Contains Nonbinding Recommendations

Draft Guidance on Theophylline

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Extended release tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo
   Strength: 600 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: 1) Exclude subjects per the current labeling for the reference product, e.g., subjects with active peptic ulcer disease, seizure disorders, or cardiac arrhythmias (not including bradyarrhythmias). 2) This drug product is classified as a narrow therapeutic index (NTI) drug. See the Explanation section for further information.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo
   Strength: 600 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above

Analyte to measure: Theophylline in plasma

Bioequivalence based on (90% CI): Theophylline

Additional strength: Bioequivalence of the 400 mg strength to the corresponding reference product strength may be demonstrated based on principles laid out in the FDA guidance on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.*

Dissolution test method and sampling times:
For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database (available at http://www.accessdata.fda.gov/scripts/cder/dissolution/), provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new

dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each of both strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

In addition to the method above, submit dissolution profiles on 12 dosage units for each of the both strengths of the test and reference products generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer). Agitation speeds may be increased if appropriate. It is acceptable to add a small amount of surfactant if necessary. Include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released to provide assurance against premature release of drug (dose dumping) from the formulation.

Explanation: FDA has concluded that theophylline is an NTI drug based on the following evidence:

- The range between the effective theophylline concentrations and the concentrations associated with serious toxicity is narrow;
- Sub-optimal theophylline concentrations lead to severe therapeutic failure or toxicity;
- Theophylline is subject to therapeutic drug monitoring based on pharmacokinetics measures;
- Theophylline has low-to-moderate within-subject variability;
- Dose adjustments are in small increments (range between 10 % and 25%) in clinical practice.

The in vivo bioequivalence studies should be of a fully replicate crossover design to

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

For details about the Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach for NTI drugs, see the guidance on warfarin sodium tablet.