*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

**Draft Guidance on Ethinyl Estradiol; Levonorgestrel**

**August 2021**

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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.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

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

**Active Ingredient:** Ethinyl estradiol; Levonorgestrel

**Dosage Form; Route:** System; transdermal

**Recommended Studies:** Three studies

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.03 mg/24 hr; 0.12 mg/24 hr
   Subjects: Healthy non-pregnant, non-lactating females, who are candidates for hormonal contraception.
   Additional comments:
   - 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 *systems*, *patches* or *extended release films*.

- Unless otherwise justified, the ethinyl estradiol; levonorgestrel TDS should be applied to the same anatomical site on all subjects, selected from among those recommended for dosing in the approved labeling for the reference product, and worn for seven days. Applicants should randomize subjects to receive either the test or reference product 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.

- 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.

- The applicant should follow FDA's current thinking in the guidance *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* for the design and conduct of the pharmacokinetic bioequivalence study.

**Analytes to measure:** Ethinyl estradiol and levonorgestrel in plasma

**Bioequivalence based on (90% CI):** Ethinyl estradiol and levonorgestrel

**Waiver request of in vivo testing:** Not applicable

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2. Type of study: Adhesion study
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.03 mg/24 hr; 0.12 mg/24 hr
   Subjects: Healthy non-pregnant, non-lactating females, who are candidates for hormonal contraception.
   Additional comments:
   - 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.

- The applicant should follow FDA's current thinking in the guidance *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs* for the design and conduct of the independent adhesion study or the combined study to evaluate both pharmacokinetic bioequivalence and adhesion.

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3. Type of study: Skin irritation and sensitization study
Design: Randomized, evaluator-blinded, within-subject repeat design in vivo
Strength: 0.03 mg/24 hr; 0.12 mg/24 hr (administered as one-half of the test and one-half of the reference)
Subjects: Healthy non-pregnant, non-lactating females, who are candidates for hormonal contraception.
Additional comments:

   - All test articles (i.e., one half of the 0.03 mg/24 hr; 0.12 mg/24 hr test product[1], one half of the 0.03 mg/24 hr; 0.12 mg/24 hr reference product, optional vehicle TDS[2] and optional negative control[3]) should be applied simultaneously to each subject at different positions on an application site recommended in the approved labeling for the reference product.

   - Sequential TDS applications should be made to the same application site weekly (i.e., every 7 days; the intended duration of wear) for a total of 21 consecutive days.

   - There is insufficient information to determine whether it is safe to simultaneously apply two whole, active, 0.03 mg/24 hr; 0.12 mg/24 hr, ethinyl estradiol; levonorgestrel TDS on the same subject during a 21-day skin irritation and sensitization study. Since the reference product has a matrix design that can be safely cut in half, one half of the reference product 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 product (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.

   - Subjects should be informed that wearing a TDS that is cut in half will not protect them from pregnancy and they are especially at risk for pregnancy during the first

[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 is an occlusion cover or device with normal saline applied on a polyester pad under the cover or within the device chamber.

- week of the induction phase, after Day 7 of the rest period, and during the entire challenge phase.

- Following the challenge phase, if a subject wishes to use the contraceptive TDS or resume oral contraceptives, she may apply a new (reference) TDS to a different site immediately or start a new pill cycle, but she should also continue using non-hormonal contraception for 7 days after starting the new hormonal contraceptive cycle. Subjects who do not wish to use a hormonal contraceptive may experience vaginal bleeding or spotting after removal of the challenge TDS.

- The applicant should follow FDA's current thinking in the guidance *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs* for the necessity, design, and conduct of the skin irritation and sensitization study.

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**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.

- Females should not be pregnant. Due to an increased myocardial risk primarily in smokers, non-smoking subjects who have previously used hormonal contraceptives without complications should be enrolled. Also, females having a BMI lower than 30 $kg/m^2$ and not exceeding 35 years of age should be considered since the reference product is contraindicated in women with a BMI $\geq$ 30 $kg/m^2$ and older women may be at a higher risk of drug-related adverse events. Baseline systolic blood pressure should be no greater than 140 mm Hg and diastolic blood pressure no greater than 80 mm Hg.

- Criteria should also be developed to discontinue subjects that reach a pre-defined maximum blood pressure throughout the study.

- Inclusion Criteria (the applicant may add additional criteria):
    a. Non-pregnant, non-lactating female subjects 18-35 years of age (inclusive) who are candidates for hormonal contraception
    b. Subjects who have previously used hormonal contraceptives without complications are the optimal candidates for this study
    c. Subjects who are willing to stop using any current hormonal contraceptive method
    d. Subjects who had a tubal ligation OR who throughout the study and for 7 days after completion of the study or premature discontinuation, agree to abstain from sexual intercourse or to use a reliable non-hormonal method of contraception (e.g., diaphragm with spermicide or condom with spermicide)
    e. Negative pregnancy test on first dosing day, prior to application of a TDS

- Exclusion Criteria (the applicant may add additional criteria):

a. Subject who is pregnant or lactating
b. Subject who is a current smoker
c. Subject who has a BMI 30 kg/$m^2$ or more
d. Subject who was a previous user of reference product
e. Subject who is currently using any long-acting hormonal method of contraception (e.g., contraceptive rod implant such as Nexplanon®, hormonal intrauterine device such as Mirena®, hormone injections such as Depo-Provera® or Depo-subQ Provera 104®) or has used them within past 3 months
f. Subject who currently has any of the following conditions:
    1. Active deep venous thrombosis, pulmonary embolism, or a history of these conditions
    2. Inherited or acquired hypercoagulopathies
    3. A past history of deep vein thrombophlebitis or thromboembolic disorders
    4. Current or history of cerebrovascular or coronary artery disease
    5. Thrombogenic valvular or thrombogenic rhythm diseases of the heart (e.g., subacute bacterial endocarditis with valvular disease or atrial fibrillation)
    6. Uncontrolled hypertension or hypertension with vascular disease
    7. Diabetes with vascular disease
    8. Headaches with focal neurological symptoms or migraine headaches
    9. Major surgery with prolonged immobilization
    10. Known or suspected carcinoma of the breast or personal history of breast cancer
    11. Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
    12. Undiagnosed abnormal genital bleeding
    13. Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use
    14. Acute or chronic hepatocellular disease with abnormal liver function
    15. Hepatic adenomas or carcinomas
    16. Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir
    17. Hypertriglyceridemia
    18. Hereditary angioedema
    19. Taking thyroid hormone replacement therapy
    20. Taking inducers of CYP3A4 such as St. John's wort, anticonvulsants, phenylbutazone, rifampin, rifabutin, nevirapine and efavirenz
    21. Taking inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, nelfinavir and grapefruit juice

- A listing of the prescription and over-the-counter drug products that are contraindicated during the study should be provided, such as:
  Hormonal contraception other than test product and reference product (e.g., oral contraceptive pills, contraceptive vaginal ring such as NuvaRing®, contraceptive rod implant such as Nexplanon®, hormonal IUD such as Mirena®, hormone injections such as Depo-Provera® or Depo-subQ Provera 104®).

- Subjects should receive the first TDS within seven days after the first day of a menstrual period. Subjects currently taking hormonal contraceptives should switch to the study drug on the day they are scheduled to start a new contraceptive cycle. This will minimize disruption of the menstrual cycle.

- Subjects should be advised to expect menstrual bleeding after each TDS is removed.

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