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Draft Guidance on Calcifediol

March 2021

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This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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This is a new draft product-specific guidance for industry on generic calcifediol.

Active Ingredient: Calcifediol

Dosage Form; Route: Extended release capsule; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.03 mg (Recommended dose: 30 x 0.03 mg extended release capsule)
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: (1) Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of calcifediol. Alternatively, a parallel study design may be considered. (2) Consider enrolling subjects with baseline calcifediol concentration lower than 30 ng/mL to determine the effect of the test and reference products after correction for baseline calcifediol concentration. (3) Submission of an Investigational New Drug Application (IND) is required prior to the conduct of a bioequivalence study (21 CFR 320.31). (4) Formulate test product qualitatively (Q1) the

same and quantitatively (Q2) similar to the reference listed drug or provide dissolution and appropriate permeation test results at different doses (e.g., 0.03 mg (therapeutic dose), 0.45 mg and 0.9 mg (supratherapeutic dose)) to demonstrate the similarity between the test and reference products.

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2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 0.03 mg (Recommended dose: 15 x 0.03 mg extended release capsule)
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above.

Analyte to measure: Calcifediol in serum

Bioequivalence based on (90% CI): Baseline-corrected calcifediol
Measure baseline calcifediol concentrations at -12, -6, and 0 hours before dosing. The mean of the pre-dose calcifediol concentrations should be used for the baseline correction.

Additional strengths: Not applicable

Dissolution test method and sampling times:
For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database, http://www.accessdata.fda.gov/scripts/cder/dissolution/, provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

In addition to the method above, submit dissolution profiles on 12 dosage units for each of the test and reference products generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer). Agitation speeds may be increased if appropriate. It is acceptable to add a small amount of surfactant if necessary. Include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released to provide assurance against premature release of drug (dose dumping) from the formulation.

Alcohol dose dumping studies:
Due to concerns of dose dumping of drug from this product when taken with alcohol, conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium as follows:

Testing Conditions: 500 mL, 0.1N HCl, USP Apparatus 2 (paddle) at 100 rpm, with or without alcohol

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl) with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Conduct testing on both test and reference products accordingly, and provide data on individual unit, means, range and %CV.

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