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July 7, 2005

Viola Sellman, Chief
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
Program Enforcement Branch II, HFZ-312
2094 Gaither Road
Rockville, Maryland 20850-4009

Re: Warning Letter, dated October 14, 2004

Dear Ms. Sellman:

I am writing in response to your Warning Letter, dated October 14, 2004. I take my obligations in participating in the conduct of a clinical trial very seriously. I also treat my obligations regarding the health and safety of my patients and individuals participating in the clinical trial with the utmost seriousness and respect.

The clinical study I participated in was sponsored by [redacted] and involved providing study subjects with [redacted] to investigate and study an experimental [redacted] device, the [redacted] developed by [redacted] Although many of study subjects received the [redacted] my participation only involved the control arm of the study. Therefore, I only provided patients with fully inspected, non-investigational devices that are accepted by the Food and Drug Administration ("FDA"). No participant receiving services from me received an investigational device and all such participant were provided treatment at the highest level and quality of care. Furthermore, I note that all the items cited in the FDA Warning Letter were procedural and none effected, in any way, the level of care and services received by participating individuals.

Moreover, as you are aware, the sponsor of this study, [redacted] encountered many difficulties in the overall conduct of this study. Due to these difficulties and my frustration with the overall conduct of the study, I made the decision to discontinue participation in the study and discontinued enrollment of subjects in [redacted] In connection with this decision, [redacted] determined it would only use results obtained in connection with [redacted] study subjects I enrolled into the study prior to [redacted] as part of the investigational device exemption submitted for the [redacted] These [redacted] study subjects executed [redacted] approved informed consent forms in connection with their participation in the study.

Notwithstanding my decision to terminate the study and [redacted] decision to only use data from certain subjects, I have continued to monitor all of the study participants that I enrolled. I did this even though no participant I enrolled received the experimental [redacted] I will continue my monitoring and oversight responsibilities until the final participant completes the two year follow up period.

I have addressed each Warning Letter Item individually below with a description of actions taken in response.

(1) Failure to obtain Investigational Review Board approval (21 CFR 812.110(a)).

[redacted] Study is the first and only clinical research study which I participated in as a principle investigator. Consequently, I relied heavily upon instruction and advice of [redacted] in undertaking my participation in the study. I believed that approval of the study by the [redacted] was sufficient for my participation in and conduct of the study. I obtained such approval prior to my enrollment of any study subjects. [redacted] accepted this approval and did not request evidence of institutional review board ("IRB") approval of my participation in this study.

[redacted] provided to me its form of informed consent and accepted my use of the form between [redacted] and [redacted] I now more fully understand that clinical research conducted under the auspicious of the FDA can only be conducted following review and approval of a properly formed IRB. Upon learning that the approval of the [redacted] was insufficient, my staff diligently pursued and obtained study approval from [redacted] functions as a non-local institutional review board for various entities on Long Island and is well versed in, and meets the FDA requirements for, functioning as a non-local IRB.

Upon receiving [redacted] notice that the original informed consent executed by each enrolled study subject should be replaced with a [redacted] approved informed consent, my staff attempted to contact each study subject and obtain an executed [redacted] informed consent. I also met with [redacted] and formulated a plan to obtain revised informed consents from each study subject. Ultimately, due to the inaccessibility of a majority of the study subjects, we were only able to obtain signatures of [redacted] study subjects on the revised informed consent. Many subjects were inaccessible because they had received a FDA approved device more than a year before and did not understand the necessity of completing a revised informed consent. Consequently, [redacted] is only using the results obtained from these [redacted] study subjects as part of the investigational device exemption submitted for the [redacted] I will ensure proper IRB approval is obtained should I decide to participate in clinical research in the future.

(2) Failure to obtain adequate informed consent (21 CFR 812.100 and 21 CFR 50.20, 50.25, and 50.27(a)).

As discussed above in responding to Item 1, I initially utilized a [redacted] supplied informed consent in connection with the study. The informed consent was approved by the

[redacted] whose approval I believed was sufficient for my participation in the control arm of the study. Due to my inexperience with clinical research studies, I was not aware, nor was I informed by [redacted] that the informed consent provided was inadequate for these purposes.

Upon [redacted] review of this informed consent, I was informed of the inadequacies of this informed consent. Thereafter, we attempted to obtain from each study subject an executed copy of the revised informed consent, approved by [redacted] Additionally, a decision was made not to include any study results received from study subjects who did not sign the revised consent in the [redacted] research study results.

With respect to my failure to obtain the original informed consent from [redacted] of the study subject's prior to those subject's undergoing pre-operative evaluations, it was my understanding that certain potential study subjects should not be enrolled in the study until after they were determined to be eligible. Unfortunately, in order to determine eligibility, certain pre-operative evaluations were required by [redacted] to be performed on each potential subjects. These evaluations were required to be completed out forty-five days prior to surgery and unfortunately, in certain cases, these evaluations were completed before the informed consent process was completed. I note, however, that an informed consent was always obtained from a study subject prior to undertaking any surgical procedure in connection with study participation. Furthermore, I routinely followed hospital guidelines in ensuring pre-operative medical clearance is obtained for each patient undergoing surgical intervention.

I now more fully understand that as principal investigator of a study it is my responsibility to ensure that the informed consent utilized in connection with a study meets all requirements of 21 CFR Part 50 and that each study subject must execute a consent prior to participation. Although I currently have no plans to act as a principal investigator in connection with any clinical research studies in the future, I will ensure proper and timely informed consent is obtained from each study subject should circumstances change.

(3) Failure to adhere to the investigational plan (21 CFR 812.100 and 812.110(b)).

In conducting the study, I attempted to comply with the investigational plan and all applicable FDA regulations and the study protocol. As part of this compliance I attempted to perform all required follow up evaluations within the protocol required timeframes. Unfortunately, due to certain miscalculations of my staff with respect to the length of such timeframes, our inexperience with protocol driven study activities and the reluctance of some study participants to return to the office for follow up visits within the required timeframes, certain follow up evaluations were not completed in a timely manner. These failures are noted in your warning letter and addressed below.

In order to ensure patient safety at all times, all necessary follow up evaluations were scheduled and conducted even though they fell outside of the required timeframes, whenever the study subject was willing to make themselves available for such evaluations. Further, we ensured that all reluctant patients, at a minimum, received all follow up that is medically necessary in connection with the [redacted] they received.

I recognize that [redacted] was included in the study even though the subject had undergone [redacted] which was an exclusion criteria for the study. Originally, when we determined the Subject met the exclusion criteria, we intended to exclude the subject. [redacted] and [redacted] advised me to keep the Subject in the study for statistical reasons. They indicated [redacted] would exclude the Subject later as they deem appropriate. I was unaware at the time that all changes in the Protocol were required to be approved by the IRB.

With respect to the specifically noted missed instances of post-operative evaluations, most such visits were conducted before the noted time frame or were missed due to patient inaccessibility. For example, [redacted] and [redacted] week post-operative evaluation were performed outside the required timeframe because of a miscalculation in the timing schedule and follow-up date. [redacted] month post-operative visit was, however, performed within the allocated timeframe, as the surgery was preformed on [redacted] and the [redacted] month follow-up was performed [redacted] The protocol allowed a plus or minus three week window for all such post-operative visits. [redacted] month visit was correctly scheduled for [redacted] however, the subject did not return to the office until [redacted] six weeks later and outside the visit window.

For [redacted] the post-operative visits were performed outside of the protocol required timeframes due to patient unavailability and scheduling. Each of these post-operative visits were performed earlier than required. [redacted] visit was also performed prior to protocol required period and [redacted] was performed later because of the timing of the Subject's surgery and discharge. The failure to perform [redacted] month [redacted] on all study subjects was an oversight.

I now more fully understand the responsibility for protocol driven requirements accepted by principal investigators. Although I currently have no plans to act as a principal investigator in connection with any clinical research studies in the future, I will ensure proper and timely completion of all follow up and protocol required evaluation for each study subject should circumstances change.

(4) Failure to maintain accurate, complete, and current records (21 CFR 812.140(a)).

In conducting the study we attempted to maintain accurate, complete and current records relating to each subject's participation in the study. Unfortunately, due to our inexperience in conducting clinical studies, certain forms were not fully completed in a timely manner. Where any study subject data is intended to be included by [redacted] in the study results, such forms were subsequently correctly completed. I have addressed the failures noted in your warning letter below.

With respect to my failure to include data required by the protocol in [redacted] I was advised by [redacted] representatives would assist us in performing these calculations. Therefore, we collected the

data but did not complete the calculations required to complete form [redacted] Subsequently [redacted] failed to provide the necessary assistance.

The narrative reports covering the operative procedures were not included in the medical reports for [redacted] as they were sent to the hospital and accidentally not included in the Subjects' medical record. This oversight has subsequently been corrected. The inconsistency in the height and weight of [redacted] was a clerical error which was subsequently corrected and initialed.

I note, however, that all such information necessary for the implantation of a FDA approved device was always included in the medical records of such Subjects on a timely basis. I now more fully understand the responsibility for completing all records undertaken by a principal investigator in a clinical trial. Although I currently have no plans to act as a principal investigator in connection with any clinical research studies in the future, I will ensure proper and timely completion of all study records for study subject should circumstances change.

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As a result of my participation in this study, I am now more fully aware of the responsibilities and obligations accepted by a principal investigator in agreeing to conduct a clinical study. I currently have no plans to conduct any clinical studies in the future. However, should I determine to undertake such an exercise in the future, I will ensure compliance with all FDA requirements and regulations. Further, before participating in research I will implement the necessary policies and procedures regarding research, ensure I have adequate and trained staff, institute the necessary relationship with IRB and otherwise take the steps to ensure all such research conducted in compliance with all applicable laws and regulations.

Very truly yours,

Louis C. Rose, M.D.