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Draft Guidance on Estradiol

February 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Spray; 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: 1.53 mg/spray
   Subjects: Non-smoking, postmenopausal women with no contraindication to estrogen therapy
   Additional comments:
   1. 3.06 mg (2 sprays) of estradiol 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).

2. 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 the most recent version of the FDA guidance for industry on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application*[a] 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 analyses 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:

This product is a drug-device combination product. 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*.[a] An abbreviated new drug application for a proposed generic drug-device combination product should include complete comparative analyses.

Unique Agency Identifier: PSG_022014

[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