

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2003D-0549]

RMB

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Certifier G. P. [Signature]

**Draft Guidance for Industry: Clozapine Tablets: In Vivo Bioequivalence and In Vitro Dissolution Testing, Revision; Availability**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

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**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "Clozapine Tablets: In Vivo Bioequivalence and In Vitro Dissolution Testing." This draft guidance provides recommendations for sponsors of abbreviated new drug applications (ANDAs) on the design of bioequivalence studies for generic clozapine products. This draft guidance is being issued because an earlier guidance on this topic published in November 1996 needed to be revised to reflect current agency recommendations. Because of significant potential adverse effects, the agency no longer recommends in vivo bioequivalence testing in healthy subjects.

**DATES:** Submit written or electronic comments on the draft guidance by *[insert date 60 days after date of publication in the Federal Register]*. General comments on agency guidance documents are welcome at any time.

**ADDRESSES:** Submit written requests for single copies of this draft guidance to the Division of Drug Information (HFD-240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the draft guidance to the Division

of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

**FOR FURTHER INFORMATION CONTACT:** Lizzie Sanchez, Center for Drug Evaluation and Research (HFD-650), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-5847.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

FDA is announcing the availability of a draft guidance for industry entitled “Clozapine Tablets In Vivo Bioequivalence and In Vitro Dissolution Testing.” This draft guidance is intended to provide information to sponsors of ANDAs on the design of bioequivalence studies for generic clozapine products, and revises the recommendations provided in a guidance on the same topic published in November 1996.

In the earlier version of this draft guidance, the agency recommended that doses of clozapine tablets be administered to healthy subjects in bioequivalence studies for generic clozapine products. The earlier guidance also provided the option of conducting studies in the appropriate patient population. Because a high number of healthy subjects in bioequivalence studies for clozapine products have experienced serious adverse effects such as hypotension, bradycardia, syncope, and asystole during clozapine bioequivalence studies, FDA is no longer recommending such studies be done in healthy subjects.

The draft guidance provides recommendations for two approaches to study the product in the appropriate patient population. One approach is a study

design using patients naive to clozapine. This design uses the recommended titration of dosing consistent with the reference product labeling. The alternative study design uses the appropriate patient population already stable on a dose of clozapine. This alternative also appeared in the earlier version of the guidance. The agency believes that the previously recommended design using healthy subjects was adequate to establish bioequivalence of generic clozapine products; however, the safety concerns associated with the use of clozapine in healthy subjects are significant, and the agency is no longer recommending this practice.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance represents the agency's current thinking on studies to demonstrate the bioequivalence of clozapine tablets. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes or regulations.

## **II. Comments**

Interested persons may submit written or electronic comments to the Division of Dockets Management (see **ADDRESSES**). Two copies of mailed comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guidance and received comments are available for public examination in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: 12/17/03  
December 17, 2003.

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Jeffrey Shuren,  
Assistant Commissioner for Policy.

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