Contains Nonbinding Recommendations

Draft Guidance on Estradiol

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Estradiol

Form/Route: Tablet/Vaginal

Recommended studies: 3 studies

1. Type of study: Bioequivalence (BE) with Pharmacokinetic (PK) Endpoints Study
   Design: Single-dose, two-treatment, two-period crossover, in vivo
   Strength: 10 mcg (dose: 1x10 mcg) [**NOTE**: if approval is sought only for 25 mcg, omit this study]
   Subjects: Healthy postmenopausal women with no contraindication to estrogen therapy.
   Additional comments:
   - Please perform the statistical analysis with and without baseline adjustments. Baseline estradiol levels should be measured at -1, -0.5, and 0 hours before dosing.
   - The analytical procedure for estradiol should have a lower limit of sensitivity of at least 2 pg/mL or lower.

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2. Type of study: Bioequivalence (BE) with Pharmacokinetic (PK) Endpoints Study
   Design: Single-dose, two-treatment, two-period crossover, in vivo
   Strength: 25mcg (dose: 1x25 mcg) [**NOTE**: if approval is sought only for 10 mcg, omit this study]
   Subjects: Healthy postmenopausal women with no contraindication to estrogen therapy.
   Additional comments:
   - Please perform the statistical analysis with and without baseline adjustments. Baseline estradiol levels should be measured at -1, -0.5, and 0 hours before dosing.
   - The analytical procedure for estradiol should have a lower limit of sensitivity of at least 2 pg/mL or lower.

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3. Type of study: BE with Clinical Endpoints Study
   Design: Randomized, double blind, parallel, placebo-controlled, in vivo
   Strength: 10 mcg (dose: 1x10 mcg once daily for 14 days) [**NOTE**: if approval is sought only for 25 mcg, dose with 1x25 mcg once daily for 14 days]
   Subjects: Healthy postmenopausal women with symptoms of vulvar and vaginal atrophy and no contraindication to estrogen therapy.
   Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Estradiol in plasma (Studies 1 & 2)

Bioequivalence based on (90% CI): Estradiol (for Studies 1 & 2) and clinical endpoint (for Study 3)

Waiver request of in vivo testing: BE with clinical endpoint study on the 25 mcg based on (i) acceptable BE with PK endpoints studies on the 10 mcg and 25 mcg strengths, (ii) acceptable BE with clinical endpoint study on the 10 mcg strength, (iii) proportional similarity of the 10 mcg formulation to the 25 mcg strength, and (iv) acceptable in vitro dissolution testing of both strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please 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 application.

Additional comments regarding the BE with clinical endpoints study:

1. The Office of Generic Drugs (OGD) recommends conducting a bioequivalence study with a clinical endpoint in the treatment of postmenopausal vulvar and vaginal atrophy (VVA). Subjects are to be randomized to receive the estradiol vaginal tablet test product, the reference listed drug (RLD), or placebo control, each administered as one tablet intravaginally once daily for 14 days. The primary endpoint is the proportion of subjects identified as responders on study Day 15 (i.e., one day after the administration of the fourteenth dose of study treatment).

2. This study should enroll only subjects who meet the inclusion and exclusion criteria specified in the Draft Guidance for Industry: Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation (Issued 1/2003, Posted 1/30/2003) except that a baseline endometrial biopsy is not requested.

3. The following baseline requirements are necessary for inclusion in the study:
   - ≤ 5% superficial cells on vaginal smear cytology
   - Vaginal pH > 5.0
   - At least one subject self-assessed moderate to severe symptom of vulvar and vaginal atrophy (VVA) from the following list that is identified by the subject as being most bothersome to her:
     - Vaginal dryness
     - Vaginal and/or vulvar irritation/itching
     - Dysuria
     - Vaginal pain associated with sexual activity
     - Vaginal bleeding associated with sexual activity

4. For safety considerations, it is recommended that baseline systolic blood pressure be no greater than 150 mm Hg and diastolic blood pressure be no greater than 90 mm Hg.

5. Any woman with undiagnosed vaginal bleeding or a history of significant risk factors for endometrial cancer is to be excluded.

6. Baseline vaginal ultrasonography is recommended for all women with an intact uterus to confirm an inactive endometrial lining, and subjects with an endometrial thickness of 4 mm or more should be excluded from the study.

7. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
   a. Any prescription or over-the-counter estrogen, progesterone or testosterone drug product, other than study product.
   b. Vaginal drug products other than study product (e.g., vaginal antifungals).

8. The following subject self-assessed symptoms of vulvar and vaginal atrophy should be evaluated on a scale of 0 to 3 where 0 = none and 3 = severe. Each score should be clearly defined. Each subject should specify the symptom that she identifies as the most bothersome.
    - Vaginal dryness (none, mild, moderate or severe)
    - Vaginal and/or vulvar irritation/itching (none, mild, moderate or severe)
    - Dysuria (none, mild, moderate or severe)
    - Vaginal pain associated with sexual activity (none, mild, moderate or severe)
    - Vaginal bleeding associated with sexual activity (absence vs. presence)

9. Vaginal pH and vaginal cytology should be evaluated on study Day 15 using smears collected from the lateral vaginal walls.

10. The recommended primary endpoint of the study is the proportion of subjects in the Per Protocol (PP) population that are identified as responders on Day 15 (i.e., one day after the administration of the fourteenth dose of study treatment). A responder is defined as a subject with at least a 25% reduction from baseline in the sum of % basal/parabasal + % intermediate cells on vaginal cytology AND vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5.

11. The change from baseline in the severity of most bothersome symptom should be evaluated and compared between treatment groups as a secondary endpoint. Alternatively, this endpoint can be dichotomized as a success vs. failure, with success defined a priori (for example, as a certain minimum reduction from baseline on the above severity scale or as a score of 0 to 1 at primary endpoint evaluation).

12. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
    a. The PP population includes all randomized subjects who met all inclusion/exclusion criteria, used a prespecified proportion of the scheduled applications (e.g., 75% to 125%) of the assigned product for the specified duration of the study, did not miss more than 4 consecutive doses, and completed the primary endpoint evaluation within the designated visit window (+/- 2 days) with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries, and the protocol violations that would affect the treatment evaluation.
    b. The mITT population includes all randomized subjects who met all inclusion/exclusion criteria, received study treatment, and returned for at least one post-baseline visit. The mITT population should be used to compare both test and reference products to placebo.
    c. The safety population includes all randomized subjects who received study treatment.

13. Subjects who are discontinued early from the study due to lack of treatment effect should be included in the PP population as treatment failures (i.e., non-responders). Patients discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF).

14. 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 RLD.

15. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use.

16. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy and/or systemic or local availability.

17. The method of randomization should be described in the protocol. 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 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.

18. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference and placebo 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.

19. Please 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 bioequivalence 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 (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected by each drug site prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

20. It is the sponsor's responsibility to enroll sufficient patients for the study to demonstrate bioequivalence between the products.

21. To establish bioequivalence, the 90% confidence interval of the difference in responder rates between the test product and RLD treatment groups at study Day 15 must be within [-0.20, +0.20] for a dichotomous variable ,using the PP study population.

22. As a parameter for determining adequate study sensitivity at the lower end of the dose/response curve, the test product and RLD should both be statistically superior to placebo ($p < 0.05$, two-sided) for the primary endpoint (responder rate on study Day 15), using the mITT study population and LOCF.

23. The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable (success/failure):

    Equivalence Analysis

    Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success proportions between test and reference treatment must be contained within [-0.20, +0.20] in order to establish equivalence.

    The compound hypothesis to be tested is:

    H_0: $p_T - p_R < -.20$ or $p_T - p_R > .20$
    versus
    H_A: $-.20 \leq p_T - p_R \leq .20$

where p_T = cure rate of test treatment p_R = cure rate of reference treatment.

Let

n_T = sample size of test treatment group

cn_T = number of cured patients in test treatment group

n_R = sample size of reference treatment group

cn_R = number of cured patients in reference treatment group

$\hat{p}_T$ = cn_T / n_T, $\hat{p}_R$ = cn_R / n_R,

and se = ($\hat{p}_T$(1 - $\hat{p}_T$)/n_T + $\hat{p}_R$(1 - $\hat{p}_R$)/n_R)^{½}.

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

L = ($\hat{p}_T$ - $\hat{p}_R$) – 1.645 se – (1/n_T + 1/n_R)/2

U = ($\hat{p}_T$ - $\hat{p}_R$) + 1.645 se + (1/n_T + 1/n_R)/2

We reject H_0 if L ≥ -.20 and U ≤ .20

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

24. Study data should be submitted to the OGD in electronic format.
    a. A list of file names, with a simple description of the content of each file, should be included.
    b. Please provide a "pdf" document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=Yes, N=No for analysis population).
    c. All SAS transport files should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
    d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
    e. Please provide a separate dataset for variables such as demographics, baseline admission criteria, baseline vital signs, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.

25. Please provide a summary dataset 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 Treatment (exposure): test product, RLD, placebo
    i. Duration of Treatment (total exposure in days)
    j. Completed the study (yes/no)
    k. Reason for premature discontinuation of subject
    l. Subject required additional treatment for vulvar and vaginal atrophy due to unsatisfactory treatment response (yes/no)

m. Per Protocol (PP) population inclusion (yes/no)
n. Reason for exclusion from PP population
o. Modified intent to Treat (mITT) population inclusion (yes/no)
p. Reason for exclusion from mITT population
q. Safety population inclusion (yes/no)
r. Reason for exclusion from Safety population
s. Baseline superficial epithelial cells on vaginal cell cytology (i.e., % superficial)
t. Study Day 15 superficial epithelial cells on vaginal cell cytology (i.e., % superficial)
u. Baseline intermediate epithelial cells on vaginal cell cytology (i.e., % intermediate)
v. Study Day 15 intermediate epithelial cells on vaginal cell cytology (i.e., % intermediate)
w. Baseline basal epithelial cells on vaginal cell cytology (i.e., % basal)
x. Study Day 15 basal epithelial cells on vaginal cell cytology (i.e., % basal)
y. Baseline vaginal pH
z. Study Day 15 vaginal pH
aa. Baseline most bothersome symptom of vulvar and vaginal atrophy (VVA)
bb. Baseline score of most bothersome symptom of VVA identified at baseline
cc. Study Day 15 score of most bothersome symptom of VVA identified at baseline
dd. Final designation as responder/non-responder
ee. Treatment compliance: number of missed doses per patient
ff. Concomitant medication (yes/no)
gg. Adverse event(s) reported (yes/no)

Please refer to Table 1 as an example. 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 dataset for each individual test article per subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXDUR	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs	safety	safet_rs
101	1	01	54	YEARS	F	1	A	14	Y			Y		Y		Y	
101	2	01	58	YEARS	F	1	B	14	Y			Y		Y		Y	

cyto_sb	cyto_s15	cyto_ib	cyto_i15	cyto_bb	cyto_b15	pH_b	pH_15	symp_b	score_b	score_15	responde	complian	CM	AE
4	80					6.0		1	3	2		0	Y	Y
3	78					5.5		2	2	2		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., F=Female
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:	Name of Actual Treatment (exposure), e.g. A=test product, B= RLD, C=placebo
EXDUR:	Duration of Treatment (total exposure in days)
completd:	Subject completed the study, e.g., Y=Yes, N=No
disc_rs:	Reason for premature discontinuation from the study, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment unblinded, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event
add_trt:	Subject required treatment for vulvar and vaginal atrophy due to unsatisfactory treatment response, e.g., Y=Yes, N=No
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.
mitt:	Modified Intent to Treat (mITT) population inclusion, e.g., Y=Yes, N=No
mitt_rs:	Reason for exclusion from mITT population, e.g., A=never treated etc.
safety:	Safety population inclusion, e.g., Y=Yes, N=No
safet_rs:	Reason for exclusion from Safety population, e.g., A=never treated, etc.
cyto_sb:	Baseline superficial epithelial cells on vaginal cell cytology, e.g., % superficial
cyto_s15:	Study Day 15 superficial epithelial cells on vaginal cell cytology, e.g., % superficial
cyto_ib:	Baseline intermediate epithelial cells on vaginal cell cytology, e.g., % intermediate
cyto_i15:	Study Day 15 intermediate epithelial cells on vaginal cell cytology, e.g., % intermediate
cyto_bb:	Baseline basal epithelial cells on vaginal cell cytology, e.g., % basal
cyto_b15:	Study Day 15 basal epithelial cells on vaginal cell cytology, e.g., % basal
pH_b:	Baseline vaginal pH
pH_15:	Study Day 15 vaginal pH
symp_b:	Most bothersome symptom of vulvar and vaginal atrophy (VVA) identified at baseline, e.g., 1 (vaginal dryness), 2 (vaginal and/or vulvar irritation/itching, 3 (dysuria), 4 (vaginal pain associated with sexual activity) or 5 (vaginal bleeding associated with sexual activity)
score_b:	Baseline score of the most bothersome symptom of VVA identified at baseline, e.g., 2, or 3
score_15:	Study Day 15 score of the most bothersome symptom of VVA identified at baseline, e.g., 0, 1, 2, or 3
responde:	Final designation (i.e., A=responder, B=non-responder)
complian:	Treatment compliance, e.g., number of missed doses per patient
CM:	Concomitant medication, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

26. Please provide a dataset 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 Treatment (exposure): test product, RLD, placebo control
    d. Visit number
    e. Visit date
    f. Number of days since baseline visit

g. Evaluator: identity of evaluator
h. Superficial epithelial cells on vaginal cell cytology (i.e., % superficial)
i. Intermediate epithelial cells on vaginal cell cytology (i.e., % intermediate)
j. Epithelial cells on vaginal cell cytology (i.e., % basal)
k. Vaginal pH
l. Score (e.g., 0, 1, 2, or 3) of most bothersome symptom of VVA (identified at baseline) at that visit (e.g., Visit 1, 2, etc.)
m. Concomitant medication reported during this visit (yes/no)
n. Adverse event reported during this visit (yes/no)
o. Laboratory testing during this visit (yes/no)

Please refer to Table 2 as an example. 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 dataset containing one line listing for each visit per subject

STUDYID	SUBJID	EXTRT	VISITNUM	SVSTDTC	ELTMBS	EVAL	cyto_s	cyto_i	cyto_b	pH	score	CMrpt	AErpt	LBtest
101	1	A	2	2004-07-01	14						1	Y	Y	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
EXTRT: Name of Actual Treatment (exposure), e.g. A=test product, B=RLD, C= placebo control
VISITNUM: Visit Sequence Number
SVSTDTC: Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBL: Elapsed Time since Baseline (days)
EVAL: Evaluator: identity of the evaluator
cyto_s: Superficial epithelial cells on vaginal cell cytology, e.g., % superficial
cyto_i: Intermediate epithelial cells on vaginal cell cytology, e.g., % intermediate
cyto_b: Basal epithelial cells on vaginal cell cytology, e.g., % basal
pH: Vaginal pH
score: Score (e.g., 0, 1, 2, or 3) of most bothersome symptom of VVA (identified at baseline) at Visit 1
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