

Draft Guidance on Ethinyl Estradiol; Ethynodiol Diacetate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 (EE); Ethynodiol Diacetate (EDA)

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover *in-vivo*
Strength: 0.05 mg/1 mg
Subjects: Healthy non pregnant females, general population.
Additional Comments:

2. Type of study: Fed
Design: Single-dose, two-way crossover *in-vivo*
Strength: 0.05 mg/1 mg
Subjects: Healthy non pregnant females, general population.
Additional Comments:

Analytes to measure (in appropriate biological fluid): Ethinyl Estradiol and Norethindrone (active metabolite of Ethynodiol Diacetate).

Bioequivalence based on (90% CI): Ethinyl Estradiol and Norethindrone.

Referencing/Cross-referencing of *in-vivo* testing: For the lower strength, 0.035 mg/1 mg EE/EDA submitted in a separate ANDA, based on (i) acceptable bioequivalence studies of the 0.05 mg/1 mg EE/EDA strength from a separate but related ANDA, (ii) cross-referencing of the studies above in the separate ANDA of the 0.035 mg/1 mg EE/EDA strength (iii) acceptable in vitro dissolution testing of both strengths, and (iv) proportional similarity of the formulations between two strengths.

If only the lower strength, 0.035 mg/1 mg EE/EDA (21 day or 28 day regimen), is to be marketed first, the fasting and fed studies should be conducted on this lower strength, comparing it with the equal strength of the reference product of the same bundle (linked to the current guidance). In such case, if later the higher strength, 0.05 mg/1 mg EE/EDA is to be marketed, an **additional** fasting study will be requested for this higher strength without cross-referencing of the studies of the lower strength.

Please note that if different NDA/ANDAs of Ethinyl Estradiol and Ethynodiol Diacetate Tablets, 0.035 mg/1 mg and 0.05 mg/1 mg, are referenced, 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/Guidance/ComplianceRegulatoryInformation/Guidances/ucm064995.htm>

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/index.cfm> . 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.