

## Draft Guidance on Testosterone

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active ingredient:** Testosterone

**Form/Route:** Gel/Transdermal

**Recommended studies:** 1 study

Type of study: Fasting

Design: Single-dose, two-way crossover in vivo

Strength: 1% (dose: 100 mg testosterone, i.e., contents of two 5 gm packets, each containing 50 mg testosterone in 5 gm gel)

Subjects: Hypogonadal males with no other abnormalities

Additional comments:

1. Because of significant safety concerns pertaining to the transfer of testosterone to others and the current inability of the Office of Generic Drugs (OGD) to adequately determine which new inactive ingredient(s) or change(s) in the formulation may significantly affect the safety of testosterone gel, the OGD plans to receive an abbreviated new drug application (ANDA) for a generic version of Testosterone Transdermal Gel, 1% only if it has all of the same ingredients as the reference listed drug (RLD) and the concentration or amount of each inactive ingredient in the test product differs by no more than +/- 5% of the concentration or amount for the same ingredient in the RLD [the generic drug product is qualitatively (Q1) and quantitatively (Q2) the same, i.e., Q1/Q2, to the RLD].
2. If the generic version of Testosterone Transdermal Gel, 1% is not Q1/Q2 to the RLD, the OGD recommends that the applicant contact the Office of New Drugs (OND), Division of Reproduction and Urology Products (DRUP), in order to obtain their recommendations regarding the studies necessary to support the submission of a New Drug Application (NDA) for their drug product.
3. Note that there are two RLDs for Testosterone Transdermal Gel, 1% [i.e., AndroGel® (testosterone gel), 1% and Testim® 1% (testosterone gel)]. While the active ingredients for both RLDs are the same, the Therapeutic Equivalent Code listed in the Orange Book for both RLDs is BX (i.e., drug products for which the data are insufficient to determine therapeutic equivalence). Generic sponsors must specify to which RLD they are demonstrating bioequivalence.
4. Subjects should not currently be receiving any treatment for their hypogonadism.
5. The inclusion criterion for hypogonadal males is serum testosterone levels below 2.5 ng/mL.
6. Testosterone should be applied to clean, dry, intact skin of the shoulders and/or upper arms.
7. Cumulative skin irritation/sensitization studies are not necessary when the test product is Q1/Q2 to the RLD.

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**Analytes to measure (in appropriate biological fluid):** Testosterone in serum.

Since testosterone is an endogenous substance, the serum concentrations of testosterone should be corrected for baseline endogenous levels by subtracting the mean pre-dose baseline value (average of at least three pre-dose values, e.g. -1.0, -0.5, and 0 hours). Any negative values obtained from baseline

correction at time 0 hour, should be designated as zero (0) and any subject with pre-dose concentration more than 5% of their C<sub>max</sub> should be excluded from BE statistical analysis and the 90% confidence intervals based on the remaining subjects. Please refer to the Draft Guidance on Ergocalciferol Capsule for additional information regarding endogenous compounds.

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

**Waiver request of in-vivo testing:** Not Applicable

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