DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852-1448

By Facsimile Transmission and Overnight Delivery

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August 28, 2012

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDING AND OPPORTUNITY TO EXPLAIN

Dear Dr. Richards:

Between December 6 and 30, 2011, a Food and Drug Administration (hereafter referred to as "FDA" or the "Agency") investigator conducted an inspection of the following clinical study involving a biological investigational new drug, which you conducted as a clinical investigator:

(b)(4)

The inspection was conducted as part of FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational products.

At the conclusion of the inspection, the FDA Investigator presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We have reviewed the inspection report, the documents submitted with that report, and your written response to the Form FDA 483 dated January 13, 2012. Your response is insufficient to address the matters outlined in this letter.

Based on our evaluation of information obtained by the Agency, we believe that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as set forth under Title 21 Code of Federal Regulations (CFR), Part 312. These regulations are available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312.

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether you should be disqualified from receiving investigational articles as set forth under 21 CFR § 312.70.

A listing of violations follows. The applicable provisions of the CFR are cited for each violation.

1. **You failed to protect the rights, safety, and welfare of the subjects under your care, and to conduct an investigation according to the signed investigator statement, investigational plan, and the protocol. [21 CFR § 312.60]**

When you signed Form FDA 1572, you agreed to conduct the study in accordance with the study protocol and applicable FDA regulations. Your responsibilities as a clinical investigator include ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and protecting the rights, safety, and welfare of subjects under the your care.

You failed to fulfill your obligations as a clinical investigator in the following ways:

A. You administered the wrong dosage of the investigational product to Subject (b)(6)

(b)(4)

In your letter, you admit to administering the wrong dose of the investigational product to Subject (b)(6) (b)(4)

(b)(4)

Your general responsibilities as a clinical investigator included protecting the rights, safety, and welfare of subjects under your care. Your repeated practice of failing to verify dosing amounts prior to each administration of the investigational drug exposed this subject to increased and unreasonable risk.

B. You failed to take the required (b)(4)

(b)(4)

i. (b)(4)

ii. (b)(4)

The protocol-required (b)(4) (b)(4) to determine response status for the purpose of efficacy analysis of this study. You repeatedly failed to take (b)(4) according to the protocol-required time schedule which prevented the (b)(4) from accurately determining the response status for those subjects and for the purpose of efficacy analysis of this study. As the clinical investigator, you were ultimately responsible for the conduct of this study, including the data captured at your site. The violation described above compromised the validity and integrity of the data at your site.

C. You did not follow the protocol and the study (b)(4) (b)(4)

i. (b)(4)

ii. (b)(4)

(b)(4)

(b)(4)

In your response, you explained that the (b)(4)

(b)(4)

FDA does not accept your explanation. (b)(4)

(b)(4)

(b)(4) These issues were brought to your attention numerous times by study monitors and (b)(4) (b)(4), yet you did not implement corrections. Your repeated failure to adhere to the protocol precluded the (b)(4)

(b)(4)

(b)(4) therefore exposed subjects to increased and unreasonable risk.

D. You did not conduct the (b)(4)

(b)(4)

In your letter, you explain that for this particular study, (b)(4)

(b)(4)

We do not accept your explanation. (b)(4)

(b)(4)

In summary, you repeatedly failed to conduct the above referenced study according to the investigational plan. Your failure to conduct an investigation according to the investigational plan in accordance with 21 CFR 312.60 is a violation also identified in your 2004 FDA Warning letter. Your corrective action plan in 2004 stated that you intended to "utilize greater diligence in appropriately documenting the decisions made

for the subjects in clinical trial." You also stated that you "understood the importance of collecting all data required by clinical trial protocol and wish to provide assurance that you do strive for such consistency." The violations documented above indicate that you failed to successfully implement your corrective actions.

2. **You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. [21 CFR § 312.62(a)]**

FDA's inspection found inaccurate and inadequate documentation for receipt, dispensing and destruction of the investigational drug. Examples include the following:

A. According to your accountability records for lots (b)(4) you received (b)(4) of lot (b)(4) but dispensed (b)(4) of that lot for administration to subjects. Your records also state that you received (b)(4) of lot # (b)(4) but dispensed (b)(4) of that lot. Due to your inadequate documentation practices, it cannot be determined which subject received which lot of the investigational product.

In your response, you explained that an investigation into this incident identified your use of a (b)(4) as the root cause for this error, and that the pharmacist entered the incorrect lot numbers into the (b)(4) You also explain that you have implemented a new SOP and process requiring a (b)(4) (b)(4) for each lot of investigational drug. Your corrective procedures are inadequate in part because they do not specify how you will address transcription errors.

B. Your accountability records for test article lot # (b)(4) , expiration date (b)(4) , indicates that the remaining (b)(4) were destroyed on (b)(4) However, nine days after the study site's pharmacist supposedly destroyed the (b)(4) the FDA investigator found (b)(4) of lot (b)(4) in the (b)(4) freezer.

In your response, you explained that an investigation into this incident identified "distraction as the root cause for this error." In order to prevent this type of error in the future you have adopted a new SOP requiring the pharmacist to have a witness present when destroying investigational product.

Your lack of oversight over this study, particularly with regard to inaccurate and inadequate documentation of the drug accountability log, raises significant concerns regarding subject safety. Accountability of the investigational product at the trial site is the responsibility of the investigator. While you may delegate certain study tasks to individuals qualified to perform them, you may not delegate your general responsibilities as a clinical investigator.

3. **You failed to report promptly to the Institutional Review Board (IRB) all changes in the research activity and all unanticipated problems involving risk to human subjects. [21 CFR § 312.66].**

You submitted a study renewal continuing review report to the IRB on 10/6/2010 which contained incorrect information regarding the number of subjects involved in the study and their status. The report stated that no subjects were active in the study, yet the FDA investigation found at least two subjects were active in the study prior to 10/6/2010.

In your letter you explain that "an investigation into the incorrect numbers being entered into the continuing review form submitted to the IRB on October 6, 2010 failed to identify a specific cause" and you also recognize "that transcription errors may occur in a busy research office."

Your failure to report the accurate number of subjects involved in the study and their status misled the IRB about the status of research activities at your site.

Your failure to report promptly to the IRB all changes in the research activity in accordance with 21 CFR 312.66 is a violation which was also identified in your 2004 FDA Warning Letter.

4. **You failed to prepare and maintain adequate and accurate case histories, including all observations and other data pertinent to the investigation. [21 CFR § 312.62(b)].**

An investigator is 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. As defined by 21 CFR § 312.62(b), case histories include case report forms and supporting data.

A. (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

B. According to your Corrective and Preventative Action (CAPA) form dated 10/31/2011, the site monitor trained your study staff to use the new "Response to Treatment Assessment" worksheets on 9/26/2011. The new worksheets were implemented to correct the pattern of source documentation lapses and discrepancies described above. You retrospectively completed the new worksheets for at least four subjects after the FDA inspection began on 12/6/2011. Source documents are to be completed contemporaneous to each study visit, not retrospectively. In addition, some of the newly implemented Response to Treatment worksheets you completed and signed after the inspection began revealed discrepancies compared to the eCRF. The table below provides examples of these discrepancies.

Subject/Treatment Date	**Electronic Case Report Form Response to Treatment Entry**	**"Response to Treatment Assessment" worksheet**
(b)(6)	(b)(4)	(b)(4)
(b)(6)	(b)(4)	(b)(4)

In your letter, you explain your challenges for documenting source data utilizing the site's electronic medical record (EMR) system which is the site's primary source for documentation. You explain that "response assessments were maintained in the patient's paper research chart, but inconsistently scanned into the EMR....This process rendered the primary source document incomplete." You have since implemented a SOP requiring a reference in the patient progress note to the location of source document data.

We acknowledge that in your response to the Form FDA 483 you outlined the corrective actions that you have taken to prevent this type of violation from occurring in the future. However, these corrective procedures do not specify how you will address the inaccurate entries into the eCRF by your study coordinators.

Not only does the finding above compromise the reliability of data captured at your site, but it also raises significant concerns regarding the protection of human subjects at your site. As the clinical investigator, you were ultimately responsible for the conduct of this study, including the data captured and recorded at your site.

Throughout this letter, we have identified violations which we observed both during the 2004 inspection and in the most recent inspection in 2011. The recent inspection in 2011 demonstrates that the corrective actions you promised to undertake in your response to the 2004 Warning Letter failed to prevent further violations.

This letter is not intended to contain an all-inclusive list of deficiencies with your clinical studies of investigational new drugs. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above listed violations, FDA concludes that you have repeatedly or deliberately failed to comply with the cited regulations. Accordingly, FDA proposes that you be disqualified as a clinical investigator. You may reply to the above stated findings, including an explanation of why you should remain eligible to receive investigational articles and not be disqualified as a clinical investigator, in a written response or at an informal conference in my office. This procedure is provided for by regulation at 21 CFR § 312.70(a).

Within fifteen (15) business days of receipt of this letter, write or call me to arrange a conference time or to indicate your intent to respond in writing. Your written response must be forwarded within thirty (30) business days of receipt of this letter. If you do not respond to me within fifteen (15) business days to arrange a conference time, you will have waived your right to file a response.

Your reply should be sent to:

Mary Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring with you all pertinent documents. A representative of your choosing may accompany you. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational articles. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

The Center will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR Part 16 (available at the Internet address identified on page 1 of this letter) and 21 CFR § 312.70. Before such a hearing, FDA will provide you notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer who has not participated in this matter will conduct the hearing. The Commissioner will determine whether or not you will remain entitled to receive investigational articles. You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

Sincerely yours,

Mary A. Malarkey

Mary A. Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Enclosure: Proposed consent agreement