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

Amy Holmes, M.D.
(b) (6)

Dear Dr. Holmes:

Between March 24 and April 8, 2008, Ms. Dana Daigle, representing the Food and Drug Administration (FDA), conducted an investigation and met with you via telephone to review your conduct of a clinical investigation (Protocol (b) (4), 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. Daigle 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 the April 22, 2008, written response of Mr. David Deshotels, president of Gulf Coast Research Associates, Inc., to the Form FDA 483. We do not find the April 22, 2008 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 (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 false information to the sponsor in a required report [21 CFR 312.70(a)].**

   Based on information obtained from the inspection, entries in case report forms (CRFs) appear to have been falsified.

   Protocol (b) (4), dated September 14, 2004, stated, "Study drug will be administered i.v. [intravenously] by qualified staff[,] and details of each administration will be recorded in the CRF." The April 2005 edition of the sponsor newsletter addressed self-administration of study drug in the patient's home. In the question-and-answer section of the newsletter, one of the questions read, "Is self-administration of study drugs in the patient's home permitted?" The response to the question read: "No, only Home-Care Agencies can administer the study-drugs in a patient's home." In a letter dated April 7, 2005, (b) (4), the contract research organization (CRO), stated that any outpatient-dosing plan requiring subjects to self-administer any dose at home without research staff or a visiting nurse was no longer acceptable. This decision resulted in the cessation of enrollment at your site.

   On April 8, 2005, you submitted a document summarizing your outpatient treatment procedures to the sponsor, in which you indicated that nursing personnel administered medication to subjects every 12 hours according to protocol guidelines. In an e-mail to (b) (4) and the sponsor dated April 11, 2005, you provided a detailed version of your outpatient treatment plan. An April 27, 2005, document entitled "Re: Outpatient Treatment Procedures," stated that "All study subjects treated on an outpatient basis are administered study drug in our designated 'infusion center' under the supervision of our qualified study team." This document further described the details of your outpatient treatment procedures, noting that study personnel who administered medication also performed wound assessment and documented the temperature of the study drug, the time and completion of dosing, and any adverse events. Following review of your outpatient treatment plan, the sponsor permitted you to resume enrollment on April 27, 2005. Nonetheless, subjects enrolled after this date continued to self-administer IV study drug in their homes, evidently without supervision by study personnel, even though on-site study records, including CRFs, documented that the medications were administered by study personnel. For example:

   a. Subject 1206 was enrolled in the study on April 28, 2005. Subject 1206's "Daily IV Infusion Log/Notes CRF" contains entries dated from April 28 to May 5, 2005, indicating that the study medication was administered by one of the clinical research coordinators (CRCs). However, the inspection revealed that study drug was delivered to the subject's residence and stored in her refrigerator until her spouse administered it.

   b. Subject 2275 was enrolled in the study on July 19, 2005, along with her daughter, Subject 2274. Both subjects resided at the same address. The "Daily IV Infusion Log/Notes CRF" contains entries for both subjects, dated from July 19 to 26, 2005. Many entries state, "CRC to pt's home to administer study drug to pt." However, the inspection revealed that a study coordinator or other employee

delivered the drug to the subjects' home, and that both subjects self-administered the study medication.

In the written response dated April 22, 2008, Mr. David Deshotels, speaking on your behalf, stated, "Prior to conducting the (b) (4) Protocol, the Principal Investigator made it clear to the CRO, ((b) (4)) and the Sponsor, ((b) (4)), that the standard of practice in our area (Louisiana) has moved to outpatient therapy for patients who are diagnosed with (b) (4)]." Mr. Deshotels also stated, "The first protocol amendment, (b) (4), INT-1, stated that 'Patients may receive study drug infusions as inpatients, outpatients, or through a home-care agency.' All subjects were enrolled after this amendment."

We note that protocol amendment (b) (4), INT-1, dated September 14, 2004, expressly permitted outpatient administration of study medication, but it did not permit self-administration. In addition, a document entitled "(b) (4): (b) (4) Study, Outpatient Study Drug Procedure" (final version dated May 25, 2005) expressly stated, "Note: patient self-administering of study medication is not allowed." Furthermore, we note that the April 22, 2008 written response did not address the false information contained in your CRFs which indicated that subjects received study medication from study personnel when that was not the case.

Not only does the finding above compromise the reliability of data captured at your site, but it 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 fact that false information was submitted to the sponsor.

2. **You failed to protect the rights, safety, and welfare of subjects under your care [21 CFR 312.60].**

Your general responsibilities as a clinical investigator included protecting the rights, safety, and welfare of subjects under your care. The practice of permitting subjects to self-administer IV medication in their homes without appropriate supervision by a qualified health professional, which was in direct violation of the protocol and your written outpatient treatment procedure, had the potential to expose subjects to serious harm.

3. **You failed to obtain IRB approval before making changes in the research [21 CFR 312.66].**

Protocol (b) (4) did not allow the self-administration of IV study medication by subjects in their homes. At your site, at least 12 of the 26 study subjects performed IV self-administration of the study medication in their homes, evidently without the supervision of study personnel. According to longhand notations on source documents for the baseline (pre-dose) study visit, Subjects 1009, 1010, 1011, 1014, 1037, 1039, 1041, 1043, 1186, and 1187 were instructed to self-administer

medication in their homes. A Self Administration case report form for Subject 1036 documents that the study medication "was self-administered by pt. [patient] twice a day." For Subject 1038, a home care infusion worksheet documents that the subject received instruction on the proper technique for self-administration of IV medication. However, there is no documentation that a change to the research activity for these subjects was ever submitted to the IRB for approval.

The inspection did not find any evidence that you informed the CRO or the sponsor that subjects would be self-administering study medication, nor was there any evidence that this practice was presented to and approved by the IRB. In fact, in the documents you submitted to the CRO and the sponsor detailing your outpatient treatment procedures, you indicated that either the nurse coordinator or a home health nurse visited subjects' homes and administered each dose. As noted in item 1 above, protocol amendment (b) (4), INT-1, dated September 14, 2004, expressly permitted outpatient administration of study medication, but it did not permit self-administration.

We emphasize that self-administration of IV study drug by subjects in their homes without supervision by a qualified individual had the potential to result in serious harm. Your failure to notify the IRB of this change in research activity raises significant concerns regarding the adequacy of human subject protections at your site and your commitment to conduct the study in accordance with the protocol.

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

   a. For Subject 1010, there is no explanation given for the removal of all documentation of a concomitant medication from the study records. A March 22, 2005, physician's progress note, dictated one day prior to the Test of Cure (TOC) visit on March 23, 2005, indicated that the subject was prescribed Levofloxacin for the treatment of a leg wound other than the study wound. Following a query from the monitor, documentation of this medication was removed from the study records without explanation.

   b. For Subject 1123, study documents contain conflicting information regarding a diagnosis of osteomyelitis, which was an exclusionary condition. A progress note dictated by a sub-investigator on April 25, 2005, five days after the TOC visit, indicated that the subject returned for "further evaluation and treatment of his right foot wound and his chronic refractory osteomyelitis." However, written at the bottom of the typed progress note and signed by the same sub-investigator is the phrase, "osteomyelitis not confirmed."

c. For Subject 1206, study documents contain conflicting information regarding the cause of the study wound. In the Protocol Waiver (Exception) Request Form dated April 27, 2005, the wound is described as a postoperative wound to the left lateral hip, whereas on the Baseline/Pre-dose Visit source document dated April 28, 2005, longhand notations document the wound to be a result of trauma to the left lateral side of the back from hitting the edge of a door.

d. For Subject 2274, study records contain inconsistent descriptive characteristics for the primary infection site. Documentation for the End of Treatment (EOT) visit includes conflicting information; the maximum dimension of inflammation is recorded as 1 mm by 0 mm on an EOT source document dated July 26, 2005, whereas an undated EOT CRF documents the maximum dimension of inflammation as 80 mm by 95 mm.

e. Identical Protocol Waiver (Exception) Request Forms stating, "Subject has a diabetic ulcer of the right foot," were apparently placed in the records of three different subjects (*viz*., Subjects 2672, 2673, and 2674). The forms appear to be the same except for a longhand notation in parentheses indicating the subject number ["(2672)," "(2673)," or "(2674)"], written next to the typewritten "Patient Number 140001." There was no documentation explaining why the same study record was labeled with three different handwritten subject numbers and located in these three subjects' records. The subjects' other study documents describe their wounds as an abscess on the right upper leg (Subject 2672), an abscess of the left thigh (Subject 2673), and an abscess of the left upper leg (Subject 2674).

In the April 22, 2008 written response, Mr. Deshotels stated that "subjects were evaluated at each visit by the Investigator(s), and that the coordinator or investigator recorded the necessary evaluations[,] and there is source documentation of investigator participation or knowledge of every visit and evaluation because of notes and signatures." This response is not acceptable. No documentation of this information was available on-site at the time of the inspection, and no documentation accompanied the written response.

The findings above compromise both the interpretation of and the validity of clinical data captured at your site.

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.
Director
Division 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 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.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

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

Cc:

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
12/02/2010