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Inspections, Compliance, Enforcement, and Criminal Investigations

Diaz, Leslie, M.D. 11/4/11



Department of Health and Human Services

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

WARNING LETTER

Nov 4, 2011

CERTIFIED MAIL RETURN RECEIPT REQUESTED

Leslie E. Diaz, M.D.
Infectious Disease Associates of the Palm Beaches
840 U.S. Highway #1, Suite 120
North Palm Beach, FL 33408

Ref: 11-HFD-45-10-01

Dear Dr. Diaz:

Between January 12, 2011, and March 8, 2011, Ms. Colleen Aspinwall, 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:

Protocol **(b)(4)**, titled "**(b)(4)**," of the investigational drug **(b)(4)**, performed for **(b)(4)**

Protocol **(b)(4)**, titled "**(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 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, the documents submitted with that report, and your written response dated March 11, 2011, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. At the conclusion of the inspection, Ms. Aspinwall presented you with a Form FDA 483, Inspectional Observations, and discussed the observations listed on the form with you. We wish to emphasize the following:

1. You failed to personally conduct or adequately supervise the clinical investigations [21 CFR 312.60].

When you signed the investigator statements (Form FDA 1572) for the above-referenced clinical investigations, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities include ensuring that the investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety, and welfare of subjects under your care; and ensuring control of drugs under investigation (21 CFR 312.60). In the signed investigator agreement, you specifically agreed to personally conduct the clinical studies or to supervise those aspects of the studies that you did not personally conduct. While you may delegate

certain study tasks to individuals qualified to perform them, as clinical investigator, you may not delegate your general responsibilities. Our investigation indicates that your supervision over the studies was not adequate to ensure that clinical trials were conducted according to the signed investigator statement, the investigational plan, and applicable regulations. This lack of adequate involvement in and oversight of the studies raises concerns regarding the protection of the rights, safety, and welfare of subjects enrolled into the studies and the integrity of the data from your site.

In a written affidavit signed by you on March 8, 2011, you stated that even though your practice went through multiple ownership changes, you always remained as the principal investigator for the above trials, you were fully aware that you always had the ultimate responsibility for these clinical trials, and you continued to take full responsibility for their conduct and oversight.

In your written affidavit, you acknowledged a number of significant instances of inadequate oversight and supervision, including but not limited to the following:

- "I am admitting to the Agency that as a Clinical Investigator/Principal Investigator, I had a lack of involvement and oversight in the conduct of these clinical trials."
- "In searching for study documentation, I also found letters that were sent to me that I had never opened and/or had seen before. These letters were from monitors, sponsors, and IRB's, including some of which involved the termination of my clinical studies." These letters informed you that approval of the audited protocols had been suspended or terminated, due to your failure to submit continuing review reports; inability to contact you after multiple attempts; or your failure to respond to multiple communications.
- "I acknowledge that adverse experiences for [(b)(4)] and the (b)(4) trials ... were not evaluated/graded as required by study protocols."
- "I am also admitting to having ignored the clinical trials. I also did not keep track of the mail as far as what was coming in or going out."
- "All study documentation ended in early December 2007 after my study coordinator left."
- "I had no knowledge of how these studies were monitored."

We wish to emphasize again that as the clinical investigator, it was your ultimate responsibility to ensure that the studies were conducted properly and in compliance with FDA regulations, in order to protect the rights, safety, and welfare of study subjects and to ensure the integrity of the study data. The statements in your affidavit, when taken in conjunction with the violations described below, indicate systemic failures in your conduct of investigational research. As a result, we have significant concerns about the safety and welfare of subjects enrolled into these studies and the integrity of the data from your site.

2. 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 an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations. You have failed to conduct Protocols (b)(4) and (b)(4) according to the investigational plans. Examples of this failure include but are not limited to the following:

a. For Protocol (b)(4):

- Protocol Section 2.3 specified that subjects with severe renal insufficiency were to be excluded from the study. Source records available at your clinical site during the FDA inspection showed that Subject 02145 was screened for enrollment into the study on May 8, 2007. However, the medical history showed that this subject had continuing chronic renal failure prior to enrollment. Thus, the enrollment of this subject into the study violated the investigational plan.
- Protocol Section 3.3.6 and Table 3-1 provided instructions for evaluating adverse events (AEs) and stated that an investigator who was a qualified physician was to evaluate all AEs with regard to maximum intensity, seriousness, duration, action taken, and relationship to test drug. In your written affidavit, you acknowledged that for Protocol (b)(4), AEs that included the clinical symptoms recorded in the subjects' charts were not evaluated or graded, as required by the protocol. For example, for Subjects 02145 and 01323, AEs were recorded in the subjects' medical evaluation source documents; however, these were not evaluated or graded according to protocol requirements.
- Protocol Section 3.3.5.1 specified that any serious adverse experience (SAE), including death due to any cause, that occurs to any subject entered into this study or within 14 days following cessation of treatment or within the established off-therapy follow-up period for safety as described in the protocol, whether or not related to the investigational product, must be reported to the sponsor within 24 hours.

Subject 00996 was enrolled into the study on March 2, 2007. Records show that between May and early June 2007, when the subject was still in the study, the subject underwent cardiac catheterization that revealed an SAE of triple-vessel coronary artery occlusive disease and required surgery. Also, we note that you characterized this SAE as "immediate[ly] life-threatening" on the sponsor's SAE reporting form. However, you did not report this SAE to the sponsor until July 30, 2007, which was beyond the 24-hour window specified by the protocol. In addition, you did not provide all of the information requested on the sponsor's SAE form, including whether the SAE was related to the study drug.

b. For Protocol **(b)(4)**, Section 5.4.1 specified that the subject was to receive the investigational medication (**(b)(4)**) once eligibility was confirmed after completion of the screening form and evaluation by the sponsor or its designee. Source records indicate that Subject 214-002102 was dispensed study drug on June 27, 2007, nearly two weeks before you received confirmation of the subject's eligibility for enrollment by the sponsor or its designee on July 9, 2007. You therefore failed to follow the protocol requirements by dispensing investigational medication to a subject prior to confirming the subject's enrollment into the study.

To summarize, you have failed to ensure that the investigations were conducted in accordance with the investigational plan, because you enrolled ineligible subjects, failed to properly evaluate AEs, failed to properly report SAEs, and dispensed investigational medication to subjects prior to confirming their enrollment. Furthermore, in your signed affidavit, you acknowledge that you had a lack of involvement and oversight in the conduct of these clinical trials, did not document the process for confirming subject eligibility, and did not evaluate AEs according to the protocol.

These statements, when taken in conjunction with the violations described above, indicate systemic failures in your conduct of investigational research. As a result, we have significant concerns about the safety and welfare of subjects enrolled into these studies and the integrity of the data from your site.

3. You did not return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR 312.59 [21 CFR 312.62(a)].

During our inspection, unreturned investigational drugs for both the **(b)(4)** and **(b)(4)** studies were found at your site. In your written affidavit, you stated that in searching for documentation for the audited studies, you found a box of study drug product which had never been returned to the sponsors. The box contained full, partially full, and empty bottles of study drug.

The identification of these unreturned investigational drugs at your site raises significant concerns regarding the adequacy of your oversight and control of investigational drugs. In your signed affidavit, you admit to a lack of involvement and oversight in the conduct of these clinical trials. This general lack of oversight, when taken in conjunction with your failure to maintain control of investigational drugs, serves to undermine the confidence we have in your drug dispensation to subjects. As a result, we have significant concerns about the safety and welfare of subjects enrolled into these studies and the integrity of the data from your site.

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.

We note that in your written affidavit, you state that you are currently not involved in any FDA-regulated trials and do not have any intentions of ever conducting an FDA-regulated clinical trial in the future. Nevertheless, it is your responsibility to ensure compliance with FDA regulations. Therefore, 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. Further, we request that, if your plans should change in the future and you should decide to begin conducting FDA-regulated research, you promptly notify this office of your intention to become a clinical investigator.

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.
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,

/S/

Leslie K. Ball, M.D.

Acting Director

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