



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

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Suresh Gupta, M.D.
Research Institute of Greater Dayton
1010 Woodman Drive
Dayton, Ohio 45432

Dear Dr. Gupta:

Between June 20 and August 28, 2007, Ms. Marianne Allen, 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

[] performed for [] and [] and [] respectively:

[] "A 4-Week, Randomized, Double-Blind, Cohort Study to Evaluate the Safety and Tolerability of Converting from [] Release (IR) to [] Extended Release (XR) Formulation in Patients with [] and []

[] "A Randomized, Double-Blind, Phase 3 Study of the Efficacy and Safety of [] in Subjects Requiring NSAID Treatment."

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. Allen presented and discussed with you the items listed on Form FDA 483, Inspectional Observations, regarding Protocol [] (trial). We have reviewed the inspection report, the documents submitted with that report, and your written response to the Form FDA 483 dated October 10, 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)].

Information reviewed indicates that you submitted false information to [] in required reports for the [] trial. You enrolled 5 subjects (541, 542, 543, 544, and 545) and you submitted information stating that the subjects met all entry criteria to the sponsor in the electronic case report forms (e-CRFs) required for the clinical investigation. The [] protocol for the trial required a physical exam at the screening visit to determine whether subjects met all entry criteria and were qualified to be enrolled in the study. Section 6.2.2 of the protocol states that "[a] full physical examination will be conducted by a physician or other individual who is licensed to perform physical exams under local laws." Our investigation revealed that the physical exams were not performed by you or another qualified individual, but rather were performed by the Director of Clinical Research (an unlicensed physician). The CRFs contain false information, by affirmative representation, in that they falsely represent subjects as being eligible for the study when in fact no qualified physician made that determination. These CRFs were submitted to the sponsor pursuant to the [] protocol.

2. You failed to personally conduct or supervise the investigation [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 trial or to supervise those aspects of the trial 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 for the [] trial was not adequate to ensure that the clinical trial was conducted according to the signed investigator statement, the investigational plan, and applicable

regulations, and in a manner that protects the rights, safety, and welfare of human subjects.

Our investigation revealed that you were minimally involved with the [] trial and that you delegated study responsibilities to the Director of Clinical Research (an unlicensed physician) and to the study coordinator. Evidence indicates that you delegated tasks to unqualified individuals and failed to maintain adequate supervision and involvement in the ongoing conduct of the study. For example, you did not see patients on an ongoing basis or review data from site visits in a timely manner. We note that you documented your involvement with the 5 subjects enrolled in the study in a Memo to File placed in each subject's chart. Subjects were enrolled (completed Baseline Visit) between June 30, 2006 and August 15, 2006. The last subject enrolled, subject 545, was seen for a Baseline Visit on 8/15/06 and completed the study on 9/20/06. For all subjects, your Memo to File is dated September 22, 2006; therefore, these memoranda were created after all subjects had completed the study. Your lack of supervision of this study led to the observations discussed below.

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

- a. Our investigation revealed that for the [] trial an unlicensed physician performed screening physical exams on study subjects and evaluated laboratory and ECG results. For 5 of 5 enrolled subjects, there is a Protocol Deviation Request/Waiver in the charts stating that [] performed the initial physical exam. Mr. [] curriculum vitae states that he trained as a medical doctor in India, but is not licensed to practice medicine in the United States. Accordingly, Mr. [] was not authorized to perform screening examinations for the [] trial, nor was he qualified to analyze laboratory and ECG results.

During the inspection, you stated that Protocol Deviation Request/Waiver forms were placed in the charts in error. You state in your August 23, 2007, affidavit, obtained during FDA's inspection, that you performed the physical exams. You repeat the same explanation in your written response to Form FDA 483. We have information that physical examinations were not conducted by you or another licensed physician and that laboratory and ECG results were not evaluated by you or another licensed physician. Although you signed the physical exam forms, information obtained during the FDA inspection indicates that you or another licensed physician did not perform the physical exams or have laboratory and ECG results appropriately evaluated, thereby failing to protect the rights, safety, and welfare of the subjects under your care.

- b. The [] trial required the completion of Clinical Global Impressions Scales [Severity of Illness (CGI-S) and Global Improvement (CGI-I)] by the clinical investigator at the Baseline/Randomization Visit and at Week 1, Week 2, Week 3, Week 4, and Early Termination visits. The protocol states that the CGI-S scales allow "the investigator to rate the severity of subjects' illness considering their total clinical experience." [] Protocol, section 6.3.2) Similarly, describing the

utility of the CGI-I scales the protocol states, "The CGI-I allows the investigator to rate the subject's global improvement or worsening compared with the condition at Baseline." [] Protocol, section 6.3.2) It is clear from the protocol that these scales are intended for use by the investigator or someone with a clinical background. Our investigation revealed that for several subjects' visits, these scales were completed by the study coordinator. For example,

- For subject 541, the study coordinator completed the CGI-S and CGI-I for all visits.
- For subject 542, the study coordinator completed the CGI-S and CGI-I for all visits.
- For subject 543, the study coordinator completed the Baseline and Week 1 CGI-S and CGI-I.
- For subject 544, the study coordinator completed the Baseline CGI-S.
- For subject 545, the study coordinator completed the Baseline CGI-S.

We note that in your written response to Form FDA 483, you state the protocol does not require the CGI scales to be completed by the principal investigator (PI) or sub-investigator (Sub-I). As the clinical investigator for the study, you may only delegate study responsibilities to personnel who are qualified by education and training to perform the duties delegated to them. The CGI-S requires clinical experience with a particular population in order to make a determination regarding the severity of the subject's illness; the CGI-I requires the rater to make a clinical judgment as to whether the subject's improvement is related entirely to drug treatment. As a medical assistant, the study coordinator does not have the clinical background required to make these determinations. In addition, the study coordinator documented in a Protocol Deviation Request/Waiver that she had not been trained on the CGI scales.

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

The [] trial specified an inclusion criterion requiring subjects to be on a stable dose of once daily [] IR at a dose of 1, 2, or 4 mg for at least 2 weeks prior to study entry/Baseline Visit.

Subject 542 was on a divided dose of [] IR (1.5 mg at 5 pm and 2.5 mg at 10 pm) at study entry/Baseline Visit; therefore, this subject did not qualify for the study. According to your written response, you made a decision as clinical investigator to deviate from the protocol by accepting Subject 542 and you informed the sponsor about that decision on August 18, 2006. However, we are not aware of any evidence that the sponsor approved this protocol deviation.

5. You failed to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

- a. Mr. [] documented in the progress notes, part of the case histories, for subjects 541 and 545 enrolled in the [] trial, that the physical exam was performed by you and that you or Dr. [] (sub-investigator) signed all physical exam forms. Thus, the case histories state that physical exams were performed by a licensed physician. As stated above, information obtained during our investigation indicates that the physical exams were not performed by a licensed physician, and therefore the case histories are inaccurate.
- b. Your site used electronic case report forms (eCRFs) for the [] trial and other studies at your site. During the inspection, our inspector learned that study data you purportedly entered into eCRFs (including your electronic signature), was actually entered by Mr. [] using your password.

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.

Page 6 – Suresh Gupta, M.D.

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.

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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
09/12/2008