Draft Guidance on Progesterone

Active Ingredient: Progesterone

Dosage Form; Route: Gel; vaginal

If the test product is qualitatively (Q1) and quantitatively (Q2)[1] the same as the reference product, the following two studies are recommended to document bioequivalence (BE) of the test product to the reference product:

Recommended Studies: Two studies

1. Type of study: BE study with pharmacokinetic (PK) 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
    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. 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. Analyze the data using both uncorrected and corrected data. Applicants may consider using a reference-scaled average BE approach for progesterone (see draft guidance on progesterone capsule/oral, 200 mg).

---

2. Type of study: BE study with clinical endpoint
    Design: Randomized, double-blind, multiple-dose, 2-treatment, parallel, in vivo
    Strength: 45 mg [12 separate QOD (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 hypothalamic amenorrhea or premature ovarian failure
    Additional comments: Specific recommendations are provided below

---

Analytes to measure (in appropriate biological fluid): Progesterone in plasma (for PK endpoint)

---

[1] Potential applicants may propose an alternative approach for a specific non-Q1/Q2 product, but are encouraged to discuss the approach with OGD via a pre-ANDA meeting request.

Bioequivalence based on (90% CI): Progesterone (for PK endpoints) and bleeding (for clinical endpoint)

Waiver request of in vivo testing: 4% (45 mg) strength based on (i) acceptable BE study with PK endpoints on the 8% (90 mg) strength, (ii) acceptable BE study with clinical endpoint on the 4% (45 mg) strength, iii) proportional similarity of the formulations across all strengths, and (iv) acceptable in vitro dissolution test of all strengths

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods Web site, available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Additional comments regarding the BE study with clinical endpoint:

1. OGD recommends a BE study with clinical endpoint in the treatment of secondary amenorrhea due to hypothalamic amenorrhea or premature ovarian failure (POF). Subjects are randomized to receive the 4% strength of the generic progesterone vaginal gel or the 4% strength of the reference listed drug (RLD). 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 premature ovarian failure (defined as a follicle-stimulating hormone value of > 40 mIU in woman $\leq$ age 45). Perform assays for luteinizing hormone (LH), follicle stimulating hormone (FSH), dehydroepiandrosterone sulfate (DHEAS), thyroid-stimulating hormone (TSH), triiodothyronine (T_3), T_3 resin uptake, thyroxine (T_4), 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 (DUB).
    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 PP 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 safety population includes all randomized subjects.

8. Subjects discontinued prematurely before completing dosing with 10 doses of progesterone vaginal gel should be excluded from the PP population.

9. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of an AE should include date of onset, description of AE, severity, relation to study medication, action taken, outcome, and date of resolution. This information is relevant to FDA's determination of whether the incidence and severity of adverse reactions is different between the test product and RLD.

10. The method of randomization should be described in the protocol and the randomization schedule provided as an SAS transport file. FDA recommends that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor 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.

11. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test and reference products 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.

12. Refer to 21 CFR 320.38, 320.63 and the guidance for industry *Handling and Retention of BA and BE Testing Samples* regarding retention of study drug samples and 21 CFR

320.36 for requirements for maintenance of records of BE testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, *Good Clinical Practice: Consolidated Guideline*, for retention of study records and data in order to conduct their studies in compliance with good laboratory practices (GLPs) and good clinical practices (GCPs). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

13. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate BE between the products.

14. FDA recommends that the following compound hypotheses be evaluated to demonstrate equivalence:

$$H_0:\ \pi_T - \pi_R \leq \Delta_1\ \ \text{or}\ \ \pi_T - \pi_R \geq \Delta_2\ \ \text{versus}\ \ H_A:\ \Delta_1 < \pi_T - \pi_R < \Delta_2$$

where π_T = the proportion of subjects with a therapeutic cure for the test group, and
π_R = the proportion of subjects with a therapeutic cure for the reference group.

The null hypothesis, H_0, is rejected with a type I error (α) of 0.05 (two one-sided tests) if the 90% confidence interval for the difference of the proportions between test and reference products ($\pi_T - \pi_R$) is contained within the interval $[\Delta_1, \Delta_2]$, where $\theta_1 = -0.20$ and $\theta_2 = 0.20$.

Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

15. Study data sets should be submitted to the OGD in electronic format. All data sets should be submitted as SAS transport files.
 a. Include a list of file names, a description of the content of each file, an explanation of the variables within each file, and a description of all variable codes (for example, for the treatment variable, A = RLD and B = TEST).
 b. Provide two primary data sets: one with No Last Observation Carried Forward (NO-LOCF – pure data set) and one with the Last Observation Carried Forward (LOCF – modified data set).
 c. Provide a separate data set for demographic, vital sign, adverse event, disposition (including reason for discontinuation of treatment), concomitant medication, medical history, compliance, and comment variables.

16. Provide a summary data set containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
 a. Study identifier
 b. Subject identifier
 c. Site identifier: study center
 d. Age
 e. Age units (years)
 f. Sex
 g. Race

h. Name of Actual Progesterone Treatment (exposure): test product, RLD
i. Duration of Progesterone Treatment (total number of doses administered)
j. Duration of Estrogen Treatment (total number of days)
k. Per Protocol (PP) population inclusion (yes/no)
l. Reason for exclusion from PP population
m. Safety population inclusion (yes/no)
n. Reason for exclusion from safety population
o. Final designation as success/cure (yes/no)
p. Progesterone Treatment compliance: number of missed progesterone doses per subject
q. Estrogen Treatment compliance: number of missed estrogen doses per subject
r. Concomitant medication (yes/no)
s. Adverse event(s) reported (yes/no)

Table 1 provides an example. Note: this sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 1: Example of a summary data set containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT_p	EXDUR_p	EXDUR_e	pp	pp_rs	safety	safe_rs	success	compli_p	compli_e	CM	AE
101	1	01	22	YEARS	F	1	A	6	56	Y		Y		N	0	0	Y	Y
101	2	01	30	YEARS	F	1	B	6	56	Y		Y		Y	0	0	N	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final, dated 11/12/08.

STUDYID: Study Identifier
SUBJID: Subject Identifier for the Study
SITEID: Study Site Identifier
AGE: Age
AGEU: Age units (years)
SEX: Sex, e.g., M=Male, F=Female, U=Unknown
RACE: Race, e.g., 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
EXTRT_p: Name of Actual Progesterone Treatment (exposure), e.g., A=test product, B= RLD
EXDUR_p: Duration of Progesterone Treatment (total number of doses administered), e.g., 1, 2, 3…12
EXDUR_e: Duration of Estrogen Treatment (total exposure in days)
pp: Per Protocol (PP) population inclusion, e.g., Y=Yes, N=No
pp_rs: Reason for exclusion from PP population, e.g., A=prematurely

discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.

safety: Safety population inclusion, e.g., Y=Yes, N=No
safe_rs: Reason for exclusion from Safety population, e.g., A=never treated, etc.
success: Final designation e.g., Y=Yes (therapeutic success/cure), N=No (failure)
compli_p: Progesterone Treatment compliance, e.g., number of missed doses per subject
compli_e: Estrogen Treatment compliance, e.g., number of missed doses per subject
CM: Concomitant medication, e.g., Y=Yes, N=No
AE: Adverse event(s) reported, e.g., Y=Yes, N=No

17. Provide a data set containing a separate line listing for each visit per subject (if data exist) using the following headers, if applicable:
   a. Study identifier
   b. Subject identifier
   c. Name of Actual Progesterone Treatment (exposure): test product, RLD
   d. Visit number
   e. Visit date
   f. Number of days since baseline visit
   g. Ultrasound endometrial thickness (if done)
   h. Any vaginal bleeding since last visit (yes/no)
   i. Therapeutic success/cure (yes/no)
   j. Concomitant medication reported during this visit (yes/no)
   k. Adverse event reported during this visit (yes/no)
   l. Laboratory testing during this visit (yes/no)

Table 2 provides an example. Note: this sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of data set containing one line listing for each visit per subject

STUDYID	SUBJID	EXTRT_p	VISITNUM	SVSTDTC	ELTMBS	endothic	bleeding	success	CMrpt	AErpt	LBtest
1	1	A	1	2004-07-01	0	JB	0		Y	N	Y

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final, dated 11/12/08.

STUDYID: Study Identifier
SUBJID: Subject Identifier for the Study
EXTRT_p: Name of Actual Progesterone Treatment (exposure), e.g., A=test product, B=RLD
VISITNUM: Visit Sequence Number

SVSTDTC: Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBL: Elapsed Number of Days since Baseline Visit (days)
endothic: Ultrasound endometrial thickness (if done) in millimeters, e.g., 1, 2, 3, 4, etc.
bleeding: Any vaginal bleeding since last visit, e.g., Y=Yes, N=No
success: Therapeutic success/cure, e.g., Y=Yes, N=No
CMrpt: Concomitant Medication reported during this visit, e.g., Y=Yes, N=No
AErpt: Adverse Event reported during this visit, e.g., Y=Yes, N=No
LBtest: Laboratory Testing performed during this visit, e.g., Y=Yes, N=No

18. These recommendations are specific to this product and may not be appropriate for BE studies of any other product, including any other dosage form or strength of progesterone.