

*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

**Draft Guidance on Etonogestrel**

**August 2022**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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This is a new draft product-specific guidance for industry on generic etonogestrel.

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<b>Active Ingredient:</b>	Etonogestrel
<b>Dosage Form; Route:</b>	Implant; implantation
<b>Recommended Studies:</b>	One in vitro bioequivalence study with supportive characterization studies and one in vivo bioequivalence study with pharmacokinetic endpoints

To be eligible for the bioequivalence studies recommended in this guidance, the test product should meet the following criteria:

1. Qualitatively (Q1) and quantitatively (Q2) the same as the Reference Listed Drug (RLD)
2. Same dimensions with respect to length, diameter and skin thickness of the implant as the Reference Standard (RS) products

3. Acceptable comparative physicochemical and mechanical characteristics of the test and the RS products including: 1) particle size and size distribution of the active pharmaceutical ingredient (API); 2) crystalline form of the API; and 3) mechanical properties of the implant, including but not limited to tensile strength and hardness

**One in vitro bioequivalence study with supportive characterization studies:**

**Comparative in vitro drug release:**

Acceptable comparative in vitro drug release of etonogestrel from the test and RS products (i.e., in water, 37°C) throughout the intended period of product use (3 years).

**Additional comments:** A real time release study that is shorter than 3 years may be acceptable when an accelerated dissolution method that correlates to the real-time drug release behavior is developed and validated. It is recommended that applicant should submit a proposed accelerated dissolution method for the Agency's consideration through a controlled correspondence or as part of a pre-ANDA meeting request.

**One in vivo bioequivalence study with pharmacokinetic endpoints:**

1. Type of study: In vivo bioequivalence study with pharmacokinetic endpoints  
Design: 6 months, single-dose, randomized, parallel  
Strength: 68 mg/implant  
Subjects: Healthy premenopausal, non-pregnant females

Prerequisite: Six months of in vitro etonogestrel drug release data demonstrating comparable release profiles for the test product and the RS product should be available prior to administering the test product in study subjects.

**Analyte to measure:** Etonogestrel in plasma

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

The 90% confidence interval for the ratio of the geometric means of the pharmacokinetic parameters (AUC and  $C_{max}$ ) should be within 80-125%. Residual amount of etonogestrel at month 6 should be submitted as supportive data.

**Waiver request of in vivo testing:** 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 all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

**Additional information:**

## Device:

The reference listed drug (RLD) product is presented as a removable implant in a disposable applicator. The implant and the applicator are device constituents used to administer the drug.

FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD devices when designing the test devices including the following characteristics:

- Radiopaque implant
- Preloaded, single-use applicator
- Gauge and length of applicator needle

## User Interface Assessment:

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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**Unique Agency Identifier:** PSG\_021529

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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>.