

Draft Guidance on Estradiol

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Cream 0.01%/Vaginal

Recommended studies: 2 studies

1. Type of study: Bioequivalence (BE) with Pharmacokinetic (PK) Endpoints Study
Design: Single-dose, two-treatment, crossover in vivo
Strength: 4 grams (dose: 1x4 grams)
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.
 - A pilot study to determine the intersubject variability of the PK parameters and the appropriate number of subjects required to obtain adequate statistical power for the pivotal bioequivalence study is recommended.
-
2. Type of study: BE with Clinical Endpoints Study
Design: Randomized, double blind, parallel, placebo-controlled in vivo
Strength: 2 grams (dose: 1x2 grams once daily for 7 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 (for PK study)

Bioequivalence based on (90% CI): Estradiol (for PK study) and clinical endpoint (for clinical endpoint study)

Waiver request of in vivo testing: Not Applicable

Dissolution test method and sampling times: Not Applicable

Additional comments regarding the BE with clinical endpoints study:

- 1) The Office of Generic Drugs (OGD) recommends a clinical endpoint bioequivalence study comparing the estradiol vaginal cream 0.01% test product versus the reference listed drug (RLD) and placebo, each administered as 2 grams once daily for 7 days, with the primary endpoint evaluation on study Day 8 (one day after the last dose of vaginal cream).
- 2) It is the sponsor's responsibility to enroll sufficient patients for the study to demonstrate bioequivalence between the products.
- 3) Assignment of the test product, RLD, and placebo should be randomized. 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. 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 for each application site on each subject.
- 4) 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.
- 5) This study should enroll only patients 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.
- 6) 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 patient 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

- 7) 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.
- 8) Any woman with undiagnosed vaginal bleeding or a history of significant risk factors for endometrial cancer is to be excluded.
- 9) Baseline vaginal ultrasonography is recommended for all women with an intact uterus to confirm an inactive endometrial lining, and patients with an endometrial thickness of 4 mm or more should be excluded from the study.
- 10) The following patient 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 patient 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)
- 11) Vaginal pH and vaginal cytology should be evaluated on study Day 8 using smears collected from the lateral vaginal walls.
- 12) The recommended primary endpoint of the study is the proportion of patients in the per protocol (PP) population that are identified as responders at the end of the treatment period. A responder is defined as a patient 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.
- 13) The change from baseline in the 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).
- 14) To establish bioequivalence, the 90% confidence interval of the difference in responder rates between the test product and RLD treatment groups at study Day 8 must be within (-0.20 and +0.20), using the PP study population.
- 15) To ensure that the study design is sensitive enough to show a difference between products, the test product and RLD should both be statistically superior to placebo ($p < 0.05$) with regard to the responder rate on study Day 8, using the intent-to-treat (ITT) study population and Last-Observation-Carried-Forward (LOCF).
- 16) The accepted PP population used for bioequivalence evaluation includes all randomized patients who use the majority of prescribed doses (e.g. 75% to 125%) of the assigned

product for the specified duration of the study and complete the evaluation within the designated visit window 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 patient diaries.

- 17) The usual ITT population includes all patients who are randomized, use at least one dose of study product, and return for at least one post-baseline visit.
- 18) Patients 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 ITT population, using LOCF.
- 19) 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, 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.
- 20) 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.
- 21) 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.
- 22) 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 should be contained within (-.20, +.20) in order to establish equivalence.

The compound hypothesis to be tested is:

$$H_0: p_T - p_R < -.20 \text{ or } p_T - p_R > .20$$

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
 $c n_T$ = number of cured patients in test treatment group
 n_R = sample size of reference treatment group
 $c n_R$ = number of cured patients in reference treatment group

$$\hat{p}_T = c n_T / n_T, \quad \hat{p}_R = c n_R / n_R,$$

$$\text{and se} = \left(\hat{p}_T (1 - \hat{p}_T) / n_T + \hat{p}_R (1 - \hat{p}_R) / n_R \right)^{1/2}.$$

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

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

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

We reject H_0 if $L \geq -.20$ and $U \leq .20$

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

23) Study data should be submitted to the OGD in electronic format.

- a. A list of file names included in the CD or diskette(s), 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 each study to include such variables as demographics, baseline admission criteria, baseline vital signs, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.

24) 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. Per Protocol (PP) population inclusion (yes/no)
- k. Reason for exclusion from PP population
- l. Intent to Treat (ITT) population inclusion (yes/no)
- m. Reason for exclusion from ITT population
- n. Safety population inclusion (yes/no)
- o. Reason for exclusion from safety population
- p. Baseline superficial epithelial cells on vaginal cell cytology (i.e., % superficial)
- q. Study Day 8 superficial epithelial cells on vaginal cell cytology (i.e., % superficial)
- r. Baseline intermediate epithelial cells on vaginal cell cytology (i.e., % intermediate)
- s. Study Day 8 intermediate epithelial cells on vaginal cell cytology (i.e., % intermediate)
- t. Baseline basal epithelial cells on vaginal cell cytology (i.e., % basal)
- u. Study Day 8 basal epithelial cells on vaginal cell cytology (i.e., % basal)
- v. Baseline vaginal pH
- w. Study Day 8 vaginal pH
- x. Baseline most bothersome symptom of vulvar and vaginal atrophy (VVA)
- y. Baseline score of most bothersome symptom of VVA identified at baseline
- z. Study Day 8 score of most bothersome symptom of VVA identified at baseline
- aa. Final designation as responder/non-responder
- bb. Treatment compliance: number of missed doses per patient
- cc. Concomitant medication (yes/no)
- dd. 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	pp	pp_rs	itt	itt_rs	safety	safet_rs	cyto_sb	cyto_s8
101	1	01	54	YEARS	F	1	A	14	Yes		Yes		Yes		4	80
101	2	01	58	YEARS	F	1	B	14	Yes		Yes		Yes		3	78

cyto_ib	cyto_i8	cyto_bb	cyto_b8	pH_b	pH_8	symp_b	score_b	score_8	responde	complan	CM	AE
				6.0		1	3	2		0	Yes	Yes
				5.5		2	2	2		0	No	No

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 Draft dated 7/25/07.

STUDYID:	Study Identifier
SUBJID:	Subject Identifier for the Study
SITEID:	Study Site Identifier
AGE:	Age
AGEU:	Age units (years)
SEX:	Sex, e.g., M, F, U for Male, Female, Unknown
RACE:	Race, e.g. 1, 2, 3, 4, 5 (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)
pp:	Per Protocol (PP) population inclusion, e.g., Y, N (Yes or 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.
itt:	Intent to Treat (ITT) population inclusion, e.g., Y, N (Yes or No)
itt_rs:	Reason for exclusion from ITT population, e.g., A=never treated, etc.
safety:	Safety population inclusion, e.g., Y, N (Yes or 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_s8:	Study Day 8 superficial epithelial cells on vaginal cell cytology, e.g., % superficial
cyto_ib:	Baseline intermediate epithelial cells on vaginal cell cytology, e.g., % intermediate
cyto_i8:	Study Day 8 intermediate epithelial cells on vaginal cell cytology, e.g., % intermediate
cyto_bb:	Baseline basal epithelial cells on vaginal cell cytology, e.g., % basal
cyto_b8:	Study Day 8 basal epithelial cells on vaginal cell cytology, e.g., % basal
pH_b:	Baseline vaginal pH
pH_8:	Study Day 8 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_8: Study Day 8 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, N (Yes or No)

AE: Adverse event(s) reported, e.g., Y, N (Yes or No)

25) These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of estradiol.