Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Progesterone

November 2022

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Active Ingredient: Progesterone

Dosage Form; Route: Gel; vaginal

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 in vivo bioequivalence study with clinical endpoint

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 gel, 8% using a combination of in vitro studies and an in vivo 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 that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and reference standard 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. The test product and reference standard should have the same physicochemical and structural (Q3) attributes, based upon acceptable comparative Q3 characterization tests with a minimum of three batches of the test product and three batches (as available) of

the reference standard. The test product and reference standard batches should ideally represent the product at different ages throughout its shelf life. Refer to the most recent version of the FDA guidance for industry on *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*[a] for additional information regarding comparative Q3 characterization tests. The comparison of the test product and reference standard should include characterizations of the following Q3 attributes:

a. Characterization of visual appearance and texture
b. Characterization of phase states and structural organization of matter
    - Microscopic examination with representative high-resolution microscopic images at multiple magnifications
    - Analysis of particle size distribution, crystal habit, and polymorphic form of progesterone in the drug product
    - Analysis of globule size distribution
c. Characterization of rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:
    - A characterization of shear stress vs. shear rate and viscosity vs. shear rate. At minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
    - A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
    - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
    - The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported. Any non-linear viscosity behavior over a range of shear rates should also be investigated, measured and reported.
d. Characterization of pH
e. Characterization of specific gravity
f. Characterization of any other potentially relevant Q3 attributes

3. The test product and reference standard should have an equivalent rate of progesterone release based upon an acceptable in vitro release test (IVRT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVRT method.

    Type of study: Bioequivalence study with IVRT endpoint
    Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an occluded pseudo-infinite dose, in vitro
    Strength: 8%
    Test system: A synthetic membrane in a diffusion cell system
    Analytes to measure: Progesterone in receptor solution
    Equivalence based on**:** Progesterone (IVRT endpoint: drug release rate)
    Additional comments: The IVRT study should be conducted at 37°C based on the route of administration of this drug product. Refer to the most recent version of the FDA guidance for industry on *In Vitro Release Test Studies for Topical Drug*

Products Submitted in ANDAs[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test product and reference standard evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized.

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

Type of study: Bioequivalence study with pharmacokinetic endpoints
Design: Single-dose, two-treatment, partial or fully replicated, crossover, fasting, in vivo
Strength: 90 mg (dose: 1x8% intravaginal)
Subjects: Healthy postmenopausal females, general population
Analyte to measure: Progesterone in plasma
Equivalence based on: Progesterone, using baseline-corrected data
Additional comments: 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 and reference drug products. 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 reference standard. 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 reference standard evaluated in the in vivo pharmacokinetic study should be the same as those evaluated in the IVRT bioequivalence study.

Waiver request for 4% strength: The 4% strength of the gel product containing sufficient data may be approved based on (i) acceptable demonstration of bioequivalence of the 8% strength using the bioequivalence approach outlined within Option 1, (ii) the formulations of the lower and higher strengths of the test product are exactly the same, except for the amount of progesterone and the corresponding change in the amount of the diluent, and have the same manufacturing process, (iii) acceptable comparative Q3 characterization tests using a minimum of three batches of the lower strength of the test product and three batches of the higher strength

of the test product; the relationship of the Q3 attributes of the two strengths of the test product should be compared to the relationship of the Q3 attributes of the two strengths of the reference standard, and (iv) an acceptable IVRT study comparing a minimum of one batch of the lower and higher strengths of the test product using an appropriately validated IVRT method. The relationship of the release rates of progesterone from the two strengths of the test product should be proportional to the relationship of the release rates between the two strengths of the reference standard.

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

To demonstrate bioequivalence for progesterone vaginal gel 4% and 8% strengths using a combination of in vivo bioequivalence study with pharmacokinetic endpoints and in vivo bioequivalence study with clinical endpoint, the following criteria should be met: (i) acceptable in vivo bioequivalence study with pharmacokinetic endpoints on the 8% strength, (ii) acceptable in vivo bioequivalence study with clinical endpoint on the 4% strength, and (iii) the formulations of the lower and higher strengths of the test product are exactly the same, except for the amount of progesterone and the corresponding change in the amount of the diluent, and have the same manufacturing process.

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, two-treatment, partial or fully replicated, crossover, fasting, in vivo
   Strength: 90 mg (dose: 1x8% intravaginal)
   Subjects: Healthy postmenopausal females, general population
   Analyte to measure: Progesterone in plasma
   Equivalence 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 I.

2. Type of study: Bioequivalence study with clinical endpoint
   Design: Randomized, double-blind, multiple-dose, 2-treatment, parallel, in vivo
   Strength: 45 mg (12 separate every other day doses of 1x4% intravaginal, on Days 15, 17, 19, 21, 23, and 25 of the second and third 28-day cycle)
   Subjects: Females aged 18-45 years with secondary amenorrhea due to hypothalamic amenorrhea or premature ovarian failure (POF)
   Additional comments: Specific recommendations are provided below.

To develop a single strength of progesterone vaginal gel using the bioequivalence approach outlined in Option 2, a combination of an in vivo bioequivalence study with pharmacokinetic endpoints and an in vivo bioequivalence study with clinical endpoint should be performed using the single strength of the test product and reference standard. For applicants intending to develop only progesterone vaginal gel 8%, FDA recommends submitting questions related to the study design of the in vivo bioequivalence study with clinical endpoint through an appropriate communication pathway prior to conducting the study. Refer to the most recent version of the FDA guidance for industry on *Controlled Correspondence Related to Generic Drug Development*[a] and 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 comments regarding the in vivo bioequivalence studies with clinical endpoint:

1. FDA recommends a bioequivalence study with clinical endpoint in the treatment of secondary amenorrhea due to hypothalamic amenorrhea or POF. Subjects are randomized to receive the 4% strength of the generic progesterone vaginal gel or the 4% strength of the reference standard. Subjects are to receive conjugated estrogens 0.625 mg once daily for the entire three 28-day cycles in the study. A total of 12 doses of progesterone vaginal gel, 4% are to be administered by inserting one applicatorful of progesterone vaginal gel, 4% into the vagina on Days 15, 17, 19, 21, 23, and 25 of cycles 2 and 3. The primary endpoint, vaginal bleeding, is to be evaluated beginning at the time of first dosing with study drug on Day 15 of cycle 2 through Day 28 of cycle 3.

2. Inclusion Criteria (the sponsor may add additional criteria):
    a. Females aged 18 to 45 years with secondary amenorrhea due to hypothalamic amenorrhea (defined as eugonadotropic hypoestrogenic-amenorrhea and the exclusion of hyperprolactinemia, thyroid dysfunction, and hyperandrogenism) or POF (defined as a follicle-stimulating hormone value of >40 mIU in woman ≤ age 45). Perform assays for luteinizing hormone, follicle stimulating hormone, dehydroepiandrosterone sulfate, thyroid stimulating hormone, triiodothyronine (T_3), T_3 resin uptake, thyroxine, prolactin, testosterone, and estradiol at screening visit.
    b. Negative pregnancy test at screening visit.
    c. Serum progesterone concentration of < 2 ng/mL at screening visit.
    d. Willingness to use condom, diaphragm, and/or contraceptive foam, jelly, or cream at least 6 hours before or after insertion of vaginal progesterone, unless (1) not sexually active, (2) sterilized (tubal), or (3) sexually active with a sterilized partner or female partner.

3. Exclusion Criteria (the sponsor may add additional criteria):
    a. Hysterectomy
    b. Subject bled two or more pads/tampons for two or more consecutive days at any time during the four months prior to screening visit
    c. Endometrial thickness ≥ 10 mm by ultrasound at screening visit
    d. History of hyperprolactinemia, pituitary tumor, or polycystic ovarian disease
    e. History of uterine pathology, e.g., uterine fibroids, or unresolved dysfunctional uterine bleeding
    f. History of hypersensitivity or allergy to progesterone and/or any of the progesterone vaginal gel ingredients
    g. Liver disease
    h. Known or suspected breast cancer
    i. Active arterial or venous thromboembolism, or severe thrombophlebitis or a history of these events

j. Pregnant, breast feeding, or planning to become pregnant during the study period
k. Use of any hormonal medication (e.g., estrogen-containing product, progestin-containing product, oral contraceptive, or clomiphene citrate) within 6 weeks prior to screening visit
l. Obesity; however, patients diagnosed with POF are exempt from this exclusion criterion

4. The following subjects should be prematurely discontinued from the study:
    a. Any subject with evidence of spontaneous ovulation (i.e., plasma progesterone > 2 ng/mL) during the study prior to first administration of progesterone vaginal gel on Day 15 in cycle 2
    b. Any subject with insufficient estrogenic stimulation (i.e., endometrial thickness < 5 mm by ultrasound) during cycle 2 on Day 12, 13, or 14
    c. Any subject who bled two or more pads/tampons for two or more consecutive days at any time from screening visit until first administration of progesterone vaginal gel on Day 15 of second cycle

5. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited or limited to particular periods during the study, such as:
    a. Use of any condom, diaphragm, or contraceptive vaginal foam, jelly, or creams less than 6 hours before or after insertion of vaginal progesterone.
    b. Use of any vaginal infection product (e.g., antifungal products) less than 48 hours before or after insertion of vaginal progesterone.
    c. Use of any vaginal products other than study treatment or those with time limitation listed above in 5a and 5b.
    d. Use of any estrogen-containing product, progestin-containing product, oral contraceptive, or clomiphene citrate, other than study treatments.

6. The recommended primary endpoint of the study is the proportion of subjects with therapeutic cure, defined as any vaginal bleeding during Day 15 of cycle 2 through Day 28 of cycle 3 occurring subsequent to the first dose of progesterone vaginal gel in those women who demonstrated an adequate response to estrogen therapy (by ultrasound) on Day 12, 13, or 14 of cycle 2; who did not bleed two or more pads/tampons for two or more consecutive days prior to the first dose of progesterone vaginal gel on Day 15 of cycle 2; and who received their assigned study drug every other day for 12 doses on Days 15, 17, 19, 21, 23, and 25 of cycles 2 and 3. Bleeding is to be recorded by the subject in her diary on a daily basis as light, moderate, or heavy, along with the number of pads/tampons used each day.

7. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT), and safety populations.
    a. The accepted PP population used for BE evaluation includes all randomized subjects who met all inclusion/exclusion criteria; had an endometrial thickness of at least 5 millimeters during cycle 2 on Day 12, 13, or 14; were compliant with estrogen dosing; received at least 10 doses of progesterone vaginal gel; and completed the final visit within the designated visit window (within 10 days after

receiving 12th and final dose of progesterone vaginal gel). The protocol should provide a definition of subject compliance for conjugated estrogen (e.g., used at least 75% and no more than 125% of study estrogen doses) and specify how compliance will be verified (e.g., by the use of subject diaries).

b. The mITT and safety population includes all randomized subjects who use at least one dose of product.

8. Subjects who are discontinued early from the study due to lack of treatment effect should be included in the PP population using last observation carried forward (LOCF). Subjects whose condition worsens and who require alternate or supplemental therapy for the treatment of their condition during the treatment phase of the study should be discontinued, included in the mITT and PP population analyses using LOCF, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using LOCF. Applicants should provide a pre-specified definition of lack of treatment effect.

9. The start and stop calendar date (e.g., mm/dd/yyyy) and study day (e.g., Day X) of concomitant medication use should be provided in the data set in addition to the reason for the medication use. The applicant should clearly note whether the medication was used prior to baseline visit, during the study, or both.

10. All Adverse Events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and reference standard.

11. All pregnancies should be reported, including outcome information.

12. If the inactive ingredients are different than those contained in the Reference Listed Drug (RLD)/Reference Standard or in significantly different amounts, then the applicant is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy, or systemic or local availability of the drug. Inactive ingredients used should provide adequate margins of safety for the proposed clinical exposure in the target population.

13. The method of randomization should be described in the protocol and the randomization schedule should be provided. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The applicant may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

14. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test product and reference standard should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.

15. Refer to 21 CFR 320.38, 320.63 and the most recent version of the FDA guidance for industry on *Handling and Retention of BA and BE Testing Samples*[a], regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6 *Good Clinical Practice: Consolidated Guideline*[a] for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices and Good Clinical Practices. Retention samples should be randomly selected from the drug supplies received for each shipment prior to dispensing to subjects. Retention samples should not be returned to the applicant at any time.

16. It is the applicant's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

17. To establish bioequivalence for a dichotomous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

    $H_O: \pi T - \pi_R < \Delta_1$ or $\pi_T - \pi_R > \Delta_2$ versus $H_A: \Delta 1 \leq \pi_T - \pi_R \leq \Delta_2$

    where π_T = the success rate of the primary endpoint for the treatment group, and
    π_R = the success rate of the primary endpoint for the reference group.

    The null hypothesis, H_O, is rejected with a type I error (α) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the difference of the success rates between test product and reference standard ($\pi_T - \pi_R$) is contained within the interval $[\Delta_1, \Delta_2]$, where $\Delta_1 = -0.20$ and $\Delta_2 = 0.20$. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

18. The protocol should include a section with fully detailed statistical analysis plan.

19. 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 progesterone treatment (exposure): test product, reference standard
k. Date/time of first exposure to treatment
l. Date/time of last exposure to treatment
m. Duration of progesterone treatment (total number of doses administered)
n. Duration of estrogen treatment (total number of days)
o. PP population flag (yes/no)
p. Reason for exclusion from PP population
q. mITT population flag (yes/no)
r. Reason for exclusion from mITT population
s. Safety population flag (yes/no)
t. Reason for exclusion from safety population
u. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
v. Final designation as success/cure (yes/no)
w. Progesterone treatment compliance rate (%)
x. Estrogen treatment compliance rate (%)
y. Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
z. Concomitant medication (yes/no)
aa. AE(s) reported (yes/no)

20. 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 progesterone treatment
    f. Name of actual progesterone 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 designated window (yes/no)
    m. Number of days since baseline visit
    n. Ultrasound endometrial thickness (if done)
    o. Any vaginal bleeding since last visit (yes/no)
    p. Therapeutic success/cure (yes/no)
    q. Additional treatment required during the visit (yes/no)
    r. Concomitant medication reported during this visit (yes/no)
    s. AE reported during this visit (yes/no)
    t. Laboratory testing during this visit (yes/no)

21. Refer to the study data standards resources, https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

Additional information:

Device:
The RLD product is presented in an assembly-required, single-dose, prefilled vaginal applicator that is a device constituent.

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 (T) device.

User interface assessment:
An Abbreviated New Drug Application (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 web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.