

Inspections, Compliance, Enforcement, and Criminal Investigations

Harris, Barbara A 7/27/09

[hhsbluebird](#)Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Rockville, MD 20857

WARNING LETTER

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

Ref: 09-HFD-45-07-03

Barbara A. Harris, Ph.D.
Psypharma Clinical Research, Inc.
4045 E. Union Hills, #122
Phoenix, AZ 85050

Dear Dr. Harris:

Between January 13 and 16, 2009, Mr. Mark C. Saale and Dr. Michelle Chuen and, on March 25, 2009, Ms. Cheryl D. McCall, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol Number **(b)(4)** entitled "**(b)(4)**") of the investigational drug **(b)(4)**, performed for **(b)(4)**.

This inspection is a part of 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 the study 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. Mark C. Saale and Dr. Michelle Chuen presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed 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)].

a. According to the protocol, an electroencephalogram (EEG) was to be performed on subjects approximately 1.5 hours after study drug administration. The case histories demonstrated multiple inconsistencies in instances where the study drug administration time was changed from a time outside of the 1.5 hours interval to a time within the interval. There was no supporting documentation that explains these study drug administration time changes. In addition, the times recorded on the Case Report Forms (CRFs) were not necessarily consistent with the times recorded on the progress notes.

i. For Subject #002, on 6/20/07, the time of EEG recording was 13:18, and the study drug administration time documented in the progress notes, signed and dated by the study coordinator, **(b)(6)** was 11:40. This time was changed to 11:50, and initialed and dated by BH. However, the time recorded on the CRF was 11:40.

ii. For Subject #002, on 6/27/07, the time of EEG recording was 11:37, and the study drug administration time documented on the laboratory request sheet and in the progress notes, signed and dated by **(b)(6)**, was 09:30. This time was changed to 10:00 on the laboratory request sheet and in the progress notes, and was initialed and dated by BH. The following is documented in the progress notes signed and dated by **(b)(6)**: "pt & caregiver arrived to EEG lab late pt out of window by 32 min." The amended time of 10:00 is inconsistent with this note.

iii. For Subject #002, on 7/25/07, the time of EEG recording was 13:40, and the study drug administration time documented on the laboratory request sheet, signed and dated by **(b)(6)**, was 12:00. This time was changed to 12:10, initialed and dated 1/25/07 (i.e., 6 months before the visit date) by BH.

iv. For Subject #008, on 11/2/07, the time of EEG recording was 10:24, and the study drug administration time documented on the laboratory request sheet was 8:00. This time was changed to 9:00. However, the time recorded on the CRF was 8:00.

b. The case history for Subject #002 had two different copies of CRF page 12 from Visit 1. One copy was a pink duplicate copy of CRF page 12, signed and dated as having been completed by Barbara Harris on May 10, 2007. The second copy was a photocopy of CRF page 12, also signed and dated as having been completed by Barbara Harris on May 10, 2007, but apparently filled out by a different person (as evidenced by different handwriting) and contains different information from the

first copy. There was no explanation in the case history for the existence of two different versions of the same source record for Subject #002. Having 2 versions of a single CRF page for a given subject compromises case history accuracy.

c. For Subject #008, on 11/2/07, the time of electrocardiogram (ECG) originally documented on the laboratory request sheet was 8:22. This time was changed to 10:22. However, the time recorded on the ECG and on the CRF was 8:22. There was no supporting documentation for the ECG time change on the laboratory request sheet.

d. For Subject #002, the EEG report was missing for Visit 2 (5/30/07).

e. For Subject #014, according to the ECG tracing obtained on 12/4/07, the P-R interval was 175 msec, the QRS interval was 108 msec, the QT interval was 456 msec, and the QTc interval was 438 msec. On the corresponding CRF, the P-R interval, QRS interval, and QT interval were initially documented in accordance with the ECG tracing, but were changed to 174 msec, 104 msec, and 470 msec, respectively. The QTc interval on this CRF was initially documented in accordance with the ECG tracing, but was changed to 444 msec on 3/21/08 and to 452 msec on 6/10/08. These changes appear to be initialed by **(b)(6)**. There was no supporting documentation to explain these changes to the ECG results on the CRF.

f. CRF page 54 for Subject #002 incorrectly identifies the subject number as #001.

g. There was no start or finish time documented for the CIBC-plus on page 84 of the CRF (Visit 7, Week 12) for Subject #007, despite the fact that the CRF indicated that this information should be entered.

2. You failed to ensure the investigation was conducted according to the investigational plan [21 CFR 312.60].

The protocol required that all findings regarding adverse events experienced by a patient, irrespective of the suspected causality, be reported on the Adverse Events (AE) page in the CRF. Progress notes dated 6/13/07 for Subject #002 document that the patient complained of light headedness 2 hours after dosing at home. This was not reported on the AE page in the CRF. We note your statement during the inspection interview that it was the opinion of the doctor that the lightheadedness was most probably due to alcohol. However, there is no documentation of this opinion. The protocol required that all findings regarding adverse events experienced by a patient, irrespective of the suspected causality, be reported on the AE page in the CRF.

3. You failed to maintain adequate records of the disposition of the drug,

including dates, quantity, and use by subjects [21 CFR 312.62(a)].

a. The investigational accountability log on 11/2/07 for Subject #008 indicates that 84 tablets were dispensed; however, the CRF for that date indicates that the amount dispensed was 42. It is unclear which number is correct, and there is no explanation in the record for this discrepancy.

b. The case history for Subject #002 had two different copies of CRF page 77 from Visit 7. One copy indicated that 168 tablets were dispensed on 8/22/07, while the other copy had 168 crossed out and 140 written instead on 10/10/07, with no documentation to support this change.

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 K BALL
07/27/2009