



Inspections, Compliance, Enforcement, and Criminal Investigations



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Tuller, Betty Ph.D. 11/21/11



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

November 21, 2011

UNITED PARCEL SERVICE (UPS)

Ref: 12-HFD-45-11-01

Betty Tuller, Ph.D.

(b)(6)

Dear Dr. Tuller:

Between January 18, 2011, and February 14, 2011, Mr. Sean Creighton, representing the U.S. Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations of the investigational drug **(b)(4)**:

(b)(4)

The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of Title 21, Code of Federal Regulations (CFR) Part 312 if the criteria in 21 CFR 312.2(b)(1) are met. However, the studies listed above do not meet these criteria because they involved a route of administration or dosage level that significantly increased the risks (or decreased the acceptability of the risks) associated with the use of this drug product [21 CFR 312.2(b)(iii)]. Therefore, these studies were subject to 21 CFR Part 312 [21 CFR 312.2(a)] and should have been conducted under an Investigational New Drug (IND) application [21 CFR 312.20]. As a result, your conduct as the clinical investigator for these studies was required to conform to the requirements in 21 CFR Part 312.

During the time you conducted these studies, you were working at the following address: Florida Atlantic University, Center for Complex Systems and Brain Sciences, 777 Glades Road, Boca Raton, FL 33431.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help 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, Mr. Creighton presented and discussed with you the

inspectional findings. We wish to emphasize the following:

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

As the investigator, it was your responsibility to obtain informed consent in accordance with 21 CFR Part 50 [21 CFR 312.60]. 21 CFR 50.25(a) describes the basic information that must be provided to each subject when seeking informed consent. However for four of the five studies listed above **(b)(4)** and **(b)(4)**, you failed to ensure that subjects were provided with all of the basic information required by 21 CFR 50.25(a).

Specifically, the informed consent documents used for these four studies failed to include the following required elements:

- a. Identification of any procedures which are experimental [CFR 50.25(a)1)].
- b. A disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the subject [21 CFR 50.25(a)4)].
- c. A statement noting the possibility that the Food and Drug Administration may inspect the records [21 CFR 50.25(a)5)].
- d. An explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs; and, if so, what they consist of, or where further information may be obtained [21 CFR 50.25(a)6)].
- e. A description of any reasonably foreseeable risks or discomforts to the subject [21 CFR 50.25(a)2)].

The informed consent documents for these studies indicate that "Risks from the **(b)(4)** are primarily hypoglycemia." However, according to the **(b)(4)** label found in study records at your site, the risks associated with the use of **(b)(4)** products also include, but are not limited to, hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. **(b)(4)** administered **(b)(4)** has a rapid onset of action. Therefore, this modality of **(b)(4)** therapy should be used with caution in subjects at risk for hypokalemia (e.g., patients using potassium-lowering medications and patients taking medications sensitive to serum potassium concentrations), and potassium should be monitored frequently when **(b)(4)** is administered **(b)(4)** to avoid fatal hypokalemia.

You failed to inform subjects of the reasonably foreseeable risk of developing hypokalemia and its complications. This is a critical omission in the information provided to subjects when seeking informed consent, and represents a significant human subject protection concern.

Your failure to inform subjects of the reasonably foreseeable risk of hypokalemia and its complications, along with your failure to inform subjects of the additional required elements of consent listed above, denied the subjects an opportunity to assess the risks and benefits of their participation in the clinical investigations. Additionally, by not providing the subjects under your care with the information they were entitled to receive to assist them in making an informed decision about whether to participate in the studies, you compromised the rights, safety, and welfare of those subjects.

2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

As the clinical investigator, you were required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)]. Case histories include information related to subjects' enrollment and participation in, and completion of, the study. However, during the inspection, you indicated to Mr. Creighton that you did not keep records of how many subjects were enrolled, how many subjects withdrew from the study, and how many subjects completed the study. As a result, it appears that you failed to maintain adequate and accurate case histories as required by 21 CFR 312.62(b).

Your failure to maintain adequate and accurate case histories, including information related to subject enrollment and completion of the study, impacts the ability to accurately characterize subject participation in your studies; raises concerns about subject safety and data integrity; and compromises the interpretation and validity of the investigational endpoints.

3. You failed to promptly report to the IRB all unanticipated problems involving risk to human subjects or others [21 CFR 312.66].

As the clinical investigator, you were required to promptly report to the IRB all unanticipated problems

involving risk to human subjects or others [21 CFR 312.66]. Our investigation revealed that you collected lists of adverse events that occurred during the conduct of the five studies listed above, between 2004 and 2009, including some adverse events that resulted in hospitalization of subjects. However, during the course of our investigation, you indicated to Mr. Creighton that you reported there were "no adverse events" in these studies on all of your submissions to the IRB. Moreover, during our investigation, we did not find any records to indicate that you reported any of the unanticipated problems involving risk to human subjects, which were recorded on your lists of adverse events, to the responsible IRB.

Your failure to ensure that the IRB was notified of all unanticipated problems involving risk to subjects, raises concerns about the extent to which subjects' rights, safety, and welfare were protected. Without a complete listing of the unanticipated problems involving risks to the subjects, the IRB was unable to make an informed determination regarding the continued safety of the subjects enrolled in your investigations.

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 ongoing 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 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 Cullity, 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 Cullity (formerly Lewin), M.D., M.P.H.
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Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

/s/

/Leslie K. Ball, M.D./
Leslie K. Ball, M.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

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