

Contains Nonbinding Recommendations

Draft Guidance on Theophylline

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Active ingredient: Theophylline

Form/Route: Tablet, Extended Release/ Oral

Recommended studies: 4 studies

1. Type of study: Fasting Bioequivalence study
Design: Single-dose, two-treatment, two-period crossover, *in vivo*
Strength: 450 mg
Subjects: Healthy males and nonpregnant females, general population
Additional Comments:

2. Type of study: Fed Bioequivalence study
Design: Single-dose, two-treatment, two-period crossover *in vivo*
Strength: 450 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments:

3. Type of study: Fasting Bioequivalence study
Design: Single-dose, two-treatment, two-period crossover, *in vivo*
Strength: 200 mg
Subjects: Healthy males and nonpregnant females, general population
Additional Comments:

4. Type of study: Fasting Bioequivalence study
Design: Single-dose, two-treatment, two-period crossover, *in vivo*
Strength: 100 mg
Subjects: Healthy males and nonpregnant females, general population
Additional Comments:

Analytes to measure (in appropriate biological fluid): Theophylline in plasma

Bioequivalence based on (90% CI): Theophylline

Waiver request of *in-vivo* testing: 300 mg based on (i) acceptable bioequivalence studies on the 450 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable *in vitro* dissolution testing of 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.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please 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. Specifications will be determined upon review of the data submitted in the application.