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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

Matthew J. Guy, M.D.
119-15 Rockaway Beach Boulevard
Rockaway Park, New York 11694

Dear Dr. Guy:

Between August 2, 2004 and December 8, 2004, Andrew Paglia, D.P.M., representing the Food and Drug Administration (FDA), conducted an inspection to review your conduct of the following clinical investigations:

- Protocol[ ]"A Double Blind, Multi-Center, Randomized, Placebo-Controlled, Parallel Group Dosing Study Evaluating the Effects of Nebivolol on Blood Pressure in Patients with Mild to Moderate Hypertension" performed for Mylan Pharmaceuticals, Inc.; and

- Protocol[ ]"A Multi-Center, Double-Blind, Parallel Group Extension Study to Determine the Safety and Efficacy of Long-Term Nebivolol Exposure in Patients with Mild to Moderate Hypertension" performed for Mylan Pharmaceuticals, Inc.

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.

Based on our evaluation of information obtained by the Agency, we believe that you have 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 312.70 (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. All violations cited below concern Protocol[ ]

1. **You submitted false information to FDA or the sponsor in a required report [21 CFR 312.70(a)].**

   Our investigation found that for Protocol[ ]you maintained two separate sets of source documents for study subjects; one set consisted of actual private practice notes which predated the subjects' entry into the study and the other consisted of re-created clinic records that were dated on or after the subjects' entry into the study and that were used to support the data entered into the study case report forms (CRFs). (As noted at the end of this section, the protocol expressly defined "source documents"). Comparison of the two sets of medical records revealed that 9 of 12 subjects you enrolled into the study had a pre-existing condition that should have excluded them from the study. In all cases, the re-created source documents did not contain the subjects' pre-existing medical conditions that would have rendered them ineligible for enrollment into the study. These documents contain false information, either by omission or affirmative representation, in that they falsely represent subjects as being eligible for the study when they were not in fact eligible. These documents were used to support the CRFs, which were then submitted to the sponsor during monitor visits.

   a. For subject 0194 enrolled on 9/6/02, review of at least 31 private practice notes dated 11/15/01 - 8/29/02 showed the subject had known Lupus, Chronic Obstructive Pulmonary Disease (COPD) and experienced panic attacks. However, the re-created private practice note, the study source document and the case report form dated 9/6/02, did not record a history of Lupus, COPD or panic attacks. In addition, our investigation found that you signed a "New York City Application for a City Parking Permit for People with Disabilities" on 3/12/02, stating that the subject had Emphysema, Asthma and Dyspnea. You also sent a letter dated 9/22/00 to the Long Island Power Authority (LIPA) requesting LIPA not to turn off the electricity for this subject because the subject was under your care for heart disease and asthma and required the use of electrically operated equipment. Per the protocol, COPD and asthma are conditions that would have excluded this subject from participation in the study. Moreover, your notes and March 12, 2002 letter state that this subject suffered from panic attacks, lupus, emphysema, and dyspnea, while the[ ]Worksheet does not indicate that this subject suffered from these conditions. The study protocol states that the exclusionary criteria include the "[p]resence of any condition that may, in the judgment of the investigator, jeopardize the participant's adherence to the protocol or ability to complete the trial."

   b. For subject 1261 enrolled on 9/13/02, review of the private practice notes dated 5/23/02 – 9/10/02 showed the subject received monthly respiratory treatment, and the Pulmonary Function Tests dated 8/1/02, 4/18/02, and 3/14/02 showed the subject had Severe Restrictive Lung Disease (SRLD). However, the study source documents and the case report form, both dated 9/13/02, did not record a history of SLRD or document the monthly respiratory treatment, and the protocol

exclusion criteria includes the history or presence of asthma, bronchospasm, COPD, and any condition that may jeopardize the participant's ability to complete the trial.

c. For subject 1164 enrolled on 9/13/02, review of the private practice notes dated 4/1/02 - 8/29/02 showed the subject had COPD and received multiple inhaler prescriptions. However, the study source documents and the case report form, both dated 9/13/02did not record a history of COPD.

d. For subject 2813 enrolled on 10/11/02, review of the Chief Complaints section of the private practice notes dated 5/5/02 - 10/10/02 and the Pulmonary Function Test dated 7/11/01 showed the subject had severe COPD. However, review of the study source documents shows that the reference to severe COPD was omitted from the Chief Complaints section of the October 11, 2002 private practice notes and remained only under the Allergies section of that form and was omitted from the case report form, dated 10/11/02.

e. For subject 0388 enrolled on 9/6/02, review of the "impressions" section of the private practice notes dated 8/22/02 - 9/3/02 showed the subject had COPD. However, the study source documents and the case report form, both dated 9/6/02, did not record a history of COPD.

f. For subject 0873 enrolled on 9/13/02, review of at least 28 private practice notes dated 9/13/01 - 9/25/02 showed the subject had severe COPD. However, review of the study source documents and the case report form, both dated 9/13/02, did not record a history of COPD. A note was added to the worksheet indicating that the subject had COPD but that a waiver had not been sought, as it was not deemed clinically significant; however, this note was not made until July 3, 2003.

g. For subject 2910 enrolled on 10/30/02, review of the Pulmonary Function Test dated 6/6/01, showed the subject was diagnosed with SRLD as of 6/6/01 and that the subject was continuing with respiratory therapy for COPD through 5/29/04. However, review of the study source documents and the case report forms, both dated 10/30/02, did not record SRLD or continued respiratory therapy for COPD.

h. For subject 0485 enrolled on 9/6/02, review of the Pulmonary Function Test dated 7/12/01 showed the subject was diagnosed with mild obstructive lung disease, and review of at least 15 private practice notes dated 7/12/01 - 9/5/02 document either COPD or severe COPD. However, review of the study source documents and the case report forms, both dated 9/6/02, did not record obstructive lung disease or COPD.

i. For subject 1649 enrolled on 9/20/02, review of the Pulmonary Function Test dated 3/7/02 showed the subject was diagnosed with mild obstructive lung disease, and private practice notes dated 3/7/02 - 10/17/02 showed the subject had COPD. However, study source documents and the case report form, both dated 9/20/02, did not record a diagnosis of mild obstructive lung disease or COPD.

We note that Protocol[ ]defines source documents as follows:

> original documents, data and records. They include all original recordings of clinical findings, observations or other activities necessary for the evaluation and reconstruction of the study.
>
> Examples of source documents are hospital records, clinical and office charts, laboratory notes, patients' diaries or evaluation checklists, pharmacy dispensing records recorded data from automated instruments, etc.

In addition, the protocol requires monitoring by the sponsor or monitor at regular intervals. The protocol further explains:

> During site visits, the field monitor will review informed consents, patient records, case report forms, drug accountability records, and document retention.
>
> The purpose of these visits is to verify adherence to the protocol, the completeness and accuracy of the CRF, and drug dispensing and inventory record. Case report forms and all original data should be readily available for review during scheduled monitoring visits. All case report forms should be carefully reviewed by the study coordinator and/or the investigator for completeness prior to the monitoring visit.

In addition, in many instances, you kept two sets of progress notes for the same subject after the subject's entry into the study. During the course of the inspection, you were asked by the FDA investigator on multiple occasions if you had provided all study related documents because review of certain documents you provided found many examples of medical progress notes for the same subject for the same day containing different information. On December 8, 2004, the investigator specifically told you that there were many instances where the progress notes withheld information such as adverse events, prior and concomitant medications, and exclusion criteria. In your written response dated 12/29/04, you explained that you set up a folder for each subject for study visits and "source documents," and separately maintained "regular chart notes" for each subject. In addition, you stated that the study visit file notes and "regular" chart notes were not identical as they dealt with different issues. Although your 12/29/04 written response stated that both sets of folders were on the premises and available to the FDA investigator at all times of the inspection visits, it was not until the close out interview of the inspection that you indicated you kept separate records.

Your response is inadequate. By maintaining separate and often conflicting study related records and clinic charts to support the information contained in the CRFs, you submitted false information to FDA or the sponsor in a required report. These falsified study reports permitted the enrollment of subjects that were ineligible for participation, (see item 2 below).

2. You failed to conduct the study or ensure the study was conducted according to the approved protocol [21 CFR 312.60].

a. Protocol[ ]excluded subjects with a history or presence of asthma, bronchospasm, or COPD; subjects who were diabetics with hemoglobin A1C (HbA1C) ≥ 10% during the screening period; and subjects with significant thyroid, renal or hepatic disease [TSH > 1.5 times upper limit of normal, urine protein > 1+, creatinine > 2.2 mg/dL; AST (SGOT) and/or ALT (SGPT) greater than twice the upper limit of normal]. In addition to our finding that ineligible subjects were enrolled into the study as noted in item 1 above, our investigation found the following:

i. Subject 2619 was enrolled into the study on 9/27/02 although the screening HbA1C was 10.2. The subsequent HbA1C values were 10.7 on 11/8/02 and 10.2 on 11/22/02.

ii. Subject 1261 was enrolled into the study on 9/13/02 although the screening urinalysis demonstrated 2+ urine protein. The subsequent urinalysis demonstrated 2+ urine protein on 10/11/02 and 3+ urine protein on 1/3/03.

iii. Subject 1358 was enrolled into the study on 9/13/02 although the screening ALT was 147, three times the upper limit of normal and the screening urinalysis demonstrated 2+ urine protein. In addition, the screening HbA1C test was not performed.

b. Protocol[ ]prohibited the use of all antidepressants with blood pressure altering effects. Our investigation found the following:

i. According to your private practice records dated 8/29/02, 9/23/02, and 10/8/02, subject 1164 was receiving 30 mg of amitriptyline, a prohibited antidepressant medication.

c. Protocol[ ]required blood pressure measurements to be taken in the supine, sitting, and standing positions. Specifically, the supine blood pressure and heart rate were to be measured and recorded three times at two-minute intervals after the subject had been at rest in the supine position for at least five minutes. After sitting for one minute, three blood pressure and heart rate measurements were to be measured and recorded at two-minute intervals; and after standing for one minute, three more blood pressure and heart rate measurements were to be measured and recorded at two-minute intervals. If performed according to the protocol, this process should have taken at least 20 minutes from start to finish. The investigator informed you that the study records showed multiple study procedures were performed on several subjects at the same time or within several minutes of each other. You responded that three people were performing multiple procedures. Although the blood pressure readings were recorded in 1-2 minute intervals, you admitted that there may have been cases where the blood pressure measurements were not performed and recorded within the 1-2 minute interval.

In addition, the protocol required that the blood pressure and heart rate measurements be taken prior to the required blood draws. According to the study records, several subjects' blood draws were performed prior to blood pressure measurements. For example:

Subject	Visit Date	Visit	BP/ HR Time	ECG Time	Labs Drawn Time
2619	9/27/02	V1	7:30	NA	7:10
2619	10/25/02	V3	9:03	NA	8:00
2619	11/8/02	V4	9:40	NA	9:00
*1358	9/13/2002	V1	9:30	NA	9:40
**0194	9/06/2002	V1	08:01	NA	08:00

* Subject 1358 should have been continuing to have his or her blood pressure measured at 9:40.
** A note to file indicates that the blood was drawn at 8:30, which would be consistent with the protocol; however, this note was not recorded until May 23, 2003.

In your written response dated 12/29/04, you stated the following, "I believed that using common sense and my almost 30 years of clinical practice experience allowed me to interpret the protocol just as I would interpret all guidelines in everyday clinical medicine. I thought that I was to use my own clinical judgment.... As Principal Investigator I should have mastered the regulations known as Good Clinical Practice [GCP]. I should have known that GCP was a specific set of rules and regulations and not assumed, as I did, that this meant "good medical practice".... I now know that a Clinical Research Protocol is a strict set of rules, not just guidelines." You also conceded that, "I should have better understood the protocol and regulations and not relied solely on the guidance of the CRO, Monitor and the Sponsor" and that the monitor had not made you aware of the errors you were making in the[ ]study until most of the subjects had been enrolled.

In your response letter, you explained that the timestamp on your EKG machine was "not accurate" and that the phlebotomist recorded the approximate times of the blood draws, despite your instruction to record precise times. You admitted that, "[h]aving others work under me doing bloods, EKG's, etc. in the setting of a timed clinical research project was a new experience for me" and that "I simply did not have the experience to organize this properly."

Your response is inadequate. When you signed the Statement of Investigator, Form FDA 1572 in July 2002, you agreed to the responsibilities of a clinical investigator that included ensuring that the study is conducted according to the protocol to protect the safety, rights or welfare of the subjects and to comply with all the obligations of a clinical investigator and all other pertinent requirements in 21 CFR 312. We remind you that as a clinical investigator, you retain responsibility for the conduct of the study.

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

   a. As noted in item 1 above, our investigation determined that you maintained two sets of medical records for study subjects covering the same time period which contained numerous discrepancies. In many instances, conditions recorded in private practice notes predating the subject's entry into the study detailed pre-existing conditions that would have precluded that subject's participation in the study. These conditions were omitted from the study source documents and case report forms. In addition, there were instances in which you kept two sets of documents for the same subject for the time period following their entry into the study. One set of documents omitted information such as adverse events, prior and concomitant medications, or exclusion criteria.

   b. You failed to report all concomitant medications in the case report forms. For example,

      i. Your private practice clinic records dated 8/29/02 for subject 0194 document that the subject was taking Atrovent PRN, Albuterol and Flovent via nebulizer; Combivent Inhaler; MS Contin 15 mg; Diazepam 10 IM; Darvocet N 100 PRN; Fiornal PR; and Librax PRN; however, these medications were not documented in the Prior Medications Section or the Concomitant Medications Section of the CRF. We note that the Prior Medications Section lists the patient number as 0776; however, the patient initials are [ ] which otherwise correlates with subject number 0194. Thus, it appears that the reference to patient number 0776 was in error.

      ii. Your private practice clinic records dated 8/29/02, 9/23/02, and 10/8/02, for subject 1164 document that the subject was taking 30 mg of Amitryptiline; however, this medication was not documented in the Prior or Concomitant Medications Section of the CRF.

   c. You failed to report complete medical histories in the case report forms. For example,

      i. The source documents dated 9/27/02 for subject 2619 document that the subject had a history of diabetes; however, in the "Informed Consent and Demographic Information" Section of the CRF, you checked "no" to indicate that the subject did not have diabetes mellitus, nor was it checked off in the "Cardiovascular Risk Factor Profile" section.

      ii. Your private practice clinical records dated 5/23/02 – 5/29/03, for subject 1261 document that the subject reported poor vision and/or dizziness; however, this was not recorded in the Medical History section of the CRF.

4. You failed to personally conduct or adequately supervise the above-referenced clinical trials [21 CFR 312.60]

When you signed the investigator statement (Form FDA 1572) for the above-referenced clinical investigations, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities (21 CFR 312.60) include ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations and protecting the rights, safety and welfare of subjects under the investigator's care. You specifically agreed to personally conduct the clinical studies or to supervise those aspects of the studies that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as clinical investigator, you may not delegate your general responsibilities. 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 investigational plan.

You failed to adequately supervise individuals to whom you delegated study tasks. As discussed above, in your response letter, you explained that the timestamp on your EKG machine was "not accurate" and that the phlebotomist recorded the approximate times of the blood draws, despite your instruction to record precise times. You admitted that, "[h]aving others work under me doing bloods, EKG's, etc. in the setting of a timed clinical research project was a new experience for me" and that "I simply did not have the experience to organize this properly." In addition, during your initial interview with the investigator, you stated that you, your wife, and a lab technician performed the blood pressure readings. You first stated that the blood pressures were taken in 1 and 2 minute intervals. Later during this interview, however, you stated that the blood pressures were not performed and recorded during the 1-2 minute intervals. Your failure to personally conduct or adequately supervise the clinical trials resulted in the failure to adhere to study protocols.

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, 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 (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.
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. After such a hearing, the Commissioner 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, HFD-45
Office of Compliance
Center for Drug Evaluation and Research

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