

Draft Guidance on Ergocalciferol

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Capsule/Oral

Recommended studies: In Vitro Study and/or In Vivo Studies (2 studies)

In Vitro Option

If the test product formulations are qualitatively (Q1) (i.e., contain all of the same inactive ingredients and quantitatively (Q2) the same as the reference listed drug (RLD) with respect to inactive ingredients and that inactive ingredient used in the test product is of comparable grade to that used in the RLD, bioequivalence (BE) may be established based solely on an in vitro method (quantitative capsule rupture test) described below that assures equivalent release of API from the capsules.

Quantitative Capsule Rupture Test

Quantitative capsule rupture test is performed in the following conditions on 12 units of the Test and Reference products:

Medium: 0.5 N NaOH with 0, 5%, and 10% Triton-X-100 in DI water
Apparatus: II (Paddle)
Speed: 100 rpm
Volume: 500 mL
Sampling Times: 15, 30, 45, 60, and 90 minutes and/or until 80% of the labeled amount of Ergocalciferol dispersed in the medium if appropriate

Based on the information available to the Agency, as well as the recommendation given in the USP Pharm Forum,¹ USP Apparatus 4 (flow-through cell) is the most appropriate apparatus for drugs with poor solubility, compared with the conventional USP Apparatus 1 (basket) and Apparatus 2 (paddle). In addition, the use of surfactant is also critical in the in vitro drug release method development for Ergocalciferol drug product. Therefore, alternatively, a second method using USP Apparatus 4 (flow-through cell) maybe developed in conjunction with the method using USP Apparatus 2. For details on method development and parameter optimization, please refer to the 'Draft Guidance on Omega-3-Acid Ethyl Esters'.

¹ Marques, MRC., Cole E. et al. (2009). Stimuli to the Revision Process : Liquid-filled Gelatin Capsules. USP Pharm Forum. 35(4), 1029-1041.

In Vivo Option

If the test product formulations are not Q1/Q2 same as the RLD with respect to inactive ingredients and that inactive ingredient used in the test product is not of comparable grade to that used in the RLD, bioequivalence (BE) may be established by conducting in vivo studies with pharmacokinetic endpoints. Two in vivo BE (fast and fed) studies are recommended.

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 1.25 mg (50,000 IU)
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: To assist with achieving a stable plasma ergocalciferol baseline, subjects should receive a stable diet for a period preceding dosing and during plasma sample collection. Subjects should avoid all active vitamin D compounds and vitamin D-supplemented foods. In addition, subjects should avoid prolonged, direct sunlight for at least 10 days prior to- and during the study periods/washout.

2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 1.25 mg (50,000 IU)
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: Please see comments above.

Analytes to measure (in appropriate biological fluid): Ergocalciferol in plasma.

Since ergocalciferol (vitamin D2) is an endogenous substance, for both fasting and fed studies, the plasma concentrations of ergocalciferol should be corrected for baseline endogenous levels by subtracting the mean value of four pre-dose levels at -24, -16, -8 and 0 hour baseline time points from each subsequent ergocalciferol concentration obtained after dosing and used for all pharmacokinetic calculations. Any negative values obtained from baseline correction at time 0 hour, should be designated as zero (0) and any subject with pre-dose concentration more than 5% of their C_{max} should be excluded from BE statistical analysis and the 90% confidence intervals based on the remaining subjects. *See appendix for additional information regarding endogenous compounds.

Bioequivalence based on (90% CI): Ergocalciferol

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.

Appendix:

Endogenous compounds are drugs that are already present in the body either because the body produces them or they are present in the normal diet. Because these compounds are identical to the drug that is administered, determining the amount of drug released from the dosage form and absorbed by each subject can be difficult. We recommend that applicants measure and approximate the baseline endogenous levels in blood (plasma) and subtract these levels from the total concentrations measured from each subject after the drug product is administered. In this way, you can achieve an estimate of BE of the products. Depending on whether the endogenous compound is naturally produced by the body or is present in the diet, the recommended approaches for determining BE differ as follows:

- When the body produces the compound, we recommend that you measure multiple baseline concentrations in the time-period before administration of the study drug and subtract the baseline in an appropriate manner consistent with the pharmacokinetic properties of the drug.
- In addition, when there is dietary intake of the compound, we recommend that you strictly control the intake both before and during the study. Subjects should be housed at a clinic before the study and served standardized meals containing an amount of the compound similar to that in the meals served on the pharmacokinetic sampling day.

For both of the approaches above, we recommend that you determine baseline concentrations for each dosing period that are period specific. If a baseline correction results in a negative plasma concentration value, the value should be set equal to 0 before calculating the baseline-corrected AUC. Pharmacokinetic and statistical analysis should be performed on both uncorrected and corrected data. Determination of BE should be based on the baseline-corrected data.