

State Enforcement Notifications—21 CFR 100.2(d) (OMB Control Number 0910-0275)—Extension

Section 310(b) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 337(b)) authorizes States to enforce certain sections of the act in their own names, but provides that

States must notify FDA before doing so. Section 100.2(d) (21 CFR 100.2 (d)) sets forth the information that a State must provide to FDA in a letter of notification when it intends to take enforcement action under the act against a particular food located in the State. The information required under § 100.2(d) will enable FDA to identify the food

against which the State intends to take action and advise the State whether Federal action has been taken against it. With certain narrow exceptions, Federal enforcement action precludes State action under the act.

FDA estimates the burden of this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN¹

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours Per Response	Total Hours
100.2(d)	1	1	1	10	10

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

The reporting burden for § 100.2(d) is insignificant because enforcement notifications are seldom used by States. During the last 3 years, FDA has not received any enforcement notifications. Since the enactment of section 403A(b) of the act (21 U.S.C. 343-1(b)) as part of the Nutrition Labeling and Education Act of 1990, FDA has received only a few enforcement notifications. Although FDA believes that the burden will be insignificant, it believes these information collection provisions should be extended to provide for the potential future need of a State government to submit enforcement notifications informing FDA when it intends to take enforcement action under the act against a particular food located in the State.

Dated: June 14, 2005.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2003D-0549]

Guidance for Industry on Clozapine Tablets: In Vivo Bioequivalence and In Vitro Dissolution Testing; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry entitled "Clozapine Tablets: In Vivo Bioequivalence and In Vitro Dissolution Testing." The guidance was originally published in November 1996. However, because of potentially significant

adverse effects seen in healthy subjects who had not previously used clozapine, FDA proposed a revision to the guidance in a draft published in December 2003. FDA did not receive comments on the draft guidance during the comment period. This final version of the 2003 draft guidance includes a change in the recommended patient population as well as other minor changes that are based on current information available to FDA.

DATES: Submit written or electronic comments on agency guidances at any time.

ADDRESSES: Submit written requests for single copies of this 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 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 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 guidance for industry entitled "Clozapine Tablets: In Vivo Bioequivalence and In Vitro Dissolution Testing." This guidance is being issued

because of necessary changes to recommendations provided in a previous guidance on the same topic that published in November 1996. In the **Federal Register** of December 30, 2003 (68 FR 75262), FDA published a document that proposed revisions to the 1996 guidance and that provided information to the pharmaceutical industry regarding the design of bioequivalence studies for generic clozapine products.

In the 1996 guidance, FDA recommended that doses of one-half of a 25 milligram clozapine tablet be administered to healthy subjects in bioequivalence studies for generic clozapine products. The guidance also provided an option for conducting studies in the appropriate patient population. However, in the 2003 draft guidance, FDA proposed that such studies not be conducted in healthy subjects because a high number of healthy subjects experienced serious adverse effects such as hypotension, bradycardia, syncope, and asystole during clozapine bioequivalence studies. FDA did not receive comments on the 2003 draft guidance during the comment period.

This final version of the 2003 draft guidance has been further revised to provide recommendations describing the use of an appropriate patient population that is already stable on a dose of clozapine. The use of healthy subjects who had not previously used clozapine is no longer recommended in this final version of the guidance, which will ensure the safety of subjects in bioequivalence studies on clozapine.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the agency's current thinking on clozapine tablets: in vivo and in vitro dissolution testing. 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 and regulations.

II. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

III. Electronic Access

Persons with access to the Internet may obtain the document at either <http://www.fda.gov/cder/guidance/index.htm> or <http://www.fda.gov/ohrms/dockets/default.htm>.

Dated: June 9, 2005.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2005D-0223]

Draft Guidance for Industry on Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals." The purpose of this draft guidance is to provide recommendations to industry for designing nonclinical toxicity studies to determine potential late radiation toxicities (radiation-induced injuries occurring after a latency period of several months to years) of therapeutic radiopharmaceuticals administered systemically. The purpose of such studies is to help minimize the risk of late-occurring irreversible

radiation toxicities in clinical studies of therapeutic radiopharmaceuticals.

DATES: Submit written or electronic comments on the draft guidance by September 19, 2005. General comments on agency guidance documents are welcome at any time.

ADDRESSES: Submit written requests for single copies of the 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: Adebayo Laniyonu or Renee Tyson, Center for Drug Evaluation and Research (HFD-160), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-7510.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled "Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals." The objective of this guidance is to provide recommendations to industry for designing nonclinical toxicity studies to determine potential late radiation toxicities of therapeutic radiopharmaceutical agents. This guidance is not intended for diagnostic radiopharmaceuticals or for radiobiologicals (e.g., radiolabeled monoclonal antibodies).

Late radiation toxicity differs from early or acute radiation toxicity. Acute radiation toxicity (e.g., bone marrow failure, nausea, vomiting, diarrhea, and oral mucositis) occurs within days to weeks of an acute dose of radiation and is often self-limiting and reversible. In contrast, late radiation toxicity (e.g., renal failure, pulmonary fibrosis, and chord transection) occurs after a latency period of several months to years, during which relatively normal organ function continues. Late radiation toxicity is usually progressive and irreversible.

Therapeutic radiopharmaceuticals are typically administered systemically to treat cancer. The radiation absorbed

doses delivered by therapeutic radiopharmaceuticals may be comparable to those delivered with external beam radiotherapy (XRT). At therapeutic doses of radiation, the late radiation toxicities commonly associated with XRT (e.g., brain necrosis, paralysis, pulmonary fibrosis, liver or kidney failure, and hemorrhagic cystitis) can also be seen with therapeutic radiopharmaceuticals. With XRT, if the total dose given to an organ is less than its tolerance dose, the probability of symptomatic late radiation toxicity to that organ will be minimal. The tolerance doses of most human organs for conventional fractionated XRT are known, and are routinely used to direct the safe administration of XRT. In FDA's experience, however, there are few clinical data from which to estimate organ tolerance doses for therapeutic radiopharmaceuticals. Furthermore, late radiation toxicity has been observed when Medical Internal Radiation Dose (MIRDose) estimates of radiation absorbed doses delivered by therapeutic radiopharmaceuticals to target organs were substantially below the published XRT organ tolerance doses.

Therefore, there is a need to gain additional knowledge in this area to support the safe administration of therapeutic radiopharmaceuticals to humans. Because studies in humans would be unethical, the best means to gain insight into this issue is by conducting nonclinical late radiation toxicity studies. These studies will aid in identifying organs at risk and establish a margin of safety for late radiation toxicity. As a result, these studies will help to minimize the risk of late-occurring radiation toxicities in clinical studies of therapeutic radiopharmaceuticals.

This draft guidance focuses solely on late radiation safety concerns that are unique to therapeutic radiopharmaceuticals, and provides recommendations for late radiation toxicity nonclinical study designs including issues regarding good laboratory practices, species selection, dose selection, timing of study, and study parameters.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the agency's current thinking on nonclinical evaluation of late radiation toxicity of therapeutic radiopharmaceuticals. 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