Dear Dr. Fandino:

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 May 6 and May 22, 2013. Mr. Craig A. Garmendia, representing the FDA, reviewed your conduct of the following clinical investigations:


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, Mr. Garmendia presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your June 3, 2013 written response to the Form FDA 483.

From our review of the establishment inspection report, the documents submitted with that report, and your June 3, 2013 written response, 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 wish to emphasize the following:
1. **You failed to personally conduct or supervise the clinical investigations [21 CFR 312.60].**

When you signed the Statement of Investigator (Form FDA 1572) for the above-referenced clinical trials, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities as a clinical investigator include ensuring that the clinical trials are 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]. By signing Form FDA 1572, you specifically agreed to personally conduct the clinical trial or to supervise those aspects of the trial that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as a clinical investigator you may not delegate your general responsibilities. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trials were conducted according to the signed investigator statement, the investigational plan and applicable regulations, and in a manner that protects the rights, safety, and welfare of human subjects.

Specifically, you failed to adequately supervise individuals to whom you delegated study tasks. Your failure to adequately supervise the conduct of the studies referenced above led to many of the violations noted in this letter. These violations include, but are not limited to, enrollment of ineligible subjects in Protocols (b)(4) and (b)(4), and failure to take adequate precautions to prevent theft or diversion of the investigational drug (b)(4), a Schedule II controlled substance. Had you provided adequate oversight, you may have been able to prevent many of these violations from occurring.

In your June 3, 2013 written response to the Form FDA 483, you explained that one probable cause of the protocol violations was lack of proper supervision due to lack of or limited clinical investigator experience and supervision in delegating responsibilities to unqualified staff. You also noted that you increased your supervision of clinical research, that you and your staff were retrained, and that you implemented new standard operating procedures about delegation of responsibilities, investigator and sub-investigator responsibilities, investigator review of essential study documents, source document and case report form creation, pharmacy operations and pharmacy diversion policy.

Your written response is inadequate because your corrective action plan is not sufficient to prevent similar violations in the future. Specifically, we find your Standard Operating Procedures (SOPs) insufficient and note that you did not provide details regarding the training that you and your staff underwent.

Your SOP titled “Principal Investigator and Sub-Investigator Responsibilities” does not address how you personally will ensure adequate oversight of study procedures, activities of study coordinators and protocol training for you and your study staff. In addition, your SOP lists some responsibilities of a clinical investigator, and states that it is not an all-inclusive list. However, please note that you are responsible for compliance with all regulations applicable to your conduct as a clinical investigator, not just those which are listed as responsibilities in your SOP.

Regarding the training that you and your staff underwent, you did not provide details regarding the training. Without having the details of this training, we are unable to determine whether it appears adequate to help prevent similar violations in the future.

As the clinical investigator, it was your ultimate responsibility to ensure that these studies were conducted properly and in compliance with FDA regulations to protect the rights, safety, and welfare of study subjects and ensure the integrity of study data. Your lack of supervision and oversight over the clinical studies raises significant concerns about the adequacy of your protection of study subjects enrolled at your site in the studies mentioned above, and also raises concerns about the integrity of the data generated at 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 your clinical studies are conducted in accordance with the investigational plans. The investigational plans for Protocols (b)(4) and (b)(4) required you to ensure that subjects met all eligibility criteria prior to the subjects’ participation in the studies. You failed to adhere to these requirements. Specifically:

a. Protocol (b)(4) requires subjects to have (b)(4) diagnosed by a medical professional, in accordance with the American Diabetes Association guidelines, and within 5 years prior to consenting to participate in this study.

Subjects 016, 018, 020 and 022 (4 of the 10 subjects who you enrolled) were diagnosed with (b)(4) more than 5 years before they consented to participate in Protocol (b)(4) and, thus, were ineligible for the study.

i. Subject 016 consented to participate in Protocol (b)(4) on March 23, 2012, and was randomized into the study on April 24, 2012. However, study records show that Subject 016 was diagnosed with (b)(4) in 2001.

ii. Subject 018 consented to participate in Protocol (b)(4) on April 2, 2012, and was randomized into the study on April 26, 2012. However, study records show that Subject 018 was diagnosed with (b)(4) in 2005.

iii. Subject 020 consented to participate in Protocol (b)(4) on April 5, 2012, and was randomized into the study on April 27, 2012. However, study records show that Subject 020 was diagnosed with (b)(4) in 2003.

iv. Subject 022 consented to participate in Protocol (b)(4) on April 10, 2012, and was randomized into the study on April 30, 2012. However, study records show that Subject 022 was diagnosed with (b)(4) in 2005.

As noted above, Subjects 016, 018, 020 and 022 represent 4 of the 10 subjects who you enrolled. Your inappropriate enrollment of 4 out of 10 subjects in this study raises significant concerns about the adequacy of your protection of study subjects enrolled at your site and also raises concerns about the integrity of the data generated at your site for Protocol (b)(4).

b. Protocol (b)(4) requires that new subjects (defined as subjects not previously treated with (b)(4)) be on a stable regimen of 30 to 1000 mg oral morphine daily or an equivalent analgesic dose of one or more listed opioid therapies for at least 4 weeks before screening for non-cancer-related pain with no anticipated change in opioid dose requirement over the proposed study period as a result of disease progression. Subjects 030 and 014, who were enrolled as new subjects, were not on an opioid regimen that complied with this protocol requirement.

i. Subject 030: Subject 030’s opioid regimen at enrollment was 120 mg of codeine daily, taken in the form of a combination product (300 mg acetaminophen and 30 mg codeine) every 6 hours. However, the subject needed to be taking 300 mg codeine daily to meet the protocol-required minimum equivalent of 30 mg oral morphine daily. Subject 030 was randomized into the study on September 15, 2011, and remained in the study until August 10, 2012.

On October 6, 2011, your site notified your Institutional Review Board (IRB) of this protocol violation and explained that it happened because the morphine-equivalent conversion dose for this subject was miscalculated. Yet, after finding the error, you continued Subject 030 in this study until August 10, 2012, 11 months after the subject was randomized and 10 months after reporting the violation to the IRB.
Subject 014: Subject 014’s opioid regimen at enrollment was 100 mg of Tramadol daily. However, the subject needed to be taking 135 mg of Tramadol daily to meet the protocol-required minimum equivalent of 30 mg oral morphine daily. Subject 014 was randomized into the study on August 12, 2011, and remained in the study until June 22, 2012.

On August 17, 2012, approximately one year after Subject 014 was randomized into Protocol (b)(4), you prepared a Memo to File regarding the subject’s Tramadol dosing. In this memo, you indicated that a previous study coordinator falsified the Tramadol dosing frequency from once daily to 4 times daily to make the subject appear eligible for the study. On August 29, 2012, you amended Subject 014’s Eligibility Checklist to reflect that the subject did not meet the study requirement regarding opioid regimen.

Your study records show that Subject 014 remained enrolled for nearly a year in Protocol (b)(4) even though the subject did not meet eligibility requirements for the study.

In your June 3, 2013 written response to the violations noted in Item 2 above, you stated that the studies were conducted without proper follow-through or supervision. In addition, you acknowledge your failure to review eligibility criteria effectively at screening and at randomization visits to ensure that subjects were eligible for study participation. You also noted that you have, for example, increased your supervision of clinical research, that you and your staff were retrained, and that you implemented new standard operating procedures about delegation of responsibilities, investigator and sub-investigator responsibilities, investigator review of essential study documents, and source document and case report form creation.

Your written response is inadequate because your corrective action plan is not sufficient to prevent similar violations in the future. Specifically, we find your Standard Operating Procedures (SOPs) insufficient. In addition, you have not provided details regarding the training that you and your staff underwent. Without having the details of this training, we are unable to determine whether it appears adequate to help prevent similar violations in the future.

Your SOP titled “Delegation of Responsibilities, Conduct and Completion of Study Activities” is of concern to us because it appears to have delegations pre-set without regard to study-specific requirements. A study protocol may contain requirements regarding delegation of responsibilities, conduct, and completed study activities that are not aligned with this SOP. We are uncertain how you would meet the requirements of your own SOP and study protocols when your SOP conflicts with directions or requirements contained in study protocols.

Your SOP titled “Sources [sic] Document/Case Report Form Creation” notes the following, which is of concern to us:

- The assigned study coordinator will start drafting study source documents at or about the time the study is approved by the Institutional Review Board
- The assigned study coordinator will be the primary author of source documents and Case Report Forms, with the investigator’s role being that of Quality Assurance Reviewer and Editor

We are unclear on what type of source documents you would have a study coordinator start drafting at or about the time a study is approved by an IRB. Study-specific activities, including creation of source documents, generally cannot be undertaken until after IRB approval of the study.

We are also concerned with the statement that a study coordinator will be the primary author of source documents and Case Report Forms, with your role being that of reviewer and editor. Placing responsibility on a study coordinator for authorship of all source documents and Case Report Forms in all studies raises concern about the adequacy of your oversight of studies. We do not find it acceptable for you to assign these responsibilities to study coordinators without first considering the...
specifics and requirements of each study that you undertake and determining the extent, if any, to which the study coordinator is qualified to be the primary author of all source documents and Case Report Forms.

We are further concerned that, where revisions to source documents or Case Report Forms may be required based on a protocol amendment, the SOP does not indicate who is responsible for ensuring that any document revisions are appropriate, accurate, and complete.

With respect to the sample Case Report Form that you provided, we are unable to determine the purpose of this sample Case Report Form and when you plan to use it. We are concerned that you may introduce error into future studies by using Case Report Forms that are not study-specific.

We emphasize our concern that you failed to fully evaluate eligibility criteria for subjects that were designed specifically for each research study to optimize interpretability of collected data and minimize foreseeable harm to enrolled subjects. Enrollment of subjects who do not meet eligibility criteria jeopardizes subject safety and welfare and raises concern about the validity and integrity of the data collected at your site. We are particularly concerned that 4 of the 10 subjects in Protocol (b)(4) were enrolled despite being ineligible for the study.

3. You failed to take adequate precautions to prevent theft or diversion of an investigational drug that is subject to the Controlled Substances Act [21 CFR 312.69].

As a clinical investigator, when handling an investigational drug that is subject to the Controlled Substances Act, you are required to take adequate precautions to prevent theft or diversion of the substance into illegal channels of distribution. These precautions include the storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited. The investigational drug for Protocol (b)(4), (b)(4), is classified by the U.S. Drug Enforcement Administration as a Schedule II controlled substance based on structural relatedness to noroxymorphone. You failed to take adequate precautions to prevent theft or diversion of (b)(4). Specifically, you failed to store (b)(4) in a securely locked enclosure. Rather, you stored the investigational drug in an unlocked and unsecured room. A police report from the City of Miami Police Department indicates that approximately 900 (b)(4) tablets were stolen from your site on November 3, 2011.

In your June 3, 2013 written response to the violation noted in Item 3 above, you acknowledged that the theft of (b)(4) at your site was “due to the lack of stringent security monitoring and measures.” You indicated that, to prevent similar violations in the future, you implemented the following:

- Two new standard operating procedures:
  - Pharmacy Operations (Version 1, dated March 16, 2012)
  - Pharmacy Diversion Policy (Version 1, dated March 16, 2012)
- Use of new surveillance cameras and an alarm system in hallways leading to and inside the pharmacy
- Moving the pharmacy to a more secure location
- Use of a locked cabinet system for storing investigational drugs classified as controlled substances
- Limiting access to these investigational drugs classified as controlled substances to designated employees
- Changing pharmacy door locks and reassigning new keys to designated employees only

Your response is inadequate because you failed to provide a copy of the new standard operating procedures about pharmacy operations and pharmacy diversion prevention policy. As a result, we
are unable to determine whether your corrective actions appear sufficient to prevent a recurrence of similar violations.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational drugs. 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 believe you have complied with FDA regulations, include your reasoning and any supporting information for our consideration.

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
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10903 New Hampshire Avenue
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Sincerely yours,

{See appended electronic signature page}

Sean Y. Kassim, Ph.D.
Acting 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/
SEAN Y KASSIM
04/30/2014

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Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.