

## Draft Guidance on Ethinyl Estradiol; Levonorgestrel

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active ingredient:** Ethinyl Estradiol; Levonorgestrel

**Form/Route:** Tablets/Oral

**Recommended studies:** 3 studies

1. Type of study: Fasting  
Design: Single-dose, two-treatment, two-period crossover *in-vivo*  
Strength: 0.03 mg/0.15 mg tablet of ethinyl estradiol and levonorgestrel  
Subjects: Healthy nonpregnant females, general population.  
Additional Comments:

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2. Type of study: Fed  
Design: Single-dose, two-treatment, two-period crossover *in-vivo*  
Strength: 0.03 mg/0.15 mg tablet of ethinyl estradiol and levonorgestrel  
Subjects: Healthy nonpregnant females, general population.  
Additional Comments:

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3. Type of study: Fasting (If Applicable)  
Design: Single-dose, two-treatment, two-period crossover *in-vivo*  
Strength: 0.01 mg tablet of ethinyl estradiol  
Subjects: Healthy nonpregnant females, general population.  
Additional Comments:

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**Analytes to measure (in appropriate biological fluid):** Ethinyl estradiol and levonorgestrel in plasma for the combination tablets. Only ethinyl estradiol for the single component tablet.

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

### Cross-referencing of *in-vivo* bioequivalence testing:

1. Please note that when referencing different NDAs of Ethinyl Estradiol and Levonorgestrel Tablets, 0.03 mg/0.15 mg, and 0.02 mg/0.1 mg as designated in the RLD application number column, separate applications must be submitted. Please refer to the Guidance for Industry, *Variations in Drug Products that May Be Included in a Single ANDA* located at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064995.htm>

2. For applications containing the same strength (of Ethinyl Estradiol/Levonorgestrel Tablets or Ethinyl Estradiol Tablets) as that used in the bioequivalence studies but submitted in a separate ANDA, you may cross-reference based on (1) acceptable bioequivalence studies of this strength in another related ANDA, (2) acceptable in vitro dissolution testing of both formulations of the same strength, and (3) proportional similarity of the formulations of the same strength.
3. For the lower strength, 0.02 mg/0.1 mg Ethinyl Estradiol/Levonorgestrel strength, submitted in a separate ANDA, based on (1) acceptable fasting and fed bioequivalence studies of the higher strength, 0.03 mg/0.15 mg Ethinyl Estradiol/Levonorgestrel, in another related ANDA, (2) acceptable in vitro dissolution testing of both formulations, and (3) proportional similarity between the 0.03 mg/0.15 mg and 0.02 mg/0.1 mg Ethinyl Estradiol/Levonorgestrel formulations.

If only the lower strength, 0.02 mg/0.1 mg Ethinyl Estradiol/Levonorgestrel (together with the 0.01 mg Ethinyl Estradiol strength), is to be marketed first, the fasting and fed studies should be conducted on the 0.02 mg/0.1 mg Ethinyl Estradiol/Levonorgestrel, and a fasting study should be conducted on the 0.01 mg Ethinyl Estradiol strength, comparing them with the respective equal strengths of the reference product. However, if the higher strength, 0.03 mg/0.15 mg Ethinyl Estradiol/Levonorgestrel is to be marketed at a later time after *the in vivo* studies of the 0.02 mg/0.1 mg Ethinyl Estradiol/Levonorgestrel and 0.01 mg Ethinyl Estradiol were conducted, an **additional** fasting study will be requested for the higher combination strength.

#### **Dissolution test method and sampling times:**

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.