NCAL

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

Howard W. Marker, M.D.
Sarah Cannon Research Institute
6005 Park Ave, Suite 805
Memphis, TN 38119

Dear Dr. Marker:

Between April 28 and May 2, 2008, Ms. Barbara Wright, representing the Food and Drug Administration (FDA or Agency), conducted an investigation and met with you, to review your conduct of the following clinical investigations:

- Protocol (b) (4) entitled "A Phase 3, 53 Weeks Study on Analgesic Efficacy and Safety of (b) (4) 26-Week, Randomized, Parallel-Group, Double-Blind, Placebo (13 Weeks)- and Naproxen (26 Weeks)-Controlled, Multicenter Study of (b) (4) with a 26-Week Naproxen-Controlled Safety Follow-up in Subjects with Osteoarthritis of the (b) (4), and a 1-week Post-treatment Safety Follow-up," of the investigational drug (b) (4), performed for (b) (4).

- Protocol (b) (4) entitled "A Phase III, Open Label, Long-Term Safety Study of Tramadol Hydrochloride Extended Release and Meloxicam QD Combination in the Treatment of Moderate to Moderately Severe Pain Associated with Osteoarthritis," of the investigational drug tramadol hydrochloride, performed for Biovail.

- Protocol (b) (4) entitled "A 6-Month, Phase 3, Randomized, Double-blind, Parallel-group, Controlled, Multi-center Study to Evaluate the Incidence of Gastric Ulcers Following Administration of Either (b) (4) or Naproxen in Subjects Who Are at Risk for Developing NSAID-associated Ulcers," of the investigational drug (b) (4), performed for (b) (4)

- Protocol (b) (4) entitled "A Phase III, 12-week, Multicentre, Double-blind, Double-dummy, Randomised, Placebo- and Active Comparator-Controlled, Parallel Group study to investigate the Efficacy and Safety of (b) (4) administered orally once daily, in adults with Osteoarthritis of the (b) (4)," of the investigational drug (b) (4), performed for (b) (4).

- Protocol (b) (4) entitled "A 13-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial of (b) (4) o.d. in patients with primary (b) (4) osteoarthritis using celecoxib (200 mg o.d.) as a positive control," of the investigational drug (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, Ms. Wright 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, your written response to the Form FDA 483 dated May 13, 2008, and additional information obtained by the Agency. 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 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.

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)].**

   a. Based on additional information obtained by the Agency, you did not perform physical examinations for a number of study subjects. However, you signed the study records, indicating that you had performed the physical examinations. Examples include, but are not limited to, the following:

Subject Number	Protocol
061-003	(b) (4)
061-004	(b) (4)

061-005
061-012
0001
0002

(b) (4)
(b) (4)
(b) (4)
(b) (4)

b. Study records for the following four subjects indicated that you performed their physical examinations on November 06, 2007: Subject 061-012 enrolled in protocol (b) (4); subject 401-0003 enrolled in protocol (b) (4); and subjects 138-113 and 138-148 enrolled in protocol (b) (4). However, your research appointment book noted that you were out of the office all week.

We note that in your May 13, 2008 written response to the Form FDA 483 you stated that you arrived at the research office at approximately 6:30 am on November 06, 2007 and performed assessments on "a couple of subjects" prior to leaving for the airport to attend a professional meeting. You stated that while you did not personally examine the other study subjects, your research staff performed the examinations and later you reviewed their findings and subsequently signed the date that the visit occurred. You stated that you realize that this is not standard practice and your staff should not have signed as completing the exam. You also stated that you should have dated your signature the date you reviewed the exams. We note that you did not specify which subjects you examined and which ones were examined by your research staff. You stated that you do not contest this inspection observation.

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

Protocol (b) (4) excluded subjects who participated in another drug or device study during the three months prior to baseline/randomization visit. Subject (b) (6) participated in protocol (b) (4) between the February 25, 2005 and June 6, 2005. The subject was subsequently enrolled in protocol (b) (4) on July 5, 2005 in violation of the protocol. You stated in your May 13, 2008 written response that you do not dispute this observation.

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 at 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
Food and Drug Administration

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
01/29/2009