthy, and between the ages of 18 and 65 years

Additional comments:

- All test articles (i.e., 2 mg/24 hr test product¹, 2 mg/24 hr reference product, optional vehicle TDS² and optional negative control³) should be applied simultaneously to each subject at different positions on an 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 24 hours, for a total of 21 consecutive days. The TDS applied on Day 21 should be removed on Day 22.
- The sponsor 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.

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.

- Inclusion Criteria (the applicant may add additional criteria):
 - a. Healthy, hypogonadal male subjects aged at least 18 years with no contraindication to testosterone therapy
 - b. Baseline systolic blood pressure no greater than 140 mm Hg and diastolic blood pressure no greater than 80 mm Hg

¹ The test TDS evaluated should be the actual product 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.

- Exclusion Criteria (the sponsor may add additional criteria):
 - a. Female subject
 - b. Medical history of carcinoma of the breast, carcinoma of the prostate, benign prostatic hyperplasia, polycythemia, venous thromboembolism, pulmonary embolism, stroke, cholestatic jaundice, hypertension, serious heart problems, heart failure, myocardial infarction, ventricular arrhythmia, exertional chest pain, insulin dependent diabetes, hypercholesterolemia, hypertriglyceridemia, impaired liver function, or significant renal dysfunction
 - c. Taking insulin, oral anticoagulants, or corticosteroids.
 - d. Within 3 months prior to dosing, testosterone pellet drug therapy
 - e. Within 4 weeks prior to dosing, transdermal testosterone therapy
 - f. Within 2 weeks prior to dosing, short-acting testosterone esters drug therapy (such as testosterone cypionate or testosterone enanthate
 - g. Within 24 hours prior to dosing, oral testosterone therapy