

Draft Guidance on Levonorgestrel

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

Active Ingredient:	Levonorgestrel
Dosage Form; Route:	Intrauterine Device; intrauterine
Strength:	52 mg
Recommended Studies:	Two studies: in vitro and in vivo/ex vivo

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

- Qualitatively (Q1) and quantitatively (Q2) the same as the Reference Listed Drug (RLD).
- Equivalent physicochemical and mechanical characteristics including 1) particle size and size distribution of the active pharmaceutical ingredient (API); 2) Degree of crosslinking of poly(dimethylsiloxane) elastomer (PDMS) used in the drug reservoir and the drug rate controlling membrane; 3) Mechanical properties of the drug reservoir and the drug rate controlling membrane; 4) Appearance, memory, mechanical properties of the T-body; and 5) Breaking force of the removal thread comparable to the Reference Standard (RS).
- Same dimensions with respect to each component as the RS.

A. Comparative in vitro drug release

Acceptable comparative in vitro drug release of levonorgestrel from the test and RS products throughout the intended period of product use (5 years). Any accelerated dissolution 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-ANDA meeting request.

B. In vivo/ex vivo clinical study

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: 52 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 test product and the RS product should be available prior to placing the test product in study subject.

Analytes to measure:

1. Residual amount of Levonorgestrel (following test product implantation and removal of test product at months 3, 6, and 12)
2. Levonorgestrel in serum at months 1, 3, 6, and 12 (collect serum sample prior to LNG-IUS removal for subjects scheduled for removal on the same day)

Bioequivalence based on (90% CI of T/R ratio of residual amount of levonorgestrel should be within 95.00%-105.26%): Residual amount of Levonorgestrel at month 12

Additional comments: The following elements should be incorporated into BE study designs:

1. **Inclusion criteria:**

- Healthy premenopausal, nonpregnant females, ages 18 to 45 years (inclusive), who are not using other hormonal contraceptive methods and are willing to use an intrauterine contraceptive to prevent pregnancy for 3 – 12 months. (Women are eligible if they have a prior bilateral tubal ligation).
- Investigator finds that patient has suitable general and uterine conditions for inserting the levonorgestrel intrauterine system.
- Has regular menstrual cycles (21 - 35 day cycles) without hormonal contraceptive use
- If subjects at increased risk for infectious endocarditis (prosthetic heart valves, rheumatic heart disease, previous endocarditis) are not excluded from the study population, the protocol should state, *prophylactic antibiotics should be considered prior to insertion and removal of intrauterine contraception in high risk patients.*

2. **Exclusion criteria:**

- Women with a prior transcervical tubal sterilization procedure (e.g., Essure)
- Postmenopausal woman
- Known or suspected pregnancy
- Lactating
- Use of another hormonal contraceptive within 30 days of levonorgestrel intrauterine system placement for the study
- Vaginal delivery, cesarean delivery, or abortion within six weeks prior to levonorgestrel intrauterine system insertion (uterus should be fully involuted before a postpartum insertion).
- History of ectopic pregnancy
- Women with a uterine cavity that measures less than 6 cm or greater than 10 cm
- Congenital or acquired uterine anomaly, including fibroids if they distort the uterine cavity
- Acute pelvic inflammatory disease (PID) or a history of PID unless there has been a subsequent intrauterine pregnancy
- Postpartum endometritis or infected abortion in the past 3 months
- Known or suspected uterine or cervical neoplasia
- Known or suspected breast cancer or other progestin-sensitive cancer, now or in the past
- Uterine bleeding of unknown etiology

- Untreated acute cervicitis or vaginitis, including bacterial vaginosis or other lower genital tract infections
- Acute liver disease or liver tumor (benign or malignant)
- Conditions associated with increased susceptibility to pelvic infections
- A previously inserted intrauterine device that has not been removed
- Hypersensitivity to any component of the product

3. Screening procedures:

- Physical examination should include evaluation of uterine position and size and for abnormal pelvic masses or cervical discharge.
- Perform appropriate tests for any forms of genital or other sexually transmitted infections consistent with the U.S. Centers for Disease Control and Prevention and U.S. Preventive Services Task Force recommendations. Currently this includes:
 - Annual chlamydia screen for sexually active women < 25 years old
 - Annual chlamydia screen for sexually active women 25 years and older at increased risk
 - Annual gonorrhea screen for sexually active women at increased risk
 - High risk factors include: new or multiple sexual partners, inconsistent condom use, and sex work)
- Serum pregnancy test

4. Procedures related to levonorgestrel intrauterine system (LNG-IUS) insertion:

- Pregnancy tests must be obtained prior to all LNG-IUS insertions.
- Insert the LNG-IUS into the uterine cavity within seven days of the onset of menses or at six weeks postpartum.
- Follow all labelling insertion instructions exactly.
- Counsel subjects with all labelled Patient Counselling Information (Section 17 of Prescribing Information) including pelvic infection symptoms and instructions on how to check for the removal threads.
- Provide FDA-Approved Patient Labelling to each subject.

5. Use of an additional contraceptive method during the study:

- Subjects may not use another hormonal contraceptive method at any time during the study (subjects may instead choose to use a barrier method of contraception such as male or female condom, diaphragm, or cervical cap).
- See “LNG-IUS Removal and Contraception” below.

6. Adverse event monitoring and reporting:

- Pregnancy testing should be done at screening, baseline, immediately before LNG-IUS removal, and at other interim visits if pregnancy suspected.
- Report pregnancies and IUD expulsions as adverse events.
- Provide narratives for any pregnancies that occur in the seven-day window after IUS removal.
- Report uterine perforations as serious adverse events.

- If a subject is diagnosed with a sexually transmitted infection during the study, follow current CDC treatment recommendations.
- If a subject develops PID during the study, follow current CDC treatment recommendations. Once treatment is initiated, the investigator should determine, based on clinical judgment, whether to remove the LNG-IUS or leave it in place.
- If a subject has an abnormal cervical cytology result that requires further evaluation, with or without treatment, follow current recommendations from the American College of Obstetrics and Gynecology and the American Society for Colposcopy and Cervical Pathology (ASCCP).
- If a subject becomes pregnant during the study with an LNG-IUS in place, the pregnancy is more likely to be ectopic. The subject should be given ectopic pregnancy warnings and followed closely until an intrauterine pregnancy is confirmed or ruled out and appropriate treatment provided.

7. LNG-IUS removal and contraception before and after LNG-IUS removal:

- Pregnancy tests must be obtained prior to all LNG-IUS removals.
- LNG-IUS removal should be performed during menses when possible (if the woman is still experiencing regular menses).
- At interim visit prior to end of study visit, counsel subject about post-study contraception. If LNG-IUS removal will occur at a time other than during the first few days of menses (or if the subject is no longer having regular menses), inform the subject to start using condoms or another barrier contraceptive method at least seven days before LNG-IUS removal. If LNG-IUS removal occurs at times other than during menses and the woman had intercourse in the week prior to removal, she is at risk of pregnancy.
- All enrolled subjects who do not have a tubal ligation should be offered insertion of a Mirena IUS when the study IUS is removed.
- Remove LNG-IUS if pregnancy occurs with LNG-IUS in place and counsel regarding risks.

8. The inserter for an LNG-IUS proposed under a 505(j) regulatory pathway should have similar look, feel, and operation compared to the RLD. The applicant should refer to the FDA Guidance for Industry “Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (January 2017)¹”, which provides the Agency’s current thinking on the identification and assessment of any differences in the design of the user interface for a proposed generic drug-device combination product when compared to its RLD.

¹ <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf>