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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

Bertrand Agus, M.D.
251 East 33rd Street, 4th Floor
New York, NY 10016

Dear Dr. Agus:

Between October 25, 2006 and February 7, 2007, Andrew Paglia, D.P.M., representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical study:

Protocol [ ] entitled "A Multicenter, Standard of Care-Controlled Study to Evaluate the Long-Term Safety of [ ] for the Treatment of Chronic Low Back Pain." This study of the investigational drug [ ] was performed for [ ]

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 the study have been protected.

Based on our evaluation of information obtained by the Agency, we believe that you have submitted false information to the sponsor 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.

A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

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

When you signed the investigator statements (Form FDA 1572) for the above referenced clinical investigation, you agreed to take on the responsibilities of a clinical investigator at your site. 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. 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 inspection indicates that you failed to personally conduct or supervise the clinical investigation. Our inspection revealed that you had little personal involvement in the conduct of the study beyond conducting a limited number of physical examinations, reviewing a limited number of electrocardiograms (ECGs), and treating study related emergencies, and 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, in a manner that protected the rights, safety, and welfare of human subjects.

Specifically, during the FDA inspection you informed the FDA investigator that you did not personally meet with the sub-investigator (Dr.[ ]who conducted the study, nor review his research or clinic records regarding the subjects he enrolled. You also stated that you did not review the inclusion criteria, treatment outcomes, protocol deviations, or adverse event documentation for the subjects enrolled by this sub-investigator.

The subject screening/randomization log, and the randomization and treatment assignment listing document that [redacted] subjects were enrolled in the study; however, during the inspection you stated that you can only remember [redacted] subjects [redacted] and [redacted] who were seen by you during the screening period. You admitted to the FDA investigator that you never saw the remaining [redacted] subjects. The FDA inspection revealed that there were no study records (e.g., medical records/charts, case report forms) available for review at the clinical site for 8 subjects who participated in the study. The inspection report also indicates that you did not know if any periodic reports were submitted to the sponsor. During the inspection, you stated that you did not know how electronic case report forms entries were made as you did not check or log into the electronic data capture system entitled[ ]You also stated that you did not know if any adverse events were reported to the sponsor.

Your failure to provide supervision and lack of personal involvement in the study resulted in submission of false information to the sponsor, protocol violations, inadequate records, and other violations that jeopardized the rights, safety, and welfare of the subjects under your care (see violations 2 through 7).

2. **You failed to conduct the clinical investigation according to the investigational plan [21 CFR 312.60].**

a. The Inclusion Criteria section of the protocol included that s[redacted] during the screening period. In addition, the protocol required that potential subjects be excluded from the study if they had taken any c[redacted] or [redacted] within [redacted]ks prior to Baseline Visit. The following subjects failed to meet the study eligibility criteria described above and were enrolled in the study:

i. The laboratory report dated 12/7/05 for subject[redacted] documents that the subject had a positive drug screening test for [redacted] However, the case report form (CRF) documents that the subject met the inclusion criteria and did not meet any of the exclusion criteria.

ii. The laboratory report dated 1/31/06 for subject[redacted] documents that the subject had a positive drug screening test for [redacted] However, the CRF documents that the subject met the inclusion criteria and did not meet any of the exclusion criteria.

iii. Subject[redacted] was enrolled in the study; however, there is no laboratory report to substantiate any drugs of abuse screening test. Therefore, we cannot determine whether or not this subject was eligible to participate in the study.

iv. The case report form dated 1/18/06 for subject[redacted] documents a negative result for drugs of abuse screening test. However, there is no laboratory report to substantiate any drugs of abuse tests.

v. The laboratory report dated 2/6/06 for subject[redacted] documents that the subject had a positive drug screening test for [redacted] and [redacted] However, the CRF documents that the subject met the inclusion criteria and did not meet any of the exclusion criteria.

b. The protocol required that potential subjects be excluded from the study if they had an [redacted] and [redacted]N or had a [redacted] The laboratory report dated 2/22/06 for subject[redacted] documents that the subject had critical high values for [redacted] and [redacted] of [redacted] and [redacted] respectively. Further, the laboratory report documents that the subject was positive for [redacted]. However, the subject was enrolled in the study. The CRF documents that the subject met the inclusion criteria and did not meet any of the exclusion criteria.

c. The protocol required that subjects start medication on [redacted] and they may reduce their dose for reasons of tolerability only, first to [redacted], then, if necessary, [redacted]. Further, subjects who did not tolerate the study drug

[redacted] should have been withdrawn from the study. The following subjects were not administered the dose of study drug required by the protocol:

i. The CRF documents that subject [redacted]'s first dose was at 400 mg BID (12/2/05), and subsequent doses were at 150 mg BID (12/6/05), 200 mg BID (12/7/05), 300 mg BID (12/9/05) and 200 mg BID (12/13/05).

ii. The CRF documents that subject [redacted]'s first dose was at 400 mg BID (12/8/05), and subsequent doses were at 50 mg BID (12/21/05), 100 mg BID (12/22/05), 150 mg BID (12/23/05), 200 mg BID (12/24/05) and 300 mg BID (12/25/05).

d. Section 9.1 of the protocol states, "Adequate and accurate case records and source documents will be maintained and all relevant observations and data related to the study will be recorded." The inspection revealed that you failed to maintain study records for subjects.

3. You submitted false information to the sponsor [21 CFR 312.70].

As the clinical investigator who signed the Form FDA 1572, you were responsible for activities of the sub-investigator who submitted false information to the sponsor on your behalf. The following were noted during the inspection:

a. Specifically, case report forms were submitted to the sponsor that document that subjects [redacted] and [redacted] met the inclusion criteria and did not meet any of the exclusion criteria. Review of the subjects' laboratory screening reports revealed that these subjects failed to meet the study eligibility criteria, as detailed above [items 2(a)(i),(ii) (v) and 2(b)]. The case report forms falsely report that these subjects met protocol inclusion criteria and did not meet any exclusion criteria.

b. The inspection report indicates that the FDA investigator conducted a phone interview with a subject on 11/14/2006 and the subject stated that he was only at the site for two visits. Review of the CRFs revealed that there were entries for a total of six visits for this subject. The CRFs document a screening visit on 1/19/06 and a baseline visit conducted on 2/9/06. Additional entries were made in the electronic CRFs for the week one, week two, month one and month 2, none of which were attended by the subject.

c. The inspection report indicates that the FDA investigator conducted a phone interview with a subject on 11/20/06. The subject stated that no ECG or physical examination was performed on him by either you or Dr. [redacted] The subject also stated that he had medication left over, and that no one had followed up with him. The CRFs document that the subject had an [redacted] taken on 2/3/2006 and the result was normal. The protocol required subjects to have a [redacted] at the screening (de novo) or baseline visit (rollover).

d. The inspection report indicates that the FDA investigator conducted a phone interview with a subject. This subject stated that he remembered being examined by two physicians and having blood and urine samples taken and stated that he did not return after the second visit. Review of the CRFs revealed that there were entries for a total of six visits for this subject. The CRFs document a screening visit on 1/31/06 and a baseline visit conducted on 2/9/06. Additional entries were made in the electronic CRFs for the week one, week two, month one and month 2, none of which were attended by the subject.

4. **You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60].**

Informed consent must be documented by the use of a written consent form approved by the Institutional Review Board (IRB) and signed and dated by the subject or the subject's legally authorized representative at the time of consent. The subject screening/randomization log documents that subjects[ ]were screened/evaluated for enrollment; however, there is no documentation that you obtained informed consent from these subjects prior to initiation of any study-related procedures.

Further, the FDA investigator was able to locate only two signed informed consent documents for subject[redacted] and[redacted] There is no documentation that you obtained informed consent from 12 of the[redacted] subjects enrolled in the study.

5. **You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation [21 CFR 312.62(b)].**

The inspection revealed serious deficiencies in study documentation, including the lack of case report forms and source documentation. You did not adequately maintain source documents for the subjects participating in the study. The available records are inadequate to evaluate whether the study was performed according to the investigational plan. Examples include, but are not limited to, the following:

a. There were no study records (e.g., medical records/charts, case report forms) available for review at the clinical site for subjects[redacted]. An[redacted] was the only study record found for subject 6380005.

b. The medical charts for subject[redacted] revealed limited screening source documentation. Further, the source documentation was written in pencil. The protocol required that all entries in study documents should be clearly written with a blue or black ballpoint pen.

c. The screening/randomization log documents that subjects[ ]and[ ]were assigned the same screening numbe[redacted]

d. The laboratory reports for tests conducted in November 2005 document that subject[ ]was assigned the screening numbe[redacted]However, the laboratory reports for tests conducted in December 2005 document that subject[ ]was assigned the screening numbe[redacted]

6. You failed to maintain adequate records of the disposition of the investigational drug [21 CFR 312.62(a)].

FDA's inspection found inaccurate and inadequate documentation for receipt, dispensing, and reconciling of the investigational drug. Drug accountability records are inadequate to reconcile the amount of drug dispensed to and returned by subjects. Examples include, but are not limited, to the following:

a. There are no investigational drug, randomization source document worksheets for the baseline visit for subjects[redacted]and[redacted] Further, there are no study drug return and dispensation source document worksheets for the week 1 and 2 visit.

b. There are no investigational drug, randomization source document worksheets for the baseline visit for subject[redacted] Further, there were no study drug return and dispensation source document worksheets for the week 1, week 2, month 1, month 2 and month 3 visits.

c. For subjec[redacted], the CRF documents that the study drug was returned and dispensed on 3/3/06, 3/28/06 and 4/21/06. However, the study drug accountability log, and test article reconciliation and return forms do not reflect the dispensation or return of the study drug for those respective dates. The subject drug accountability, and test article reconciliation and return forms document the dispensation of the study drug on 1/31/06, 2/24/06, 3/21/06, and 4/14/06.

d. For subject[redacted], the CRF documents that the study drug was returned and dispensed on 3/6/06 and 3/31/06. However, the study drug accountability log, and test article reconciliation and return forms do not document the dispensation or return of the test article for those respective dates. The drug accountability log documents a month 1 visit date on 3/3/06, indicating that 104 tablets were dispensed and four tablets were returned. However, the comments section indicates a quantity of zero return written by the respective contract research organization personnel dated 5/24/06.

e. For subject[redacted], the CRFs document that the study drug was returned and dispensed on 3/8/06 and 4/3/06. However, the subject drug accountability log,

and test article reconciliation and return forms document the dispensation of the study drug on 2/8/06, 3/3/03, 3/29/03, 3/3/06, 3/29/06, and 4/25/06.

7. **You failed to retain records for the requisite time period [21 CFR 312.62(c)]**

Per regulation, investigators shall retain records that are required to be maintained under this part for two years following the date a marketing application is approved for the drug being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. You failed to retain a copy of all study-related documents, including case report forms, when the sponsor terminated the study.

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 exposed human subjects to undue risks and jeopardized the data integrity, 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 (240) 276-8817 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.
Acting Director
Division of Scientific Investigations, HFD-45
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
7520 Standish Place, Room # 103
Rockville, Maryland 20855

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.
Acting Director
Division of Scientific Investigations, HFD-45
Office of Compliance
Center for Drug Evaluation and Research

Enclosures:
#1 - 21 CFR 312.70
#2 - 21 CFR 312.60
#3 - 21 CFR 312.62
#4 - 21 CFR 50
#5 – 21 CFR 56
#6 - 21 CFR 16
#7 - Consent Agreement

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Leslie Ball
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