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

David Craig Loucks, M.D.
14100 E. Arapahoe Road
Suite B370
Centennial, Colorado 80112

Dear Dr. Loucks:

Between April 15, 2008 and May 7, 2008, Ms. Linda M. Cherry, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of a clinical investigation entitled, (b) (4) ," of the investigational drug (b) (4) , performed for (b) (4)

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Ms. Cherry 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 June 4, 2008. We do not find your response to be acceptable in addressing the matters under complaint, which are described below.

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.

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 false information to the sponsor or the Agency in required reports [21 CFR 312.70(a)]. Specifically,**

   A number of study-specific documents were signed and/or initialed by persons other than you, using your name, as indicated by you during the FDA audit, conducted April 15, 2008 through May 7, 2008, and in your affidavit dated May 7, 2008. Your falsified signature was present on a Form FDA 1572 investigator statement for the (b) (4) protocol, and on protocol-specified laboratory reports/source documents, resulting in the appearance that you understood your responsibilities as a clinical investigator and that you evaluated subjects, directed or performed study-related procedures, and reviewed results of study-required laboratory tests. This Form FDA 1572 and the source documents and/or the information contained within them were submitted to the sponsor in support of the (b) (4) Study.

   For example,

   a. Your falsified signature was present on a Form FDA 1572 investigator statement for the (b) (4) protocol, signed and dated on August 22, 2006 by persons other than you, using your name. The Form FDA 1572 was then submitted by you to the sponsor, (b) (4) who in turn submitted your Form FDA 1572 investigator statement to FDA under an Investigational New Drug Application (IND).

   b. For Subject 5006, the following Blood Chemistry Laboratory Reports contained your falsified signature:

      i) Specimen collection date 9/22/06; report signed and dated on 9/25/06.
      ii) Specimen collection date 10/3/06; report signed and dated on 10/9/06.
      iii) Specimen collection date 10/12/06; report signed and dated on 10/20/06.
      iv) Specimen collection date 10/16/06; report signed and dated on 10/20/06.
      v) Specimen collection date 11/13/06; report signed and dated on 11/16/06.

   c. For Subject 5008, the following Hematology Laboratory Report and Nurse's Orders contained your falsified signature:

      i) Specimen collection date 10/10/06; report signed, but not dated.
      ii) Nurses orders – signed and dated 10/10/06.

d. For Subject 5014, the following Blood Chemistry Laboratory Report contained your falsified signature: Specimen collection date 10/10/06; report signed and dated on 10/13/06.

e. For Subject 5016, the following Laboratory Reports and Nurse's Orders contained your falsified signature:

i) Blood Chemistry Laboratory Report – specimen collection date 10/16/06; report signed and dated on 10/23/06.
ii) Nurse's Orders – signed and dated on 10/17/06.
iii) Blood Chemistry Laboratory Report – specimen collection date 11/27/06; report signed and dated on 11/30/06.

2. You failed to personally conduct or supervise the clinical investigation [21 CFR 312.60].

The required Investigator Statement Agreement (Form FDA 1572) for the above-referenced clinical investigation outlines the responsibilities of a clinical investigator at your site. Your general responsibilities (21 CFR 312.60) 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. Your responsibilities require that you personally conduct the clinical studies or supervise those aspects of the studies that you do 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 of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trial was conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protected the rights, safety, and welfare of human subjects.

We note that your failure to adequately supervise this study led to significant problems identified with the conduct of the study. For example,

a. A number of study-related documents were signed and/or initialed by persons other than you, using your name, as indicated by you during the FDA audit, conducted April 15, 2008 through May 7, 2008, and in your affidavit dated May 7, 2008. Your falsified signature was present on a Form FDA 1572, IRB correspondence, and subject informed-consent documents, resulting in the appearance that you adequately controlled and/or personally conducted the study, were aware of IRB correspondence content, and personally obtained informed consent from study subjects. For example,

i) Form FDA 1572 investigator statement for the (b) (4) protocol was signed and dated on August 22, 2006 by persons other than you, using your name. The Form FDA 1572 was then submitted by you to the sponsor, (b) (4)

who in turn submitted your Form FDA 1572 investigator statement to FDA under an Investigational New Drug Application (IND). The submission of this investigator statement led the Agency to believe that you understood your responsibilities as a clinical investigator, and that you were committed to conducting the study in accordance with the investigational plan and applicable regulations. You enrolled the first subject into the (b) (4) study on August 29, 2006.

ii) (b) (4) IRB *Application for a Protocol/Consent Form Amendment (Change) Addendum (New),* adding (b) (4) to the study, was signed and dated on 8/31/06.

iii) (b) (4) IRB *Application for Continuing Review* and the *Breakdown of Participants in Randomized Trials* were signed and dated on 2/1/07.

iv) Subject 5003 had a Serious Adverse Event, aspiration pneumonia, on 9/15/06. The SAE report to (b) (4) IRB was signed and dated on 1/29/07.

v) (b) (4) IRB *Summary Information Sheet* designating study sites was signed and dated 8/28/06.

vi) Informed Consent Forms for Subjects 5016 and 5018 were each signed and dated on 10/16/06.

b. You failed to ensure that protocol-specific assessment worksheets and source documents were reviewed by you or your delegate, evidenced by your signature and date contained on those documents, during the subjects' active treatment period (Day 1 to Day 12 ± 2), or during the subjects' study specified follow-up period (Day 13 ± 2 to Day 42 ± 5). Instead, for all 24 subject records audited by FDA, there was one or more instance in which the clinical assessment worksheets and/or source documents were not reviewed by you or your delegate until after the subject had completed the study, post Day 42 ± 5. For example,

i) For Subject 5002, Day 0 was on (b) (6) and Day 13 was on (b) (6); however, the worksheets/source documents associated with these study visits were not reviewed until 11/25/07.

ii) For Subject 5003, Day 0 was on 9/11/06; however, the Day 0 worksheet was not reviewed until 11/25/07.

iii) For Subject 5006, Day 0 was on (b) (6); however, the Day 0 worksheet was not reviewed until 11/25/07. Day 1 was on 10/3/06, but the worksheet was not reviewed until 3/3/08. Day 6 was on 10/12/06, but the worksheet was not reviewed until 3/30/07. Day 13 was on 10/16/06, but the worksheet was not reviewed until 3/3/08. Day 42 was on 11/13/06, but the worksheet was not reviewed until 3/3/08.

3. You failed to conduct the study or ensure it was conducted according to the investigational plan [21 CFR 312.60]. Specifically,

a. The protocol (b) (4) procedures require that on Day 0 (defined as up to 14 days prior to Day 1), the informed consent must be obtained by the investigator; a physical examination with assessment of vital signs must be done; medical history must be obtained; blood samples must be drawn for clinical chemistry, hematology, and coagulation parameters; and an ECG must be performed. Day 1 is defined as the day of surgery, on which additional clinical assessments are conducted prior to and after surgery. These procedures were not always followed. For example, of the 24 subjects audited at your site, 12 subjects had Day 0 procedures conducted on Day 1. For example,

i) For Subject 5002, Day 0 and Day 1 study procedures were done on the same day, (b) (6) . Day 0 study procedures conducted on (b) (6) included pre-operation procedures (beginning at 0640 AM), 12-lead ECG (0701 AM) and phlebotomy (0710 AM) for laboratory evaluations (hematology, chemistry, coagulation, and serology), obtaining informed consent and medical history, and conducting physical exams. Day 1 procedures included surgery, which was initiated at 0811 AM, with the time of anesthesia induction at 0738 AM.

ii) For Subject 5017, Day 0 and Day 1 procedures were done on the same day, (b) (6) . Day 0 procedures performed on Day 1 included obtaining informed consent (9:45 AM), the blood draws, which were done at 1015 AM for required labs (hematology, chemistry, coagulation, and serology), and ECG evaluation, which was done at 1038 AM. Day 1 procedures included surgery, which was initiated at 1111 AM, with the time of anesthesia induction at 1041 AM.

iii) For Subject 5019, Day 0 was on 11/1/06; however, blood samples for hematology were not collected and the ECG was not conducted until Day 1, on (b) (6) .

iv) Of the 24 subjects audited at your site, eight were consented on the day of surgery, Day 1. For example,

(1) Subject 5002 was admitted to the hospital for elective (b) (6) surgery on (b) (6) , with pre-operation procedures beginning at 0640 AM, including medical history and vital signs. The informed consent was signed by the subject on (b) (6) at 0645 AM, followed immediately by surgery, which was initiated at 0811 AM, with the time of anesthesia induction at 0738 AM.

(2) Subject 5086 was admitted to the hospital for elective (b) (6) surgery on (b) (6) , with study-specific pre-operation procedures beginning at 0941, including medical history and vital signs. The informed consent was signed by the subject on the day of surgery,

(b) (6) . Surgery was initiated at 1043, with the time of anesthesia induction at 1007.

b. The protocol specified that on Day 6, a physical examination with assessment of vital signs will be performed, and blood sampling for hematology, clinical chemistry, and coagulation parameters will be done for all subjects. The blood sampling for coagulation parameters will be done twice, shortly before intake of the study drug or placebo, and 2 to 4 hours after intake of the study drug or placebo. On Day 13, the protocol specified that a physical examination with assessment of vital signs will be performed, and blood sampling (taken before venography) for hematology, clinical chemistry, and coagulation parameters will be done for all subjects. A bilateral venography must be performed on Day 13, the day after the last intake of study medication. On Day 42 a final physical examination and assessment for DVT/PE must be conducted. For seven of the 24 subjects audited at your site, these procedures, as well as Day 0 procedures, were not always performed. For example,

i) For Subject 5007 and Subject 5008, Day 6 Coagulation Peak Samples (blood drawn 2-4 hours after subject ingests study tablet) were not collected. The corresponding Day 6 worksheet indicated that this blood sample was not drawn due to nursing error.

ii) For Subject 5014, Day 0 blood sample for hematology was not collected. Day 6 and Day 13 hematology samples were collected, but hematology was not done.

iii) For Subject 5024, Day 0 blood samples for chemistry, coagulation, and serology were not collected.

c. The Protocol (b) (4) required that severe adverse events (SAEs) be reported, in part according to local law and regulations, to the local Ethics Committee and regulatory authorities. According to the inspectional findings, you failed to report 12 SAEs to your local IRB (b) (4) IRB), in accordance with local requirements, within 48 hours for nonfatal SAEs or 24 hours for death. For example,

i) Subject 5003 developed aspiration pneumonia on 9/15/06; however, this SAE was not reported to the IRB until 1/29/07, four months later. In addition, as described above under item 2.a.iv, this SAE report was signed by a person other than you, using your name.

ii) Subject 5008 developed infrapopliteal deep-vein thrombosis on 10/20/06; however, this SAE was not reported until 6/19/07, eight months later.

iii) Subject 5061 developed severe confusion on March 15, 2008, according to the (b) (4) IRB SAE Report Form; however, this date is likely a transcription error, since the date of treatment was March 15-18, 2007; the SAE was reported on January 23, 2008, 10 months later.

4. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21 CFR 312.62(b)]. For example,

a. For seven of 24 subjects, laboratory records were missing from their record files. For example,

i) For Subject 5013, Day 6 hematology results were not in the subject binder. A (b) (4) -specific protocol deviation/waiver request form documented that Day 6 hematology results could not be found; however, the sampling request form indicated that the sample was collected on Day 6.

ii) For Subject 5015, Day 6 and Day 13 hematology results were not in the subject binder. However, Day 6 and Day 13 worksheets indicated that blood samples were collected for these tests.

iii) For Subject 5016, Day 6 and Day 13 hematology results were not in the subject binder. Day 6 and Day 13 worksheets indicate that blood samples were collected for these tests.

b. You failed to accurately document concomitant medications of subjects enrolled in the study. For example,

i) For Subject 5021, not all medications administered in the hospital were documented or reported to the Sponsor. (b) (4) discharge reports listed all medication given to the subject during the hospital stay. It listed, for example, hydrochlorothiazide, Quinapril, Clonazepam, and Oxycodone, all of which were administered to subject 5021 on November 9, 2006. However, these drugs were not listed on the subject's electronic Case Report Form (eCRF) or reported to the Sponsor.

ii) For Subject 5046, the concomitant medication Versed was listed on the concomitant medications worksheet for this subject but was not entered into the subject's eCRF or reported to the sponsor.

iii) For Subject 5023, not all medications administered in the hospital were documented or reported to the Sponsor. (b) (4) discharge reports listed all medication given to the subject during the hospital stay. They listed Docusate sodium and Oxycodone HCl; the anesthesiologist's orders included Meperidine (Demerol). However, these drugs were not listed on the concomitant medication worksheet or the eCRF.

c. The inspection revealed that the original six-page worksheet/source documents that captured the periodic assessments defined by the protocol by study day were destroyed. You indicated to the FDA field investigator that the study records for Subjects 5001-5018 had been "recopied" by the study coordinators, and that the original six-page worksheets/source documents had been destroyed. Without the

original worksheets/source documents, we are unable to verify the accuracy of the information for these 18 subjects.

d. Protocol deviation reports that were required to be maintained at the site were reportedly sent to the Sponsor's medical monitor and not retained at the site.

5. You failed to report promptly to the IRB all unanticipated problems involving risk to human subjects [21 CFR 312.66].

An investigator is required to promptly report to the IRB all unanticipated problems involving risk to human subjects, in accordance with 21 CFR 312.66. The (b) (4) Protocol describes anticipated problems involving risks to human subjects under section 7.0, Adverse Events, and refers to the (b) (4) Investigators Brochure for the known side-effect profile of the study drug. Neurological disorders such as severe confusion are not identified as known side effects for the study drug in the (b) (4) protocol or in the Investigators Brochure, Version 13, dated January 15, 2008. Subject 5061 developed severe confusion on March 15, 2008, according to the (b) (4) IRB SAE Report Form; however, this date is likely a transcription error, since the date of treatment was March 15-18, 2007. The SAE was reported to the (b) (4) IRB on January 23, 2008, 10 months later.

Per the report to the Center and your response letter, dated June 4, 2008, you concur with these observations. You stated that you take complete responsibility for the conduct of the study, but that the fault lies with your "unqualified study coordinators." You stated that you were not aware that your signature had been forged on study-related documents until November 2007. You stated, "… in retrospect I did not fulfill my commitments as outlined in the Form FDA 1572." Your written response, dated June 4, 2008, offered no detailed corrective action plan.

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 must be forwarded within thirty (30) days of receipt of this letter.

Your reply should be sent to:

Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 51, Rm. 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 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.

Sincerely yours,

{See appended electronic signature page}

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

Enclosures:
Consent Agreement
21 CFR 312.70
21 CFR 312.60
21 CFR 50
21 CFR 56
21 CFR 16

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

/s/

LESLIE K BALL
08/18/2009