DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

SEP 30 2004

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

CERTIFIED MAIL - RESTRICTED DELIVERY
RETURN RECEIPT REQUESTED

Emad Dean Nukta, M.D.
West Side Cardiology Associates
Cleveland Cardiovascular Research Foundation
18099 Lorain Avenue, Suite 404
Cleveland, Ohio 44111

Dear Dr. Nukta:

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 Title 21 of the Code of Federal Regulations (CFR), Section 812.119.

Food and Drug Administration (FDA) investigators conducted inspections on July 29 – August 9, 2002, December 3 – December 12, 2002, and January 27 – February 6, 2003 of the following clinical studies in which you participated:

- [redacted] sponsored by
- [redacted] sponsored by
- [redacted] sponsored by

These inspections were conducted as part of the FDA's Bioresearch Monitoring Program which includes inspections designed to monitor the conduct of research involving investigational products.

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), Parts 50 and 812 (copies enclosed).

We acknowledge receipt of your August 5, 2002, letter and the September 9, 2002, January 16, and March 6, 2003, letters from Ms. Mary J. Giganti of Waldheger & Coyne, on your behalf, in response to the items on the Form FDA-483s issued by Ms. Kondas and Mr. Kilker. We note that you acknowledge the observations, provide explanations, and describe plans to take corrective actions to address the violations. While those responses indicate some corrective actions have been undertaken, or dispute some factual observations of the Cincinnati District, they do not provide adequate documentation to support your explanations. Further, in some instances, violations you claim to have corrected for one study were found to recur in FDA inspections related to other studies. Your responses collectively, and the results of the inspections conducted on July 29 – August 9, 2002, December 3 – 12, 2002, and January 27 – February 6, 2003, by Ms. Kondas and Mr. Kilker, indicate that you repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products as published under 21 CFR Parts 50 and 812.

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

1. **Failure to conduct the study in accordance with the investigational plan, the investigator's agreement, and conditions of approval imposed by the IRB [21 CFR 812.110(b)]. Failure to submit progress reports at least annually to the IRB [21 CFR 812.150(a)(3)].**

In all three studies as to which you were inspected, you failed to follow some conditions of approval imposed by the reviewing IRB, failed to conduct the study in accordance with the signed investigator agreement, and failed to follow the investigational plans, as required by 21 CFR 812.110(b). In addition, you also failed to submit complete, accurate, and timely progress reports, as required by 21 CFR 812.150(a)(3), for all three of these studies.

[redacted] Study

The IRB requires you to submit and receive approval for all changes and modifications to protocols before they are implemented to ensure the continued protection of the rights, safety, and welfare of research subjects. You implemented two protocol amendments that changed study eligibility requirements, without IRB review and approval. In one case, you never sought IRB review and approval, and in the other, you submitted the amendment for IRB review only after a study monitor repeatedly noted the lack of IRB approval.

The IRB requires that you report any unanticipated problems, injuries, and deaths immediately, as stated in their January 18, 2000, letter. In addition, adverse events should be submitted in progress reports at least annually to the IRB [21 CFR 812.150(a)(3)]. You reported serious adverse events, including deaths, months after their occurrence to the IRB. For example, on October 12, 2001, you

notified the IRB about serious adverse events that occurred several months earlier in the year for subjects [redacted] and [redacted]. On July 25, 2002, you notified the IRB about serious adverse events for subjects [redacted] and [redacted] that occurred in the calendar year of 2001 and subject [redacted] that occurred in the calendar year of 2000.

You failed to enroll subjects according to the inclusion / exclusion criteria. For example, you enrolled subject [redacted] who had a vessel diameter below 3.0 mm, the minimum inclusion value. Subjects [redacted] and [redacted] had coronary interventions within thirty days of their index procedure. Subjects [redacted] and [redacted] each had an acute myocardial infarction (AMI) within 48 hours of the study procedure.

[redacted] Study

For this study, the IRB requires that you report any unanticipated problems, injuries, and deaths immediately as stated in their procedures / instruction forms. In addition, adverse events should be submitted in progress reports at least annually to the IRB [21 CFR 812.150(a)(3)]. You reported serious adverse events to the IRB long after they occurred. For example, in November 2002, you notified the IRB about serious adverse events of several randomized and registry subjects which occurred in the calendar years of 2000 and 2001.

You failed to enroll subjects according to the inclusion / exclusion criteria. Subjects [redacted] and [redacted] had elevated cardiac enzymes and therefore did not meet the CK and CK-MB cardiac enzyme result for eligibility.

Furthermore, numerous other protocol violations occurred. For example, testing was not done at eight-hour intervals to follow levels of elevated cardiac enzymes until they returned to 50% of the peak value for subjects [redacted] and [redacted]. You failed to measure CK and CK-MB cardiac enzymes within protocol specified times in three subjects and you treated at least four patients with a non-qualifying lesion in another blood vessel during the same procedure and did not receive prior approval of these deviations from the sponsor or the IRB according to the investigator agreement. You failed to measure [redacted] every 30 minutes during the procedure in several subjects. You failed to measure creatinine and blood urea nitrogen (BUN) in a subject. You also failed to perform electrocardiograms in two subjects.

[redacted] Study

The IRB requires that you report any unanticipated problems, injuries, and deaths immediately, and any other adverse event should be submitted to the IRB in progress reports at least annually. In your final report to the IRB, dated October 1, 2002, you stated that you previously submitted reports of adverse events. However, there is no record of your submitting reports of adverse events until January 22, 2003. If you did in fact submit the data earlier to the IRB, but the IRB refused it, you should have correspondence to support this and none was available during the inspection. In

addition, there were adverse events from 2001 that were included in the January 2003 report but were not submitted previously in the annual progress report.

You failed to enroll subjects according to the inclusion / exclusion criteria. For example, subjects [redacted], and [redacted] had coronary inventions within thirty days of their procedure. Subjects [redacted] had renal failure. You failed to follow the study treatment procedure when you implanted subjects [redacted] (November 27, 2001) and [redacted] (December 1, 2001) with a device from another clinical investigation, the [redacted] study. You did not report these protocol deviations before the IRB reviewed your final report on October 9, 2002. Instead, you reported these deviations to the IRB on November 14, 2002. In addition, the investigator agreement required you to receive prior approval from the sponsor for protocol exceptions.

You failed to perform all required tests at study visits. Your records contained numerous instances where study procedures, including laboratory testing, either were not performed or were not consistently followed at scheduled examinations. Subjects [redacted] did not have CK and CK-MB results of their measurements. Subjects [redacted] and [redacted] did not have CK and CK-MB measurements performed according to established procedures. Subjects [redacted] and [redacted] did not have ECG performed according to established procedures. Subject [redacted] did not have a follow-up to check for major adverse [redacted] events ([redacted]) within specified period. Subjects [redacted] and [redacted] did not achieve an [redacted] within protocol limitations. Subjects [redacted] and [redacted] did not have any [redacted] values.

Summary

It is important to understand that treatment of study subjects must adhere to the requirements of the investigational plan (21 CFR 812.110). Changes to and deviations from the investigational plan must generally have prior approval from the sponsor [21 CFR 812.150(a)(4)]. In circumstances where changes affect the rights, safety, or welfare of study subjects or the scientific soundness of the study, FDA and IRB approval are also required. See 21 CFR 812.150(a)(4), 812.35(a). Only in an emergency where deviation from the investigational plan is necessary to protect the life or physical well-being of the subject may the investigation go forward without prior approval, but you must report this deviation to the sponsor and reviewing IRB as soon as possible, and no more than 5 working days, after its occurrence [21 CFR 812.150(a)(4)].

2. Failure to prepare and maintain accurate, complete, and current records relating to your participation in the investigation [21 CFR 812.140(a)(3)]

In one study as to which you were inspected, you failed to prepare and maintain adequate records as required by 21 CFR 812.140(a)(3).

[redacted] Study

You failed to prepare and maintain complete case histories of subjects participating in the clinical investigation. The original case report forms (dated December 30, 1999) used to document demographics (study data) were not available for subjects [redacted].

You failed to prepare and maintain accurate information regarding the review of study data and study eligibility. Dates provided in documentation of your review of study data in the case histories of subjects [redacted] are inaccurate. The study eligibility forms were also incorrectly marked for subjects [redacted].

In addition, you failed to maintain accurate, complete and current records of informed consent as required by 21 CFR sectrion 50.27 and 812.140(a)(3). Records show that subjects [redacted] signed informed consent documents after they were randomized and study-specific procedures performed. You contend that these subjects signed appropriate informed consent documents prior to participation in the study, but that these forms were accidentally discarded.

Summary

It is important to understand that your participation in an investigation must adhere to the record keeping requirements in accordance with 21 CFR 812.140(a)(3).

3. Failure to obtain informed consent (21 CFR Part 50 and 21 CFR 812.100).

In all three studies as to which you were inspected, you failed to ensure that informed consent was obtained in accordance with 21 CFR Part 50.

[redacted] Study

You did not meet the basic requirements for informed consent specified in 21 CFR 50.25. The informed consent documents used and signed by the 117 subjects did not disclose the expected 12-month duration of the research or include specifics about the schedule of required follow-up visits and the testing procedures that would be performed, as required by 21 CFR 50.25(a)(1). These informed consent documents do not describe details of procedures encountered by the subject during the investigation such as the echocardiogram required during the one-month follow-up visit, the post-treatment use of aspirin along with either [redacted]® or [redacted]®, or a 12-month follow-up assessment. The informed consent documents also did not adequately disclose the risks of participation as required by 21 CFR 50.25(a)(2), as they did not discuss the possibility of an [redacted] procedure in the event of an [redacted] or [redacted].

In addition, five subjects signed informed consent documents that were not the most recently approved IRB version.

[redacted] Study

You failed to ensure that informed consent was obtained from each research subject before that subject participated in the research study, as required by 21 CFR 50.20. Subjects [redacted] and [redacted] did not sign the informed consent documents. In your response, you state that the sponsor permits a patient's family member to sign the informed consent document and that an "X" mark as a signature is adequate to acknowledge the patient's consent during duress such as during a heart attack and / or being under the influence of pain medication.

FDA requires clinical investigators to obtain legally effective informed consents from subjects or the subject's legally authorized representative. See 21 CFR 50.20. An investigator must seek consent only under circumstances that provide the prospective subject or his representative sufficient opportunity to consider whether to participate and that minimize the possibility of coercion or undue influence. The entire informed consent process involves giving a subject or the representative adequate information concerning the study, providing adequate opportunity for the subject or the representative to consider all options, responding to questions, ensuring that the subject or representative has comprehended the information, obtaining the subject's voluntary agreement to participate or the representative's permission and, continuing to provide information as the subject or situation requires. Consequently, obtaining a patient's consent under conditions of physical distress – such as during a heart attack – would not satisfy this regulation.

Your response indicates this would be allowed by the protocol. In an emergency situation when consent is not able to be obtained, or in exceptional cases when consent is difficult to obtain, then the case should have been documented and reported to the IRB and to the sponsor within five days in compliance with the investigator agreement.

You failed to ensure that a legally effective informed consent was obtained from several study subjects. For example, subjects [redacted] and [redacted] signed consent forms applicable to different branches of the study from those in which they were participating. Furthermore, the only records of consent for fourteen subjects ([redacted] and [redacted]) are outdated consent forms for the investigational study. Subjects [redacted], and [redacted] signed an unapproved informed consent.

[redacted] Study

You failed to ensure that informed consent was obtained from each research subject before that subject participated in the research study, as required by 21 CFR 50.20 The informed consent documents used and signed by 30 subjects do not describe and identify all procedures in the study,

as required by 21 CFR 50.25(a)(1). Electrocardiograms are not described. The informed consent document does not describe foreseeable risks, as required by 21 CFR 50.25(a)(2). These consent forms do not describe treatment and compensation for physical injuries, as required by 21 CFR 50.25(a)(6).

In addition, you are required to seek consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence (21 CFR 50.20). Informed consent documents should not contain unproven claims of effectiveness or certainty of benefit, either explicit or implicit, that may unduly influence potential subjects. Overly optimistic representations in the potential benefit section of the informed consent document, such as [redacted] and [redacted] is a safe and effective treatment ... The success rate is more than 90 percent ... Previous studies with [redacted] have proved promising" are misleading and violate the requirement to minimize the possibility of coercion or undue influence (21 CFR 50.20).

Summary

The July 29 – August 9, 2002, FDA inspection found that you treated study subjects without benefit of proper informed consent and revealed protocol violations that included treatment of subjects outside of the inclusion / exclusion criteria. You responded that you would take corrective actions on all issues; however, the December 3 – 12, 2002, and the January 27 – February 6, 2003, FDA inspections revealed additional violations similar to those found during the July 29 – August 9, 2002, inspection.

Concerning activities that you plan to initiate as part of your corrective actions, you should amend your organizational procedures regarding clinical investigations for which you are the principal investigator. These procedures need to include measures to assure that personnel responsible for the informed consent process are knowledgeable of the inclusion / exclusion criteria of the study in question and have access to pertinent information about the potential study subject. The informed consent process needs to stress the importance of the subject adhering to the study requirements. Once these procedures have been amended, a training program needs to be arranged for all personnel who have responsibilities with regard to investigational studies.

4. Failure to prepare and maintain accurate, complete, and current records relating to your receipt, use, or disposition of a device [21 CFR 812.140(a)(2)].

In one study as to which you were inspected, you failed to maintain adequate records in accordance with 21 CFR 812.140(a)(2).

[redacted] Study

The study monitor report noted the failure to account for [redacted]. Study records failed to include any documents to verify the return of these [redacted]

Summary

It is important to understand that an investigator should maintain adequate records for the receipt, use, or disposal of a device.

General Discussion

Although your responses to the FDA-483s attribute many violations to your employees, delegating work to research staff does not relieve you of the responsibility to supervise the clinical investigation. You are responsible for the accuracy and completeness of the study records and for any discrepancies found in the records. In signing the investigator's agreement, you agreed to conduct the study according to the investigational plan and in accordance with FDA regulations. See 21 CFR 812.100 and 812.110. Your response indicates that you did not conduct certain study procedures because they were not standard in the industry. Despite your explanation, these tests were a requirement of the investigational plan. If you disagreed with these tests, you should have discussed them with the sponsor prior to signing the investigator agreement.

According to your study records, you are actively participating in the clinical investigation of the following applications: IDE [redacted] IDE [redacted] IDE [redacted] IDE [redacted] and IND [redacted]. You are also actively participating in the post-marketing study of PMA [redacted]. We recommend that you review your activities in these studies to ensure compliance with FDA regulations to ensure good clinical practices and to protect the rights, safety, and welfare of the human subjects.

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 repeatedly or deliberately failed to comply with the cited regulations and it 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 812.119(a).

Within fifteen (15) days of receipt of this letter, write or call Dr. Michael Marcarelli at (240) 276-0125 to arrange a conference time or to indicate your intent 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:

Michael E. Marcarelli, Pharm.D.
Director
Division of Bioresearch Monitoring, HFZ-310
Office of Compliance
Center for Devices and Radiological Health
Food and Drug Administration
2098 Gaither Road
Rockville, Maryland 20850

In your response, provide a complete list of your investigational studies and post-marketing studies, including the name of the study sponsor, the date of IRB approval, application number, and status. The list of clinical studies you provided to Mr. Kilker during the January 27 – February 6, 2003, inspection is incomplete. For example, the status and application of the [redacted] sponsored by [redacted], and the application of the [redacted], sponsored by [redacted] are not included in the list.

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 you may be accompanied by a representative of your choosing. 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 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 Part 16 and 21 CFR 812.119. 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,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

Enclosures – Consent Agreement
21 CFR Parts 16, 50, and 812