

## Draft Guidance on Phenytoin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Dosage Form; Route:** Chewable tablets; oral

**Recommended Studies:** Two studies

1. Type of study: Fasting  
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicated crossover in-vivo  
Strength: 300 mg dose (6×50 mg) and use a washout period of at least 14 days  
Subjects: Normal healthy males and females, general population.  
Additional Comments: The tablets should be swallowed whole.
  
2. Type of study: Fed  
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicated crossover in-vivo  
Strength: 300 mg dose (6×50 mg) and use a washout period of at least 14 days  
Subjects: Normal healthy males and females, general population.  
Additional Comments: The tablets should be swallowed whole.

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

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

**Waiver request of in-vivo testing:** Not Applicable

**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).

**Explanation:** FDA has concluded that phenytoin is a narrow therapeutic index (NTI) drug based on the following evidence:

- The range between phenytoin concentrations and the concentrations associated with serious toxicity is narrow;

- Sub-optimal doses or concentrations lead to therapeutic failure or severe toxicity;
- Phenytoin is subject to therapeutic monitoring based on pharmacokinetics measures;
- Phenytoin has low-to-moderate within-subject variability;
- Doses are adjusted in small increments (less than 20%) in clinical practice.

The study should be a fully replicated crossover design in order to

- Scale bioequivalence limits to the variability of the reference product; and
- Compare test and reference product within-subject variability.

For details about Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach for narrow therapeutic index drugs, please refer to Guidance on Warfarin Sodium.