

**Draft Guidance on Ethinyl Estradiol; Segesterone Acetate**

**May 2023**

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**Active Ingredients:** Ethinyl estradiol; Segesterone acetate

**Dosage Form; Route:** Ring; Vaginal

**Strength:** 0.013mg/24hr; 0.15mg/24hr

**Recommended Studies:** Two options: (1) one in vitro comparative drug release study with supportive characterization studies and one in vivo bioequivalence study with pharmacokinetic endpoints (3 cycles) or (2) one in vivo bioequivalence study with pharmacokinetic endpoints (13 cycles)

**I. Option 1: One in vitro comparative drug release study with supportive characterization studies and one in vivo bioequivalence study with pharmacokinetic endpoints (3 cycles)**

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

1. The test and reference listed drug (RLD) formulations are qualitatively (Q1)<sup>1</sup> and quantitatively (Q2)<sup>2</sup> the same;
2. Comparative physicochemical and mechanical characteristics of the test and reference standard (RS) products including, a) degree of crosslinking of the silicone polymers, b) mechanical properties (hardness, tensile strength, elongation at break), and fatigue testing; and
3. Same physical dimensions including geometry of the ring and the inner cores as the RLD.

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

<sup>2</sup> Q2 (Quantitative sameness) means that the amount of the inactive ingredient(s) used in the test product are within ± 5% of those used in the RLD product.

### **One in vitro comparative drug release study with supportive characterization studies:**

1. Type of study: Comparative in vitro drug release testing of ethinyl estradiol and segesterone acetate  
Strength: 0.013 mg/24hr; 0.15 mg/24hr  
Additional comments: In vitro drug release of ethinyl estradiol and segesterone acetate from the test and the RS products should follow 21/7 days in/out schedule for thirteen 28-day cycles (the intended period of product use). The ring should be stored in the co-packaged container during the 7-day out interval after being cleaned with warm water and mild soap, dried with a clean cloth towel or paper towel per label instruction. Testing should be carried out to capture both initial burst release and sustained release at each cycle.

### **One in vivo bioequivalence study with pharmacokinetic endpoints (3 cycles):**

1. Type of study: Bioequivalence study with pharmacokinetic endpoints  
Design: Three 28-day cycles, single-dose, randomized crossover or parallel in vivo  
Strength: 0.013 mg/24hr; 0.15 mg/24hr  
Subjects: Healthy premenopausal, non-pregnant, non-smoking females  
Additional comments:
  - Study subjects should have a BMI  $\leq 29$  kg/m<sup>2</sup>, no contraindication for use of hormonal contraceptives and should not use any other vaginal products (e.g., rings, creams, gels, and devices) during the study.
  - The last blood sample should be collected right before the ring removal.
  - Determine residual amount of ethinyl estradiol and segesterone acetate in the retrieved test and the RS products at the end of the 3<sup>rd</sup> cycle.

**Analytes to measure:** Ethinyl estradiol in plasma, segesterone acetate in plasma, residual amount of ethinyl estradiol and segesterone acetate following removal of the ring at the end of the 3<sup>rd</sup> cycle

**Bioequivalence based on (90% CI):** Ethinyl estradiol and segesterone acetate in plasma

The 90% confidence intervals of the log-transformed AUC<sub>0-21d</sub> and C<sub>max</sub> of Cycle 3 for ethinyl estradiol and segesterone acetate should meet the acceptable limits of 80.00% - 125.00%.

Log-transformed AUC<sub>0-21d</sub> and C<sub>max</sub> of Cycles 1 and 2 for both ethinyl estradiol and segesterone acetate serve as supportive information. The residual amount of ethinyl estradiol and segesterone acetate in retrieved rings serve as supportive information.

**Waiver request of additional strengths:** Not applicable

## II. Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints (13 cycles)

In vivo bioequivalence study with pharmacokinetic endpoints described below is recommended for any generic segesterone acetate and ethinyl estradiol vaginal ring that cannot meet the criteria described in Option I.

1. Type of study: Bioequivalence study with pharmacokinetic endpoints  
Design: Thirteen 28-day cycles, single-dose, crossover or parallel in vivo  
Strength: 0.013 mg/24hr; 0.15 mg/24hr  
Subjects: Healthy premenopausal, non-pregnant, non-smoking females  
Additional comments:
  1. Study subjects should have a BMI  $\leq 29$  kg/m<sup>2</sup>, no contraindication for use of hormonal contraceptives and should not use any other vaginal products (e.g., rings, creams, gels, and devices) during the study.
  2. The last blood sample should be collected right before the ring removal.
  3. Determine residual amount of ethinyl estradiol and segesterone acetate in the retrieved test and RS products at the end of the 13<sup>th</sup> cycle.
  4. Additional data and information may be necessary to address potential risk posed by the differences in inactive ingredients or formulation differences between the test and the RLD. It is recommended that an applicant should contact FDA before designing any such studies to ensure the proposed studies are appropriate for supporting an 505(j) submission.

**Analytes to measure:** Ethinyl estradiol and segesterone acetate in plasma, residual amount of ethinyl estradiol and segesterone acetate following removal of the ring at the end of 13<sup>th</sup> cycle

**Bioequivalence based on (90% CI):** Ethinyl estradiol and segesterone acetate in plasma

The 90% confidence intervals of log-transformed AUC<sub>0-21d</sub> and C<sub>max</sub> of the 1<sup>st</sup> and 13<sup>th</sup> cycles for ethinyl estradiol and segesterone acetate should meet the acceptable limits of 80.00% - 125.00%.

Log-transformed AUC<sub>0-21d</sub> and C<sub>max</sub> of Cycles 3 and 7 for both ethinyl estradiol and segesterone acetate serve as supportive information. The residual amount of ethinyl estradiol and segesterone acetate in retrieved rings serve as supportive information.

**Waiver request of additional strengths:** Not applicable

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, <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).

**Additional information:**

Device:

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*.<sup>a</sup>

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<sup>a</sup> 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>.