Regulatory Information

CDER: Notice of Initiation of Disqualification Proceeding And Opportunity to Explain (NIDPOE); Date Issued: 02/21/2008

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Notice of Initiation of Disqualification Proceeding And Opportunity to Explain (NIDPOE)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Pramod Raval, M.D.
24661 Coolidge Highway
Oak Park, Michigan 48237-1449

Dear Dr. Raval:

Between May 17 and June 7, 2005, Ms. Catherine Quinlan, representing the Food and Drug Administration (FDA or agency), conducted an investigation to review your conduct of the following
clinical studies:

> **Protocol**: **[redacted]** entitled: "A Randomized Double-Blind, Multicenter, Active-Control Study Evaluating the Efficacy and Safety of **[redacted]** in Subjects with Moderate to Severe Osteoarthritis Pain" performed for **[redacted]**

and

Protocol [redacted] entitled: "An Open-Label, Randomized Study to Evaluate the Safety of 4 mg Nicotine Lozenges in Comparison with 4 mg Nicotine Gum in Smokers with Certain Underlying Disease Restrictions Specified in the Label" performed for GlaxoSmithKline.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research 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. Quinlan 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 responses to the Form FDA 483 dated July 13 and August 8, 2005. We do not find your responses to be acceptable in addressing the matters under complaint, which are described below.

Based on our evaluation of the information obtained by the agency, the Center for Drug Evaluation and Research (the Center) believes that you 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) and that you have repeatedly or deliberately submitted false information in required reports to FDA or the sponsor (21 CFR 312.70).

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 312.701]

As part of the subject qualification procedures for study **[redacted]** subjects were to document opioid usage for a two week screening period. In the first week (Week 1), subjects were to maintain a diary of opioid intake and document the use of an opioid analgesic for pain at the primary osteoarthritis (OA) pain site at a dose of $\geq$30 mg and $\leq$80 mg/day of opioid equivalents (on four or more days of the seven day period). The protocol specifies that subjects would qualify for continuance into the second week of the study (Week 2 or the opioid-tapering phase) provided that they documented the requisite use of opioids in the first week and that their diaries were completed appropriately and legibly. In Week 2, subjects were to document the tapering of their opioid medication, dependent on the investigator's assessment of the subject's level of pain and the implementation of the recommendations in the "American Pain Society Opioid Tapering Algorithm" as appropriate. Subjects who reported pain scores during Week 2 that fell within protocol specified limits were eligible to enter the open-label Run-in period, during which subjects who tolerated the 10 mg study drug **[redacted]** were to be titrated upwards to the 20 mg **[redacted]**

For the majority of subjects randomized into this study, records either indicate that the subjects did not meet the above qualification criteria or fail to show. whether the subjects met these criteria. However, statements in the CRFs indicate that subjects qualified for entry into the Run-in period of the study. For example:

a. Pain Medications diaries for subjects 39006 and 39008 are blank; therefore, there is no documentation of the baseline opioid dosage (Week 1) nor is there documentation of opioid tapering (Week 2). Despite this lack of documentation, the CRFs completed by sub-investigator **[redacted]** state that the diaries were reviewed, found complete, appropriate, and legible, and that the subjects took the protocol-specified amounts of opioids. These statements are not supported by the subjects' diaries.

b. Subject 39009's Pain Medications diaries document only the use of Advil, a non-opioid, for Weeks 1 and 2. The CRFs completed by sub-investigator **[redacted]**, state that the diaries were reviewed, found complete, appropriate, and legible, and that the subject took the protocol-specified amounts of opioids. These statements are not supported by the subject's diaries.

c. Subject 39011's Pain Medications diaries document only the use of a non-opioid analgesic (Motrin) for Weeks 1 and 2. The CRFs completed by sub-investigator **[redacted]** state that the diaries were reviewed, found complete, appropriate, and legible, and that the subject took the protocol-specified amounts of opioids. These statements are not supported by the subject's diaries.

d. Subject 39012's Pain Medications diaries document only the use of non-opioid analgesics (Vioxx, Excedrin, and Bextra) for Weeks 1 and 2. The CRFs completed by sub-investigator **[redacted]** state that the diaries were reviewed, found complete, appropriate, and legible, and that the subject took the protocol-specified amounts of opioids. These statements are not supported by the subject's diaries.

e. Subject 39014's Pain Medications diary for Week 1 documents only the use of non-opioid analgesics (Vioxx, Motrin, and Advil). The Week 2 diary notes the use of Celebrex, Motrin, and Vicodin. Vicodin, the only opioid analgesic used, was used one time on one day during Week 2. The CRFs completed by sub-investigator **[redacted]** state that the diaries were reviewed, found complete, appropriate, and legible, and that the subject took the protocol-specified amounts of opioids. These statements are not supported by the subject's diaries.

2. You failed to ensure that the clinical trial was conducted according to the signed investigator statement, in that you failed to adequately supervise the clinical trial [21 CFR 312.60].

Your general responsibilities as a clinical investigator (21 CFR 312.60) include ensuring that the investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety and welfare of subjects under your care; and ensuring control of drugs under investigation. When you signed the investigator statement (Form FDA 1572) for the above-referenced clinical investigation, you committed to taking on the responsibilities of a clinical investigator at your site. You specifically agreed to personally conduct or supervise the clinical study, and to ensure that all associates, colleagues, and employees assisting in the conduct of the study were informed about their obligations. While you may delegate certain study tasks to individuals qualified to perform them, as clinical investigator, you must adequately supervise those to whom you delegate authority. 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 protected the rights, safety, and welfare of human subjects.

You delegated substantial responsibilities in the conduct of protocol **[redacted]** to your sub-investigator, **[redacted]**. You failed to adequately supervise **[redacted]** in the conduct of delegated tasks. For example, as described in item 1 above, six subjects had blank diaries or documented that they used no opioids whatsoever

during the Weeks 1 and 2 screening period even though lack of opioid use during this period was an exclusion criterion for the study. Despite these subjects having blank diaries or documenting no opioid use, your sub-investigator documented these individuals as having filled out diaries that were complete, appropriate, and legible, that the subjects had taken the protocol-specified amounts of opioids, and that the subjects were eligible for the Run-in phase of the study. Had you provided adequate oversight of the study, it would have been obvious from a review of the subject's diaries that these six subjects were clearly ineligible for study continuation according to the protocol.

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

In protocol **[redacted]** subject 39004's diaries for Visit 1-2 of April 21-26, 2004 and Visit 2-3 of April 27-May 3, 2004, document a dose of 4-6 tablets per day of propoxyphene (Darvon). The CRF indicates that the subject tapered her opioid intake beginning on April 17, 2004. This date indicates that the tapering process began *prior*□ to Visit 1-2, the period during which the subject was only to record drug intake. Tapering, according to protocol, was to occur during the Visit 2-3 period . The screening worksheet which assessed the subject on May 4, 2004, the day after the Visit 2-3 period, states that the subject tapered her opioid intake and qualified for the Run-in period. In addition, the screening worksheet intended to capture information on non-opioid analgesic intake notes that Darvon intake was reduced from 4-6 tablets every 4-6 hours to 2 tablets every 4-6 hours. This information is not supported by data in the subject diaries. The diaries show that 32 tablets of Darvon were taken during Week 1 and 36 tablets were taken in Week 2, an increase of four tablets, contradicting the worksheet statement that opioid use had been tapered. Subject 39004 continued into the Run-in phase of the study where she recorded pain levels of 8-10 for seven out of seven days. The protocol required that subjects record pain levels at the primary OA site of $\leq$ 4 for six of seven days in order to qualify for the randomization phase of the study. The subject, though not qualified because of excessive pain scores, was entered into the randomization phase of the study. The subject dropped out of the study because of intolerable pain.

In addition, Subject 39010's Pain Medications diaries document only the use of non-opioid analgesics (ibuprofen, aspirin, and Motrin) for Weeks 1 and 2. The CRFs state that the diaries were reviewed, found complete, appropriate, and legible, but that the subject did not take the protocol-specified amounts of opioids. Nevertheless, the subject was continued in the study. Also, though lack of opioid use during this period was an exclusion criterion for the study, as described under item 1, six other subjects were continued in the study who had blank diaries or documented that they used no opioids whatsoever during the Weeks 1 and 2 screening period.

In summary, of 14 subjects screened for this study, at least eight subjects were continued in the study despite meeting protocol-specified exclusion criteria regarding the use of opioids for pain control. Thus, the rights, safety, and welfare of these subjects were not protected, and subject 39004 in particular experienced severe pain for an extended period because of a lack of adherence to the protocol and a lack of monitoring of the subject's self-reported condition in the diary.

4. You failed to conduct the study according to the investigational plan [21 CFR 312.60].

a. Five subjects (003, 006, 007, 008, and 009) completed study **[redacted]**. The protocol specified visits at intervals of two, four, six, and twelve weeks after the quit date for Visits 2, 3, 4, and 5, respectively. However, review of the Enrollment Log indicates that these five were seen every two weeks beginning with Visit 1. Thus, the timing between visits for these subjects was inconsistent with the protocol-specified intervals. Your written response is inadequate. If subsequent visits were scheduled from Visit 1 per protocol requirements and per your written explanation, the interval between Visit 1 and Visit 5 would have remained approximately 12 weeks. Furthermore, as confirmed in your written response, these subjects do not have a documented "committed quit date" nor was there documentation of follow-up contact with the subjects 7-8 days after this date to confirm use of the assigned product as required by protocol.

b. Subjects 39006 and 39011 in protocol **[redacted]** did not undergo pregnancy testing as required by protocol. The protocol requires that subjects receive pregnancy tests at Visits 1 an d 10 or at study discontinuation. Both subjects had blood samples drawn at Visit 10; however, there is no documentation that either subject was tested for pregnancy.

c. Subject 39006 in Protocol **[redacted]** was not discontinued from the study despite documenting two days with Subjective Opiate Withdrawal Scale (SOWS) scores of 26 and 24 during the. opioid tapering period . Per protocol, a subject experiencing a SOWS score exceeding 23 on any given day during this phase must be discontinued from the study.

d. Subject 39010 in protocol **[redacted]** did not have two consecutive days of pain scores $\geq$ 5 during the opioid tapering period, and, therefore, did not qualify for continued study-eligibility since the protocol required two consecutive days with pain scores $\geq$ 5 during this period.

e. Pain scores reported by subjects 39006, 39008, 39010, and 39011, all in protocol **[redacted]** should have resulted in their discontinuation from the study. Per protocol, subjects must not report pain scores greater than four at the primary OA site for six of seven days during the Run-in period to remain eligible to enter the Double-blind Phase of the study. Each of these subjects reported pain scores exceeding this protocol-specified maximum.

f. Subjects 002 and 009 in study **[redacted]** were taking Diovan HCT and Lexapro, respectively; however, these concomitant medications were not listed in the Current/Concomitant Medications CRF as required by protocol. Your written response states that this failure to list these concomitant medications was a transcription error.

g. Some subjects experienced adverse events that were not documented on the Adverse Events CRF as required by protocol. For example:

i. Subject 3001 in study protocol **[redacted]** experienced incidents of headache and sore throat that were not reported on the Adverse Events CRF.

ii. Subjects 39003 an d 39010 in study protocol **[redacted]** reported that the **[redacted]** were itchy while subjects 39011 and 39012 in the same study reported that the **[redacted]** made them feel sleepy. None of these adverse events were reported on the Adverse Events CRF.

5. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subject [21 CFR 312.62(a)].

a. At Visit 5 on May 17, 2004, subject 39003 for study **[redacted]** returned a **[redacted]** and rescue medications, had an old **[redacted]** removed and a new **[redacted]** applied, and was dispensed new rescue medications according to the progress note. The Master Drug Accountability Log contains no documentation of the dispensation or return of these **[redacted]** for this visit.

b. At Visit 3 on May 4, 2004, subject 39008 for study **[redacted]** had a **[redacted]** applied and was dispensed rescue medications according to the progress note. The respective Master Drug Accountability Logs do not

document the dispensation or return of [**redacted]** and rescue medications.

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.

On the basis of the above listed violations, FDA asserts that you have submitted false information to FDA or the sponsor in a required report and that you have repeatedly or deliberately failed to comply with the cited regulations. Accordingly, 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) 796-3392 to arrange a conference time or to indicate your intent to respond in writing. Your written response should 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
Building 51, Room 5342
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

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 you make to this proceeding. 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,

(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:
#I - Consent Agreement
#2 - 21 CFR 16
#3 - 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
02/21/2008