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*Draft – Not for Implementation*

## **Draft Guidance on Theophylline**

**May 2022**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

In February 2010, FDA issued a draft product-specific guidance for industry on generic theophylline. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

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**Active Ingredient:** Theophylline

**Dosage Form; Route:** Tablet, extended release; oral

**Recommended Studies:** Three in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting  
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo  
Strength: 450 mg  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments: This drug product is classified as a narrow therapeutic index (NTI) drug. See the Explanation section for further information.

2. Type of study: Fed  
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo  
Strength: 450 mg  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments: See comments above.
3. Type of study: Fasting  
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo  
Strength: 100 mg  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments: See comments above. Conduct with 3 units of the 100 mg test product and 1 unit of the 300 mg reference product.

**Analyte to measure:** Theophylline in plasma

**Bioequivalence based on (90% CI):** Theophylline

**Additional strengths:** Bioequivalence of the 200 mg and 300 mg strengths to the corresponding reference product strengths may be demonstrated based on acceptable bioequivalence studies on the 100 mg and 450 mg strengths respectively and principles laid out in the most recent version of the FDA guidance for industry on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.<sup>a</sup>

**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 Dissolution Methods database, <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 strength of the test and reference products. Specifications will be determined upon review of the ANDA.

In addition to the method above, submit dissolution profiles on 12 dosage units for each strength 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 (e.g., 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, refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.<sup>a</sup>

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**Revision History:** Recommended February 2010; Withdrawn August 2020; Revised May 2022

**Unique Agency Identifier:** PSG\_085328

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<sup>a</sup> For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.