

*Contains Nonbinding Recommendations*

**Draft Guidance on Levonorgestrel**

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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:** Levonorgestrel

**Form/Route:** Tablets/Oral

**Recommended studies:** 2 studies

1. Type of study: Fasting  
Design: Single-dose, two-way crossover in-vivo  
Strength: 1.5 mg  
Subjects: Healthy nonpregnant females, general population.  
Additional Comments:

2. Type of study: Fed  
Design: Single-dose, two-way crossover in-vivo  
Strength: 1.5 mg  
Subjects: Healthy nonpregnant females, general population.  
Additional Comments: Please refer to the Amantadine hydrochloride tablet guidance for additional information regarding fed studies.

**Analytes to measure (in appropriate biological fluid):** Levonorgestrel in plasma

**Bioequivalence based on (90% CI):** Levonorgestrel

**Waiver request of in-vivo testing:** 0.75 mg based on (i) acceptable fasting and fed BE studies on the 1.5 mg strength, (ii) proportional similarity in the formulations across all strengths, and (iii) acceptable dissolution testing across all strengths.

Since Levonorgestrel Tablets, 1.5 mg and 0.75 mg are the subject of two separate applications, two separate Abbreviated New Drug Applications (ANDAs) must be submitted. A waiver of *in vivo* bioequivalence testing of the 0.75 mg strengths may be requested if the criteria are met. The *in vivo* bioequivalence studies conducted on 1.5 mg may be cross-referenced, along with the in-vivo waiver request. Refer to the Guidance for Industry, *Variations in Drug Products that May Be Included in a Single ANDA* located at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072892.pdf>.

If only the lower strength, 0.75 mg, is to be marketed first, please conduct the studies recommended above comparing the test 0.75 mg strength to the corresponding strength of

the reference product. However, if the higher strength, 1.5 mg, is to be marketed at a later time after the in vivo studies on the 0.75 mg strength were conducted, an additional fasting study will be requested for the 1.5 mg 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.