

Draft Guidance on Cyclophosphamide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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 Ingredient: Cyclophosphamide

Dosage Form; Route: Tablet; oral

Recommended Studies: Two options: BCS or in vivo study

I. BCS (in vitro study) option:

Upon request, it may be possible to receive a waiver of in vivo testing for all strengths of this product, provided that the appropriate documentation regarding high solubility, high permeability, and rapid dissolution—as detailed in the guidance for industry *Waiver of In Vivo Bioavailability and Bioequivalence for Immediate-Release Solid Oral Dosage Forms Based on the Biopharmaceutics Classification System*—is submitted in the application. You may use information contained in the approved labeling of the reference product. Peer-reviewed articles may not contain the necessary details of the testing for the Agency to make a judgment regarding the quality of the studies. A decision regarding the acceptability of the waiver request can only be made upon review of the data submitted in the application.

II. In vivo study option: 1 study

Type of study: Steady-state

Design: Two-way crossover, in vivo

Strength: 50 mg; doses of cyclophosphamide tablets should be calculated on the basis of body surface area. Cyclophosphamide tablets should be administered at the current dose of cyclophosphamide: the patient should receive his/her own recommended dose during the study and not be switched to a different dose or regimen for purposes of study enrollment.

Subjects: Adult patients taking oral cyclophosphamide as monotherapy or as part of combination therapy. The subjects must not only be indicated for treatment with oral cyclophosphamide, but must also already be in an established treatment regimen using this drug product. Furthermore, each patient should have comparable health status between the two periods of the study.

Additional comments:

1) Submission of an Investigational New Drug Application (IND) is required prior to the conduct of a bioequivalence (BE) study for a cytotoxic drug product such as cyclophosphamide tablets (see 21 C.F.R. § 320.31).

- 2) If it becomes necessary to adjust a patient's dosing regimen during the study, the patient should be dropped from the BE study.
 - 3) Equal numbers of patients should be randomized to receive the test (Treatment A) or reference (Treatment B) products for 5 days each for two periods.
 - 4) Period I should begin on the first day of a treatment cycle. Pharmacokinetic sampling should take place on Day 5 of Periods I and II. Blood sampling should occur over a dosing interval starting on the morning of Day 5 to assess the concentration-time curve at pre-dose (0 hour) and at appropriate post-dose sampling times.
 - 5) Blood samples should be collected at -24, -48, and -72 h before the morning dose of Day 5 in each period to ensure that steady-state blood plasma levels are achieved.
 - 6) On the day following Day 5 of Period I, patients should be switched to receive the other treatment in Period II.
-

Analytes to measure: Cyclophosphamide in plasma, using an achiral assay

Bioequivalence based on (90% CI): Cyclophosphamide

Waiver request of in vivo testing: 25 mg strength based on (i) an acceptable BE study on the 50 mg strength, (ii) proportional similarity of the formulations between both strengths, and (iii) acceptable in vitro dissolution testing of both strengths

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods Web site, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. 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 abbreviated new drug application (ANDA).