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Draft Guidance on Levonorgestrel

November 2024

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Active Ingredient:	Levonorgestrel
Dosage Form:	System
Route:	Intrauterine
Strength:	13.5 mg
Recommended Studies:	One in vitro bioequivalence study with supportive comparative studies and one in vivo/ex vivo bioequivalence study

To be eligible for the bioequivalence studies recommended in this guidance, the test (T) product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference listed drug (RLD) product that may significantly affect the local or systemic availability of the active ingredient. For example, the T product can be qualitatively (Q1) [1] and quantitatively (Q2) [2] the same as the reference standard (RS) product to satisfy no difference in inactive ingredients. [3]

[1] Q1 (Qualitative sameness) means that the T product uses the same inactive ingredient(s) as the RLD product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T product are within ±5% of those used in the RLD product.
[3] If quantitative differences more than 5% in inactive ingredients exist, prospective applicants should provide data and information justifying that such differences would not impact the proposed drug product in terms of safety and efficacy and the studies recommended in this guidance may still be suitable for establishing bioequivalence.

One in vitro bioequivalence study:

1. Type of study: In vitro drug release testing (IVRT) of levonorgestrel from the T and RS throughout the intended period of product use (3 years)
   Design: Should be performed on three batches each of both T and RS products
   Strength: 13.5 mg
   Additional comments:
   a. A properly developed and validated method that can detect potential formulation differences should be provided. The prospective applicant should identify relevant critical manufacturing parameters and/or quality attributes of the drug product that can impact product performance in terms of drug release and develop the IVRT methodology to discriminate meaningful differences in these attributes. [4,5]
   b. A complete IVRT method development and validation report should be provided.
   c. Equivalence in levonorgestrel release should be established using a proper statistical method from at least three batches of T and RS products. One suggested approach is a model independent similarity (f2) factor. For more information on calculation of f2 factor, refer to the most recent version of the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.[b]
   d. Any accelerated IVRT method that correlates to the real-time drug release behavior may be submitted for the Agency's consideration through either a controlled correspondence or as part of a pre-abbreviated new drug application (pre-ANDA) meeting request.

Bioequivalence based on: Release profiles of levonorgestrel

Comparative characterization studies:

Comparative physicochemical and mechanical characterization of the T and RS products. The comparative study should be performed on at least three batches each of both the T[6] and RS products and should include:

- Particle size and size distribution of levonorgestrel
- Degree of crosslinking of poly (dimethylsiloxane) elastomer (PDMS) used in the drug reservoir and the drug rate controlling membrane
- Mechanical properties of the drug reservoir and the drug rate controlling membrane
- Appearance, memory, mechanical properties of the T-body
- Breaking force of the removal thread
- Dimension of each component

[4] Bao Q, Zou Y, Wang Y, Kozak D, Choi S, Burgess DJ. Drug release testing of long-acting intrauterine systems. Journal of Controlled Release, 2019. 316: 349-358. https://doi.org/10.1016/j.jconrel.2019.11.015

[5] Fanse S, Bao Q, Zou Y, Wang Y, Burgess DJ. Impact of manufacturing variables on product performance of contraceptive levonorgestrel intrauterine systems. International Journal of Pharmaceutics. 2024. 660:124343. https://doi.org/10.1016/j.ijpharm.2024.124343

[6] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

One in vivo/ex vivo clinical study:

1. Type of study: In vivo/ex vivo study of residual levonorgestrel and serum levonorgestrel
   Design: One year, single-dose, randomized, parallel in vivo study
   Strength: 13.5 mg
   Subjects: Healthy premenopausal, nonpregnant females, ages 18 to 45 years (inclusive), who are not using other hormonal contraceptive. The enrolled population should include a sufficient number of nulliparous women.
   Prerequisite: Twelve months of in vitro levonorgestrel drug release data demonstrating comparable release profiles for the T product and the RS product should be available prior to placing the T product in study subject.
   Additional comments: Refer to the most recent version of the FDA product-specific guidance on *Levonorgestrel Intrauterine System* (NDA 021225) [a] for additional considerations for the study design of the in vivo/ex vivo bioequivalence study; the residual amount of levonorgestrel at months 3, 6, and 12 should be provided to support that the T and RS products have a comparable in vivo release pattern.

Analytes to measure:

a. Residual amount of levonorgestrel (following intrauterine system (IUS) implantation and removal of IUS at months 3, 6, and 12)
b. Levonorgestrel in serum at months 1, 3, 6, and 12 (collect serum sample prior to levonorgestrel intrauterine system removal for subjects scheduled for removal on the same day)

Bioequivalence based on (90% CI): Residual amount of levonorgestrel at month 12 (90% CI of T/R ratio of residual amount of levonorgestrel should be within 95.47% - 105.65%)

Waiver request of in vivo testing: Not applicable

Additional information:

Device:
The RLD is presented as two integrated devices: (1) a single-use levonorgestrel-containing IUS partially preloaded in a (2) single-use, disposable delivery system. The IUS and delivery system constitute the device constituent parts of the product.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the T device including:

- Size, shape, and flexibility of IUS
- Visibility of IUS under ultrasound and radiograph
- Monofilament removal thread
- IUS integrated with delivery system
- Delivery system inserter tube length, diameter, curvature, and flexibility
- Delivery system inserter tube measurement scale in centimeters located on two sides of tube
- Delivery system with single-hand operation

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.*[b]

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[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm
[b] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.