

Draft Guidance on Dapagliflozin; Metformin Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredients: Dapagliflozin; Metformin hydrochloride

Dosage Form; Route: Extended release tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 10 mg; 1 g
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: 1) Females should practice abstinence or contraception during the study. 2) To avoid hypoglycemic episodes, the drug products should be administered with 240 mL of a 20% glucose solution in water, followed by 60 mL of the glucose solution administered every 15 minutes for up to 4 hours after dosing.

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 10 mg; 1 g
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See above comments

Analytes to measure (in appropriate biological fluid): Dapagliflozin and metformin in plasma

Bioequivalence based on (90% CI): Dapagliflozin and metformin

Additional strengths: Bioequivalence of the 2.5 mg; 1 g, 5 mg; 500 mg, 5 mg; 1 g, and 10 mg; 500 mg strengths to the corresponding reference product strengths may be demonstrated based on principles laid out in the FDA guidance on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.

Dissolution test method and sampling times:

For modified release drug products, FDA recommends that applicants develop specific discriminating dissolution methods. Applicants may also use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database (available at <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 for the modified release drug product, FDA recommends that the submission includes 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 strength of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

In addition to the method above, dissolution profiles on 12 dosage units for each strength of the test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted. 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.

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium as follows:

Testing conditions: 1000 mL, pH 6.8 phosphate buffer, Apparatus I (basket, 20 mesh) @ 100 rpm, with or without alcohol:

Test 1: 12 units tested according to the proposed method (with pH 6.8 phosphate buffer), 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

Both test and reference products should be tested accordingly, and data should be provided on individual unit, means, range, and %CV on both strengths.