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

Massachusetts charged you with executing a scheme and artifice to defraud Pfizer, Inc. in connection with the delivery of and payment for health care benefits, items and services. On Jan. 8, 2010, you signed a plea agreement in which you plead guilty to one count of health care fraud in violation of 18 U.S.C. §1347. In doing so, you acknowledged that although you entered into an Independent Research Grant Agreement with Pfizer to conduct a study entitled "Perioperative Administration of Celecoxib [Celebrex] as a Component of Multimodal Analgesia for Outpatient Anterior Cruciate Ligament Reconstruction Surgery," you did not actually enroll any subjects in the study. You admitted that the results reported both to Pfizer and to Anesthesia and Analgesia Journal and in turn to the public were wholly made up and therefore false.

Based on our evaluation of information obtained by the Agency, we believe that you have 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 312.70 (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 failed to conduct the studies or ensure they were conducted in accordance with the signed statement of investigator and the investigational plan [21 CFR 312.60].**

   a. Protocol (b) (4), Section 6.2, "Exclusion Criteria," states that subjects will not be included in the study if they have a known allergy to sulfonamides. Section 7.3.1, "Screening Visit," states that laboratory test results will be used to determine if a subject is eligible for the study. You failed to ensure that the following study subjects met the protocol criteria for study subject selection:

      i. Subject 1013 had a history of allergy to sulfonamides and was enrolled into the study.

      ii. Subject 1015's and Subject 1016's screening laboratory results were not reviewed for exclusionary values until after their enrollment into the study.

   b. Protocol (b) (4), Section 9.0, "Concomitant Therapy," states that Non Steroidal Anti-Inflammatory Drugs (NSAIDS) and oral or injectable corticosteroids are specifically excluded from use during the treatment period:.

      i. Subjects 1003 and 1004 were administered dexamethasone preoperatively.

      ii. Subjects 1013 and 1016 took NSAIDS postoperatively.

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