

*Contains Nonbinding Recommendations*  
*Draft – Not for Implementation*  
**Draft Guidance on Deutetrabenazine**  
**May 2025**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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<b>Active Ingredient:</b>	Deutetrabenazine
<b>Dosage Form:</b>	Tablet, extended release
<b>Route:</b>	Oral
<b>Strengths:</b>	6 mg, 12 mg, 18 mg, 24 mg, 30 mg, 36 mg, 42 mg, 48 mg
<b>Recommended Studies:</b>	Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 48 mg  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments: Exclude subjects with risk factors for prolonged QTc interval and Torsades de Pointes. CYP2D6 poor metabolizers are likely to have much higher systemic exposure of the active dihydro-metabolites of deutetrabenazine and experience adverse events. Exclude CYP2D6 poor metabolizers.
2. Type of study: Fed  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 48 mg  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments: See comments above.

**Analyte to measure:** Deutetrabenazine in plasma using an achiral assay

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

**Additional strengths:** Bioequivalence of the 6 mg, 12 mg, 18 mg, 24 mg, 30 mg, 36 mg, and 42 mg strengths to the corresponding reference listed drug (RLD)<sup>1</sup> strengths 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 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 (T) product and RLD.<sup>1</sup> Specifications will be determined upon review of the abbreviated new drug application.

In addition to the method above, submit dissolution profiles on 12 dosage units for each strength of the T product and RLD 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.

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

Testing Conditions: 500 mL, 0.1N HCl, USP Apparatus 2 (paddle) at 75 rpm, with or without alcohol

Test 1: 12 units tested according to the proposed method (with 0.1 N 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

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<sup>1</sup> If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions*.

Conduct testing on both T product and RLD accordingly, and provide data on individual unit, means, range and %CV.

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