

## Draft Guidance on Capecitabine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

<b>Active ingredient:</b>	Capecitabine
<b>Form/Route:</b>	Tablet; Oral
<b>Recommended studies:</b>	2 Options: BCS waiver or In-Vivo Study

### I. BCS Waiver option:

It may be possible to request a waiver of in-vivo testing 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 the 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 option:

1. Type of study: Fed  
Design: Single-dose, two-way, crossover in-vivo  
Strength: 500 mg  
Subjects: Cancer patients already receiving a stable twice-daily dosing regimen as prescribed by the reference product label (i.e. 1250 mg/m<sup>2</sup>, twice daily, equivalent to 2500 mg/m<sup>2</sup> total daily dose, for two-weeks followed by a one-week rest period given as three-week cycles)  
Additional Comments: See comments below:

Submission of a Bio Investigational New Drug Application (BioIND) is required prior to the conduct of a bioequivalence study for a cytotoxic drug product such as capecitabine (see 21CFR § 320.31).

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

**Bioequivalence based on (90% CI):** Capecitabine

**Waiver request of in-vivo testing:** 150 mg based on (i) acceptable bioequivalence study on the 500 mg strength, (ii) acceptable *in vitro* dissolution testing all strengths, and (iii) proportional similarity of the formulations across all strengths.

**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.

**Additional comments regarding the bioequivalence study:**

- The patients shall receive their own established capecitabine dosing regimen during the study as multiples of the 500 mg tablet. The dose administered to each patient should be the same between the two study periods. After the study is completed, the patients should be continued on their current regimens for Capecitabine Tablets. Since each patient in the study will be receiving different doses, dose should be included in the statistical model. Correction for differing dosing regimens by dose-normalization is not recommended.
- Due to the short half life of capecitabine and its metabolites (< 1 hour), the test and reference products may be dosed on two consecutive days. If the products are administered on two consecutive days, the test product and RLD treatments should be administered at the same time of the day, e.g., both in the morning (or both in the evening) of Day 1 (Period 1 of the study) and Day 2 (Period 2 of the study). Since the patients are on a twice daily dosing regimen, the patients should receive their usual dose of capecitabine as per their dosing regimen between the two periods. The drug product used to administer the dose between the two periods does not have to be the same as that used in the first study period, instead can be the same as that used by the patients for their current dosing regimen.
- Applicants may consider using a reference-scaled average bioequivalence approach as available evidence suggests that this is a highly variable drug substance/product. Please provide evidence of high variability in the bioequivalence parameters, AUC and/or Cmax (i.e., within-subject variability  $\geq 30\%$ ) when using this approach. For general information on this approach, please refer to Haidar *et al.*, Bioequivalence Approaches for Highly Variable Drugs and Drug Products, *Pharm. Res.* 25:237-241 (2008). You may also refer to the Progesterone Capsules Individual Product guidance on this website for additional useful information.
- Pregnant and geriatric cancer patients ( $\geq 80$  years), and cancer patients with a prior history of coronary artery disease, receiving concomitant therapy of warfarin, and dihydropyrimidine dehydrogenase deficiency, should be excluded to avoid serious adverse events. Cancer patients with hepatic impairment and severe renal impairment

should be excluded from the study due to possible effect on pharmacokinetics of capecitabine and its metabolites and due to potential adverse events. Investigators should refer to the Boxed Warning, Contraindications, Warnings, Precautions and Adverse Reactions in the FDA-approved labeling and follow the label recommendations closely.

- Cancer patients with monotherapy are generally recommended for the BE studies. However, cancer patients receiving concomitant drug(s) are allowed to participate, provided:
  - The concomitant medication is the same for both study and clearly documented.
  - The subjects should follow the same dosing regimen for the concurrent medications for both periods of the BE study. Each concurrent medication should be well documented and clearly stated in the protocol.
  - Patients do not change their concurrent medications during the BE study.