Inspections, Compliance, Enforcement, and Criminal Investigations

Joseph-Vempilly, Jose, MD 5/14/13

Department of Health and Human Services

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

MAY 14, 2013

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 13-HFD-45-05-01

Jose Joseph-Vempilly, M.D.
155 N. Fresno Street
Fresno, CA 93701-2302

Dear Dr. Joseph-Vempilly:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between September 13 and October 11, 2012. Gulshan Anand, Ph.D., representing the FDA, reviewed your conduct of a clinical investigation (Protocol **(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 FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Dr. Anand presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your October 16, 2012, written response to the Form FDA 483.

From our review of the establishment inspection report, the documents submitted with that report, and your October 16, 2012, written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We wish to emphasize the following:

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

As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. You failed to adhere to these requirements. Specifically:

a. The investigational plan requires that subjects be using an approved dose of an inhaled corticosteroid for at least 12 weeks preceding Visit 1, and a stable dose for at least 4 weeks preceding Visit 1. Subjects with changes in asthma medication occurring between Visits 1 and 2 (excluding albuterol/salbutamol inhalation aerosol provided at Visit 1) were to be excluded from treatment randomization.

i. Subject 00621 was taken off an inhaled corticosteroid (asthma medication) at Visit 1 and was not given a prescription for an inhaled corticosteroid during the period between Visits 1 and 2. This subject was not excluded from treatment randomization.

ii. Subject 00624 stopped using an inhaled corticosteroid before Visit 1. This subject was not excluded from treatment randomization.

iii. Subject 00625 was taken off an inhaled corticosteroid at Visit 1 and was not given a prescription for an inhaled corticosteroid during the period between Visits 1 and 2. This subject was not excluded from treatment randomization.

iv. Subject 00626 stopped using an inhaled corticosteroid one day prior to Visit 1.This subject was not excluded from treatment randomization.

b. The investigational plan prohibits subjects from using leukotriene antagonists starting at Visit 1. However, Subject 00638 continued to use a leukotriene antagonist after Visit 1.

Enrollment of subjects who do not meet eligibility criteria, and failure to ensure discontinuation of prohibited medications as required by the protocol, jeopardize subject safety and welfare and raise concerns about the validity and integrity of the data collected at your site.

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 a clinical investigator, you are 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. Case histories for Protocol **(b)(4)** include records of blood pressure, pulse rate, and body temperature that were required to be taken at every visit during the study. You have failed to maintain adequate and accurate case histories with respect to these measurements. Specifically:

a. Blood-pressure readings, pulse rates, and body temperatures were recorded for Subject 00621 when these measurements were not taken. A July 18, 2011, progress note documents that the subject stated that blood pressure, pulse rate, and temperature were not taken at every visit.

b. Blood-pressure readings were recorded for Subject 00623 when these measurements were not taken. A July 14, 2011, progress note documents that the subject reported that blood pressure was not measured at every visit.

c. Blood-pressure readings, pulse rates, and body temperatures were recorded for Subject 00628 when these measurements were not taken. A July 15, 2011, progress note documents that the subject stated that these measurements were not taken at every visit.

Other than the examples above, we are unable to determine the extent to which the above-mentioned subjects' vital signs (i.e., blood pressure, pulse rate, and body temperature) were falsified. However, in your October 16, 2012, written response, you acknowledged that data for vital signs were entered into the case report forms for the above-mentioned subjects when such data had not been collected.

By failing to maintain adequate and accurate case histories, and specifically, by failing to ensure that the data recorded were accurate, you have compromised the validity and integrity of data captured at your site.

We acknowledge your October 16, 2012, written response that indicates that you promptly reported these findings to the sponsor and IRB when you became aware of them in July 2011. We also acknowledge your statement that you contacted all other subjects to inquire about the performance of vital sign measurements.

We acknowledge the following corrective action plan that is noted in your October 16, 2012, written response and that addresses the violations in Items 1 and 2 above:

- The research coordinator who falsified data was terminated;
- All investigators and staff must attest that they have read and will adhere to the department's Standard Operation Procedures when conducting research;
- The department will conduct comprehensive standardized training and competency validation for all new research coordinators;
- The Department of Medicine research manager and staff will perform continuous internal monitoring of studies;
- Study-specific enrollment criteria for all studies will be reviewed at weekly department research meetings, and investigators will be required to sign eligibility checklists; and
- Research teams will be required to obtain mandatory continuing education.

Your response is inadequate because you have not provided sufficient information to enable us to evaluate the adequacy of your corrective action plans. Specifically, you have not provided documentation of the corrective actions that you have implemented. In addition, your response is inadequate because you have only referenced actions that your department is taking, and you have failed to include any corrective actions that you, as a clinical investigator, are implementing to prevent similar violations in the future.

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 address the violations noted above adequately and promptly 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, M.D., M.P.H.
Branch Chief
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,

{See appended electronic signature page}

Thomas N. Moreno, M.S.
Acting Office Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

THOMAS N MORENO
05/14/2013

Page Last Updated: 05/24/2013
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