

Draft Guidance on Estradiol

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:	Estradiol
Dosage Form; Route:	Insert, extended release; vaginal
Strength:	0.0075 mg/24hr
Recommended Studies:	Two options: in vitro/in vivo or in vivo

I. In vitro/in vivo option:

To be eligible for this option all of the following criteria should be met:

- The test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)¹ and quantitatively (Q2)² the same (Q1/Q2).
- Comparative physicochemical and mechanical characteristics of the test and reference standard (RS) products including, 1) degree of crosslinking of the silicone polymers; and 2) mechanical properties (hardness, tensile strength, elongation at break).
- Same dimensions as the RLD

1) Comparative in vitro drug release testing³

Acceptable comparative in vitro drug release of estradiol from the test and the RS products throughout the intended period of product use (90 days).

2) Type of study: In vivo bioequivalence with pharmacokinetic (PK) endpoints

Design: 28 days, crossover or parallel

Strength: 0.0075 mg/24hr

Subjects: Healthy postmenopausal women with no contraindication to estrogen therapy.

Additional comments:

- a. Statistical analysis with and without baseline adjustments should be performed. Baseline estradiol levels should be measured at -1, -0.5, and 0 hours before dosing.
- b. The analytical procedure for estradiol should have a lower limit of sensitivity of at least 2 pg/mL or lower.

¹ Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.

² Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within $\pm 5\%$ of those used in the RLD product.

³ Please note that, if determined to be warranted, an in vitro release test (IVRT) method used as part of the quality control specifications may and/or can ultimately be different than the IVRT method developed to support bioequivalence determination and will be assessed at the time of review of the ANDA.

- c. Retrieve the ring at day 28 following insertion and determine residual amount of estradiol as supportive information.

Analytes to measure (in appropriate biological fluid): Estradiol in plasma and residual amount of estradiol following removal of the ring

Bioequivalence based on (90% CI): Estradiol in plasma

The 90% confidence intervals of the following PK parameter must meet the acceptable limits of [80.00-125.00]: Log-transformed AUC_{0-28d} , and C_{max} , where AUC_{0-28d} is the area under the plasma-concentration vs. time curve from 0 to day 28, and C_{max} is the maximum plasma concentration

II. In vivo option

1. Type of study: Bioequivalence with pharmacokinetic (PK) endpoints
Design: 28 days, crossover or parallel
Strength: 0.0075 mg/24hr
Subjects: Healthy postmenopausal women with no contraindication to estrogen therapy.
Additional comments:
 - a. Statistical analysis with and without baseline adjustments should be performed. Baseline estradiol levels should be measured at -1, -0.5, and 0 hours before dosing.
 - b. The analytical procedure for estradiol should have a lower limit of sensitivity of at least 2 pg/mL or lower.
2. Type of study: Bioequivalence with clinical endpoints
Design: Randomized, double blind, parallel, placebo-controlled in vivo
Strength: 0.0075 mg/24hr
Subjects: Postmenopausal women with symptoms of vulvar and vaginal atrophy and no contraindication to estrogen therapy, general population.
Additional comments:
 - 1) Specific recommendations regarding the bioequivalence study with clinical endpoints are provided below.
 - 2) If the test product is not Q1/Q2 to the RLD, an additional clinical study or studies to identify any increased risk posed by the differing inactive ingredients or formulation differences between the test product and the RLD may be necessary.
 - 3) Depending upon the specific clinical study or studies recommended, e.g., vaginal safety study, a test drug product that is not Q1/Q2 to the RLD may need to be submitted in a NDA to the Office of New Drugs.

Analytes to measure: Estradiol in plasma (for PK study) and residual amount of estradiol (for clinical endpoints study).

Bioequivalence based on (90% CI): Estradiol in plasma (for PK study) and clinical endpoints (for clinical endpoints study)

The 90% confidence intervals of the following PK parameter must meet the acceptable limits of [80.00-125.00]: Log-transformed AUC_{0-28d} , and C_{max} ,

where AUC_{0-28d} is the area under the plasma-concentration vs. time curve from 0 to day 28, and C_{max} is the maximum plasma concentration

Additional comments regarding the bioequivalence study with clinical endpoints:

- 1) The Office of Generic Drugs (OGD) recommends a clinical endpoint bioequivalence study in the treatment of postmenopausal vulvar and vaginal atrophy (VVA). Subjects are to be randomized to receive the estradiol extended release vaginal insert product, the reference listed drug (RLD), or placebo control, each administered as one ring insert intravaginally once for 12 weeks. The primary endpoint is the proportion of subjects identified as responders at the end of Study Week 12.
- 2) Inclusion Criteria (the applicant may add additional criteria):
 - a. Non-smoking, postmenopausal female subjects with VVA and no contraindication to estrogen therapy.
 - “Postmenopausal” is defined as 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone levels > 40 mIU/ml or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.
 - b. $\leq 5\%$ superficial cells on vaginal smear cytology
 - c. Vaginal pH > 5.0
 - d. At least one patient self-assessed moderate to severe symptom of VVA from the following list that is identified by the subject as being most bothersome to her:
 - Vaginal dryness
 - Vaginal and/or vulvar irritation/itching
 - Dysuria
 - Vaginal pain associated with sexual activity
 - Vaginal bleeding associated with sexual activity
 - e. Baseline systolic blood pressure should be no greater than 140 mm Hg and diastolic blood pressure no greater than 80 mm Hg
 - f. Subjects >40 years have documentation of a negative screening mammogram (obtained at screening or within 9 months of study enrollment) and a normal clinical breast examination prior to enrollment in study.
 - g. Subjects with an intact uterus have baseline vaginal ultrasonography demonstrating inactive endometrial lining with endometrial thickness less than 4 mm.
- 3) Exclusion Criteria (the applicant may add additional criteria):
 - a. Male subject
 - b. Premenopausal, perimenopausal, pregnant or lactating subject
 - c. Undiagnosed abnormal genital bleeding
 - d. Known, suspected, or history of breast cancer
 - e. Known or suspected estrogen-dependent neoplasia

- f. History of endometrial cancer or risk factors for endometrial cancer
 - g. Subject with tobacco use or body weight >90 kg
 - h. Active deep venous thrombosis, pulmonary embolism, or a history of these conditions
 - i. High risk of venous thrombosis or arterial thrombosis
 - j. Active arterial thromboembolic disease (e.g., stroke and myocardial infarction), or a history of these conditions
 - k. Anaphylactic reaction or angioedema with the reference product
 - l. Liver impairment or disease
 - m. Protein C, protein S, or antithrombin deficiency, or other thrombophilic disorders.
 - n. History of cholestatic jaundice, hypertension, coronary heart disease or other serious heart problems, diabetes, hypercholesterolemia, hypercalcemia, hypoparathyroidism, hypertriglyceridemia, systemic lupus erythematosus, renal impairment, residual endometriosis post-hysterectomy, asthma, epilepsy, migraine, porphyria, hepatic hemangiomas
 - o. History of narcotic abuse, drug abuse or alcoholism
 - p. Within 6 months prior to dosing, estrogen pellet therapy or progestin injectable drug therapy
 - q. Within 3 months prior to dosing, progestin implants and estrogen alone injectable drug therapy
 - r. Within 8 weeks prior to dosing, oral estrogen and/or oral or intrauterine progestin therapy
 - s. Within 4 weeks prior to dosing, transdermal estrogen alone or transdermal estrogen/progestin products
 - t. Within 1 week prior to dosing, vaginal hormonal products (rings, creams, gels)
 - u. Within 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization
 - v. Taking thyroid hormone replacement therapy
 - w. Taking inducers of CYP3A4 such as St. John's wort, anticonvulsants, phenylbutazone, rifampin, rifabutin, nevirapine and efavirenz
 - x. Taking inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, nelfinavir and grapefruit juice
- 4) A listing of the prescription and over-the-counter drug products that are contraindicated during the study should be provided, such as:
- a. Antihypertensives and pressor agents
 - b. Estrogens, other than study medication
- 5) The recommended primary endpoint of the study is the proportion of subjects in the Per Protocol (PP) population that are identified as responders at Week 12. A responder is defined as a subject with:
- a. At least a 25% reduction from baseline in the sum of % basal/parabasal + % intermediate cells on vaginal cytology;
 - b. Vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5;
 - c. Improvement in severity of the most bothersome symptom of VVA.

- 6) Please provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
- a. Study identifier
 - b. Unique Subject identifier
 - c. Subject identifier for the study
 - d. Study site identifier (if applicable)
 - e. Age
 - f. Age units (years)
 - g. Sex
 - h. Race
 - i. Name of planned treatment
 - j. Name of actual treatment
 - k. Safety population flag (yes/no)
 - l. Reason for exclusion from safety population
 - m. Modified Intent-to-Treat (mITT) population flag (yes/no)
 - n. Reason for exclusion from mITT population
 - o. Per-Protocol (PP) population flag (yes/no)
 - p. Reason for exclusion from PP population
 - q. Randomized population flag (yes/no)
 - r. Date/time of first exposure to treatment
 - s. Date/time of last exposure to treatment
 - t. End of study date
 - u. End of study status
 - v. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
 - w. Baseline intermediate epithelial cells on vaginal cell cytology (i.e., % intermediate)
 - x. Study Week 12 intermediate epithelial cells on vaginal cell cytology (i.e., % intermediate)
 - y. Baseline basal/parabasal epithelial cells on vaginal cell cytology (i.e., % basal)
 - z. Study Week 12 basal/parabasal epithelial cells on vaginal cell cytology (i.e., % basal)
 - aa. Baseline vaginal pH
 - bb. Study Week 12 vaginal pH
 - cc. Baseline score of most bothersome symptom of VVA identified at baseline
 - dd. Study Week 12 score of most bothersome symptom of VVA identified at baseline
 - ee. Final designation as responder/non-responder
 - ff. Compliance rate (%)
 - gg. Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
 - hh. Adverse event reported (yes/no)
 - ii. Concomitant medication (yes/no)
- 7) Please provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
- a. Study identifier
 - b. Unique subject identifier
 - c. Subject identifier for the study
 - d. Study site identifier (if applicable)

- e. Name of planned treatment
 - f. Name of actual treatment
 - g. Safety population flag (yes/no)
 - h. Modified ITT population flag (yes/no)
 - i. Per-Protocol (PP) population flag (yes/no)
 - j. Analysis date
 - k. Analysis visit
 - l. Study visit within the designated window (yes/no)
 - m. Analysis timepoint (e.g., hour 0, hour 2) (if applicable)
 - n. Baseline intermediate epithelial cells on vaginal cell cytology (i.e., % intermediate)
 - o. Study Week 12 intermediate epithelial cells on vaginal cell cytology (i.e., % intermediate)
 - p. Baseline basal/parabasal epithelial cells on vaginal cell cytology (i.e., % basal)
 - q. Study Week 12 basal/parabasal epithelial cells on vaginal cell cytology (i.e., % basal)
 - r. Baseline vaginal pH
 - s. Study Week 12 vaginal pH
 - t. Baseline score of most bothersome symptom of VVA identified at baseline
 - u. Study Week 12 score of most bothersome symptom of VVA identified at baseline
 - v. Final designation as responder/non-responder
 - w. Additional treatment required during the visit (yes/no)
 - x. Adverse event reported during the visit (yes/no)
 - y. Concomitant medication during the visit (yes/no)
- 8) Please refer to the product-specific guidance on adapalene; benzoyl peroxide topical gel, 0.3%; 2.5% entitled *Guidance on Adapalene; Benzoyl Peroxide* for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.
- 9) Study data should be submitted in a standardized format⁴.
- 10) Retrieve the ring at the last day of the study to determine residual amount of estradiol.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

⁴ Study Data Standards for Submission to CDER and CBER available at: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>