

Draft Guidance on Cyclobenzaprine Hydrochloride

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient:	Cyclobenzaprine hydrochloride
Dosage Form:	Capsule, extended release
Route:	Oral
Strengths:	15 mg, 30 mg
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: 30 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments:
 - Exclude geriatric subjects due to increased risk of central nervous system effects. Monitor vital signs and electrocardiogram during the study. Subjects should be evaluated prior to discharge for cognitive impairment and instructed not to drive or operate machinery until their cognitive function returns to baseline level.
 - Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of cyclobenzaprine. Alternatively, a parallel study design may be considered.
2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 30 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above.

3. Type of study: Fasting, sprinkle-in-applesauce
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 30 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above.

Analyte to measure: Cyclobenzaprine in plasma

Bioequivalence based on (90% CI): Cyclobenzaprine

Additional strengths: Bioequivalence of the 15 mg strength to the corresponding reference list drug (RLD)¹ 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*.^a

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 product and RLD. 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 test 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: None

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

¹ 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*.