Draft Guidance on Phenytoin

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.