



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

George J. Brewer, M.D.
University of Michigan Medical School
205 Zina Pitcher Rd.
Ann Arbor, MI 48109

Dear Dr. Brewer:

Between May 20 and June 9, 2008, Ms. Nancy Bellamy, Ms. Laureen Kononen, and Dr. Virginia Elgin, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct as both sponsor and investigator of the following clinical investigations of the investigational drug (b) (4):

- Study (b) (4) : Clinical Trial of (b) (4) in the Initial Treatment (b) (4) ;
- Study (b) (4) : Double Blind Trial of (b) (4) in (b) (4) ; and
- Study (b) (4) : Phase III Study of (b) (4) Dose Regimen in Initial Neurological (b) (4)

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Bellamy and Ms. Kononen presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

VIOLATIONS RELATED TO INVESTIGATOR RESPONSIBILITIES [21 CFR 312.60, 312.66, 312.62(a), and 312.62(c)]

1. You failed to obtain informed consent of subjects involved in research in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60].

21 CFR 50.20 requires that except as provided in sections 50.23 and 50.24, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. In addition, the FDA regulations require that informed consent be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent [21 CFR 50.27(a)].

- a. There were no signed and dated informed consent documents on file for subjects [REDACTED] and [REDACTED] enrolled in study (b) (4).
- b. There is no signature of the subject or the subject's legally authorized representative on the informed consent document for subject [REDACTED] enrolled in study (b) (4) at the 8/31/00 visit.
- c. There is no signature of the subject or the subject's legally authorized representative on the informed consent document for subject [REDACTED] enrolled in study (b) (4) for the follow-up visit on 1/14/03.
- d. Regarding study (b) (4), study procedures were conducted prior to obtaining informed consent from subjects [REDACTED] and [REDACTED]. Specifically, for subject [REDACTED], an MRI of the brain was conducted on 10/4/88, but informed consent was not signed by the subject until 10/06/88. For subject [REDACTED], a liver biopsy was performed on 10/4/94, but informed consent was not signed by the subject until 10/5/94.
- e. The information that was given to the subject or the subject's legally authorized representative was not in a language understandable to the subject or the subject's legally authorized representative. Specifically, non-English speaking subjects were given informed consent documents written in English. Examples include, but are not limited to, the following: Subjects [REDACTED] enrolled in study (b) (4), and subjects [REDACTED] enrolled in study (b) (4).

2. You failed to assure that an Institutional Review Board (IRB) complying with applicable regulatory requirements was responsible for the continuing review and approval of a clinical study [21 CFR 312.66].

You continued to perform research activities during timeframes when the IRB's study approval was expired. Examples include, but are not limited to, the following:

- a. Study (b) (4) lapsed in IRB approval from 3/19/93 until 4/29/93. During this timeframe subject [REDACTED] was enrolled (4/15/93). The study also lapsed in IRB

approval from 7/14/95 until 9/28/95. During this timeframe subject [REDACTED] was enrolled (7/18/95).

- b. Study (b) (4) lapsed in IRB approval from 6/30/05 until 9/08/05, and from 9/7/06 until 10/05/06. Subjects were receiving study medications or seen for evaluations during these time periods.

3. You failed to maintain adequate and accurate records for disposition of the investigational drug [21 CFR 312.62(a)].

Regarding study (b) (4), a report dated 7/20/04 to the Data Safety Monitoring Board (DSMB) and IRB indicated that the (b) (4) made an error by including placebo capsules in a bottle that should have contained only the investigational drug. The report indicated that this involved one subject for a period of one week, during which the subject received between 50 and 90% of the correct investigational drug. A memorandum dated 4/20/04 describes a dispensing error in medication on 2/17/04 when capsules were dispensed for subjects [REDACTED]

4. You failed to conduct the studies according to the investigational plan [21 CFR 312.60].

The research plan for study (b) (4) specified that subjects with concurrent seizure activities should be excluded. Subject [REDACTED] had tonic-clonic seizures on 5/8/99, but was enrolled in the study in violation of the study.

VIOLATIONS RELATED TO SPONSOR RESPONSIBILITIES [21 CFR 312.53(c)(1), 312.56(a), 312.57(a), and 312.57(c)]

5. You failed to obtain an investigator statement, Form FDA 1572, before permitting an investigator to participate in an investigation [21 CFR 312.53(c)(1)].

Specifically, regarding study (b) (4), you allowed a clinical investigator to participate in the investigation prior to obtaining a signed investigator statement containing:

- a. The name and address of the investigator;
- b. The name and code number, if any, of the study(s) in the IND identifying the study(ies) to be conducted by the investigator;
- c. The name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted;
- d. The name and address of any clinical laboratory facilities to be used in the study;
- e. The name and address of the IRB that is responsible for review and approval of the study(ies);
- f. A commitment by the investigator that he or she:

- i. Will conduct the study(ies) in accordance with the relevant, current study(s) and will only make changes in a study after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;
- ii. Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;
- iii. Will personally conduct or supervise the described investigation(s);
- iv. Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;
- v. Will report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 312.64;
- vi. Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and
- vii. Will ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

6. You failed to monitor the progress of all clinical investigations being conducted under your IND [21 CFR 312.56(a)].

The FDA inspection disclosed that you did not maintain any documentation to indicate that the above studies conducted under an IND were adequately monitored. In your August 13, 2008 response letter to the Form FDA 483, you stated that you were personally involved in the care and treatment of every subject and treatment of every subject who participated in the (b) (4) studies at the University of Michigan, and monitored their progress. You stated that during the last several years, a DSMB monitored the data collected during the studies to assure patient safety. You stated that it is true that you relied on individuals at the University of Michigan to help assure that the research was properly conducted in Ann Arbor, and on a colleague at an academic institution in (b) (4) to do the same at his site. However, you acknowledged that you failed to document monitoring activities adequately.

7. You failed to maintain adequate records showing the shipment of the investigational drug [21 CFR 312.57(a)].

Regarding study (b) (4), during the inspection you did not have any documentation showing the shipment of investigational drugs to the clinical investigator at the (b) (4) site.

8. You failed to retain records for the requisite time period [21 CFR 312.57(c)].

21 CFR 312.62(c) requires that a sponsor retain the records and reports required by 21 CFR Part 312 for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after

shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified. A curriculum vitae or other statement of qualifications of the investigator showing the education, training, and experience that qualifies the investigator as an expert in the clinical investigation of the drug for the use under investigation required to be obtain by 21 CFR 312.53(c)(2) could not be located for the clinical investigator conducting study (b) at the (b) (4) Sites. During the inspection you told the FDA investigators that you did have the clinical investigator's curriculum vitae on file at the start of the study, but could not locate it.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken or will be taking to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Lewin, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Leslie Ball
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