
Guidance for Industry

Clozapine Tablets: In Vivo Bioequivalence and In Vitro Dissolution Testing

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**June 2005
BP**

Revision I

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Clozapine Tablets: In Vivo Bioequivalence and In Vitro Dissolution Testing

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1 **Guidance for Industry¹**
2 **Clozapine Tablets: In Vivo Bioequivalence and In Vitro Dissolution**
3 **Testing**
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6 This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It
7 does not create or confer any rights for or on any person and does not operate to bind FDA or the public.
8 You can use an alternative approach if it satisfies the requirements of the applicable statutes and
9 regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for
10 implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate
11 number listed on the title page of this guidance.
12

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14 **I. INTRODUCTION**
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16 This guidance provides recommendations for sponsors of abbreviated new drug applications
17 (ANDAs) designing bioequivalence studies for generic clozapine products. This document
18 revises the recommendations provided in a guidance on the same topic issued in November
19 1996. In the 1996 guidance, the Agency recommended that doses of clozapine tablets be
20 administered to healthy subjects as well as to the appropriate patient population in
21 bioequivalence studies for generic clozapine products. Because a high number of healthy
22 subjects experienced serious adverse effects such as hypotension, bradycardia, syncope, and
23 asystole during clozapine bioequivalence studies, FDA is recommending that studies not be
24 conducted using healthy subjects. In addition, a single-dose study using a 12.5 mg dose is no
25 longer recommended. Instead, this guidance recommends a multiple-dose bioequivalence study
26 conducted in patients using the highest dosage strengths (e.g., 100 mg tablets).
27

28 The protocols described in this guidance are designed to reduce the likelihood of adverse events
29 or, if adverse events should occur, to ensure that adequate treatment is available.
30

31 FDA's guidance documents, including this guidance, do not establish legally enforceable
32 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
33 be viewed only as recommendations, unless specific regulatory or statutory requirements are
34 cited. The use of the word *should* in Agency guidances means that something is suggested or
35 recommended, but not required.
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38 **II. BACKGROUND**
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40 Clozapine, a dibenzodiazepine derivative with potent antipsychotic properties, is indicated for
41 the management of patients with severe schizophrenia who fail to respond adequately to standard

¹ This guidance has been prepared by the Office of Generic Drugs (OGD) in the Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration.

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42 antipsychotic drug treatment. A significant risk of agranulocytosis and seizures associated with
43 its use is a major factor restricting wide use of clozapine in psychiatric practice.

44
45 The FDA recommends that treatment with clozapine begin with one-half of a 25 milligram (mg)
46 tablet (12.5 mg) once or twice daily and that treatment be continued with daily dosage
47 increments of 25-50 mg per day, if well tolerated, to achieve a target dose of 300 to 400 mg per
48 day by the end of 2 weeks. While many patients respond adequately at doses between 300 and
49 600 mg per day, it may be necessary to raise the daily dose to between 600 and 900 mg to obtain
50 an acceptable response. Dosing should not exceed 900 mg per day.

51
52 In humans, clozapine from 25 mg and 100 mg tablets is equally bioavailable relative to a
53 clozapine solution. Following a dosage of 100 mg twice a day, the average steady-state peak
54 plasma concentration occurs at an average of 2.5 hours (range 1-6 hours) after dosing. Food
55 does not appear to affect clozapine systemic bioavailability. The mean elimination half-life of
56 clozapine after a single 75 mg dose is 8 hours (range 4-12 hours), compared to a mean steady-
57 state half-life of 12 hours (range 4-66 hours) following 100 mg twice a day dosing. The
58 elimination half-life increases significantly upon multiple dosing relative to single-dose
59 administration, raising the possibility of concentration dependent pharmacokinetics. However,
60 at steady-state, linearly dose-proportional changes have been observed in AUC, peak, and
61 minimum clozapine plasma concentrations after administration of 37.5 mg, 75 mg, and 150 mg
62 (twice daily).

63
64 Orthostatic hypotension with or without syncope can occur with clozapine treatment.
65 Orthostatic hypotension is more likely to occur during initial titration in association with rapid
66 dose escalation and may even occur with the first dose. Due to the hypotensive effects
67 associated with administration of clozapine to healthy subjects, the original recommendations in
68 a guidance on clozapine tablets published in November 1996 are being changed. This document
69 revises and supersedes the previous version of the guidance. The Agency currently recommends
70 that steady-state studies to evaluate the bioequivalence of clozapine products be performed only
71 on patients who are already receiving an established maintenance dose of an approved clozapine
72 product and have failed to respond adequately to standard antipsychotic drug treatment. The
73 Agency believes that the previously recommended study design using half tablets in healthy
74 subjects was adequate to establish bioequivalence of generic clozapine products; however, the
75 safety concerns associated with the use of clozapine in healthy subjects are significant, and it is
76 recommended that this practice not be continued.

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79 **III. IN VIVO STUDIES**

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81 **A. Product Information**

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83 *1. FDA Designated Reference Product*

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85 Applicants may consult FDA's *Approved Drug Products with Therapeutic Equivalence*
86 *Evaluations (Orange Book)* for the appropriate reference product.

87 2. *Batch size*

88
89 The test batch or lot should be manufactured under production conditions and should be
90 at least 10% of the size of the largest lot planned for full production, or a minimum of
91 100,000 units, **whichever is larger**.

92
93 3. *Potency*

94
95 The assayed potency of the reference product should not differ from that of the test
96 product by more than 5%.

97
98 **B. Steady-State Bioequivalence Study**

99
100 The objective of this steady-state bioequivalence study is to compare the rate and extent
101 of absorption of a generic formulation with a reference formulation when administered at
102 equal doses, as labeled.

103
104 Potential sponsors should consider the following study design. This study is appropriate
105 for institutionalized or noninstitutionalized patients. Procedures should be in place to
106 ensure medication compliance in either setting.

107
108 1. *Steady-State Study in Patients Receiving a Stable Dose of Clozapine*

109
110 The study would be conducted in patients who are receiving a stable daily dose of
111 clozapine administered in equally divided doses at 12-hour intervals. Patients who are
112 receiving multiples of 100 mg every 12 hours would be eligible to participate in the study
113 of the 100 mg strength by continuing their established maintenance dose. According to
114 the randomization schedule, an equal number of patients would receive either the generic
115 formulation (Treatment A) or the reference formulation (Treatment B) in the same dose
116 as administered prior to the study every 12 hours for 10 days.

117
118 Patients would then be switched to the other product for a second period of 10 days. No
119 washout period is necessary between the two treatment periods. After the study is
120 completed, patients could be continued on their current dose of clozapine using an
121 approved clozapine product as prescribed by their clinicians.

122
123 2. *Procedures for the Study*

124
125 Before the study begins, the proposed protocol must be approved by an institutional
126 review board (IRB).²

127
128 The FDA recommends that applicants enroll a sufficient number of patients to ensure
129 adequate statistical power.

130

² See 21 CFR 314.94(a)(7)(iii).

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131 Patients should receive study treatment A or B with 240 milliliters (ml) of water at fixed
132 12-hour intervals for 10 days, using multiples of the 100 mg strength.

133
134 Blood samples should be collected over a dosing interval on day 10, following
135 preliminary sampling on days 7, 8, and 9 to confirm steady-state conditions. The last
136 dose of clozapine to be taken before blood sampling for each period should be
137 administered at the clinical site to assure exact timing of sampling.

138 139 *3. Patient Entry Criteria and Facilities*

140
141 To enter into this study, patients should be appropriate candidates for clozapine therapy
142 (as stated in product labeling) and have been taking a stable dose of clozapine for at least
143 three months. Patients should be otherwise healthy as determined by physical
144 examination, medical history, and routine hematologic and biochemical tests.

145
146 Outpatients should be hospitalized for at least 2 days during the collection of each set of
147 pharmacokinetic samples. The clinical and analytical laboratories used for the study
148 should be identified in the study report, along with the names, titles, and curriculum vitae
149 of the medical and scientific/analytical directors.

150 151 *4. Safety Monitoring*

152
153 White blood cell (WBC) counts should be monitored and clozapine treatment modified, if
154 necessary, in accordance with the agranulocytosis warning in the labeling of the
155 reference listed drug product. Patients requiring modification of clozapine treatment
156 should be dropped from the study and provided with prompt medical care. Blood
157 pressure, heart rate, and body temperature should be monitored during the study and
158 immediate medical care provided for any significant abnormalities.

159 160 *5. Restrictions*

161
162 Patients should fast for at least 8 hours prior to and 4 hours after the administration of the
163 morning dose of the test or reference treatment on day 10 of each period (i.e., the days on
164 which blood samples are to be collected to assess the concentration-time curve). All
165 meals on day 10 should be standardized during the study.

166
167 Water may be allowed, except for 1 hour before and 1 hour after drug administration,
168 when no liquid should be permitted other than that needed for drug dosing.

169
170 Patients with any of the following should be excluded from the study:

- 171
- 172 • A history of allergic reactions to clozapine or other chemically related psychotropic
173 drugs
 - 174
 - 175 • Concurrent primary psychiatric or neurological diagnosis, including organic mental
176 disorder, severe tardive dyskinesia, or idiopathic Parkinson's disease

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- A total white blood cell count below 4000/ml, or an absolute neutrophil count below 2000/ml
 - A history of granulocytopenia or myeloproliferative disorders (drug-induced or idiopathic)
 - Significant orthostatic hypotension (i.e., a drop in systolic blood pressure of 30 mm Hg or more and/or a drop in diastolic blood pressure of 20 mm Hg or more on standing)
 - Concurrent use of antihypertensive medication or any medication that might predispose to orthostatic hypotension
 - A medical or surgical condition that might interfere with the absorption, metabolism, or excretion of clozapine
 - A history of epilepsy or risk for seizures
 - Concurrent use of other drugs known to suppress bone marrow function
 - Expected changes in concomitant medications during the period of study
 - Positive tests for drug or alcohol abuse at screening or baseline
 - A history of alcohol or drug dependence by *Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)* criteria during the 6-month period immediately prior to study entry
 - Compliance with outpatient medication schedule not expected
 - History of multiple syncopal episodes

6. Blood Sampling

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Venous blood samples should be collected after the day 10 morning dose to assess the concentration-time curve at predose (0 hours) and at 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0 hours. The predose blood sampling should include at least three successive trough level samples (C_{\min}). These samples should be collected on the last 3 days of dosing in each period to ensure that steady-state blood plasma/serum levels are achieved in each study period.

222 **C. Other Recommendations**

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1. *Precautions and Safety Issues*

- Patients should be confined for at least 12 hours after the first dose of the test and reference products.
- Patients should remain in the supine position for the first 6 hours after the first dose, even if they were previously on a stable dose of clozapine.
- Patients should be adequately hydrated. This may be achieved by administering 240 ml of water before the overnight fast, 240 ml of water one hour before dosing, 240 ml of water with the study dose, and 240 ml of water every 2 hours for 6 hours post-dosing.
- Patients must be adequately informed of possible cardiovascular adverse effects in the consent form.³

2. *Statistical Analysis of Pharmacokinetic Data (Blood Plasma/Serum)*

The following pharmacokinetic data should be used for the evaluation of bioequivalence of the multiple dose study:

- Individual and mean blood drug concentration levels
- Individual and mean trough levels ($C_{\min \text{ SS}}$)
- Individual and mean peak levels ($C_{\max \text{ SS}}$)
- Calculation of individual and mean steady-state $AUC_{\text{interdose}}$ ($AUC_{\text{interdose}}$ is AUC during a dosing interval at steady-state)
- Individual and mean percent fluctuation [$=100 * (C_{\max \text{ SS}} - C_{\min \text{ SS}})/C_{\text{average SS}}$]
- Individual and mean time to peak concentration

The log-transformed AUC and C_{\max} data should be analyzed statistically using analysis of variance. The 90% confidence interval for the ratio of the geometric means of the pharmacokinetic parameters (AUC and C_{\max}) should be within 80-125%. Fluctuation for the test product should be evaluated for comparability with the fluctuation of the reference product. The trough concentration data should also be analyzed statistically to verify that steady-state was achieved prior to Period 1 and Period 2 pharmacokinetic sampling.

³ See 21 CFR 50.25.

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3. *Clinical Report and Adverse Reactions*

Patient medical histories, physical examination and laboratory reports, and all incidents of possible adverse reactions should be reported.

IV. IN VITRO TESTING CRITERIA

A. Dissolution Testing

Dissolution testing on 12 dosage units of the test product versus 12 units of the reference product should be conducted for all strengths. The lot used in the biostudy should be used for dissolution testing as well. The United States Pharmacopeia (USP) method is recommended for this product. Sampling times of 15, 30, 45 and 60 minutes are recommended.

The percent of label claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, the range (highest, lowest) of dissolution, the coefficient of variation (relative standard deviation), and similarity comparisons of dissolution profiles (f2 calculations) should be reported.

B. Content Uniformity Test

Content uniformity testing on the test product lots should be performed as described in the latest edition of the USP.

V. WAIVER REQUIREMENTS

Waiver of in vivo bioequivalence study requirements for the lower strengths of a generic product can be granted if the following conditions are met:⁴

1. The in vivo study on the 100 mg tablet is acceptable.
2. The strengths are proportionally similar in active and inactive ingredients to the strength tested in vivo.
3. All strengths meet an appropriate in vitro dissolution test.

⁴ See 21 CFR 320.22(d)(2)