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

Miguel Zabalgoitia, M.D.
Prairie Cardiovascular
619 East Mason Street, Suite 4B57
Springfield, Illinois 62701

Dear Dr. Zabalgoitia:

Between July 24, 2007 and September 11, 2007, Mr. Joel Martinez, representing the Food and Drug Administration (FDA), conducted an investigation and met with you and your staff, to review your conduct of a clinical investigation of the following protocols:

- **Protocol** (b) (4) : (b) (4) , performed for (b) (4)
- **Protocol** (b) (4) : (b) (4) performed for (b) (4)
- **Protocol** (b) (4) : (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, Mr. Martinez 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 responses to

the Form FDA 483 dated October 22, 2007. We do not find your response, including your proposed corrective actions, to be acceptable in addressing the matters under complaint, which are described below, and to prevent similar violations from recurring in future studies.

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)].**

   Our investigation found that for Protocol AI-700-33 and Protocol (b) (4), physical examinations were conducted on study subjects and medical orders/progress notes were entered with your signature while you were out of town. You admitted that you did not have access to a virtual private network (VPN) that would allow you remote access to study records for signature. This was confirmed by an email from Dr. (b) (6), Associate Chief of Staff of Research and Development, (b) (4). Specifically,

   Protocol AI-700-33

   a. An American Airlines (AA) passenger itinerary obtained at your site, documented your flight from San Antonio to Dallas and then to your final destination of San Juan, Puerto Rico on 9/7/05 at approximately 7:40 am. The itinerary further showed your return flight to San Antonio occurred on 9/10/05 at approximately 7:09 pm. However,

      i. Source documents for Subject 49-055 indicate through your signature that you performed a discharge physical exam on 9/8/05 and performed the 72-hour follow-up physical exam on 9/9/05. An (b) (4) computerized patient recording system (CPRS) documented that progress notes were written and entered into the CPRS on 9/7/05 at 15:58 (3:58 pm) and were electronically signed by you on 9/7/05 at 15:59 (3:59 pm).

      ii. The (b) (4) CPRS documented that progress notes were written for Subject 49-057 on 9/8/05 and were electronically signed by you on 9/8/05 at 15:51 (3:51 pm).

iii. Medical Order Details records documented that you wrote and entered orders on 9/7/05 at 15:59 (3:59 pm) for Subject 49-055 and 9/8/05 at 16:13 (4:13 pm) for Subject 49-057.

b. An AA passenger itinerary documented your flight AA 1049 from San Antonio, TX to Dallas, TX on 1/10/06 at approximately 2:35 pm and on to Los Angeles, CA. You then returned to San Antonio on 1/11/06.

i. The (b) (4) CPRS documented that progress notes were written for Subject 49-084 stating, "He tolerated the procedures well. A physical exam and safety labs were collected prior to discharge from the research clinic." This progress note was electronically signed by you on 1/10/06 at 15:23 (3:23 pm).

ii. The (b) (4) CPRS medical record documented that progress notes were written for Subject 49-085 and entered into CPRS on 1/10/06 using your code and electronically signed by you at 15:24 (3:24 pm).

c. A hotel receipt from Fiesta Americana Guadalajara documented your stay in the hotel from 3/31/05 through 4/3/05. However, medical orders from CPRS for Subject 49-026 indicated that you electronically signed these orders on 4/1/05 at 11:08 am.

Protocol (b) (4)

d. A Chicago Marriott Downtown guest folio indicated that you arrived on 10/19/03 at 13:53 (1:53 pm) and departed on 10/20/03 at 10:05 am. However, a CPRS Medical Order Details record documented for Subject 158011, a "New Order entered by ZABALGOITIA, MIGUEL (PHYSICIAN)" on 10/20/03, 10:52 am, and electronically signed by you at 10:53 am.

e. An AA passenger receipt documented your flight from San Antonio, TX to Dallas, TX and then to Guadalajara, Mexico on 9/25/03. The AA passenger receipt further shows your return flight to San Antonio, TX on 9/28/03. However, a CPRS Medical Order Details record documented for Subject 158012 that new orders were entered on 9/26/03 by you and that you electronically signed the orders on 9/26/03 at 16:14, (4:14 pm).

Based on this evidence, medical orders and progress notes were written and entered into the (b) (4) CPRS under your name and electronically signed by others using your passcode for at least 5 subjects in Protocol (b) (4) and 2 subjects in Protocol (b) (4). During the investigation, you explained to our investigator that you authorized your assistants (Drs. (b) (6) and (b) (6)) to enter "routine things" on your behalf. You further stated that Drs. (b) (6) and (b) (6) were using your electronic signature code to enter and sign notes, something you later acknowledged was not authorized.

In your written response dated October 22, 2007, you claim that it was not your intention to give a misimpression, but you believed this was within the scope of

allowable actions. You further stated that your assistants "were used as extenders for administrative expediency" in the research. You instructed them to enter progress notes in the CPRS so you could later access the computer, review their entries, and sign off and that they were not authorized to use your signature code. Your explanations provided during the inspection and in your written response are unacceptable. When asked if you had access to a VPN that would allow you to access the CPRS while on travel, you stated that you did not. Therefore, it is not possible that you reviewed and signed off on entries into the CPRS system when you were not physically present at the (b) hospital. The use of your signature on medical orders and progress notes that you did not enter or review constitutes the submission of false information.

It is noted that under a separate investigation conducted by the (b) hospital, you admitted that you released your username and password to your assistants, contrary to the institution's policy. In addition, you claimed that you did not knowingly release your signature authority. However, we note that on December 6, 2006, you received a five day suspension for the improper use of your security password.

2. **You failed to conduct the investigation according to the signed investigator statement and to adequately supervise the clinical investigations [21 CFR 312.60].**

When you signed the Statement of Investigator, Form FDA 1572, you agreed to take responsibility for the conduct of the clinical investigation at your site. You specifically agreed to personally conduct the clinical investigation or to supervise those aspects of the clinical investigation that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as clinical investigator you many 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 protects the rights, safety and welfare of human subjects. Specifically,

a. You failed to adequately supervise individuals to whom you delegated study tasks.

As noted in item 1 above, our investigation determined that you were not present at the clinical trial site when physical examinations were conducted. These examinations were conducted by your research assistant, Dr. (b) (6), who is not licensed to practice medicine in the United States and whose J-1 Visa, according to your written statement of 10/2/07, only allowed him to have "incidental patient contact" under your supervision. You stated that you had direct supervision of his physical examinations. As noted in item 1 above, physical examinations were conducted by Dr. (b) (6) while you were on travel; therefore, you were unable to provide direct supervision.

In your 10/22/07 response, you state that Dr. (b) (6) was never allowed to exercise independent medical judgment and that the physical examination

pertinent to research was not intended to change diagnosis or to establish treatment. This response is inadequate. As noted in item 1 above, Dr. (b) (6) signed off on physical examinations, medical orders, and progress notes for subjects as if he did have medical authority.

b. You delegated certain tasks to individuals not qualified to perform such tasks.

Our investigation determined that when you were not present at the site, you delegated conduct of the trial, including conducting physical examinations and writing medical orders and progress notes to persons who were not qualified to perform these tasks. Specifically, our investigation found that for Protocol CSP 127-006, Dr (b) (6) performed physical examinations on at least 109 of the 116 subjects. Dr. (b) (6), who you describe as "a graduated physician from El Salvador" was, as noted above, in the United States on a J-1 Visa that only allowed him to have "incidental patient contact" under your supervision. Therefore, Dr. (b) (6) was not qualified to conduct physical examinations, write medical orders or progress notes.

In your 10/22/07 response, you state that Dr. (b) (6) completed three years of cardiology training in Mexico and that you felt comfortable with his skills, approach, and findings. However, this does not address the fact you delegated performing physical examinations, writing medical orders and progress notes to an individual who was not qualified to do so.

3. You failed to conduct the studies or ensure the studies were conducted according to the investigational plan [21 CFR 312.60].

Our investigation determined that study procedures were reviewed and assessed by individuals not listed on the Form FDA 1572. Specifically,

Protocol AI-700-33

a. For Subjects 49-054 and 49-100, the readers for the coronary angiogram-left ventriculography (ANGIO-LVG) were (b) (6) and (b) (6), respectively; however, these individuals were not listed on the Form FDA 1572 as sub-investigators.

Protocol CSP 127-006

b. For Subjects 21604, 21640, 21641 and 21649, (b) (6) signed the Physical Examination Form for Study Day 2; however, she was not listed on the Form FDA 1572 as a sub-investigator.

Your 10/22/07 response is inadequate. Your response discusses including the initials of the doctor who reviews the angiogram on the CRF, but does not address the failure to list sub-investigators on the Form FDA 1572.

4. You failed to maintain adequate and accurate drug disposition records [21 CFR 312.62(a)].

Protocol AI-700-33

a. Our investigation found that the (b) (4) and (b) (4) Packing Lists for Lot (b) (4) documented the receipt of 174 vials. Specifically, (b) (4) Nuclear Medicine Pharmacy records accounted for 144 vials for Subjects 49-024 through 49-098; however, there is no usage record for Subjects 49-096 through 49-101.

b. Our investigation found discrepancies between the (b) (4) Nuclear Medicine Pharmacy Records and the Study Regulatory Binder. Specifically, the study Regulatory Binder records accounted for 151 vials; however, there is no usage record for Subjects 49-069 through 49-075 and 49-099 through 49-101 in the (b) (4) Nuclear Medicine Pharmacy Records, leaving 8 vials unaccounted.

c. Our investigation found discrepancies between what was recorded on the vial label, the (b) (4) and the corresponding case report form (CRF). For example,

Subject	CRF	(b) (4)	Vial Labeling
49-027	27.5	25	25 (Image Session II)
49-059	26	No (b) (4)	25 (Image Session I)
49-059	28	No (b) (4)	25 (Image Session II)
49-100	31.3	35.3	35.3 (Image Session I)

Your 10/22/07 response is inadequate. You provided a copy of a drug accountability record for lots (b) (4) and (b) (4). However, you do not address any of the discrepancies described above.

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

Protocol (b) (4)

Our investigation found that three subjects' hospitalizations were not promptly reported to the IRB. For example,

a. Subject 158001 was hospitalized with unstable angina on 12/23/02; however, this was not reported to the IRB until 2/21/03.

b. Subject 158002 was hospitalized with respiratory distress and somnolence on 10/17/05; however, this was not reported to the IRB until 12/28/05.

We note that in your 10/22/07 response you stated that in your view, the subjects' hospitalizations were unrelated to the study, but that does not obviate your duty to promptly report any hospital admission as a serious adverse event to the IRB.

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.

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.

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. To enter into this agreement, 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 signature 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

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
06/08/2009