DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN (NIDPOE)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Scott S. Reuben, M.D.
296 Concord Street
Longmeadow, MA 01106

Dear Dr. Reuben:

Between April 20 and May 21, 2009, Ms. Patty Murphy, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of the following clinical investigations of the investigational drug Celecoxib (Celebrex), performed for Pfizer, Inc.:

- (b) (4), entitled "(b) (4)," and
- (b) (4), entitled "(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. Murphy prepared and sent to your legal representative Form FDA 483, Inspectional Observations. We have reviewed the inspection report and the documents submitted with that report. You did not respond to the matters under complaint, which are described below.

FDA's inspection raised numerous concerns about your conduct of studies, including potential fabrication of study subjects, fabrication of study data, and failure to follow the investigational plan. This matter was referred to FDA's Office of Criminal Investigations (OCI) for further investigation. Subsequently, the U.S. Attorney for the District of

c. Protocol (b) (4), Section 7.2, "Study Schedule," states that the surgical procedure will be performed under general anesthesia, using fentanyl 1-3 mcg/kg, with an injection of marcaine 0.25% with epinephrine, 20 cc total dose at the index joint.

   i. Subjects No. 1003, 1004, 1011, 1013, 1015, 1016, 1024, 1025, 1027 and 1029 did not receive the specified dose of marcaine with epinephrine per the study protocol.

   ii. Subjects No. 1006 and 1008 did not receive the specified dose of fentanyl per the study protocol.

d. Protocol (b) (4), Section 7.7.5, "Study Drug Administration," states that Bottle B is dispensed to the subject after surgery, with instruction to take as needed upon the first occurrence of pain. If the subject requires additional pain medication after 30 minutes of taking the second dose of study medication from Bottle B, subject will be provided rescue analgesic medication (Bottle C). You failed to ensure that study medications were dispensed at the prescribed times.

   i. Subject 1022 was administered rescue analgesic medication (Bottle C) twelve minutes after receiving the dose from Bottle B.

   ii. Subject 1008 was administered rescue analgesic medication (Bottle C) ten minutes after receiving the dose from Bottle B.

e. Protocol (b) (4), Section 7.7.5, "Study Drug Administration," states that Bottle B is dispensed to the subject after surgery, with instruction to take as needed upon the first occurrence of pain. If the subject requires additional pain medication after 30 minutes of taking the second dose of study medication from Bottle B, [the] subject will be provided rescue analgesic medication (Bottle C). You failed to ensure that study medications were dispensed at the prescribed times for Subject 1009, who was administered rescue analgesic medication (Bottle C) fifteen minutes after receiving the dose from Bottle B.

f. Protocol (b) (4) Section 7.2, "Study Schedule," states that the surgical procedure will be performed under general anesthesia, using fentanyl (up to 4 mcg/kg), with an injection of marcaine 0.25% with epinephrine (up to 20 cc total dose at the index joint). You failed to ensure that the marcaine was administered according to the investigational plan for Subjects 1008 and 1013, who were administered 30 cc of marcaine.

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 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.

In the normal course of a disqualification proceeding, following receipt of this notice, you would have been entitled to/offered an opportunity to explain the matter either in writing or during an informal conference. You would have been entitled to, or offered the opportunity to 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. If your written or oral responses to our allegations were unsatisfactory, in the normal course of a disqualification proceeding, you would have been entitled to/offered a regulatory hearing before FDA, pursuant to 21 CFR 16 and 21 CFR 312.70. A presiding officer free from bias or prejudice and who has not participated in this matter would have conducted the hearing to determine whether or not you would remain entitled to receive investigational products.

However, pursuant to section 4 of your plea agreement, you agreed to enter into a disqualification agreement with FDA within 21 days of receiving FDA's NIDPOE. You further agreed not to contest the disqualification proceedings, to waive your opportunity to provide a written explanation, to waive your right to attend an informal conference, and to waive your right to any regulatory hearing pursuant to 21 CFR Parts 16 and 312.70. The following paragraphs include instructions for entering into the disqualification agreement with FDA.

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.

To enter into the enclosed consent agreement with FDA, thereby terminating this disqualification process, you must:

(1) Initial and date each page of this Agreement;
(2) Sign and date the last page of this Agreement; and
(3) Return this Agreement initialed, signed, and dated to the signature below.

A copy of the fully executed Agreement will be mailed to you.

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

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
03/17/2010