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

JUL 21 2004

Jacques R. Caldwell, M.D.
C/o Earnest H. Delong, Esq.
Delong, Caldwell, Novotny and Bridgres
Centennial Tower, 101 Marietta Street, Suite 3100
Atlanta, Georgia 30303

Dear Dr. Caldwell:

By FDA letter dated June 10, 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 10, 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 in care of your attorney, Ernest H. Delong, as he requested. This NIDPOE is identical to the NIDPOE dated June 10, 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 MD

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

Jacques R. Caldwell, M.D.
C/o Earnest H. Delong, Esq.
Delong, Caldwell, Novotny, and Bridgres
Suite 3100
Centennial Tower
101 Marietta Street
Atlanta, Georgia 30303

Dear Dr. Caldwell:

Between February 19 and April 3, 2002, Ms. Brunilda Torres, representing the Food and Drug Administration (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 entitled, "Double-blind, randomized dose-titration, parallel-group comparison of the efficacy and safety of Tramadol (Tramadol and placebo in the treatment of osteoarthritis of the knee." This study of the investigational drug Tramadol was performed for

Protocol entitled, "Open label assessment of the safety and effectiveness of Tramadol (Tramado , in the treatment of chronic non-malignant pain." This study of the investigational drug Tramadol was performed for

Protocol entitled, "A comparative efficacy and safety study of Nexium (Esomeprazole Magnesium) delayed-release capsules (40mg and 20mg qd) versus placebo for the prevention of gastric ulcers associated with daily NSAID use in patients at risk." This study of the investigational drug Nexium (Esomeprazole Magnesium) was performed for AstraZeneca.

This inspection is 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 inspection, Ms. Torres 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 response to the Form FDA 483 dated June 21, 2002, and consider your response to be unacceptable in addressing the matters outlined in this letter. We conclude that you submitted false information to the sponsor 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. 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 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 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.

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. 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, evaluated whether subjects met inclusion/exclusion criteria, documented subjects' medical histories, assessed symptoms and adverse events, and took blood pressure measurements. Of note, in your discussions with our investigator, you admitted that some study assessments were completed in error by your study coordinator.

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. It appears that you also failed to review study records generated by your staff with reasonable care. For example, your study coordinator admitted fabricating standing blood pressure measurements in case reports forms (CRFs) for certain subjects in Protocol[ ]In almost all cases, the fabricated readings for standing blood pressure were not clinically plausible when compared with the measurements obtained for seated blood pressure. Had you reviewed these CRFs with reasonable care, it would have been obvious to you that many of the measurements were fabricated.

Your lack of supervision and personal involvement, and inappropriate delegation of study tasks, resulted in submission of false information to the sponsor, failure to protect the safety and welfare of study subjects, failure to adhere to study protocols, and failure to maintain adequate and accurate study records, as described below.

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

a. You submitted CRFs that contained fabricated blood pressure measurements.

Protocols[ ]and[ ]required that subjects "... be assessed for syncope, fainting spells, orthostatic hypotension (10-20 mmHg drop in blood pressure from supine or sitting to standing position), dizziness and drop attacks," "... at Screening and every study visit thereafter." Inspection of subject records revealed standing blood pressure measurements for multiple subjects that did not appear to be clinically plausible when compared to seated blood pressure measurements for those subjects. For example, there are many subjects for which standing blood pressure (diastolic or systolic) measurements were usually $\geq$ 2 mmHg higher than the sitting blood pressure. It is a well-known physiologic fact that the transition from a seated to a standing position normally causes a decrease in blood pressure. In your written response to the Form FDA 483 dated June 21, 2002, you admit that standing blood pressure readings and a laboratory report were falsified during the conduct of these studies. In particular, you stated that "... the coordinator assistant admitted that she only took seated blood pressure measurements and had not taken standing blood pressure measurements. When she realized the standing blood pressure measurements also were needed, she fabricated the standing measurements...". The following are examples:

Protocol[ ]

Subject #	Visit	Sitting Pressure	Standing Pressure
003 –[ ]	Screening	140/76	140/80
	Baseline	140/76	140/82
	V-3	140/78	140/80
	ET (Early Termination)	130/80	130/82
006 –[ ]	Screening	120/80	122/82
	ET	118/60	120/64
012 –[ ]	V-4	130/78	130/80
	V-6	128/80	130/80
	V-7	138/70	140/70
013 –[ ]	V-6	130/70	130/72
015-[ ]	Baseline	140/70	140/78
	V-5	140/80	140/82
016-[ ]	Baseline	110/70	110/70 (corrected to 76)
	V-4	130/70	130/70 (corrected to 76)
018-[ ]	V-3	120/80	120/82
021-[ ]	Baseline	120/80	120/82
026-[ ]	Baseline	140/82	142/82
028-	ET	130/72	132/72

Protocol [redacted]

Subject #	Visit	Sitting Pressure	Standing Pressure
002[redacted]	Screening	140/84	142/86
	V-2	130/80	132/82
	V-3	140/80	140/82
	V-7	130/80	130/82
[redacted]	V-1	140/78	140/80
	V-2	130/76	130/78
[redacted]	V-1	130/78	132/78
	V-2	122/84	122/86
[redacted]	V-1	120/80	122/82
	V-2	122/70	124/72
	V-4	120/68	120/70
	V-5	120/80	122/80
[redacted]	V-3	130/80	130/82
[redacted]	Screening	140/80	140/82
	V-4	140/84	140/86
	V-6	140/78	140/80
	V-2	130/90	132/90
	V-6	120/78	122/80
	V-7	102/70	110/72

b. You submitted falsified lab results for Protocol [redacted]

There were two reports for the campylobacter-like-organism (CLO) test for subject [redacted] in the Nexium study: one was positive and the other was negative. Only one of these lab results can be correct. A positive result would have excluded the subject from the study. Your signature appears on both the positive and the negative results and both of your signatures were dated 4/11/01. The subject was enrolled into the study. Of note, you admitted in your June 21, 2002 letter that this lab report was falsified.

c. Your calendar indicates that you were only at the Gainesville site once a week on Mondays, and study records indicate that you had little or no contact with study subjects. Multiple source documents, including physical examinations 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 on those dates, and signed documents representing that you had, the documents contain false information. Although you stated in your letter of June 21, 2002, that your physician assistant performed many of these exams, there is no documentation to that effect. Furthermore, even if your physician assistant had performed the exams, you are required to be physically present or within reasonable physical proximity to provide supervision and oversee the examinations. Some examples follow:

Protocol[ ]

1) The consent forms signed by subject[ ]are dated 1/23/01 and 1/30/01. Your signatures are dated on the same day. However, your schedule shows that you were working in Daytona on these dates.

2) Your signature on the consent form for subject[ ]is dated 1/26/01. However, your schedule shows that you were in Geneva on that date.

Protocol[ ]

4) Your signatures on the baseline visit date, baseline gastrointestinal symptom assessment and the physical examination sections of the CRF are dated 3/29/01 for subject[ ] However, your schedule shows that you were "...at the Capitol."

5) Your signatures on the baseline gastrointestinal symptom assessment and the physical examination sections of the CRF are dated 4/20/01 for subject[ ] However, your schedule shows that you were working in New Smyrna Beach on that date.

3. You failed to protect the rights, safety, and welfare of subjects under your care [21 CFR 312. 60].

An investigator is responsible for protecting the rights, safety and welfare of subjects under the investigator's care. You failed to ensure the safety and welfare of your study subjects in that for subjects enrolled in Protocol[ ] you failed to evaluate adverse events in a timely manner or to take appropriate action to protect subjects who experienced adverse events. For example:

a. Subject[ ]reported experiencing dizziness on 1/28/01, 2/4/01, 2/13/01, and 2/18/01. She also reported sweating on 2/18/01, and flu on 2/20/01. Dizziness is a known and expected adverse reaction of the investigational drug as noted in the protocol. The protocol requires that subjects be evaluated and closely monitored for syncope,

orthostasis, dizziness, drop attacks, and flushing. You did not evaluate the adverse events until 8/13/01, and only then at the sponsor's request. Therefore, the subject continued on the study without appropriate medical oversight.

b. Subject [ ] suffered dizziness on 1/08/01 while on 300mg of the investigational drug. Dizziness is a known and expected adverse reaction of the investigational drug as noted in the protocol. The protocol requires that subjects be evaluated and closely monitored for syncope, orthostasis, dizziness, drop attacks, and flushing. Notwithstanding the subject's complaint of dizziness, you increased the dose to 400 mg on 1/10/01. This subject continued to experience dizziness despite having stopped taking the drug on her own on 1/13/01, and, subsequently, requested to be removed from the study on 2/14/01. There is no indication that you evaluated the adverse event or provided appropriate medical oversight.

4. You failed to conduct the study according to the protocol [21 CFR 312. 60].

a. Protocol [ ] requires that physician assessments be performed by the investigator or another physician designated for this task. There is no documentation that the protocol-required *physician* assessments were always performed by you or a physician at each visit:

1) The "Physician Assessment" for subject [ ] was marked "yes" indicating that it was completed by a physician. An accompanying note read "Assessment was completed on 2/28/01(Wednesday), PI (principal investigator) signed source at a later date," followed by your signature and date on 4/2/01. You calendar indicates that you were in Daytona on 2/28/01. There is no documentation that another physician performed the exam on 2/28/01.

2) The "Physician's Global Assessments" performed at the Gainesville site on 2/28/01 for subject [ ] had no signature or initials. The assessments performed at the Gainesville site on 3/14/01 and 3/21/01 for subject [ ] bear your signature. The assessments performed at the Gainesville site on 4/18/01 and 6/15/01 for subject [ ] had no documentation that they were completed by you or another physician. Your calendar indicates that you were not in Gainesville on any of the dates listed.

3) The "Physicians Global Assessments" for subject [ ] at the Gainesville site had no signature for assessments performed on 3/09/01, 3/24/01, 4/20/01, 5/18/01, and 6/15/01. There is no documentation that you or a qualified physician investigator performed these "Physician Global Assessments". The assessment on 3/29/01 for subject [ ] bears your signature. However, your calendar indicates you were not in Gainesville on any of these dates (although it does indicate you were on call on 3/24/01).

b. Protocol inclusion and exclusion criteria were not always followed.

1) Subject[ ]was enrolled in protocol [ ]despite a blood glucose level of 303 mg/dl on 12/27/2000, indicating diabetes mellitus. The protocol-specified exclusionary criteria include "... a recognized risk of seizure such as head trauma, metabolic disorder, alcohol or drug withdrawal, or central nervous system (CNS) infection." On the basis of the existence of a metabolic disorder, i.e. uncontrolled diabetes mellitus (as indicated by a blood glucose level of 303 mg/dl), this subject should have been excluded from participating in the study.

2) Subject[ ] enrolled in protocol[ ] received Darvocet from 2/3/01 to 2/27/01. According to the protocol, Darvocet, an opioid analgesic, was a prohibited concomitant medication.

3) Subject[ ]was enrolled in protocol[ ]without documentation of either gastric or duodenal ulcer within the antecedent 5 years as required by the protocol. Of note, you admitted enrolling this subject in the study "in error" in your October 22, 2001, "Memo to file."

c. Protocol [ ]specifies that "Gastrointestinal (GI) Symptom Investigator Assessments" must be performed by the investigator. The study monitor wrote a letter to you on May 1, 2001, and clarified that only the principal investigator (or his designee with similar qualifications) should perform these "Gastrointestinal (GI) Symptom Investigator Assessments." However, for subjects[ ]and[ ]the "Gastrointestinal (GI) Symptom Investigator Assessments" were not done by the principal investigator or a similarly qualified designee. Mr.[ ]the physician assistant, signed a "Memo to file" stating that he obtained GI symptom assessment from subject[ ] on visit 3, and from subject[ ]on visits 3 and 4.

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

The violations listed above also document multiple instances of failure to prepare and maintain adequate and accurate study records, including fabricated, contradictory, and misdated records.

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 June 21, 2002, letter 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