DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

July 20, 2004

Howard L. Offenberg, M.D.
18 Foxford Chase
Ormand Beach, Florida 32174

Dear Dr. Offenberg:

By FDA letter dated June 8, 2004, FDA's Center for Drug Evaluation and Research (the Center) issued a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) to you at the address of Radiant Research, 1014 NW 57th Street, Suite A, Gainesville, Florida 32605.

Radiant Research notified FDA that the NIDPOE dated June 8, 2004 was forwarded to you. Radiant Research further informed FDA that you are no longer in their employ. For this reason, we are re-issuing the NIDPOE to you at your address. This NIDPOE is identical to the NIDPOE dated June 8, 2004, except for the address and the introductory paragraph which now states that you conducted the research at issue while employed at Radiant Research.

Enclosed you will find a copy of the NIDPOE.

Sincerely yours,

Joanne L Rhoads M.D

Joanne L. Rhoads, M.D., MPH
Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Enclosures:
#1 – NIDPOE

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 - RESTRICTED DELIVERY
RETURN RECEIPT REQUESTED

JUN 8 2004

Howard L. Offenberg, M.D.
18 Foxford Chase
Ormand Beach, Florida 32174

Dear Dr. Offenberg:

Between February 26, and March 29, 2002, Ms. Brunilda Torres, representing the Food and Drug Administration (FDA), conducted an inspection of the following clinical study, and met with you to review your conduct as the clinical investigator of the study. At the time you performed the study, you were employed by [redacted].

Protocol [redacted] entitled: "A Multicenter, Double-Blind, Randomized Study to Compare the Safety and Efficacy of Nizatidine [redacted] 150 mg twice daily (BID), Nizatidine [redacted] 300 mg daily (QD) and Placebo in the Treatment of Subjects with Symptomatic, Endoscopically Confirmed Erosive Gastroesophageal Reflux Disease (GERD)." This study of the investigational drug was performed between April and August, 2001, for [redacted]

In addition, between January 27 and February 14, 2003, Ms. Shari Hromyak and Mr. Ronnie Jackson, also of FDA, conducted an inspection of the following clinical studies and met with you to review your conduct as the clinical investigator of these studies. At the time you performed these studies, you were employed by Radiant Research of Gainesville, Florida.

Protocol [redacted] entitled: "A two part study to characterize the histology and clinical features of rash associated with gemifloxacin and to assess the potential for cross-sensitization to another quinolone in healthy female volunteers." The study of the investigational drug gemifloxacin was performed between May and August, 2001, for [redacted]

Protocol [redacted] entitled: "A Randomized, Double-Blind, Placebo-Controlled Study Evaluating Acetaminophen [redacted] in the treatment of Osteoarthritis of the Hip or Knee." The study of the investigational drug acetaminophen [redacted] was performed beginning in April 2002, for [redacted]

These inspections are a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to ensure that the rights and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspections, Ms. Torres and Ms. Hromyak presented and discussed with you the items listed on the Forms FDA 483, Inspectional Observations. We have reviewed the inspection reports, the documents submitted with those reports, and your written responses dated April 15, 2002 and March 10, 2003, respectively, addressed to FDA Investigator Brunilda Torres and Joanne L. Rhoads, M.D., MPH of the Division of Scientific Investigations. We consider your response dated April 15, 2002, to be unacceptable in addressing the matters outlined in this letter, and we consider your response dated March 10, 2003, to be partially unacceptable as detailed by the violations below. We conclude that you 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. In summary:

1. **You failed to adequately supervise the above-referenced clinical trials [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 (21 CFR 312.60) 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 the investigator's 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 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 that 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 individuals not qualified to perform such tasks.

   When you were not present at the Gainesville site, you permitted employees without appropriate medical qualifications to perform clinical assessments of subjects. For example, your study coordinator [ ] who has no medical qualifications, and others without medical training (e.g. [ ]

evaluated whether subjects met inclusion/exclusion criteria, documented subjects' medical histories, and assessed symptoms and adverse events.

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

Our investigation indicates that you had little personal involvement in the conduct of the study, and individuals to whom you delegated study functions had little or no supervision or training in the conduct of study tasks. Your calendar indicates that you were only at the Gainesville site once a week, and study records indicate that you had little or no contact with study subjects.

Your lack of personal involvement and oversight of the studies listed above also resulted in submission of false information to the sponsor, protocol violations, and record keeping deficiencies described below.

2. You submitted false information to the sponsor [21 CFR 312.70].

Your calendar indicates that you were only at the Gainesville site once a week on Tuesdays, and study records indicate that you had little or no contact with study subjects. Multiple source documents, including consent forms, patient screening forms, and lab reports generated at the Gainesville site were signed and dated as completed by you on dates that you were not physically present at the Gainesville site. Therefore, as you were unable to complete examinations of subjects, for example, on those dates, and signed documents representing that you had, the documents contain false information. Some examples follow:

a) Protocol[ ]

1) Subject[ ]Your signature appears on the consent form, dated 4/17/01; on the Visit 2 day and night assessment dated 4/30/01: and on the Visit 3 assessment dated 5/21/01. There were no other signatures on these assessments except yours. This implies that you obtained the informed consent and performed the assessments on those dates. According to your calendar, you were at Deltona, Daytona, and Phoenix, respectively.

2) Subject[ ]Your signature appears on the Visit 1 screening form dated 4/20/01; on the Visit 2 assessment dated 4/26/01; and on the Visit 3 assessment dated 5/15/01. There were no other signatures on these assessments except yours. This implies that you performed the assessments on those dates. According to your calendar, you were at New Smyrna Beach (NSB), Ocala, and Deltona, respectively.

3) Subject[ ]Your signature appears on the Visit 1 "Exclusion Criteria" dated 4/20/01, and on the Visit 2 assessment dated 5/4/01. There were no other signatures on these assessments except yours. This implies that you performed the assessments on those dates. According to your calendar, you were at NSB on both dates.

4) Subject[ ]Your signature appears on the consent form and on the Visit 1 screening form for Physical Examination, both dated 4/23/01, while your calendar showed that you were at Daytona. Moreover, the abnormal findings that were listed as hiatal hernia, rheumatoid arthritis, and depression on 4/23/01 (which could be exclusionary criteria) were crossed out on 7/18/01, almost 3 months later and no explanation was provided. Your signature was found on the Visit 2 assessment dated 5/4/01, and on the Visit 3 assessment dated 5/25/01. There were no other signatures on these assessments except yours. This implies that you performed the assessments on those dates. According to your calendar, you were at NSB on both dates.

5) Subject[ ]Your signature appears on the Visit 2 day and night assessment dated 4/26/01; on the Visit 3 assessment dated (and corrected as) 5/17/01, with your signature dated 5/15/01; and on the Visit 5 Physical Examination assessment dated 7/20/01, with your signature dated 7/24/01. There were no other signatures on these assessments except yours. This implies that you performed the assessments on those dates. According to your calendar, you were at Ocala, Deltona and Deltona, respectively.

b) Protocol[ ]

On 4/25/01, you signed the "Personnel Roles and Responsibilities Form," used to delegate responsibilities from yourself to the study dermatologist, prior to the dermatologist completing the form by adding the delegations on 5/2/01. Your signature on the form was the documentation that you had reviewed the form and agreed to the delegated responsibilities. Therefore, you signed an incomplete form that did not specify the responsibilities you intended to delegate to the dermatologist. Submission to the sponsor of the form that changed after you signed it, thus constitutes the submission of false information. Of note, you admitted signing the form before completing the specific delegation duties in your letter dated 3/10/03.

3. You failed to conduct the study according to the protocol [21 CFR 312.60].

Protocol[ ]

a. The protocol specified that the frequency and severity of day and night symptoms were to be evaluated and scored by the investigator or designee, and that the person assessing the symptoms had to be the same person who made the assessment at the baseline visit. You were also informed by letter from the monitor dated April 20, 2001, following the initiation visit, that the "... study coordinator can **NOT** perform the assessments". Neither requirement was followed, and you admitted as such in your letter dated 4/15/02. These frequency and severity of day and night symptoms assessments for several subjects were not done by you, but by your coordinators, and they were entered into the case report forms that were signed by you on days when your calendar indicated you were not at the site. Your study coordinators signed the other assessments. Some examples follow:

1) Subject[ ] Baseline day and night assessment had your signature dated 4/30/01 (you were in Daytona according to your calendar); Visit 3 had your signature dated 5/21/01 (you were in Phoenix according to your calendar); the Visit 4 assessment had a notation "performed" by the study coordinator[ ] and the Visit 5 assessment was signed by another study coordinator, [ ]

2) Subject[ ] The Visit 2 and 3 assessments had your signatures dated 4/26/01 and 5/15/01 (you were in Ocala and Deltona respectively, according to your calendar). The Visit 4 assessment, dated 6/8/01, was not signed by anyone, and the Visit 5 assessment, dated 7/20/01, was signed by the study coordinator, Zabrina Horne.

3) Subject[ ] The Visit 2 assessment was dated 5/4/01, with your signature (you were in NSB according to your calendar), the Visit 4 assessment was signed by coordinator[ ] and the Visit 5 assessment was signed by another coordinator[ ]

b. You did not obtain information about adverse events and concomitant medication for all subjects at each visit, as required by the protocol, and you admitted as such in your letter dated 4/15/02. The evidence for this violation is based in part on the notes from your attempt to contact subjects at the completion of the study to obtain this information. The following are examples:

1) Subject[ ] On 6/13/01 (Visit 4), "Adverse Events Update" is marked "No" and then corrected to "Yes" on 7/31/01 and "Dysphagia moderate onset 6/6/01 and ongoing" was added at the end of the page. On the case report form of the final visit (Visit 5) dated 7/25/01, a summary of previous adverse events was written on 8/2/01 as follows: "itching, 5/4/01 and ongoing; rash shoulder and back, 5/4/01 and ongoing; dizziness, 5/2/01 and ongoing; nausea, 5/2/01 and ongoing; blurred vision 5/2/01 and ongoing; dysphagia ongoing, onset 6/6/01." A note signed and dated 8/3/01 reads "Called patient regarding ongoing adverse events at end of trial. Patient stated the adverse events of dizziness, nausea, blurred vision and dysphagia resolved 4 days after last visit. Stop date therefore is 7/29/01 for these adverse events. The patient's rash and itching are still ongoing. Questioned patient about medications he was taking at start of trial: patient stated Synthroid and Ventolin."

2) Subject[ ] The visit 5 assessment (final visit) was on 7/20/01. A note at the bottom of the page dated 7/31/01 and signed by coordinator,[ ] reads: "Late Entry, Adverse event of retrosternal pain lasted 2 weeks, stop date 5/24/01."

3) Subject[ ] Two notes were written at the end of the study. One stated: "Called patient regarding[ ] study, questioned patient about medications she was taking at the beginning of the trial..." The other stated: "Asked patient about AEs on the trial; the constipation and insomnia resolved 8/1/01; but stated she also

experienced swelling in legs and abdomen, moderate, constant, onset 5/24/01, and ongoing severity is mild now (mild – started 8/1/01). No other AEs."

Protocol[ ]

c. Subject 01352: The subject reported a rash on Day 8 of Part A of the study on 6/23/01. The protocol required that "Individuals who report rash will stop dosing with study medication until enrolled in Part B of the study." However, the subject continued to be dosed with study drug for the entire 10-day course of Part A. The subject's rash persisted during this period of continuation of treatment with the study drug, which placed the subject at risk for an allergic reaction.

4. You failed to prepare and maintain adequate and accurate case histories [21 CFR 312.62(b)].

As investigator, you are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. You failed to ensure that source documents generated during the conduct of the study were complete and represented accurate data as follows:

Protocol[ ]

Diaries for some subjects were not available during the inspection. There is no documentation or other evidence that each subject received his/her diary at the baseline visit or at all during the study, and you admit as such in your letter of 4/15/02. For example:

1) Subject[ ]A note signed after the end of the study states: "Questioned patient if she ever received a diary while on the study; the patient stated 'no'."

2) Subject[ ] A signed statement after the end of the study dated 8/16/01 states: "No, diary was never located or returned."

3) Subject[ ]A note signed by study coordinator and dated 7/31/01, 11 days after Visit 5, states: "Diary was never returned. No questions per documentation were ever asked Re: Diary."

4) Subject[ ]A note signed and dated 8/3/01 after last visit states: "Questioned patient if he ever received a diary while on this trial; he stated 'no'."

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational drugs. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations. We recognize your assertion in your

letters dated 4/15/02 and 3/10/03 that you have made changes in your research program to improve staff training and documentation. However, FDA's initiation of disqualification proceedings is based on your repeated or deliberate violations of the regulations and your failure to account for and address your lack of responsibility as a Clinical Investigator for the conduct of clinical trials and ongoing supervision.

On the basis of the above listed violations, FDA asserts that you have submitted false information and repeatedly or deliberately failed to comply with the cited regulations for investigational drugs, and it 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. Your written response must be forwarded within thirty (30) days of receipt of this letter. Your reply should be sent to:

Joanne L. Rhoads, M.D., MPH
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 choosing 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 Part 16 (enclosed) and

21 CFR 312.70 (enclosed). 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,

Joanne L Rhoads M.D.

Joanne L. Rhoads, M.D., MPH
Director
Division of Scientific Investigations (HFD-45)
Office of Medical Policy
Center for Drug Evaluation and Research

Enclosures:
#1 - 21 CFR 312
#2 - 21 CFR 16
#3 – Consent Agreement