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WARNING LETTER
Via Federal ExpressFood and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

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Dear Dr. Figgie:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site, to discuss your written response to the deviations noted, and to request a prompt reply with regard to the remaining issues. The inspection took place during the period of September 26 and November 20, 2001, and was conducted by Dr. L. Glenn Massimilla and Mr. Andrew B. Paglia, investigators from FDA's New York District Office. The purpose of the inspection was to determine if your activities as a clinical investigator in [REDACTED] study of the [REDACTED] comply with applicable FDA regulations. This [REDACTED] is a device as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Application (PMA), and Premarket Notification [510(k)] submissions are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report submitted by the district office revealed serious violations of requirements of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions, Part 50 - Protection of Human Subjects, and Section 520(g) of the Act. You received a Form FDA 483, "Inspectional Observations," at the conclusion of the inspection that listed the deviations noted and discussed with you. We acknowledge receipt of a copy of your response to Mr. Jerome Woyshner, District Director, New York District Office, dated January 4, 2002. The deviations noted on the Form FDA 483, our subsequent review of the inspection report, and your response to the Form FDA 483 items are discussed below. The deviations noted include:

Failure to obtain signed and dated study informed consent documents from all study subjects prior to surgery. (21 CFR 812.100, 50.20, and 50.27)

Several study subjects signed and/or dated the informed consent document after the surgical procedure. As stated in 21 CFR 812.100, an investigator is responsible

for ensuring that informed consent is obtained in accordance with 21 CFR Part 50. According to 21 CFR 50.20, no investigator may involve a human being in an investigational study unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. Moreover, 21 CFR 50.27 requires that informed consent is 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.

Failure to include all required elements in the informed consent document used. (21 CFR 50.25)

The consent document used did not include specifics about the schedule of required follow-up visits and the testing necessary at each visit.

Failure to provide regular progress reports to the reviewing institutional review board (IRB). (21 CFR 812.150(a)(3))

You failed to submit progress reports to the reviewing IRB during the period between 4/13/99 and 8/23/01. Investigators are required to submit progress reports to the reviewing IRB at regular intervals, but in no event less often than yearly. As a result of the lack of a progress report, the IRB was unable to perform their continuing review of your study and terminated their approval for the study by default. Five (5) subjects received the investigational device after termination of IRB approval.

Failure to obtain IRB approval of the study prior to requesting informed consent from a study subject. (21 CFR 812.110(a))

You sent a copy of the informed consent document to a potential study subject for review and signature while it was under review by the IRB. An investigator may determine whether potential subjects may be interested in participating in an investigation but cannot request written informed consent of any subject to participate before obtaining IRB approval.

Failure to report unanticipated adverse device effects to the reviewing IRB. (21 CFR 812.150(a)(1))

You failed to report to the reviewing IRB the fact that subject [REDACTED] required [REDACTED]. An investigator is required to report to the reviewing IRB any unanticipated adverse device effects as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

Failure to maintain device accountability records. (21 CFR 812.140(a)(2))

Records supplied by you during the inspection were insufficient to determine the total number of investigational devices received from the sponsor as well as their

use or disposition. A participating investigator is required to maintain accurate, complete, and current records of the receipt and use or disposition of all investigational devices. This includes: records of the type and quantity of the device, the dates of receipt, and the batch numbers or code marks; the names of all persons who received, used, or disposed of each device; and information regarding why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

Failure to conduct the study in accordance with the investigational plan. (21 CFR 812.100 and 812.110)

Numerous protocol violations give evidence to the fact that you failed to ensure that the investigational plan was followed. For example, you entered subjects [REDACTED] and [REDACTED] into the study even though they met the exclusion criteria of having an active infection. Both subjects were found to have active urinary tract infections as a result of standard pre-operative testing. Moreover, you [REDACTED] subject [REDACTED] on 6/19/99, despite the study inclusion criteria limiting the study to [REDACTED] [REDACTED], you failed to collect follow-up data for subjects [REDACTED] and [REDACTED] within the prescribed timeframes; and you chose to eliminate a prescribed visit for subject [REDACTED].

Failure to maintain accurate, complete, and current subject records. (21 CFR 812.140(a)(3))

Several case report forms (CRFs) reviewed were lacking required information and a number of discrepancies were noted between source documents and data recorded on the CRFs.

The deviations listed above are not intended to be an all-inclusive list of deficiencies that may exist in your clinical study. It is your responsibility as a clinical investigator to ensure that an investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations.

With regard to informed consent issues, your written response to the Form FDA 483 states that it is your practice to have a full consent discussion with each potential subject during the pre-operative visit. You illustrated this with copies of subject records that include notations of such discussions. Informed consent is a process and the informed consent document that is signed is not intended to be the sole communication with a subject in this regard. However, it is important that potential subjects be made aware, in writing, of all protocol requirements and all study risks. For example, when protocol requirements with regard to the timing of follow-up visits as well as the types of testing that will be required at each are provided up front, potential subjects can decide whether such a commitment of time is feasible. If such a commitment is not feasible, they should not be encouraged to participate. Missed follow-up visits and/or visits outside of the prescribed windows deplete the pool of information available to the sponsor for support of marketing submissions and place subjects unnecessarily at risk. Your contention that the follow-up

received by study subjects is no different from that you would give your regular orthopedic patients, does not mitigate the need to relay to your subjects the exact requirements of the study. Such information is important in helping to assure their compliance with these requirements.

You state that [REDACTED], your first study subject, was sent a copy of the informed consent while the IRB was reviewing the study. Since the approved informed consent document had no changes, you did not have him sign an additional copy. As noted above, regulatory requirements state that an investigator may determine whether potential subjects are interested in participating in an investigation but cannot request written informed consent of any subject to participate before obtaining IRB approval. You further state that several subjects had signed the informed consent document prior to surgery but failed to date it at the time of signature. To remedy this, you had them date it once this omission was discovered. This information should have been documented in their study files at the time the documents were dated.

With respect to subject [REDACTED], you state that the observation that this subject was “provided a complete (6-page) informed consent to read for the first time on 6/16/99, the date of surgery,” is incorrect. According to the inspection report, the subject made this statement on 11/8/01, during a telephone interview with Dr. Massimilla regarding the informed consent process.

Your response states that since the study follow-up time was two years, this probably led you to believe that IRB approval would cover that time period. The requirement to submit progress reports to the IRB no less than yearly is a regulatory requirement. It is the responsibility of a clinical investigator to know and adhere to all applicable regulations. The inspection report notes that you did not have a copy of the IRB’s request for the missing progress report, which included notice that study approval would be rescinded if no report was forthcoming. The report also notes that you stated that you do not recall receiving such a notice. Your response states that your institution’s IRB has instituted a new procedure to assure that all IRB communications, including notices of overdue progress reports, are received and acknowledged directly by the investigators.

Regarding the [REDACTED] of the investigational device as an “emergency use,” you contend that at least two of the requirements, “limb-threatening” and the lack of a generally acceptable alternative, were met. You also contend that you discussed this with the IRB Chair, though he stated at the time of the FDA inspection that he did not recall the conversation. However, as you state, there was sufficient time to notify FDA. The surgery was planned approximately two months prior to [REDACTED] according to an e-mail contained in the subject’s study file (copy enclosed). Therefore, this use of an investigational device would not be considered an “emergency use” but instead a “compassionate use.” This requires submission of an investigational device exemption (IDE) supplement by the study sponsor for FDA review and approval, if deemed appropriate.

Your response states that you believe that the deterioration of [REDACTED] was an event entirely separate from the device [REDACTED] and not an unanticipated adverse device effect that required reporting. You also state that the statement that this subject received additional surgical intervention on 3/12/01 is incorrect. Enclosed please find a copy of the physician's admitting orders for this subject that was collected as part of the inspection. It states that [REDACTED] was done under epidural anesthesia. The need for [REDACTED] of the investigational device was not an adverse effect listed in the protocol or the informed consent document and is therefore considered an unanticipated adverse device effect for this study. Investigators must report all unanticipated adverse effects to the reviewing IRB.

With regard to [REDACTED] of the investigational device in two subjects who were found to have urinary tract infections as a result of the standard pre-operative testing, you state that it is standard procedure to prescribe antibiotics pre-operatively, to proceed with surgery, and to follow-up post-operatively. While this may be standard procedure for your orthopedic patients, the first of the ten exclusion criteria in the study protocol was "active or recent infection."

Regarding the lack of device accountability, your response states that these records are part of your office records and the information can be retrieved by performing a search by protocol or patient name. You further state that Dr. Massimilla and Mr. Paglia chose to search hospital records rather than ask you for this information. In an e-mail exchange on this subject, Dr. Massimilla stated that, according to his inspection log, on 10/4/01 you stated that you would provide this information, saying that you could easily obtain it by searching your "database" or from your recollections. On 10/24/01, a spreadsheet of subjects was provided by your office in response to FDA's request. The document was unlabeled and provided a subject/medical record/device trail but not the reverse. The accountability records expected as part of an investigator's study file include records of the receipt and use or disposition of all investigational devices received from the sponsor. The specific content of these records is noted above, where this deviation is first listed. It was after receipt of the inadequate listing that FDA investigators proceeded to inquire at the hospital for device accountability records.

Your response, in general, indicates a continued lack of understanding of the regulatory requirements clinical investigators must meet and includes few corrective actions taken or planned with regard to the deviations noted during the inspection. In addition, you state at the start of your response that your personal orientation was one of "a treating physician rather than, strictly speaking, a clinical investigator." It is important for a clinical investigator to understand that unless the physical safety of a subject demands otherwise, treatment of study subjects must adhere to the requirements of the investigational plan.

Enclosed to assist you in better understanding your responsibilities as a clinical investigator are copies of 21 CFR Parts 50, 54, 56 and 812. Part 812 describes your responsibilities as a clinical investigator of an investigational medical device

