

*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

**Draft Guidance on Progesterone**

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

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

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**Active Ingredient:** Progesterone

**Dosage Form; Route:** System; vaginal

**Recommended Studies:** Two options: in vitro/in vivo studies or in vivo studies

**I. In vitro/in vivo studies option:**

To be eligible for this option all of the following criteria should be met:

1. The test and reference listed drug (RLD) formulations are qualitatively (Q1)<sup>1</sup> and quantitatively (Q2)<sup>2</sup> the same.
2. Comparative physicochemical and mechanical characteristics of the test and reference standard (RS) products including, but not limited to, 1) degree of crosslinking of the

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<sup>1</sup> Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.

<sup>2</sup> Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD product.

silicone polymers; 2) mechanical properties including hardness, tensile strength, elongation at break.

3. Same physical dimensions as the RLD.

1. Type of study: Comparative in vitro drug release testing  
Strength: 1.78 gram  
Additional comments: In vitro drug release testing should be carried out to capture both initial burst release and sustained release of progesterone.
2. Type of study: Bioequivalence (BE) study with pharmacokinetic (PK) endpoints  
Design: Single-dose, two-treatment, two-period, crossover, in vivo  
Strength: 1.78 gram  
Subjects: Postmenopausal females, general population  
Additional comments:
  1. Measure baseline progesterone levels at -1, -0.5, and 0 hours before dosing. The mean of the pre-dose progesterone levels should be used for the baseline adjustment of the post-dose levels. Baseline concentrations should be determined for each dosing period, and baseline corrections should be period specific. If a negative plasma concentration value results after baseline correction, this should be set to 0 prior to calculating the baseline-corrected AUC.
  2. Determine residual amount of progesterone in the test and reference products at the end of the study.

**Analytes to measure:** Progesterone in plasma and residual amount of progesterone in the retrieved vaginal system

**Bioequivalence based on (90% CI):** Progesterone in plasma

The 90% confidence intervals of the following PK parameters must meet the acceptable limits of [80.00-125.00]: Baseline adjusted log-transformed  $AUC_{0-\infty}$ ,  $AUC_{0-t}$  and  $C_{max}$ .

The residual amount of progesterone in retrieved system serves as supportive information.

**Waiver request of in vivo testing:** Not applicable

## **II. In vivo studies option:**

1. Type of study: BE study with pharmacokinetic (PK) endpoints  
Design: Single-dose, two-treatment, two-period, crossover, in vivo  
Strength: 1.78 gram  
Subjects: Postmenopausal females, general population  
Additional comments:
  1. Measure baseline progesterone levels at -1, -0.5, and 0 hours before dosing. The mean of the pre-dose progesterone levels should be used for the baseline adjustment of the post-dose levels. Baseline concentrations should be determined

for each dosing period, and baseline corrections should be period specific. If a negative plasma concentration value results after baseline correction, this should be set to 0 prior to calculating the baseline-corrected AUC.

2. Determine residual amount of progesterone in the test and reference systems at the end of the study.

2. Type of study: BE study with clinical endpoints  
Design: Randomized, double-blind, single-dose, parallel, in vivo  
Strength: 1.78 gram  
Subjects: Infertile women participating in an assisted reproductive technology (ART) treatment program  
Additional comments: Specific recommendations are provided below.

**Analytes to measure:** Progesterone in plasma and residual amount of progesterone in the retrieved vaginal system (for PK endpoints)

**Bioequivalence based on (90% CI):** Progesterone in plasma (for PK endpoints) and clinical pregnancy (i.e., a gestational sac with fetal heart motion present on ultrasound) are evaluated at 6 weeks and 10 weeks post embryo transfer.

The 90% confidence intervals of the following PK parameters must meet the acceptable limits of [80.00-125.00]: Baseline adjusted log-transformed  $AUC_{0-\infty}$ ,  $AUC_{0-t}$  and  $C_{max}$ .

The residual amount of progesterone in retrieved system serves as supportive information.

**Additional comments regarding the BE study with clinical endpoint:**

1. FDA recommends a BE study with clinical endpoint in women (up to and including 34 years of age) undergoing in-vitro fertilization (IVF) as part of an ART treatment program for infertility.
  - a. Prior to the embryo transfer, subjects begin with ovarian suppression and then receive ovarian stimulation treatments in accordance with investigational site's standard protocols and (or) at investigator's discretion.
  - b. During stimulation, the subjects are determined when to trigger ovulation with human chorionic gonadotropin (hCG) based on monitoring using transvaginal ultrasound and estradiol levels. Eggs are retrieved after hCG administration.
  - c. Embryo transfer is proceeded at 3 to 5 days after egg retrieval. The embryo transfer procedure is performed in accordance with investigational site's protocol and (or) American Society for Reproductive Medicine and Society for Assisted Reproductive Technology guidelines.
  - d. Subjects are randomized to receive the generic progesterone vaginal system (VS) or the reference listed drug (RLD) after a successful egg retrieval.
  - e. Subjects insert the first progesterone VS on the day after egg retrieval and a new VS is replaced weekly and continue through 10 weeks post embryo transfer.
  - f. A serum pregnancy test is initially conducted 2 weeks post-embryo transfer and repeated at scheduled visits during the period of VS placement. Subjects with a

negative pregnancy test at any visit from 2 weeks through 10 weeks post embryo transfer are withdrawn from the study and considered treatment failures. The protocol should define the positive serum pregnancy test and include schedule for a serum pregnancy test.

- g. Clinical pregnancy (i.e., a gestational sac with fetal heart motion present on ultrasound) are evaluated at 6 weeks and 10 weeks post embryo transfer.
2. Inclusion criteria (the sponsor may add additional criteria):
    - a. Pre-menopausal females aged 18 to 34 years, inclusive
    - b. Infertility due to tubal factor, ovarian dysfunction, endometriosis, male factor and idiopathic factor
    - c. Documentation of a normal uterine cavity
    - d. At least one normal menstrual cycle without reproductive hormone medication prior to the screening
    - e. Preparation of fresh sperm for ART based on semen analysis by standard criteria (e.g., WHO and/or Kruger criteria).
  3. Exclusion criteria (the sponsor may add additional criteria):
    - a. Females who have conditions that are contraindications for the use of progesterone: previous allergic reactions to progesterone or any of the ingredients of the VS, undiagnosed vaginal bleeding, severe hepatic impairment or disease, known or suspected malignancy of the breast, active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
    - b. Body Mass Index (BMI)  $>38 \text{ kg/m}^2$
    - c. Reduced ovarian function (e.g., abnormal high follicle stimulating hormone (FSH) concentration during early follicular phase)
    - d. Clinically significant gynecological diseases that could adversely affect pregnancy success such as submucosal fibroids, intramural fibroids, endometrial cancer pelvic tuberculosis, or any other conditions.
    - e. Uncontrolled hyperprolactinemia or hypothyroidism
    - f. Currently pregnant or breastfeeding
    - g. Current gonorrhea or chlamydia
    - h. History of HIV/AIDS
    - i. History of toxic shock syndrome
    - j. Any abnormal finding on the Pap smear that the Investigator considers clinically significant
    - k. History of pelvic radiation
    - l. Current use of any vaginal medications other than the study product
    - m. Use of any investigational drug or device within 30 days prior to Screening
    - n. Currently undergoing ART procedure.
    - o. History of more than one failed IVF cycle.
    - p. ART cycle or ovarian stimulation with gonadotropins or use of drugs that affect ovarian function (e.g., insulin-sensitizing agents; metformin) within 30 days or clomiphene stimulation within 90 days prior to the screening
    - q. Tobacco use three months prior to Screening

- r. History of or current medical conditions (e.g., chronic illness and cancer) that affect outcomes of ART
  - s. Male partners with non-obstructive azoospermia
4. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the treatment period, such as antifungal products, vaginal lubricants, diaphragms, and condoms.
  5. The recommended two primary clinical endpoints of the study are the clinical pregnancy rates, defined as the presence of a gestational sac and fetal heart activity at six weeks and ten weeks post-embryo transfer.
  6. The method for insertion and removal of a VS with minimum duration for use and temporary removal and precaution of concomitant use of any other vaginal products should be instructed to subjects by un-blinded study staff. Subjects should also be informed of minimum duration for use and temporary removal, precautions of concomitant drugs and storage method of the VS. A detailed description of the blinding procedure should be provided in the protocol.
  7. Subjects self-relace the VS with a new one after seven days. If the subject does not become pregnant or remain pregnant through the 10-week of pregnancy, she should stop using the VS at the time that it is determined to be non-pregnant or no longer pregnant.
  8. The VS should be removed when subjects are determined to be non-pregnant or diagnosed with a miscarriage.
  9. A multi-center study is recommended to avoid potential investigator bias. If the study was conducted at multiple clinical centers, the center should also be considered in the data analysis.
  10. Provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
    - a. Study identifier
    - b. Unique subject identifier
    - c. Subject identifier for the study
    - d. Study site identifier (if applicable)
    - e. Age
    - f. Age units (years)
    - g. Sex
    - h. Race
    - i. Name of planned treatment
    - j. Name of actual treatment
    - k. Actual treatment (character)
    - l. Safety population flag (yes/no)
    - m. Reason for exclusion from safety population
    - n. Modified Intent-to-Treat (mITT) population flag (yes/no)

- o. Reason for exclusion from mITT population
  - p. Per-Protocol (PP) population flag (yes/no)
  - q. Reason for exclusion from PP population
  - r. Randomized population flag (yes/no)
  - s. Date/time of first exposure to treatment
  - t. Date/time of last exposure to treatment
  - u. End of study date
  - v. End of study status
  - w. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
  - x. Clinical pregnancy at 6 weeks and 10 weeks post embryo transfer
  - y. Treatment compliance: hours or days (for longer than 1 hour at a time) of removal of the VS after the first insertion.
  - z. Subject had any extended removal of the VS longer than 1 hour at a time (yes/no)
  - aa. Adverse event(s) reported (yes/no)
  - bb. Concomitant medication (yes/no)
11. Provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
- a. Study identifier
  - b. Unique subject identifier
  - c. Subject identifier for the study
  - d. Study site identifier (if applicable)
  - e. Name of planned treatment
  - f. Name of actual treatment
  - g. Safety population flag (yes/no)
  - h. Modified ITT population flag (yes/no)
  - i. PP population flag (yes/no)
  - j. Analysis date
  - k. Analysis visit
  - l. Study visit within the designated window (yes/no)
  - m. Analysis timepoint (e.g., hour 0, hour 2) (if applicable)
  - n. Serum pregnancy test and (or) clinical pregnancy assessment
  - o. Abnormal vaginal discharge or bleeding (yes/no)
  - p. Additional treatment required during the visit (yes/no)
  - q. Adverse event reported during the visit (yes/no)
  - r. Concomitant medication during the visit (yes/no)
12. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)<sup>a</sup> for a recommended approach to statistical analysis and study design for BE studies with clinical endpoints.
13. Refer to the study data standards resources, <https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>.

**Waiver request of in vivo testing:** Not applicable

**Dissolution test method and sampling times:** Conduct comparative dissolution testing on 12 units each of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

**Additional Information:**

Device:

This product is a drug-device combination product. 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>b</sup> An ANDA for a proposed generic drug-device combination product should include complete comparative analyses.

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**Unique Agency Identifier:** PSG\_201110

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<sup>a</sup> For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at <https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>.

<sup>b</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>.