Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Progesterone

October 2025

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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 Ingredient:	Progesterone
Dosage Form:	Insert
Route:	Vaginal
Strength:	100 mg
Recommended Studies:	One in vitro bioequivalence study, one in vivo bioequivalence study with pharmacokinetic endpoints, and other characterization tests

To demonstrate bioequivalence for progesterone vaginal insert, 100 mg using a combination of in vitro study and an in vivo bioequivalence study with pharmacokinetic endpoints, the following criteria should be met:

1. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard (RS) that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and RS are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the most recent version of the FDA guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards*[a], and the criteria below are also satisfied, the bioequivalence of the test product may be established using a characterization-based bioequivalence approach.

2. Comparative physicochemical and structural (Q3) characterization of a minimum of three batches of the test product and three batches (as available) of the RS. The test product and RS batches should ideally represent the product at different ages throughout its shelf life. The comparison of the test product and RS should include characterizations of the following Q3 attributes:
    a. Characterization of visual appearance (dimensions) with high resolution photographs
    b. Characterization of particle size distribution, crystal habit, and polymorphic form of progesterone in the drug product (if applicable)
    c. Characterization of disintegration time

3. The test product and RS should have acceptable dissolution of progesterone. The study should be conducted using an acceptable in vitro dissolution bioequivalence study comparing a minimum of one batch each of the test product and RS using an appropriately validated and discriminatory in vitro drug dissolution method. The batches of test product and RS evaluated in the in vitro dissolution bioequivalence study should be included among those for which the Q3 attributes are characterized. The study should be conducted at 37°C based on the route of administration of this drug product. The study should be conducted at a physiologically relevant pH that is justified based on appropriate method development and validation studies. As part of the method validation, data should be provided to illustrate that the method is sensitive to changes in critical material attributes, critical process parameters, and critical quality attributes of the drug product, as appropriate.

4. The test product and RS should demonstrate bioequivalence based upon an acceptable in vivo pharmacokinetic study with one batch each of the test product and RS.

    Type of study: Bioequivalence study with pharmacokinetic endpoints
    Design: Single-dose, two-treatment, two period, crossover, fasting, in vivo
    Strength: 100 mg (dose: 1x 100 mg insert)
    Subjects: Healthy postmenopausal females
    Analyte to measure: Progesterone in plasma
    Bioequivalence based on: Progesterone, using baseline-corrected data
    Additional comments: Subjects with a history of or risk factors for arterial or venous thromboembolic disorders should be excluded. Measure baseline progesterone levels at -1.0, -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. For each subject, baseline concentrations should be determined for each dosing period, and baseline adjustments should be period-specific. If a baseline correction results in a negative plasma concentration value, the value should be set to 0 prior to calculating the baseline-corrected area under the curve (AUC). Pharmacokinetic and statistical analyses should be performed on both uncorrected and corrected data. Determination of bioequivalence should be based on the baseline-corrected data. The bioanalytical method should be sufficiently sensitive to be able to adequately characterize the pharmacokinetic profiles of the test product and RS. Applicants may consider using a reference-scaled average bioequivalence approach for progesterone. If using this

approach, the applicant should provide evidence of high variability in the bioequivalence parameters (i.e., within-subject variability ≥ 30%) for the RS. For general information on this approach and additional information regarding the analysis of the pharmacokinetic bioequivalence study refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.[a] The batches of test product and RS evaluated in the bioequivalence study with pharmacokinetic endpoints should be the same as those evaluated in the in vitro dissolution bioequivalence study.

Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the most recent version of the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*[a] for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

Additional information:

Device:
The reference listed drug (RLD) is a vaginal insert co-packaged with a vaginal applicator. The applicator is the device constituent part.

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 test device including:

- Single-dose, disposable vaginal applicator

User interface assessment:
An abbreviated new drug application 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*.[a]

Document History: Recommended September 2012; Revised August 2024, October 2025

Unique Agency Identifier: PSG_022057

[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.