

*Contains Nonbinding Recommendations*

*Draft - Not for Implementation*

**Draft Guidance on Tiopronin**

**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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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 March 2020, FDA issued a draft product-specific guidance for industry on generic tiopronin. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

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**Active Ingredient:** Tiopronin

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

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

1. Type of study: Fasting  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 300 mg  
Subjects: Males and non-pregnant, non-lactating females, general population  
Additional comments: Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of tiopronin. Alternatively, a parallel study design may be considered.

2. Type of study: Fed  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 300 mg  
Subjects: Males and non-pregnant, non-lactating females, general population  
Additional comments: See comments above.
3. Type of study: Fasting sprinkle-in-applesauce  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 300 mg  
Subjects: Males and non-pregnant, non-lactating females, general population  
Additional comments: See comments above. Administer the dose by crushing one tablet in a pill crusher or mortar and pestle and sprinkling the crushed tablet on a spoonful of applesauce, in accordance with the approved labeling of the reference product.

**Analyte to measure:** Tiopronin in plasma

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

**Additional strength:** Bioequivalence of the 100 mg strength to the corresponding reference product strength may be demonstrated based on 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 Abbreviated New Drug Application*.<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.

**Alcohol dose dumping studies:** Due to concerns of dose dumping of drug from this product when taken with alcohol, conduct additional dissolution testing on both strengths using various concentrations of ethanol in the dissolution medium as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP Apparatus 1 (basket) at 100 rpm, with or without alcohol

Test 1: 12 units tested according to the proposed method (with 0.1N HCl) with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Conduct testing on both test and reference products accordingly, and provide data on individual unit, means, range and %CV.

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**Revision History:** Recommended March 2020; Revised May 2022

**Unique Agency Identifier:** PSG\_211843

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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>.