

Draft Guidance on Theophylline

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Recommended studies: 3 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover *in-vivo*
Strength: 300 mg
Subjects: Normal healthy males and females, general population.
Additional Comments: Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study.

2. Type of study: Fed
Design: Single-dose, two-way crossover *in-vivo*
Strength: 300 mg
Subjects: Normal healthy males and females, general population.
Additional Comments: Please see comment above

3. Type of study: Fasting sprinkle-in-applesauce
Design: Single-dose, two-way crossover *in-vivo*
Strength: 300 mg
Subjects: Normal healthy males and females, general population.
Additional Comments: Please see comment above

Analytes to measure: Theophylline in plasma

Bioequivalence based on (90% CI): Theophylline

Waiver request of in-vivo testing: 100 mg, 125 mg, and 200 mg based on (i) acceptable bioequivalence studies on the 300 mg strength, (ii) acceptable dissolution testing across all strengths, and (iii) proportional similarity in the formulations across 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.fda.gov/cder/ogd/index.htm>. 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.

For modified release products, dissolution profiles 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, water) 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. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for twelve tablets. Specifications will be determined upon review of the data submitted in the application.