*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

**Draft Guidance on Alprazolam**

**November 2021**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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 September 2008, FDA issued a draft product-specific guidance for industry on generic alprazolam. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

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**Active Ingredient:** Alprazolam

**Dosage Form; Route:** Tablet, orally disintegrating; oral

**Recommended Studies:** Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 1 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: The orally disintegrating tablet should be placed on the tongue, allowed to disintegrate, and swallowed without water. Exclude geriatric subjects due to increased susceptibility to central nervous system-associated adverse events. Exclude subjects who have narrow angle glaucoma or are taking strong CYP3A inhibitors. Subjects should be instructed not to engage in potentially hazardous activities requiring complete mental alertness, such as driving a motor vehicle or operating machinery until

they have completely returned to their level of baseline cognitive functioning after taking alprazolam.

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 1 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above

**Analyte to measure:** Alprazolam in plasma

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

**Waiver request of in vivo testing:** 0.25 mg, 0.5 mg, and 2 mg based on (i) acceptable bioequivalence studies on the 1 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. 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 abbreviated new drug application.

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**Revision History**: Recommended September 2008; Revised November 2021

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