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

Ramon Ramirez, M.D.
a.k.a. Ramon Ramirez Melendez, M.D.
CLIRECO, Inc.
7421 N. University Drive, Suite 212
Tamarac, Florida 33321

Dear Dr. Ramirez:

Between April 10 and 20, 2007, Ms. Ileana Barreto-Pettit, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations of the investigational drugs (b) (4) and (b) (4), performed for (b) (4)) and (b) (4) ., respectively:

Protocol (b) (4) "A Long-Term, Open-Label, Safety Study of (b) (4) in Patients with Moderate to Severe Chronic Low Back Pain or with Moderate to Severe Chronic Pain Due to Osteoarthritis of the Hip or Knee"

and

Protocol (b) (4), "A Randomized, Multi-Center, Double-Blind, Parallel-Group Study Assessing the Analgesic Efficacy and Safety of Different Dosages of (b) (4) bid Compared to Active (b) (4) bid and Placebo bid in Subjects with Chronic Knee-Joint Osteoarthritis"

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, Ms. Barreto-Pettit 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 May 9, 2007. We do not find your response to be acceptable in addressing the matters under complaint, which are described below.

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 submitted false information to the sponsor in a required report [21 CFR 312.70(a)].**

   Our investigation revealed that your two study coordinators withdrew 7 subjects (#s 8038, 8173, 9011, 9021, 9048, 9073, and 9124) from protocol (b) (4) and enrolled them in protocol (b) (4), but continued to fill out study documents for protocol (b) (4) as if the subjects were still enrolled. Information obtained during our inspection also revealed that your study coordinators did not dispense both study drugs to the subjects who had been withdrawn from (b) (4) I and enrolled in (b) (4). The study coordinators reportedly discarded the unused (b) (4) drug in a biohazardous bin, but recorded in the (b) (4) source documents that (b) (4) drug was dispensed to subjects and manipulated drug accountability logs to maintain the illusion that these subjects were still enrolled in protocol #(b) (4)

   Case report forms (CRFs) for protocol #(b) (4) I were falsified for the following subjects:

   a. For subject 8038, the CRF indicates that at Visit 12, "Date of Last Dose" was 4/17/06 and 24 tablets were returned; at Visit 13, "Date of Last Dose" was 5/18/06 and 18 tablets were returned, and at Visit 14, "Date of Last Dose" was 6/19/06 and 16 tablets were returned. Study medication was reportedly dispensed on 4/17/06, 5/18/06, and 6/19/06. This subject was enrolled in protocol #(b) (4) on 4/17/06.

   b. For subject 9011, the CRF indicates that study medication was dispensed on 5/26/06. This subject was enrolled in protocol #(b) (4) on 5/4/06.

   c. For subject 9048, the CRF indicates that study medication was dispensed on 5/22/06. This subject was enrolled in protocol #(b) (4) on 4/20/06.

   d. For subject 9073, the CRF indicates that at Visit 13, "Date of Last Dose" was

5/26/06 and 24 tablets were returned. At the next visit in June, 28 tablets were reportedly returned. The CRF indicates that study medication was dispensed on 5/26/06. The subject was screened for protocol #(b) (4) on 5/23/06 and withdrew from protocol #(b) (4) on 6/2/06.

2. You failed to personally conduct or supervise the clinical investigations [21 CFR 312.60].

When you signed the investigator statements (Form FDA 1572) for the above-referenced clinical trials, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities (21 CFR 312.60) include ensuring that the clinical trials are conducted according to the signed investigator statements, the investigational plans, 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 trials or to supervise those aspects of the trials that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as a 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 the clinical trials were conducted according to the signed investigator statements, the investigational plans, and applicable regulations, and in a manner that protects the rights, safety, and welfare of human subjects.

Our investigation revealed that your two study coordinators withdrew 7 subjects (#s 8038, 8173, 9011, 9021, 9048, 9073, and 9124) from protocol (b) (4) and enrolled them in protocol (b) (4), but continued to fill out study documents for protocol (b) (4) as if the subjects were still enrolled. Once the contract research organization (CRO) that was monitoring both studies became aware of the situation, the sponsors terminated the studies at your site in June 2006.

a. Subject 8038 was seen for Visit 12 of protocol #(b) (4) on 4/17/06. Study records indicate that study related procedures were performed and that the dose of study medication was increased to 10 mg because the subject was no longer getting adequate pain relief. On this same day, your study coordinators enrolled the subject (new subject #1281) in protocol #(b) (4) and thereafter continued to complete study records for this subject in protocol (b) (4) I.

b. Subject 8173 was seen for Visit 11 of protocol (b) (4) on 4/25/06. Study records indicate that study related procedures were performed and that the subject was doing well on the medication. On 5/2/06, your study coordinators screened this subject for protocol (b) (4) and thereafter continued to complete study records for this subject in protocol (b) (4). Study records indicate that screening procedures were performed (new subject #1284, consent signed, medical history, vital signs, labs, ECG) before your coordinators realized that the subject did not meet inclusion criteria for protocol (b) (4) due to being < 40 years old.

c. Subject 9011 was seen for Visit 13 of protocol (b) (4) on 4/27/06. Subject records indicate that study related procedures were performed and that the subject was doing well. On 5/4/06, your study coordinators enrolled the subject (new subject #1285) in protocol # (b) (4) and thereafter continued to complete study records for this subject in protocol (b) (4)

d. Subject 9021 was seen for Visit 13 of protocol # (b) (4) on 5/5/06. Study records indicate that study related procedures were performed and that the quality of pain relief was rated as "good." On this same day, your study coordinators enrolled the subject (new subject #1554) in protocol (b) (4) and thereafter continued to complete study records for this subject in protocol # (b) (4)

e. Subject 9048 was seen for Visit 12 of protocol (b) (4) on 4/20/06. Study records indicate that study related procedures were performed and that the quality of pain relief was rated as "good." On this same day, your study coordinators enrolled the subject (new subject #1283) in protocol (b) (4) and thereafter continued to complete study records for this subject in protocol (b) (4)

f. Subject 9073 was seen for Visit 13 of protocol # (b) (4) on 5/26/06. Study records indicate that study related procedures were performed and that the subject was getting good pain relief at the 20 mg dose level. Three days prior to this visit, on 5/23/06, your study coordinators screened the subject (new subject #1556) for protocol # (b) (4) and thereafter continued to complete study records for this subject in protocol (b) (4). The subject withdrew from protocol (b) (4) on 6/2/06 because the subject was going out of town and would not be available for study visits.

g. Subject 9124 was seen for Visit 11 of protocol # (b) (4) on 4/19/06. Study records indicate that study related procedures were performed and the subject was doing well on study medication. On this same day, your study coordinators enrolled the subject (new subject #1282) in protocol (b) (4) and thereafter continued to complete study records for this subject in protocol # (b) (4).

In your April 16, 2007 affidavit, you state: "I did not know about the dual enrollment until I received a call from the (b) (4) study auditor around 6/26/06 to inform me about this situation." However, study records that you signed and dated indicate that, in some cases, you saw the same subject on the same day for two different studies. For example, you saw subject 9124/1282 for both studies on April 19, 2006 and May 17, 2006, you saw subject 8038/1281 for both studies on April 17, 2006, you saw subject 9021/ 1554 for both studies on May 5, 2006, and you saw subject 9048/1283 for both studies on April 20, 2006. Therefore, you were either aware of the dual enrollment of these subjects prior to June 26, 2006, which is the date you stated you became aware in your affidavit, or you did not actually see these subjects on these dates.

3. You failed to protect the rights, safety and welfare of subjects under your care [21 CFR 312.60].

a. Study records support that even though subjects were terminated from protocol (b) (4) and enrolled in protocol (b) (4), they continued to have labs drawn for protocol (b) (4).

For example, your study coordinators terminated subject 9021 from protocol #(b) (4) and enrolled the subject into protocol #(b) (4) on 5/5/06. The subject had safety labs (hematology and chemistry) drawn on 7/5/06 for protocol (b) (4) and safety labs (hematology and chemistry) also drawn on 7/5/06 for protocol #(b) (4). Information obtained during our investigation revealed that when subjects had visits for protocol #(b) (4), your study coordinators collected additional tubes of blood for protocol #(b) (4) in order to give the appearance that the subjects were still participating in protocol #(b) (4). Your study coordinators did not inform the subjects that the blood was being collected for this reason.

b. Protocol (b) (4) required that subjects be monitored for opioid withdrawal after Visit 15 or Early Termination Visit, if the subject had been on study drug for ≥ 4 weeks. The study center must contact patients by telephone once daily (for four days after last dose of study medication) to monitor for symptoms of opioid withdrawal. Information obtained during our investigation revealed that subjects were not monitored for opioid withdrawal after they were discontinued from protocol #(b) (4), even though subjects 8038, 8173, 9048, 9073, and 9124 had all been on study drug for over 4 weeks.

c. Protocol (b) (4) prohibited the use of any opioids other than the study drug during the treatment period. Two subjects (9048 and 9124) were taking Vicodin while they were participating in the study as discussed below.

4. You failed to ensure that the investigations were conducted according to the investigational plan [21 CFR 312.60].

a. As stated under #3 above, subjects 8038, 8173, 9011, 9021, 9048, 9073, and 9124 in protocol #(b) (4) were not monitored for opioid withdrawal when they were terminated from the study as required by the protocol.

b. Protocol (b) (4) prohibited the use of any opioids other than the study drug during the treatment period.

i. When subject 9048 was withdrawn from protocol (b) (4) and enrolled in protocol #(b) (4) on 4/20/06, the Medication Intake document for protocol #(b) (4) indicates the subject was taking Vicodin from 2004 until 4/21/06. Therefore, the subject was taking an opioid other than the study drug during the treatment period of protocol #(b) (4), in violation of that protocol.

ii. When subject 9124 was withdrawn from protocol (b) (4) and enrolled in protocol # (b) (4) on 4/19/06, the Medication Intake document for protocol (b) (4) indicates the subject was taking Vicodin ES from 2004 until 4/20/06. Therefore, the subject was taking an opioid other than the study drug during the treatment period of protocol (b) (4) in violation of that protocol.

c. Protocol (b) (4) required that the investigator maintain accurate, original site records of drug inventory and dispensing. Our investigation revealed that your two study coordinators withdrew 7 subjects (#s 8038, 8173, 9011, 9021, 9048, 9073, and 9124) from protocol (b) (4) and enrolled them in protocol # (b) (4), but continued to fill out study documents for protocol (b) (4) as if the subjects were still enrolled. Information obtained during our inspection also revealed that your study coordinators did not dispense both study drugs to the subjects who had been withdrawn from (b) (4) and enrolled in (b) (4) The study coordinators reportedly discarded the unused (b) drug in a biohazardous bin, but recorded in the (b) source documents that (b) drug was dispensed to subjects and manipulated drug accountability logs to maintain the illusion that these subjects were still enrolled in protocol (b) (4). For example:

i. Subject 8038 was terminated from the (b) (4) study on 4/17/06; however, study records indicate that the (b) (4) System (b) (4) was contacted on 4/17/06, 5/18/06, and 6/19/06 to re-supply the subject with study medication.

ii. Subject 8173 was terminated from protocol (b) (4) I on 5/2/06; however, the Subject Investigational Product Accountability Log indicates that study medication was dispensed on 5/23/06 and study records indicate that the (b) (4) was contacted on 5/23/06 to re-supply the subject with study medication.

iii. Subject 9011 was terminated from protocol (b) (4) on 5/4/06; however, the Subject Investigational Product Accountability Log indicates that study medication was dispensed on 5/26/06 and study records indicate that the (b) (4) was contacted on 5/26/06 to re-supply the subject with study medication.

iv. Subject 9021 was terminated from protocol # (b) (4) on 5/5/06; however, the Subject Investigational Product Accountability Log indicates that study medication was dispensed on 5/5/06 and 6/8/06 and study records indicate that the (b) (4) was contacted on 5/5/06 and 6/8/06 to re-supply the subject with study medication.

v. Subject 9048 was terminated from protocol # (b) (4) on 4/20/06; however, the Subject Investigational Product Accountability Log indicates that study medication was dispensed on 4/20/06 and 5/22/06 and study records indicate that the (b) (4) was contacted on 4/20/06 and 5/22/06 to re-supply the subject with study medication.

vi. Subject 9073 was terminated from protocol #(b) (4) study on 5/23/06; however, the Subject Investigational Product Accountability Log indicates that study medication was dispensed on 5/26/06 and the (b) (4) was contacted on 5/26/06 to re-supply the subject with study medication.

vii. Subject 9124 was terminated from protocol (b) (4) I on 4/19/06; however, the Subject Investigational Product Accountability Log indicates that study medication was dispensed on 4/19/06, 5/17/06, and 6/19/06 and the (b) (4) was contacted on 4/19/06, 5/17/06, and 6/19/06 to re-supply the subject with study medication.

d. Protocol (b) (4) required that the investigator save all bottles, empty or containing unused tablets, for final disposition by the Sponsor or designee. Information obtained during our investigation revealed that your study coordinators discarded unused supplies of study drug in biohazard waste containers. Because the study coordinators discarded unused supplies of drug, this protocol requirement was not followed.

e. Protocol (b) (4) had an exclusion criterion of participation in another study of investigational drugs or devices parallel to, or less than one month before enrollment, or previous participation in this study. All of the subjects who were terminated from protocol (b) (4) and enrolled in protocol (b) (4) met this exclusion criterion and should not have been enrolled.

5. You failed to maintain adequate records of the disposition of the drug [21 CFR 312.62(a)].

As discussed in #4, our investigation revealed that, although study records were created to suggest otherwise, subjects were not dispensed study medication for protocol #(b) (4) after they were enrolled in protocol #(b) (4). Your site continued to obtain the (b) (4) study drug, a controlled substance, for subjects who were no longer participating in the study, and reportedly discarded this unused supply of a controlled substance in biohazard bins while continuing to create study records that gave the illusion the subjects were still taking the drug.

6. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation [21 CFR 312.62(b)].

As stated under #2 above, source document worksheets were falsified for 7 subjects in protocol (b) (4) to give the appearance that the subjects were still enrolled in the study, when, in reality, the subjects had been terminated from the study and enrolled in protocol #(b) (4). For example,

a. Subject 8038 was terminated from protocol (b) (4) on 4/17/06; however, study records indicate that you saw this subject on 5/18/06 and 6/19/06 for protocol # (b) (4), even though the subject was no longer in this study. Your note of 6/19/06 states: "No opioid toxicities described. No A/E's. States having good pain relief. No med changes."

b. Subject 8173 was terminated from protocol (b) (4) on 5/2/06; however, study records indicate that you saw this subject on 5/23/06 and 6/29/06 for protocol (b) (4), even though the subject was no longer in this study. A Memo to File, signed by you and dated 6/14/06, states: "This memo is written to document that pain intensity level was discussed with patient at most recent visit on 5/23/06. This patient is currently on 40 mg dose of study medication. Even though patients pain level continues usually at same level, patient wishes to remain on study."

c. Subject 9011 was terminated from protocol (b) (4) on 5/4/06; however, study records indicate that you saw the subject on 5/26/06 and 6/27/06 for protocol (b) (4), even though the subject was no longer in this study.

d. Subject 9021 was terminated from protocol (b) (4) on 5/5/06; however, study records indicate that you saw the subject on 6/8/06 and 7/5/06 for protocol (b) (4), even though the subject was no longer in this study.

e. Subject 9048 was terminated from protocol (b) (4) on 4/20/06; however, study records indicate that you saw the subject on 5/22/06 and 6/30/06 for protocol # (b) (4) even though the subject was no longer in this study.

f. Subject 9073 was terminated from protocol (b) (4) I on 5/23/06; however, study records indicate that you saw this subject on 5/26/06 and 6/21/06 for protocol (b) (4), even though the subject was no longer in this study. In addition, there are two Memos to File, signed by you and dated 6/14/06 that state: "This memo is written to document that pain intensity level was discussed with patient at most recent visit…This patient is currently on 20mg dose of study medication. Patient states her pain level is tolerable and does not want to increase her dose." For both of these memos, the date of subject visit was originally recorded as 5/23/06; the date of subject visit was changed to 5/26/06 on one memo, but not the other.

g. Subject 9124 was terminated from protocol (b) (4) on 4/19/06; however, study records indicate that you saw this subject on 5/17/06, 6/19/06, and 7/5/06 for protocol # (b) (4), even though the subject was no longer in this study.

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

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.

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.

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

Enclosures:
#1 Consent Agreement
#2 21 CFR 16
#3 21 CFR 312.60
#4 21 CFR 312.70

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
10/21/2008