

*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

## **Draft Guidance on Clozapine**

**February 2022**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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 March 2011, FDA issued a draft product-specific guidance for industry on generic clozapine. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

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**Active Ingredient:** Clozapine

**Dosage Form; Route:** Tablet; oral

**Recommended Study:** One study

1. Type of study: Steady-state  
Design: Two-treatment, two-period crossover in vivo  
Strength: 100 mg  
Subjects: Schizophrenia patients who have been receiving a stable dose of clozapine at the same multiples of 100 mg every 12 hours for at least three months

**Additional comments:**

1. Exclude patients if their smoking status or concomitant medications of known inhibitors or inducers of CYP3A4 or CYP1A2 is expected to change during the study.
2. Administer the same individualized dose for both the test and reference products for 10 days to each patient with no washout period between the two treatments.
3. Monitor absolute neutrophil count and blood pressure during the study.
4. Discontinue patients from the study if they require any dosage modification of clozapine treatment during the study.
5. Clozapine tablets are approved under a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU), which restricts its use. All pertinent elements of the REMS/ETASU must be incorporated into the protocol and informed consent.

**Analyte to measure:** Clozapine in plasma

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

**Additional Strengths:** 25 mg, 50 mg, and 200 mg strengths based on (i) acceptable bioequivalence study on the 100 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 for each of all strengths of the test and reference products. Specifications will be determined upon evaluation of the abbreviated new drug application.

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**Revision History:** Recommended March 2011; Revised February 2022

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