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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Jamie Kapner, M.D.
Scottsdale Reproductive and Urological Associates
10250 North 92nd Street, Suite 100
Scottsdale, Arizona 85258

Dear Dr. Kapner:

Between February 16 and April 6, 2005, Mr. Charles Larson and Ms. Tonia Sawyer, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of the following clinical investigations:

Protocol (b) (4), "A Multicenter, Randomized, Double-Blind, Parallel Group Trial to Demonstrate the Efficacy of Fondaparinux Sodium in Association with Intermittent Pneumatic Compression Used Alone for the Prevention of Venous Thromboembolic Events in High Risk Patients Undergoing Major Abdominal Surgery" performed for (b) (4).

Protocol (b) (4), "A Double-Blind, Placebo Controlled, Multicenter Study to Evaluate the Effects of (b) (4) in Decreasing the Risk of (b) (4) Cancer (b) (4) Study)" 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.

Based on our evaluation of information obtained by the Agency, and your April 18, 2005, letter in response to FDA's inspectional observations, we believe that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational new drugs and the protection of human subjects, as published under Title 21, Code of Federal Regulations (CFR), Parts 312, 50, and 56 (copies 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 FAILED TO PERSONALLY CONDUCT OR SUPERVISE THE CLINICAL INVESTIGATION [21 CFR 312.60].

When you signed the investigator statement (Form FDA 1572) for the above referenced clinical investigations, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities include ensuring that an 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. You specifically agreed to personally conduct the clinical studies or to supervise those aspects of the studies that you did 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 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.

a. You delegated certain tasks to an individual who was not qualified to perform such tasks.

Ms. (b)(6) served as study coordinator for the above referenced clinical investigations. In your April 18, 2005 letter to FDA you stated that Ms. (b)(6) had performed several previous studies; had been trained by the (b)(4), a study management organization; and had attended educational conferences with respect to her role as study coordinator. According to study records, Ms. (b)(6) performed study related tasks such as dispensing study medication to the nursing floor, and for Protocol # (b)(4), administering study medication by subcutaneous injection directly to hospitalized subjects. Study records also indicate that Ms. (b)(6) represented herself as a licensed practical nurse (LPN) or a registered nurse (RN).

Our investigation found, however, that Ms. (b)(6) was not qualified to perform many of these study-related activities because she was not a licensed nurse and she was not a credentialed staff member at the hospital. It is FDA' s understanding that Ms. (b)(6) received a "Cease and Desist" letter from the Arizona Board of Nursing on (b)(6), after it was reported that Ms. (b)(6) had represented herself to patients and others as a licensed nurse. The Arizona Board of Nursing found that Ms. (b)(6) is not licensed as a nurse, nor has she completed a nursing diploma or degree program. In addition, according to Ms. (b)(6), Pharmacist Supervisor at Scottsdale Healthcare Shea where the study was conducted, Ms. (b)(6) was not permitted to administer medication to hospitalized subjects because she was not credentialed by the hospital.

If you choose to delegate study tasks, it is your responsibility to delegate to qualified individuals by assessing their credentials and assertions and to make sure they are specifically qualified to perform the various study tasks.

b. You did not personally supervise the clinical investigations.

You told the FDA inspectors during the inspection, and reiterated in your letter of April 18, 2005, that you relied upon Ms. (b) (6) to maintain study records and letters of correspondence with the Institutional Review Board (IRB) and (b) (4), and to perform administrative tasks such as obtaining and maintaining IRB approval. You indicated in your April 18, 2005 letter that you relied upon hospital personnel such as pharmacists and nursing staff to ensure that the study drug was received and dispensed appropriately, and stated "I do not know what was done in the pharmacy at the hospital" and "I did not personally supervise the nurses on the floor as to whether they signed off on these injections or not." Further, in your April 18, 2005 letter you stated that you relied upon (b) (4), the sponsor, the study monitor, the IRB, and the study coordinator to make you aware of any problems with the study.

Not withstanding any delegation of responsibilities, it is your responsibility as clinical investigator to personally conduct the clinical investigation or supervise those aspects you do not conduct, and to ensure compliance with applicable FDA regulations.

Your lack of supervision and personal involvement, and inappropriate delegation of study tasks resulted in a failure to obtain informed consent appropriately, failure to promptly report to the IRB, failure to maintain adequate drug disposition records, failure to maintain adequate drug disposition records, failure to maintain adequate and accurate case histories, and failure to follow the investigational plan as described below.

2. YOU FAILED TO OBTAIN INFORMED CONSENT IN ACCORDANCE WITH 21 PART 50 FROM EACH HUMAN SUBJECT PRIOR TO CONDUCTING STUDY RELATED ACTIVITIES [21 CFR 50.20, 312.60].

For Protocol # (b) (4), study records indicate that Subject (b) (6) was enrolled on April 24, 2004, had surgery performed on April 27, 2004, and began study procedures on the same day as the surgery. However, the informed consent document (ICD) that the subject signed agreeing to participate is dated June 7, 2004.

3. YOU FAILED TO PROMPTLY REPORT TO THE IRB ALL CHANGES IN THE RESEARCH ACTIVITY AND ALL UNANTICIPATED PROBLEMS INVOLVING RISKS TO HUMAN SUBJECTS; AND YOU FAILED TO OBTAIN IRB APPROVAL BEFORE MAKING ANY CHANGES IN THE RESEARCH [21 CFR 312.66].

a. According to the informed consent document dated January 29, 2002 and revised March 28, 2002, your site was approved to enroll 10-15 study subjects. Over the course of the following two years, you enrolled one hundred thirty-one (131) subjects; however, you did not receive IRB approval for this large increase in the number of subjects

enrolled. Amendment #2, dated September 30, 2003 describes the sponsor's intention to increase the number of subjects enrolled nationwide. This amendment was not submitted to the IRB until May 10, 2004, and did not refer to a specific increase in enrollment for your site in particular.

The response in your April 18, 2005 letter with regard to this issue is unacceptable. As the clinical investigator of the of the clinical investigation, it is your responsibility to make sure all regulatory requirements are met. The fact that no one made you aware of any problems in terms of your exceeding the enrollment limit for your study does not absolve you of your responsibilities.

b. Study records document that the inclusion criteria for Protocol (b) (4), Amendment #2, dated September 30, 2003, was changed to read : "epidural catheter not planned to be removed within 6 hours post surgical closure". This amendment increased the allowable time an epidural catheter was permitted to remain in place from 2 hours to 6 hours post surgical closure, which might have affected subjects' willingness to participate. This amendment was not submitted to the IRB until May 10, 2004, well after the change was implemented, and the ICD was not altered to reflect such a change.

c. You did not report all unanticipated problems involving risks to human subjects (adverse events) to the IRB in a timely manner. According to the FDA investigators, and the IRB coordinator, Ms. (b) (6), you did not submit any adverse event (AE) reports to the IRB from October 2002 to March 2004. On May 7, 2004 you submitted thirteen AE reports documenting adverse events and serious adverse events that occurred from 2002 to 2004. For example, Subject (b) (6) developed a bowel obstruction requiring surgical intervention on May 18, 2003. The event was not reported to the IRB until May 7, 2004, almost one year later. Subject (b) (6) experienced acute renal failure in the immediate post-operative period, starting June 13, 2002. This serious adverse event was not reported to the IRB until May 10, 2004, almost two years later. You admit in your letter of April 18, 2005 that the "adverse event forms obviously should have been submitted..." and were not.

4. YOU FAILED TO MAINTAIN ADEQUATE RECORDS OF THE DISPOSITION OF THE DRUG, INCLUDING DATES, QUANTITY AND USE BY SUBJECTS [21 CFR 312.62(a)].

For Protocol (b) (4) there were numerous record keeping discrepancies between the Investigational Product Shipping Orders (IPSO2), the Pharmacy Services Department Investigational Drug Individual Patient Dispensing Records (IDIPDR), the Medication Administration Records (MARs), and the subjects' individual medical records, making it difficult to ascertain the amount of study drug received from the sponsor, dispensed from the pharmacy, and administered to study subjects. Furthermore, records documenting the number and disposition of subjects screened and randomized contain conflicting information. For example,

a. The IDIPDR for Subject 002 showed that two syringes were dispensed on May 21, 2002 and two more were dispensed on May 23, 2002, while the Subject

Dispensing Record CRF for this subject showed that 10 syringes were dispensed on May 21, 2002, and that one syringe was dispensed on each of the next seven days, and that two syringes were returned. Each of the entries on the CRF was crossed out with a notation that reads: "completed in error".

b. The IDIPDR for Subject (b) (6) showed that eight syringes were dispensed on June 5, 2002 and that one syringe was used on each of the next five days, and that three syringes were "returned to (b) (6) " on June 12, 2002. The Subject Dispensing Record CRF for this subject shows that 10 syringes were dispensed on June 5, 2002, seven were used on unspecified dates, and three were returned on an unspecified date.

c. Subject (b) (6) was admitted to the hospital August 12, 2003 for surgical treatment. According to the Subject Dispensing Record for this subject, 10 syringes of fondaparinux/placebo were dispensed on August 12, 2003 at an unspecified time. According to the hospital Medication Administration Record, the subject received the first dose of fondaparinux/placebo on August 12, 2003 at 2106 hours. The next medication administration occurred on August 13, 2003. The entry at 1900 hours reads: "given by (b) (6) ". The entry does not contain the full signature or initials of the individual administering the medication. Furthermore, as discussed previously, (b) (6) , the study coordinator, was not authorized by the hospital to administer medication to hospitalized subjects.

You admit in your letter of April 18, 2005 that you "were unable to reconcile the number of treatment kits from the sponsor" and that you "did not personally supervise the nurses on the floor as to whether they signed off on the injections or not." As the clinical investigator it is your responsibility to maintain accurate records regarding drug disposition.

5. YOU FAILED TO PREPARE AND MAINTAIN ADEQUATE AND ACCURATE CASE HISTORIES. [21CFR 312.62(b)]

The Screening Log shows 144 subjects were screened, and 126 randomized, while the subject Tracking Form shows 131 subjects randomized. An undated and incomplete memo from you to (b) (6) , Chairman of the IRB, states that "local enrollment changed from about 10-15 subjects to about 130 subjects." A handwritten message appended to that document reads: "Screened = 198, Randomized = 131, Completed = 129, Follow/up 0 study drug = 1, Withdrew/d/c prematurely = 3".

You state in your letter of April 18, 2005 that you do not know the exact number of patients who signed a consent form to participate but who failed screening and that such information was never made available to you. It is your responsibility to maintain accurate case histories and this includes the number of subjects who agree to participate in the study, are screened and are randomized.

6. YOU FAILED TO FOLLOW THE INVESTIGATIONAL PLAN [21 CFR 312.60].

For Protocol (b) (4) , Subjects (b) (6) did not receive standard physical exams at Visit 1 as required by the protocol.

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 repeatedly or deliberately failed to comply with the requirements of 21 CFR Part 312, Part 50, or Part 56, 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 at 21 CFR 312.70.

Within fifteen (15) days of receipt of this letter, write or call me at (301) 594-0020 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:

Gary Della'Zanna, D.O., M.Sc., Director
Division of Scientific Investigations, HFD-45
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
7520 Standish Place, Room # 103
Rockville, Maryland 20855

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.

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,

Gary Della'Zanna, D.O., M.Sc., Director
Division of Scientific Investigations, HFD-45
Office of Compliance
Center for Drug Evaluation and Research

Enclosures:
1. Consent Agreement
2. 21 CFR 16
3. 21 CFR Part 312
4. 21 CFR Part 50
5. 21 CFR Part 56
6. FDA Form 483

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

/s/

Gary DellaZanna
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