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Draft – Not for Implementation

Draft Guidance on Progesterone

August 2024

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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: Two options: (1) one in vitro bioequivalence study, one in vivo bioequivalence study with pharmacokinetic endpoints, and other characterization tests or (2) one in vivo bioequivalence study with pharmacokinetic endpoints and one comparative clinical endpoint bioequivalence study

I. Option 1: 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 studies 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.

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: Heathy 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 $\geq 30\%$) 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.

II. Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints and one comparative clinical endpoint bioequivalence study

1. 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: Heathy postmenopausal females
   Analyte to measure: Progesterone in plasma
   Bioequivalence based on: Progesterone, using baseline-corrected data
   Additional comments: Refer to the "Additional comments" section of the bioequivalence study with pharmacokinetic endpoints described in Option 1.

2. Type of study: Comparative clinical endpoint bioequivalence study
   Additional comments: Applicants intending to seek additional feedback related to the comparative clinical endpoint bioequivalence study are encouraged to submit specific question(s) and supporting information such as a protocol synopsis prior to initiating the study through a product development pre-abbreviated new drug application (pre-ANDA) meeting request with the FDA.

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 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*.[a]

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[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.