

*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

**Draft Guidance on Aripiprazole**

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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In December 2009, FDA issued a draft product-specific guidance for industry on generic aripiprazole. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

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**Active Ingredient:** Aripiprazole

**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: 10 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 aripiprazole. Alternatively, a parallel study design may be considered. The orally disintegrating tablet should be placed on the tongue, allowed to disintegrate, and swallowed without water. Exclude CYP2D6 poor metabolizers and subjects taking strong CYP2D6 inhibitors. See notes below for additional information on study design.

2. Type of study: Fed  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 10 mg  
Subjects: Males and non-pregnant, non-lactating females, general population  
Additional comments: See comments above

**Notes:** Life-threatening adverse events attributed to acute laryngeal dystonia have been reported following administration of a single dose of 30 mg aripiprazole to healthy subjects in bioequivalence studies. Although such events have not been reported at doses lower than 30 mg, because of the life-threatening nature and the unknown dose response relationship of this event, the following safety precautions are recommended for studies conducted in the general population of aripiprazole at all doses:

1. Study protocols should specify standard procedures to diagnose and treat dystonic reactions should they occur.
2. Subjects younger than 45 years of age should be excluded. There appears to be an inverse linear relationship between age and the incidence of acute dystonic reactions. Adults younger than 35 years of age were reported to have a 15-fold higher rate of neuroleptic-induced dystonia compared to a group of patients 60-80 years of age. The occurrence of dystonia appears to be rare at ages of approximately 45 years and higher.
3. Protocols should include stringent drug screening procedures to ensure that subjects are free of illicit drugs at the time of administration of each study drug dose.
4. The screening interview should include specific questions to exclude subjects with a prior personal or family history of dystonic reactions to medications. In addition, subjects should be specifically questioned about prior neuroleptic drug exposures.

Aripiprazole has been poorly tolerated by healthy subjects in some bioequivalence studies, particularly at the 15 and 30 mg dose levels. In several cases, adverse events have resulted in a high rate of dropouts. Adverse events have included nausea, vomiting, dizziness, syncope, insomnia, headache, fatigue, hypotension, hot flashes, weakness, diaphoresis and confusion. To minimize the occurrence of adverse events and to ensure the safety of healthy subjects in clinical trials of aripiprazole, the following is recommended:

1. Females of reproductive potential should be enrolled only if they are using effective contraceptives. A negative pregnancy test is needed within 24 hours prior to each dose. They should be informed of the potential teratogenicity of the study drug as part of the informed consent process.
2. The protocol should include standard procedures for the assessment and management of potential adverse events, including vital signs and ECG monitoring as appropriate for adverse events possibly associated with hypotension.
3. The protocol should include measures to prevent relative dehydration at the time of dosing, such as encouragement of water intake whenever possible prior to dosing. Consideration should be made to providing a standard meal just prior to the standard fasting period before dosing.

4. During the informed consent process, subjects should be advised of the high incidence of adverse events that have occurred in some healthy subject studies of aripiprazole.
5. Subjects should be monitored in-house for at least 3 days after dosing and until adverse events have resolved.
6. Subjects should be kept supine for at least 8 hours starting no longer than 15 minutes after each dose.
7. Subjects should be asked to use the bathroom soon before dosing. Subjects should be encouraged to use urinals or bedpans during the first 8 hours after dosing and at any time after dosing if the subject is experiencing adverse events such as nausea, dizziness, or hypotension. If subjects do use the bathroom during the first 8 hours after dosing or while experiencing adverse events such as nausea, dizziness, or hypotension, they should be assisted to and from the bathroom by study personnel.
8. At a minimum, routine 12-lead electrocardiogram (ECG) should be performed at 3-5 hours after dosing and at 8-12 hours after dosing. Continuous ECG monitoring during those time periods may be considered as an alternative.
9. Vital signs monitoring should continue post dosing throughout the period that subjects are housed, commencing no later than 30 minutes following dosing. Vital signs should be monitored frequently (at least every 0.5-1 hour) for at least the first 8 hours after dosing and the first hour after subjects are allowed to rise from the supine position.
10. Prespecified limits should be defined for reporting adverse events related to vital signs (e.g., hypotension, bradycardia, etc.). Vital sign readings that meet these predefined limits should be reported as adverse events, even if they are not performed during a scheduled assessment (e.g., vital signs performed as part of an assessment of an adverse event).

**Analyte to measure:** Aripiprazole in plasma

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

**Waiver request of in vivo testing:** 15 mg, 20 mg and 30 mg based on (i) acceptable bioequivalence studies on the 10 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity 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 for 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 December 2009; Revised November 2021

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