



NOV 18 2006

Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850**WARNING LETTER**

VIA FEDERAL EXPRESS

Bradley J. Bartholomew, M.D.
3629 Prytania Street
New Orleans, Louisiana 70115

Dear Dr. Bartholomew:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your clinical site from August 16 to August 23, 2006, by an investigator from the FDA New Orleans District Office. The purpose of this inspection was to determine if your activities and procedures related to your participation in the clinical study of the [REDACTED] [REDACTED] complied with applicable FDA regulations. The [REDACTED] is a device as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h). This letter also requests prompt corrective action to address the violations cited and discusses your August 28, 2006, written response to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval applications (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 prepared by the district office revealed several violations of Title 21, Code of Federal Regulations (21 C.F.R.) *Part 812 – Investigational Device Exemptions*. At the close of the inspection, the FDA investigator presented an inspectional observations form FDA 483 for your review and discussed the observations listed on the form with you. The deviations noted on the FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

Failure to conduct the investigation in accordance with the signed agreement, investigational plan, and conditions of approval imposed by an IRB or FDA (21 C.F.R. 812.100 and 812.110(b)).

Clinical investigators are required to ensure that investigations are conducted according to the signed agreement, the investigational plan, and applicable FDA regulations, as well as any conditions of approval imposed by the IRB or FDA pursuant to 21 C.F.R. 812.100 and 812.110(b). Examples of your failure to comply with these requirements include, but are not limited to, the following:

- Radiographic data measurements were not collected as required by the investigational plan, including the following:
 - [REDACTED] were not collected as required for [REDACTED] and [REDACTED] for the following 5 subjects, [REDACTED]
 - [REDACTED] used to measure [REDACTED] and [REDACTED] were not collected at the 6 and/or 12 month Post-Operative visits for the following 7 subjects: [REDACTED]
 - Subject [REDACTED] was missing the radiographic evaluation documentation at the Operative visit and at the 24 month Post-Operative visit.
 - Required Pre-operative radiographic data and measurements were not collected prior to implantation for subject [REDACTED]

In your response, you acknowledge that [REDACTED] and [REDACTED] were not taken. You stated that in your clinical practice you do not routinely order these [REDACTED] and therefore they were not taken or were inadvertently omitted. You acknowledge that Pre-Operative radiographs were not obtained for patient [REDACTED] as required by the protocol. Your response is inadequate in that it does not explain how you intend to prevent these deviations from occurring in future studies therefore, please submit a corrective action plan on how you plan to prevent this violation from reoccurring in the future.

The FDA investigator stated she reviewed all records for the Operative and 24 month Post-Operative visits for subject [REDACTED] however, she could not find documentation to demonstrate appropriate radiographic evaluations were taken. You stated in your response that Operative films were taken, and attached a Data Resolution Form (Attachment A) that provides Operative radiographic measurements, however, there was no resolution provided concerning the lack of radiographic evaluation for the 24 month Post-Operative visit. Your response is inadequate in that it does not provide the radiographic evaluation information for the 24 month Post-Operative visit. Please submit evidence that this evaluation was completed.

- The investigational plan was not followed in terms of determination of subject eligibility, for example subject [REDACTED] was found to be eligible more than seven and a half months prior to implantation of the device though the investigational plan states that the implantation must take place within six months of determination; and, subject [REDACTED] file did not contain documentation necessary to calculate the [REDACTED] which defines a criteria for exclusion.

In your response, you provide Data Resolution Forms (Attachments B and C) to document the eligibility of the subjects. Please note that this information should be recorded on the study worksheets at the required times rather than being “resolved” through monitoring at a later date. Your response is inadequate in that it does not explain how you intend to prevent these deviations from occurring in future studies. Please submit a corrective action plan that addresses how you plan to prevent these deviations from occurring in future studies.

Failure to maintain accurate, complete, and current records (21 C.F.R. 812.140(a)).

FDA regulations require clinical investigators to maintain accurate, complete, and current records relating to the investigator’s participation in an investigation, pursuant to 21 C.F.R. 812.140(a). Examples of your failure to adhere to these requirements include, but are not limited to, the following:

- Records of receipt, use, and disposal of a device that relate to the type and quantity, dates of receipt, and batch number or code mark of the device are not all accurate and complete. Specifically, there is no documentation of the following:
 - device accountability for the test treatment investigational [REDACTED] devices for subjects [REDACTED] and [REDACTED] for
 - for the control treatment [REDACTED] devices for subject [REDACTED]
 - the operative source worksheet for subject [REDACTED] identifies the implantation of [REDACTED] devices and [REDACTED] device, while the Operative Case Report Form (CRF) identifies the implantation of [REDACTED] device. A third document from the distributor, the [REDACTED] identifies the use of [REDACTED] devices in this subject; and,
 - source documentation for subject [REDACTED] identifies the implantation of [REDACTED] device, but the Operative CRF and information from the distributor identify the implantation of [REDACTED] devices and a third [REDACTED] device as not implanted.

In your response, you acknowledge that no device accountability inventory was used during the study as the devices were delivered to you on an as-needed basis by [REDACTED]. You state that, for patients [REDACTED] clinic records and worksheets do not include device usage information. Furthermore, you indicate that hospital charts, which generally included notations regarding the specific devices implanted, were destroyed during Hurricane Katrina. You have provided shipping invoices (Attachment D) for patients [REDACTED] and [REDACTED]. The shipping invoice provided for subject [REDACTED] as well as the Informed Consents Status Report and Operative Visit for subject [REDACTED] show a surgery date of [REDACTED] however, the

invoice ship date shown for subject [REDACTED] device is [REDACTED], which is after the surgery date for subject [REDACTED] was documented to have taken place. The Informed Consents Status Report also shows that, as of [REDACTED], all subjects enrolled in the study had been implanted with the study device. Please provide an explanation for this discrepancy.

For subject [REDACTED] you state you reviewed the records and confirmed that [REDACTED] devices were used as documented by the distributor, and you provided a copy of the CRF Correction Form (Attachment E). For subject [REDACTED] you state that the invoice (Attachment F) confirms implantation of [REDACTED] devices, with a third provided but not used; therefore, the CRF is accurate, and the study worksheet has been corrected to reflect this information. While your corrections have addressed the current discrepancies, your response is inadequate in that it does not indicate the disposition of the third device that was not implanted and how you plan to prevent this deviation from occurring in the future. Please explain how you intend to prevent these deviations from occurring in future studies.

- Records for each subject concerning anticipated and unanticipated adverse device effects are not all complete. Specifically, for subjects [REDACTED] Intercurrent Event Report Forms completed in [REDACTED] do not document the relationship to the study device, the intensity of the event, or if the event was anticipated or unanticipated.

In your response, you have provided CRF Correction Forms (Attachments H and I) that were issued following the last monitoring visit requesting clarification regarding the causal relationship of the device and the intensity of the intercurrent events noted in the observations. You note that the events were not caused by or related to the study device. The forms are dated by you on [REDACTED] and the FDA inspection concluded August 23, 2006, however, these CRF Correction Forms were not provided to the FDA investigator during the course of the inspection or at the closing meeting. Please note that the investigator's agreement and the investigational plan require that all intercurrent events, device related or not, be reported using the appropriate case report form. Your response is inadequate in that these events were not documented at the time when they occurred. Please explain how you intend to prevent these deviations from occurring in future studies.

- Records of each subject's case history are not all accurate and complete. Specifically, individual subject case history files including source documentation and CRFs contain missing or discrepant information, including, but not limited to the following:

- for subject [REDACTED], missing documentation of required physical examinations, incomplete or missing documentation regarding the placement of [REDACTED] and Complications Report or Intercurrent Event Report not completed;
- missing information regarding surgical complications, the number of devices implanted, and device accountability for subject [REDACTED] and,
- source worksheets and CRFs do not record any information or measurements regarding required evaluations for subjects [REDACTED]

In your response, you have provided Data Resolution Forms (Attachments J-O) addressing the incomplete information identified in the case history files. Please note that the investigator's agreement for this study states that you agree to prepare and maintain adequate case histories designed to record all pertinent clinical observations and other data, and that data will be collected on source documentation during clinical visits for later transcription to appropriate case report forms that are to be completed and signed. Many forms had been left blank or had missing information. All CRFs, with a few exceptions, have a statement at the bottom of the form indicating "COMPLETE ALL ITEMS. NOTE N/A OR NONE IF ITEM DOES NOT APPLY. MISSING OR INCONSISTENT DATA WILL REQUIRE ADDITIONAL QUERIES." Your response is inadequate in that it does not explain how you intend to prevent these deviations from occurring in future studies. Please submit a corrective action plan that addresses this deviation.

Failure to prepare and submit a complete and accurate report of an unanticipated adverse device effect within 10 working days after first learning of the effect, to the sponsor and the reviewing IRB (21 C.F.R 812.150(a)(1)).

- A complete and accurate report of an unanticipated adverse device effect was not prepared and submitted within 10 working days after first learning of the effect, to the sponsor and the reviewing IRB, as required per regulation. You failed to adhere to this requirement in that an Intercurrent Event CRF for subject [REDACTED] dated as completed on [REDACTED] concerning the [REDACTED] onset of a severe, unanticipated event related to the study device was not documented until revealed during a study monitoring visit and still has not been reported to the reviewing IRB as required for unanticipated adverse device effects.

In your response, you now state that this event, initially identified and documented as unanticipated, was anticipated and provided a CRF Correction Form (Attachment G). Please note that both the investigator's agreement and the investigational plan require that all intercurrent events, device related or not, be reported using the appropriate case report form. The Intercurrent Event CRF was

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still not completed until after the monitor found the adverse event, three years after the event occurred. Your response is inadequate in that it does not explain how you intend to prevent these deviations from occurring in future studies. Please submit a corrective action plan to address this deviation.

The FDA investigator also noted that you, or a designee, had not signed many of the source documents and CRFs. The investigational plan and investigator's agreement for this study require that the investigator must sign CRFs.

The violations described above are not intended to be an all inclusive list of problems that may exist with your clinical study. It is your responsibility as a clinical investigator to ensure compliance with the Act and applicable regulations.

The inspectional report notes that, in planning any future research, you will look for studies where: the investigational device is sent directly to you; adequate initial and continuing training will be provided by the sponsor; and the frequency and handling of monitoring visits and oversight is appropriate. The regulations in 21 C.F.R. Part 812 describe sponsor responsibilities as well as those of investigators. IRB responsibilities are spelled out in 21 C.F.R. Part 56, Institutional Review Boards. These three sets of responsibilities overlap to ensure appropriate conduct of clinical studies and the protection of the rights and welfare of participating subjects. Whether or not the sponsor or IRB involved in your study has fulfilled their regulatory responsibilities, you are still responsible for knowing and following the regulations pertinent to your activities as a clinical investigator in FDA-regulated studies.

Within fifteen (15) working days of receiving this letter, please provide written documentation of the additional actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future studies for which you are the clinical investigator. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 C.F.R. 812.119.

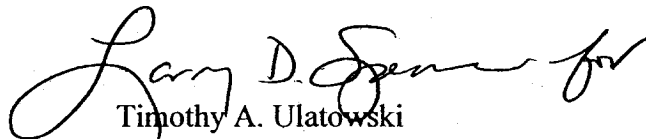
You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at <http://www.fda.gov/oc/ohrt/irbs/>. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Send your response to: Attention: Michael Marcarelli, Division Director, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring HFZ-310, 9200 Corporate Boulevard, Rockville, Maryland 20850.

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A copy of this letter has been sent to the New Orleans District Office, 297 Plus Park Boulevard, Nashville, Tennessee 37217-1003. Please send a copy of your response to that office.

If you have any questions, please contact Michael Marcarelli, Pharm.D. by phone at 240-276-0125, or by email at Michael.Marcarelli@fda.hhs.gov.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Timothy A. Ulatowski".

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