

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Estradiol; Levonorgestrel

August 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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 Ingredients:	Estradiol; Levonorgestrel
Dosage Form:	Film, extended release
Route:	Transdermal
Strength:	0.045 mg/24 hr; 0.015 mg/24 hr
Recommended Studies:	One in vivo bioequivalence study with pharmacokinetic endpoints, one in vivo adhesion study, and one in vivo skin irritation study

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 0.045 mg/24 hr; 0.015 mg/24 hr
Subjects: Non-smoking, postmenopausal women with no contraindication to estrogen therapy
Additional comments:
 - a. In this document, this dosage form is referred to as a transdermal delivery system (TDS) and includes products that may be described elsewhere or known as *patches* or *extended release films*.
 - b. Unless otherwise justified, the estradiol; levonorgestrel TDS should be applied to the same anatomical site on all subjects, as recommended for dosing in the approved labeling for the reference standard and worn for 7 days (168 hours). Applicants should randomize subjects to receive either the test product or reference standard in a given study period. When possible, the TDS administered in the second study period should be applied to the same anatomical site as in the first study period, but on the contralateral side of the body.

- c. Contact of the TDS with the skin is essential for the in vivo performance of the TDS, and the pharmacokinetics may be altered when a TDS loses its adherence to the skin. Therefore, the adhesion of each TDS should be monitored and recorded throughout the pharmacokinetic study. The applicant should prespecify their inclusion criteria for the statistical analysis of pharmacokinetic endpoints and perform their primary pharmacokinetic analysis on the per protocol population, however, pharmacokinetic samples should be collected and analyzed from all subjects at all sampling times regardless of the adhesion scores of the TDS and regardless of the inclusion criteria for the statistical analysis of pharmacokinetic endpoints. Provisions should be included in the study protocol to ensure that deliberate actions with the intent to re-apply a detached area of the TDS, to apply pressure to the TDS, or to reinforce TDS adhesion with the skin (e.g., overlays) are avoided throughout the study.
- d. The applicant should refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*^a for the design and conduct of the bioequivalence study with pharmacokinetic endpoints.

Analytes to measure: Estradiol and levonorgestrel in plasma or serum. An average baseline correction is obtained for estradiol by averaging the 3 pre-application sampling times (-1, -0.5 and 0 hours).

Bioequivalence based on (90% CI): Estradiol (using both baseline corrected and uncorrected data) and levonorgestrel.

Waiver request of in vivo testing: Not applicable

2. Type of study: Adhesion study

Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: 0.045 mg/24 hr; 0.015 mg/24 hr

Subjects: Non-smoking, postmenopausal women with no contraindication to estrogen therapy

Additional comments:

- a. The applicant may elect to evaluate the pharmacokinetic bioequivalence (study 1) and the adhesion (study 2) in a single study with a combined purpose, or in independent studies. In either case, the studies should be adequately powered to evaluate the bioequivalence, and independently, the comparative assessment of adhesion.
- b. The applicant should refer to the most recent version of the FDA guidance for industry on *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs*^a for the design and conduct of the independent adhesion study or the combined study to evaluate both pharmacokinetic bioequivalence and adhesion.

3. Type of study: Skin irritation and sensitization study
Design: Randomized, evaluator-blinded, within-subject repeat in vivo
Strength: 0.045 mg/24 hr; 0.015 mg/24 hr (Dose: One-half of a 0.045 mg/24 hr; 0.015 mg/24 hr TDS)
Subjects: Non-smoking, postmenopausal women with no contraindication to estrogen therapy
Additional comments:
- a. All test articles (i.e., one half of the 0.045 mg/24 hr; 0.015 mg/24 hr test product¹, one half of the 0.045 mg/24 hr; 0.015 mg/24 hr reference standard, optional vehicle TDS² and optional negative control³) should be applied simultaneously to each subject at different positions on an application site recommended in the approved labeling for the reference standard.
 - b. Sequential TDS applications should be made to the same application site every 7 days for a total of 21 consecutive days. The TDS applied on Day 15 should be removed on Day 22.
 - c. There is insufficient information to determine whether it is safe to simultaneously apply two whole, active, 0.045 mg/24 hr; 0.015 mg/24 hr estradiol; levonorgestrel TDS on the same subject during a 21-day skin irritation and sensitization study. Since the reference listed drug (RLD)/reference standard has a matrix design that can be safely cut in half, one half of the reference standard can be used for these studies. If the test product also has a design that can be safely cut to a smaller size, it should also be cut in half, and one half of the test product may be applied simultaneously with one half of a reference standard (to separate skin sites). It would not be acceptable to manufacture a separate batch of the test product in order to use a smaller TDS in this study. If the test TDS has a design that cannot be safely cut to a smaller size, and/or if a prospective applicant proposes a study design different than what is recommended above, the prospective applicant may submit a pre-abbreviated new drug application (pre-ANDA) meeting request to discuss the proposed approach.
 - d. The applicant should refer to the most recent version of the FDA guidance for industry on *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs*^a for the design and conduct of the skin irritation and sensitization study.

Additional comments relating to all studies:

In addition to the recommendations in the general guidances referenced above, and the product specific recommendations related to the individual studies, the following product specific recommendations should be considered.

¹ The test product evaluated should be the actual TDS to be marketed.

² The optional vehicle TDS should contain all of the inactive ingredients in the test product and be identical to the test product in every manner except for the absence of the active ingredients.

³ An example of the optional negative control treatment is an occlusion cover or device with normal saline applied on a polyester pad under the cover or within the device chamber.

1. As a safety precaution, the subject's seated blood pressure should be evaluated at all visits.
2. Inclusion criteria (the applicant may add additional criteria):
 - a. Non-smoking, postmenopausal female subjects with 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. Baseline systolic blood pressure should be no greater than 140 mm Hg and diastolic blood pressure no greater than 80 mm Hg.
 - c. 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.
 - d. 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 standard
 - 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

Additional information:

Device:

The RLD is a TDS and a drug-device combination product.

FDA recommends that prospective applicants examine the external critical design attributes of the RLD device when designing the test device.

User interface assessment:

An 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*.^a

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^a For the most recent version of a guidance, check the FDA guidance website at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.