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Draft – Not for Implementation

Draft Guidance on Testosterone

February 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Testosterone

Dosage Form; Route: Gel, metered; nasal

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

FDA recommends the following in vivo study to establish bioequivalence of the test (T) and reference (R) metered nasal gel containing testosterone.

In vivo bioequivalence study with pharmacokinetic endpoints:

FDA recommends the following pharmacokinetic study to establish BE between the T and R product:

1. Type of study: Fasting
   Design: Single-dose, two-way crossover
   Strength: 5.5 mg testosterone/0.122 gm actuation
   Dose: 11 mg of testosterone (2 pump actuations; 1 actuation per nostril)
   Subjects: Testosterone-deficient (hypogonadal) males who are otherwise healthy and between the ages of 18 and 65 years
   Additional comments:
   a. Subjects should not currently be receiving any treatments for their hypogonadism.
   b. The inclusion criterion for hypogonadal males is serum testosterone levels below 300 ng/dL.
   c. Subjects should refrain from blowing their nose or sniffing for 1 hour after dose administration.

Analyte to measure: Testosterone in serum or plasma

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 Cmax should be excluded from bioequivalence statistical analysis and the 90% confidence intervals based on the remaining subjects. Refer to the most recent version of the FDA guidance on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*[a] for additional information regarding endogenous compounds.

Equivalence based on: Baseline-corrected AUC and Cmax for testosterone. The 90% confidence intervals for the geometric mean T/R ratios of AUC and Cmax should fall within the limits of 80.00-125.00%.

Additional information:

Device:
The Reference Listed Drug (RLD) is presented as a gel in a metered nasal pump dispenser. The nasal pump dispenser is the device constituent part.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the Test (T) device including:

- Metered and multi-dose nasal pump design
- Actuator (includes nasal tip) shape and size
- Priming and cleaning processes

User interface assessment:
An Abbreviated New Drug Application (ANDA) for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[b]

Unique Agency Identifier: PSG_205488

[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[b] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.