

Draft Guidance on Clonidine Hydrochloride

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Clonidine hydrochloride

Dosage Form: Suspension, extended release

Route: Oral

Strength: 0.1 mg/mL

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 0.1 mg/mL (Recommended dose: 0.1 mg (1 mL))
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: Exclude subjects with a history of hypotension. Monitor subjects for signs and symptoms of hypotension. Subjects should be evaluated prior to discharge for cognitive impairment such as somnolence and dizziness and instructed not to drive or operate machinery until their cognitive function returns to baseline level.
2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 0.1 mg/mL (Recommended dose: 0.1 mg (1 mL))
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above.

Analyte to measure: Clonidine in plasma

Bioequivalence based on (90% CI): Clonidine

Additional strengths: Not applicable

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 of the test product and reference listed drug (RLD).¹ Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In addition to the method above, submit dissolution profiles on 12 dosage units for each 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: Due to concerns of dose dumping of drug from this product when taken with alcohol, conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium as follows:

Testing conditions: 500 mL, 0.1N HCl, USP Apparatus 2 (paddle) at 50 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 product and RLD accordingly, and provide data on individual unit, means, range and %CV.

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*.

Additional information:**Device:**

The RLD is presented in a bottle co-packaged with one or two bottle adapters and oral syringes. The oral syringes are the device constituent parts.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD devices when designing the test devices including:

- Calibrated volume markings
- Number of co-packaged oral syringes

User interface assessment:

An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.^a

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Unique Agency Identifier: PSG_217645

^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>.