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Draft Guidance on Ethinyl Estradiol; Norethindrone Acetate

October 2024

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredients: Ethinyl estradiol; Norethindrone acetate

Dosage Form: Tablet

Route: Oral, Oral-21, Oral-28

Strengths: 0.02 mg; 1 mg, 0.03 mg; 1.5 mg

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.03 mg; 1.5 mg
   Subjects: Healthy non-pregnant, non-lactating females
   Additional comments: None

Analytes to measure: Ethinyl estradiol and norethindrone in plasma

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

Waiver request of in vivo testing: 0.02 mg; 1 mg (28 day), 0.02; 1 mg (24 day), and 0.02 mg; 1 mg (21 day) based on (i) acceptable bioequivalence study on the 0.03 mg; 1.5 mg (28 day packet) strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both strengths

Cross-referencing of in vivo testing: For the same strength, 0.03 mg; 1.5 mg (21 day packet), as that used in the bioequivalence studies but submitted in a separate abbreviated new drug application (ANDA), based on (i) acceptable bioequivalence study of this strength in the separate ANDA, (ii) acceptable in vitro dissolution testing of the formulations of the same strength, and (iii) sameness (except for the colorants) of the formulations of the same strength

If only the lower strength, 0.02 mg; 1 mg is to be marketed first, then the fasting bioequivalence study should be conducted on this lower strength, comparing it with the equal strength of the reference listed drug (RLD). However, if the higher strength, 0.03 mg; 1.5 mg, is to be marketed following the in vivo studies of the lower strength, then an additional fasting study will be requested for the higher strength.

Note that if different new drug applications of the ethinyl estradiol and norethindrone acetate tablets are referenced, then separated applications must be submitted. Refer to the most recent version of the FDA guidance for industry on *Variations in Drug Products that May Be Included in a Single ANDA.*[a]

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 for each of both strengths of the test product and RLD.[1] Specifications will be determined upon review of the ANDA.

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[1] If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions.*