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Draft Guidance on Estradiol

August 2021

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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This is a new draft product-specific guidance for industry on generic estradiol.

Active Ingredient: Estradiol

Dosage Form; Route: Gel, metered; transdermal

Recommended Study: One study

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.06% (1.25 gm/activation)
   Subjects: Non-smoking, postmenopausal women with no contraindication to estrogen therapy
   Additional comments: 1.25 gm (1 pump activation) of estradiol gel may be dosed as recommended in the approved labeling for the reference product to evenly cover the same amount of skin surface area for the test and reference products. An average baseline correction may be obtained by averaging 3 pre-application sampling times (-1.0, -0.5 and 0 hours). For each subject, baseline concentrations should be determined for each dosing period, and baseline adjustments should be period specific. If a baseline correction results

in a negative plasma concentration value, the value should be set equal to 0 before calculating the baseline-corrected area under the curve (AUC).

Applicants may consider using a reference-scaled average bioequivalence approach for estradiol. If using this approach, the applicant should provide evidence of high variability in the bioequivalence parameters (i.e., within-subject variability ≥ 30%) for the reference product. For general information on this approach refer to product-specific guidance for progesterone oral capsules entitled *Guidance on Progesterone* for additional information regarding highly variable drugs.

Analyte to measure: Estradiol in plasma

Bioequivalence based on (90% CI): Estradiol, using baseline-corrected data

Pharmacokinetic and statistical analysis should be performed on both uncorrected and corrected data. Determination of bioequivalence should be based on the baseline-corrected data.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

Additional Information

Device:

Prospective applicants should refer to FDA's guidance for industry entitled *Comparative Analyses and Related Comparative Use Human Factors Studies* for a Drug-Device Combination Product Submitted in an ANDA, which, when finalized, will provide the Agency's current thinking on the identification and assessment of any differences in the design of the user interface for a proposed generic drug-device combination product when compared to its reference product.

FDA recommends that prospective applicants consider the following characteristics of the reference product when designing the test product:

- Number of doses in the reference product
- External operating principles and external critical design attributes of the reference product

Unique Agency Identifier: PSG_021166