DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN (NIDPOE)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Elmore Alexander, D.O.
(b) (6) (Home Address)

Dear Dr. Alexander:

Between November 13, 2009, and October 20, 2010, Ms. Stephanie Hubbard and Mr. LaReese Thomas, representing the U.S. Food and Drug Administration (FDA), conducted an investigation to review your conduct of the following clinical investigations of the investigational drug (b) (4), performed for (b) (4):

- Protocol (b) (4), (b) (4)";
- Protocol (b) (4), (b) (4)"; and
- Protocol (b) (4), (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.

At the conclusion of the inspection, Ms. Hubbard and Ms. Thomas attempted multiple times to present you with a Form FDA 483, Inspectional Observations. However, you refused to review the Form FDA 483 with FDA investigators. Consequently, and because

your medical office had closed during the course of the inspection, the FDA investigators left a copy of the Form FDA 483 at your residence, and observed that you retrieved it.

We have reviewed the inspection report and the documents submitted with that report. We note that you did not provide a written response to the Form FDA 483. Based on our evaluation of information obtained by the Agency, we believe that you have repeatedly or deliberately submitted false information to the sponsor or FDA in required reports, and repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products, as published under Title 21, Code of Federal Regulations (CFR), part 312 (copy enclosed).

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 products as set forth under 21 CFR 312.70. A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. **You repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report [312.70(a)].**

   Based on the information obtained during the course of the inspection, the FDA has determined that you submitted falsified subject records for three subjects enrolled in your clinical trials. The FDA inspection revealed that all of the subjects you enrolled in Protocol (b) (4) and Protocol (b) (4) were, in fact, study coordinators whom you enrolled under fictitious names.

   a. Protocol (b) (4): You enrolled your study coordinator ((b) (6)) into the study as Subject 1012 under a fictitious name (DCJ). In addition, you signed study records that showed the fictitious name for this subject. (b) (6) completed the following study-related documents for himself/herself while falsely claiming to be subject DCJ:

      - Patient medical history questionnaire for the December 3, 2008, visit date.
      - Inclusion/exclusion form on December 3, 2008.
      - Screening records for Visit 1 on December 3, 2008. On the same date, you signed the physical examination portion of these records as the physician completing the examination.
      - Informed consent document (ICD) showing falsified subject DCJ's signature on December 22, 2008. (This date was later crossed out and changed to January 23, 2009, and was initialed on February 3, 2009.) You also signed this subject's ICD on February 3, 2009.
      - Visit 2 esophagogastroduodenoscopy (EGD) report dated December 22, 2008. You signed this document on December 31, 2008.
      - Study records for Visit 3 on December 23, 2008. In addition, you signed the Investigator Symptom Assessment for this visit on the same date.
      - Study records for Visit 4 on January 23, 2009.

- Visit 4 EGD report dated January 22, 2009. Your subinvestigator, (b) (4), signed this report.

Furthermore, study records note that you signed an informed consent document executed by falsified subject DCJ; you conducted physical examinations for subject DCJ at both the screening visit on December 3, 2008, and Visit 3 on December 23, 2008; and you signed a laboratory report for laboratory samples drawn from subject DCJ on January 23, 2009. These records indicate that you were aware that you enrolled your study coordinator into Study (b) (4) under a fictitious name.

b. Protocol (b) (4): You enrolled your study coordinator ((b) (6)), who was also the Chief Executive Officer of the Site Management Organization (SMO), Clinical Trial Providers Inc., into the study as Subject 1011 under a fictitious name (MD). You and (b) (6) also signed study records that showed the fictitious name for this subject. Specifically:

- ICD (August 13, 2008, version) showing falsified subject MD's signature on November 26 and December 10, 2008. You also signed these ICDs on November 26 and December 10, 2008.
- ICD (October 30, 2008, version) showing falsified subject MD's signature on January 13, 2009. Your study coordinator (b) (6) signed as the person obtaining consent on the ICD for subject MD on this date.
- Screening records for Visit 1 on November 26, 2008. You completed and signed a physical examination form for subject MD at the screening visit on November 26, 2008. Your study coordinator (b) (6) also completed and signed screening records for Visit 1 on this date.
- Screening records for Visit 2 on December 10, 2008 (later crossed out and changed to December 9, 2008). Your study coordinator (b) (6) completed and signed these study records on December 16, 2008.
- Visit 2 EGD report for subject MD, dated December 9, 2008. You and your subinvestigator, (b) (4), signed this report on December 9, 2008.
- Visit 3 study records dated December 10, 2008. Your study coordinator (b) (6) completed and signed these study records on December 10, 2008, and you signed the Investigator Symptom Assessment section of these records on the same date.
- Visit 4 EGD report dated January 13, 2009. The signature at the bottom of this endoscopy report was not his/her true signature.
- Visit 4 EGD CRF (visit date January 13, 2009). Your study coordinator (b) (6) completed and signed the Visit 4 EGD CRF for subject MD on January 13, 2009.
- Study records for Visit 6 on January 30, 2009. Your study coordinator (b) (6) completed and signed Visit 6 study records for subject MD on January 30, 2009.

As noted above, in addition to enrolling your study coordinator under a fictitious name, you signed study records that showed the fictitious name for this subject. These records indicate that you should have been aware that you enrolled your study coordinator, (b) (6), into Study (b) (4) under a fictitious name.

c. Protocol (b) (4): You enrolled your study coordinator ((b) (6)) into the study as Subject 1012 under a fictitious name (DCJ). You also signed study records that showed the fictitious name for this subject. Furthermore, your study coordinator, (b) (6), completed these study-related documents for himself/herself while falsely claiming to be subject DCJ:

- ICD dated January 23, 2009. Your study coordinator (b) (6) completed and signed her/his own informed consent document under the false identity of DCJ, originally on December 22, 2008. On February 3, 2009, your study coordinator, using the initials DCJ, crossed out the original date and changed it to January 23, 2009.
- Inclusion/exclusion criteria form on January 23, 2009. Your study coordinator ((b) (6)) completed and signed this study record on June 8, 2009, using his/her true identity as the person completing the form but using the false identity of DCJ as the subject.
- Visit 1 study records for January 23, 2009, visit date. You signed the Investigator Symptom Assessment study record for this visit, originally on December 23, 2009, then crossed out that date and changed it to January 23, 2009. You initialed this change on February 5, 2009.
- Visit 4 study records on February 26, 2009.

As noted above, in addition to enrolling your study coordinator into Study (b) (4) under a fictitious name, you signed study records that showed the fictitious name for this subject. These records indicate that you should have known that you enrolled your study coordinator into Study (b) (4) under a fictitious name.

As the clinical investigator, it was your ultimate responsibility to ensure that these studies were conducted properly and that subjects' true identities were used on study records.

d. The signature of your subinvestigator, (b) (4), was falsified on the following documents:

- Financial disclosure form, signed and dated April 20, 2009.
- Endoscopy report dated January 13, 2009, for Subject 1011 in Study (b) (4).
- Memo dated February 4, 2009, which was attached to the November 21, 2008, endoscopy report for Subject 1004 in Protocol (b) (4).

As the clinical investigator, it is your responsibility to ensure that the data collected from study subjects are accurate and can be relied upon in all analyses of the study endpoints. As all of the collected data were based on falsified subjects, none of the data collected in support of the referenced studies are considered reliable. When you

signed the Statement of Investigator, Form FDA 1572, you agreed to provide accurate information to the sponsor, and to assure that you will comply with FDA regulations related to the conduct of the clinical investigations of the investigational drugs. You also agreed to ensure that all associates, colleagues, and employees assisting in the conduct of the studies would be informed of their obligations in meeting their commitments. Furthermore, your signature constitutes both your affirmation that you are qualified to conduct the clinical investigation, and your written commitment to abide by FDA regulations in the conduct of the clinical investigations. The use of fictitious information significantly compromises the integrity of your studies, as well as the reliability and validity of the data.

2. 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 the Form FDA 1572, you specifically agreed to personally conduct the clinical trials or to supervise those aspects of the trials 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 the study coordinators to whom you delegated 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, for example, the fabrication of records by your study coordinators; their enrollment under fictitious names in Protocols (b) (4) (Protocol (b) (4)) and (b) (4) (Protocol (b) (4)); and falsified signatures. Had you provided adequate oversight, you would have been able to prevent many of these violations from occurring.

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 ensure the integrity of the study data. Your lack of supervision and oversight of the clinical studies raises significant concerns about the protection of study subjects enrolled into the studies, and the integrity of the data from your site.

3. 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 investigations are conducted according to the signed investigator statement, the investigational plan, and applicable regulations. You 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. A sponsor newsletter, dated July 2008, prohibited the enrollment of "site staff associates" in your studies at the sites where the staff were employed. The purpose of this requirement was to avoid the introduction of bias into the study data. You violated this requirement by enrolling your study coordinators into the studies at your site. Specifically, you enrolled (b) (6) into Protocol (b) (4) in November 2008; you enrolled (b) (6) into Protocol (b) (4) in December 2008; and you enrolled (b) (6) into Protocol (b) (4) in January 2009, all of which were after the publication date of the sponsor newsletter. By enrolling your study coordinators into your studies, you introduced bias and compromised the study data.

b. Exclusion criteria for Protocol (b) (4) (version of March 24, 2008, exclusion criterion 7) and Protocol (b) (4) (version of February 11, 2008, exclusion criterion 3), require that subjects with current (b) (4) be excluded from enrollment into the study. Contrary to these exclusion criteria, you enrolled Subject 1012/DCJ (your study coordinator, (b) (6), using a fictitious identity) into Studies (b) (4) and (b) (4) despite two screening endoscopic evaluations on December 22, 2008, and January 22, 2009, documenting (b) (4) . Based on these endoscopy results, this subject should have been excluded from enrollment into both studies.

We emphasize our concern that you failed to fully evaluate the eligibility criteria, designed specifically for each clinical investigation by the sponsor to optimize the interpretability of the data to the disease process under study, and to minimize foreseeable harm to enrolled subjects due to comorbidities. Enrollment of subjects who do not meet eligibility criteria jeopardizes subject safety and welfare and compromises the interpretation and validity of the investigational endpoints.

4. You did not obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60, 21 CFR 50.20, and 21 CFR 50.27].

As a clinical investigator, you are required to obtain legally effective informed consent prior to involving a subject in research. An investigator shall seek such consent only under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. In addition, the regulations require that information given to the subject or the subject's legally authorized representative (LAR) shall be in language understandable to the subject or the LAR, and that the consent document be signed and dated by the subject or the subject's LAR at the time of consent. You failed to obtain

informed consent from subjects in accordance with these provisions of 21 CFR part 50. Examples include, but are not limited to, the following:

a. You failed to ensure that the consent documents were signed and dated by the subject or the subject's LAR at the time of consent. Specifically, you failed to obtain signatures that reflected the subjects' true identities on informed consent documents in that you permitted your study coordinators, (b) (6) and (b) (6), to enroll into studies under fictitious identities and to sign consent documents using these fictitious identities. You permitted your study coordinator, (b) (6), to sign consent documents as falsified subject DCJ in Studies (b) (4) and (b) (4), and you permitted your study coordinator, (b) (6), to sign consent documents as falsified subject MD for Study (b) (4).

b. You failed to obtain legally effective informed consent from Subject 1007 in Study (b) (4) in that you failed to ensure that the information given to the subject or the subject's LAR was in a language understandable to the subject or the LAR. Both you and your study coordinator told the Contract Research Organization (CRO) that the subject only spoke Spanish. The SMO administrator had to translate the consent form orally for this subject at the time of consent. You did not provide a Spanish version of the consent form to this subject or his/her LAR. You also did not provide a short form written consent document in Spanish to the subject, which states that the elements of informed consent required by §50.25 have been presented orally to the subject or the subject's LAR. In addition, there was no written documentation that a witness was present during the oral presentation of informed consent.

   Subject 1007 signed the ICD for Study (b) (4) on November 17, 2008, and had the endoscopy procedure with gastric biopsy for screening purposes on December 12, 2008. Endoscopy and biopsy are both invasive procedures with potential adverse events for the study subject. By not providing the subject with proper informed consent, you jeopardized this subject's safety by not assuring that he/she understood all the risks associated with screening for the study, including but not limited to the endoscopic procedure and biopsy.

c. You failed to obtain informed consent prior to involving subjects in research. Specifically, for Study (b) (4), Subject 1012 completed the patient medical history questionnaire, inclusion/exclusion form, and subject screening records on December 3, 2008. However, you did not obtain informed consent from Subject 1012 until December 22, 2008. In addition, Subject 1012's informed consent form was signed under a fictitious name.

d. You failed to obtain legally effective informed consent from your study coordinators, (b) (6) and (b) (6), in that their enrollment raised concerns regarding coercion and undue influence. As your study site staff, (b) (6) and (b) (6) were not free to give informed consent that was independent of their status as employees. You did not

minimize the potential for coercion and undue influence by enrolling them as subjects in your studies.

Your failure to ensure that informed consent documents were properly signed and dated by the subject or the subject's LAR; your failure to provide subjects with informed consent documents in a language that is understandable to the subject; and your failure to obtain informed consent prior to involving subjects in research jeopardize the safety and welfare of subjects by denying them an opportunity to assess the risks and benefits of their participation in the clinical investigation.

5. **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)].**

   As clinical investigator, you were required to prepare and maintain adequate and accurate case histories that recorded 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 include case report forms and supporting data, including, for example, subject medical records and signed and dated informed consent forms.

   As discussed above, you enrolled two members of your study staff into your study under fictitious names. Thus, you did not maintain accurate case histories for these subjects because their medical records, case report forms, and informed consent forms contained false names.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational products. 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 asserts that you have failed to protect the rights, safety, and welfare of subjects under your care; repeatedly or deliberately submitted false information to the sponsor; and repeatedly or deliberately failed to comply with the cited regulations, which placed unnecessary risks to human subjects and jeopardized the integrity of data; and the FDA proposes that you be disqualified as a clinical investigator. You may reply to the above-stated issues, including an explanation of why you should remain eligible to receive investigational products 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 21 CFR 312.70.

Within fifteen (15) days of receipt of this letter, write or call me at 301-796-3150 to arrange a conference time or to indicate your intent to respond in writing.

Should you choose to respond in writing, your written response should be forwarded within thirty (30) days of receipt of this letter.

Your reply should be sent to:

Leslie K. Ball, M.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5342
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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, and a representative of your choice 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 products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

The FDA's Center for Drug Evaluation and Research (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 16 (enclosed) and 21 CFR 312.70. Before such a hearing, FDA will provide you with 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 free from bias or prejudice and who has not participated in this matter will conduct the hearing. Such a hearing will determine whether or not you will remain entitled to receive investigational products.

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.

To enter into the enclosed consent agreement with FDA, thereby terminating this disqualification process, you must:

(1) Initial and date each page of this Agreement,
(2) Sign and date the last page of this Agreement, and
(3) Return this Agreement initialed, signed, and dated to the signer below.

A copy of the fully executed Agreement will be mailed to you.

Sincerely yours,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosures:
#1 - Consent Agreement
#2 - 21 CFR 16
#3 - 21 CFR 312.70