

Draft Guidance on Phenytoin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Suspension; 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: 125 mg/ 5 mL (dose 300 mg)
Subjects: Normal healthy males and females, general population.
Additional Comments: Washout period of at least 14 days.
2. Type of study: Fed
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicated crossover in-vivo
Strength: 125 mg/ 5 mL (dose 300 mg)
Subjects: Normal healthy males and females, general population.
Additional Comments: Washout period of at least 14 days.

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 the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

A dosage unit for a suspension is the labeled strength (5 ml). A total of 12 units from 12 different bottles should be used.

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.