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

Peggy Ann Garjian, M.D.
458 Bay Ridge Parkway
Brooklyn, NY 11209

Dear Dr. Garjian:

Between January 22 and February 25, 2008, Dr. Alia Legaux, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol (b) (4) entitled "Rheumatoid Arthritis DMARD Intervention and Utilization Study [RADIUS 2]") of the investigational drug Enbrel® (etanercept), performed for Immunex Corporation. Protocol (b) (4) entitled "Rheumatoid Arthritis Disease Modifying Anti-Rheumatic Drug (DMARD) Intervention and Utilization Study (RADIUS 1)" was also reviewed. However, we note that the RADIUS 1 study was not conducted under an investigational new drug application (IND).

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, Dr. Legaux presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We have reviewed the inspection report and the documents submitted with that report.

Based on our evaluation of information obtained by FDA's Center for Drug Evaluation and Research (CDER), we believe that you have 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), Parts 50 and 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 Part 312.

A listing of the violations pertaining to your conduct of protocol 016.0035 follows. The applicable provisions of the CFR are cited for each violation.

1. **You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].**

   Protocol (b) (4) requires that subjects who are currently or have been previously enrolled in RADIUS 1 (protocol (b) (4)) be excluded from the study. However, you enrolled subjects in protocol (b) (4) although the subjects were currently or previously enrolled in protocol (b) (4) . Examples include, but are not limited to, the following:

Subject's Initials	Protocol	Subject Number	Date Enrolled
(b) (6)	(b) (4)	(b) (6)	11/26/2002
	(b) (4)	(b) (6)	3/27/2002
(b) (6)	(b) (4)	(b) (6)	11/25/2002
	(b) (4)	(b) (6)	4/20/2002
(b) (6)	(b) (4)	(b) (6)	10/30/2002
	(b) (4)	(b) (6)	4/19/2002
(b) (6)	(b) (4)	(b) (6)	10/24/2002
	(b) (4)	(b) (6)	4/18/2002
(b) (6)	(b) (4)	(b) (6)	11/26/2002
	(b) (4)	(b) (6)	3/14/2002
(b) (6)	(b) (4)	(b) (6)	12/16/2002
	(b) (4)	(b) (6)	7/15/2002

   During the inspection you informed the FDA investigator that you were given verbal permission from the sponsor to enroll subjects in protocol (b) (4) although the subjects were currently or previously enrolled in protocol (b) (4) . You did not have any documentation of this communication with the sponsor.

2. **You failed to promptly report to the institutional review board (IRB) all changes in research activity and you made changes in research activities without IRB approval [21 CFR 312.66].**

   21 CFR 312.66 requires, in part, that an investigator assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. The change in research activities mentioned in item 1 above was not reviewed and approved by the IRB.

3. **You failed to obtain or document that informed consent was obtained from subjects [21 CFR 50.20 and 21 CFR 50.27(a)].**

21 CFR 50.20 requires that except as provided in sections 50.23 and 50.24, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. In addition, the FDA regulations require that, except as provided in section 56.109(c), informed consent be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent [21 CFR 50.27(a)].

a. There were no informed consent documents on file for subjects (b) (6) to indicate that you obtained informed consent from these subjects prior to their enrollment in the study.
b. Subject (b) (6) was enrolled on 11/4/02, but did not sign the informed consent document until 11/8/02.
c. The following subjects signed a consent form that was not approved by the IRB:

Subject Number	Date Signed
(b) (6)	December 16, 2002
(b) (6)	June 4, 2003
(b) (6)	June 2, 2003
(b) (6)	January 1, 2003
(b) (6)	May 16, 2003
(b) (6)	May 19, 2003

During the inspection, you told the FDA investigator that, during the sponsor's visits, all informed consent documents were verified. You stated that you did not know what happened to the missing consent forms. As the clinical investigator, it is your responsibility to obtain, and maintain documentation of, informed consent.

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)].**

Specifically, the Investigational Drug Accountability logs are incomplete in that between October 18, 2002, and December 23, 2002, the quantity of products returned was not consistently documented on the logs.

During the inspection you told the FDA investigator that the study nurse was responsible for completing the Investigational Drug Accountability log and that you never review the logs. As the clinical investigator, you are responsible for maintaining adequate drug accountability records.

5. **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)].**

   a. Protocol (b) (4) requires that subjects meet the 1987 American Rheumatism Association (now American College of Rheumatology) criteria for rheumatoid arthritis (RA). There was no documentation on file to indicate that subjects (b) (6) met this inclusion criterion.

   b. The same subjects have different years of RA diagnosis documented on the case report forms. For example,
      i. The year of RA diagnosis for subject (b) (6) is recorded as 1983 on the case report for protocol (b) (4) (subject number (b) (6)). However, this subject's year of RA diagnosis is reported as 1982 on the case report form for protocol (b) (4) (subject number (b) (6)).
      ii. The year of RA diagnosis for subject (b) (6) is recorded as 2001 on the case report for protocol (b) (4) (subject number (b) (6)). However, this subject's year of RA diagnosis is reported as 2002 on the case report form for protocol (b) (4) (subject number (b) (6)).
      iii. The year of RA diagnosis for subject (b) is recorded as 1998 on the case report for protocol (b) (4) (subject number (b) (6)). However, this subject's year of RA diagnosis is reported as 2001 on the case report form for protocol (b) (4) (subject number (b) (6)).

   c. Subject (b) (6) had duplicate baseline visit study records with different responses documented with regard to disease status, morning stiffness duration, joint assessment, and the health assessment questionnaire.

   d. There were no corresponding source documents on file for C-reactive protein and/or erythrocyte sedimentation rate data reported on the case report form for subjects (b) (6) (baseline visit, 10/18/02) and (b) (6) (baseline visit, 12/11/02).

   During the FDA inspection you could not provide a complete list of subjects enrolled in the study. Therefore, we could not determine the number of subjects enrolled and we were unable to determine whether you failed to maintain adequate and accurate case histories for other subjects.

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, CDER asserts that you have failed to protect the rights, safety and welfare of subjects under your care 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 CDER 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

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 CDER 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 CDER.

CDER will carefully consider any oral or written response. If your explanation is accepted by CDER, 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. After such a hearing, the Commissioner 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:
#1 - Consent Agreement
#2 - 21 CFR 16
#3 - 21 CFR 312.60
#4 - 21 CFR 312.70
#5 - 21 CFR 50
#6 - 21 CFR 56

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
08/25/2008