

Failure to conduct the study in accordance with the signed agreement with the sponsor, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by the IRB or FDA [21 CFR 812.100 and 812.110(b)].

Under FDA regulations, you are required to conduct your clinical investigation in accordance with your signed agreement with the study sponsor; your investigational plan, which includes the study protocol; FDA regulations; and any conditions of approval imposed by the IRB or FDA. The sponsor indicated in the study protocol that you must obtain the sponsor's and IRB's prior approval for all changes to the research. Also, the IRB indicated in their letters, dated 6/13/02 and 3/21/03, that you must obtain IRB pre-approval for all changes to approved research except where necessary to eliminate apparent immediate hazards to the study subjects. Our investigation and review of the inspection report and related documents revealed deviations from the study protocol and FDA regulations, including, but not limited to, the following:

1. Numerous protocol violations were found in relation to this study conducted at your site:

a.) [REDACTED] of the [REDACTED] enrolled subjects did not meet eligibility criteria to be enrolled into the study:

- Subject [REDACTED] was treated with [REDACTED] a prohibited medication, during the study.
- Subject [REDACTED] was treated with [REDACTED] and [REDACTED] prohibited medications within 1 week prior to study treatment.
- Subject [REDACTED] was treated with [REDACTED] a prohibited medication, during the study; was treated with [REDACTED] a prohibited medication within 1 week prior to study treatment; and had documentation of an allergy to [REDACTED] an exclusion criterion.
- Subject [REDACTED] was treated with [REDACTED] a prohibited medication within 1 week of study treatment.
- Subject [REDACTED] had a positive reaction to the [REDACTED] test performed prior to study treatment, which was an exclusion criterion. You stated in a memo, dated 10/2/03, that you deemed the result as negative, even though the protocol stated that any reaction such as this subject experienced would be considered a positive reaction and would exclude the subject.
- Subject [REDACTED] was treated with [REDACTED] a prohibited medication, during the study.

Federal regulations generally require that clinical investigators obtain prior approval from the sponsor before implementing any deviations from the investigational plan. 21 CFR 812.150(a)(4). If these changes or deviations affect the scientific soundness of the plan or the rights, safety, or welfare of the subjects, FDA and IRB approval in accordance with 21 CFR 812.35(a) is also required. 21 CFR 812.150(a)(4). You also signed an Investigator Agreement which states that

you would not make any changes in the research without sponsor and IRB approval.

Furthermore, you should realize that inclusion and exclusion criteria are used in a study protocol for many reasons, including limiting study subject variability, ensuring that the subjects meet the specific requirements of the study and are the appropriate types of patients to be tested with the investigational device, and most importantly, to ensure subject safety.

In response to these inspectional observations, you state that study subjects were verbally instructed not to use the prohibited medications. You also state that you have addressed this problem by changing the clinical study policy to record all verbal instructions and correspondence with the study subjects. Your response is inadequate in that the steps you have taken, or plan to take, will not prevent the recurrence of enrolling subjects who do not meet the protocol requirements. With your response to this letter, please provide detailed steps of your preventive actions for meeting protocol requirements when subjects are uncooperative, or ignore your verbal or written instructions.

- b) You enrolled, or allowed to continue in the study, subjects who underwent prohibited medical procedures. Specifically, Subject [REDACTED] underwent a [REDACTED] procedure [REDACTED] approximately one month before being enrolled in the study and again approximately four months into the study.

Your response explaining why permitting Subject [REDACTED] to participate in the study was not a protocol deviation is adequate. Please provide a copy of the revised protocol criterion, and, when available, a copy of the IRB letter approving the protocol revision.

- c) [REDACTED] of the [REDACTED] randomized subjects had one or more study visits outside the protocol-required windows:

- Subject [REDACTED] Visit 4 was performed on 10/8/02, while it should have been on 10/6/02 \pm 1 day.
- Subject [REDACTED] Visit 11 was performed on 1/6/03, while it should have been on 12/27/02 \pm 7 days.
- Subject [REDACTED] Visit 11 was performed on 1/6/03, while it should have been on 12/27/02 \pm 7 days.
- Subject [REDACTED] Visit 11 was performed on 1/10/03, while it should have been on 12/27/02 \pm 7 days.
- Subject [REDACTED] Visit 5 was performed on 10/21/02, while it should have been on 10/15/02 \pm 3 days.
- Subject [REDACTED] Visit 4 was performed on 10/10/02, while it should have been on 10/6/02 \pm 1 day. Visit 6 was performed on 10/21/02, while it should have been on 10/20/02. Visit 7 was performed on 11/7/02, while it should have been on 10/31/02 \pm 3 days. Visit 8 was performed on 11/19/02,

while it should have been on 11/14/02 \pm 3 days. Visit 10 was performed on 12/23/02, while it should have been on 12/12/02 \pm 7 days. Visit 12 was performed on 1/23/03, while it should have been on 1/9/03 \pm 7 days.

Our review of the inspection report revealed that you did not adhere to the timeframes in the protocol for the subjects who are identified above. As the Principal Investigator, you are required to inform subjects of the necessity to adhere to the study schedule for follow-up visits. If subjects cannot commit to the follow-up visits then you should take that into consideration when considering whether they should be allowed to enroll in the study. You are also required to ensure that you and your study staff understand the study follow-up visit schedule so that subjects will be seen at the correct times.

The response you submitted does not adequately address our concerns. Efficacy endpoints for this study were based on evaluations of the subjects at specific times during the study.

Failure to adhere to the protocol-required follow-up visit windows and enrolling ineligible subjects into the clinical trial could potentially impact the outcome of the study as well as place the subjects at unnecessary risk. Please provide the steps that you have taken or plan to take to correct and prevent the recurrence of not meeting the required timeframes.

2. You failed to maintain the test articles under the conditions required by the study protocol. The protocol required the investigational products to be stored at 2°C to 8°C , with the warning, " 2°C ". Your refrigerator monitoring records indicate the temperature as " 7° " on most days, with no indication of the degrees -- Centigrade or Fahrenheit. You told the FDA Investigators that the records were in Fahrenheit degrees. If this was truly the case, the investigational product was stored at 7°F temperatures throughout the study, in violation of the protocol.

In response to this observation, you state, "The temperature log for the storage refrigerator should have been recorded as centigrade. The unit $^{\circ}\text{C}$ was inadvertently not recorded." Your response is inadequate in that you do not provide detailed steps of corrective and preventive actions that you have taken or plan to take to prevent the recurrence of this problem in the future.

3. You also failed to complete the physical exam records and sign and date the source documents and Case Report Forms (CRFs) as required by the investigational plan.

In your response to observations 7 and 8, you state that for future studies, you will perform, record and sign all physical examinations, and a note was made to the file regarding the monitor's instructions about the need for you to sign and date all source documents and CRFs. Your response to observation 7 appears to be adequate; however, your response to observation 8 is incomplete in that you did not specify the

contents of the note you generated to file on December 11, 2002. Please provide a copy of the note for our review.

Failure to maintain accurate and complete records for each subject enrolled into the study [21 CFR 812.140(a)(3)].

The CRFs, which are the primary means by which the study sponsor collects study data that is reported to the FDA, did not accurately reflect the information found in the study subjects' source records or medical files. Many of the omissions and inaccuracies were related to issues that would have disqualified the subjects from being enrolled in the study. For example:

a.) Concomitant medications recorded in the study subjects' medical records were not reported in the CRFs:

- Subject [REDACTED] use of [REDACTED] and [REDACTED] received during the study.
- Subject [REDACTED] received during the study.
- Subject [REDACTED] use of [REDACTED], and [REDACTED]
- Subject [REDACTED] use of [REDACTED]

b.) Study subjects' medical histories or procedures were inconsistent or were not accurately reported in the CRFs:

- Subject [REDACTED] history of [REDACTED] was not reported. The subject was also noted as being both surgically sterile and post-menopausal, but there was no record of surgery on the medical/surgical history CRF.
- Subject [REDACTED] allergy to [REDACTED] was not reported.
- Subject [REDACTED] reported as being treated with [REDACTED] but there was no medical history to explain this. This subject was also reported as being of [REDACTED] potential.
- Subject [REDACTED] positive reaction to the [REDACTED] test was reported as negative in the CRF.
- [REDACTED] of the [REDACTED] enrolled subjects' CRFs had inconsistencies regarding reporting of vital signs. For example, subjects' temperatures were reported as ranging from 96 to 98 °C.
- Subject [REDACTED] and Subject [REDACTED] had the implant procedures performed by you on the same day and at the same time, according to the CRFs.
- Changes were made to the records, either by crossing out or writing over information, with no date or initials to indicate when the changes were made or who made them.

Also, our review of the source documents revealed that Subject [REDACTED] had an allergy to [REDACTED] which is an exclusion criterion in the study protocol but he was still included in the study. We realize that this deviation was not listed on the Form FDA 483. As

a clinical investigator, you are responsible for ensuring that all records are accurate in order to confirm findings, and that exclusion criteria are fully taken into consideration prior to allowing subjects to participate in the study.

The corrective action taken to address the failure to record Subject [REDACTED]'s allergy to [REDACTED] appears to be adequate; however, your response does not indicate what steps you have taken or plan to take to prevent this deviation from recurring in the future.

In addition, with regard to the CRFs showing that two subjects received implants on the same day at the same time, the preventive action described in your response appears to be adequate. However, your response does not identify what corrective actions you have taken or will take to address the discrepancies in the study records concerning the implantation times for Subjects [REDACTED] and [REDACTED]. Please provide such corrective action information, and a timeframe for the planned “re-instruction” of clinical staff on initialing, signing, and dating of changes to document entries.

With regard to the remaining deviations above, your response is inadequate in that you do not provide detailed steps of corrective and preventive actions you have taken or plan to take to avoid recurrence of these deviations.

- c) Two study subjects, Subjects [REDACTED] and [REDACTED] had no medical charts.

FDA regulations require clinical investigators to maintain accurate, complete, and current records of each subject's case history, including case report forms and supporting data such as medical charts. 21 CFR 812.140(a)(3). All information recorded on the CRFs should be verifiable in the subjects' medical history or source records. Failure to maintain accurate and complete medical files on study subjects raises questions as to the accuracy and integrity of data reported to the study sponsor and the FDA.

Failure to provide a copy of the Informed Consent form to subjects in an investigation [21 CFR 50.27(a)].

Investigators are responsible for ensuring that informed consent is obtained in accordance with the requirements of FDA regulations at 21 CFR Part 50 and section 812.100. One of those requirements is that subjects must be given a copy of the signed consent form. 21 CFR 50.27(a). A memo from you, dated 4/21/03, states that subjects were not given a copy of the consent form due to an oversight. You also told the FDA investigators you did not know it was a requirement to give subjects a copy of the form. In addition to the requirements prescribed by the Federal regulations cited above, the informed consent form used for the study contains a statement on the signature page which clearly indicates that subjects must be given a signed and dated copy of the form for their records.

Your response to this deficiency is inadequate because you failed to indicate the steps you have taken or plan to take to prevent the recurrence of subjects not receiving a copy of their signed and dated consent form.

Your corrective and preventive actions will be verified during a future visit.

The deviations described in this letter are not intended to be an all-inclusive list of objectionable practices that may exist at your clinical site. It is your responsibility to ensure adherence to each requirement of the Act and all pertinent Federal regulations. You are also required to directly supervise all activities conducted in performance of clinical trials for which you are the Clinical Investigator. In addition, you must ensure that any staff or personnel who are delegated study tasks are appropriately qualified by training and/or education to correctly perform those tasks.

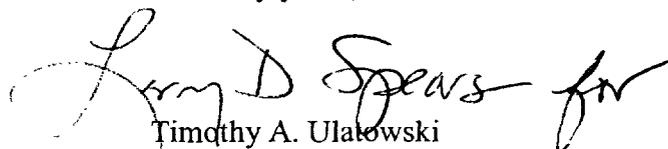
Please advise this office, in writing of the specific steps you have taken or will take to correct the noted conditions, and to prevent the recurrence of similar conditions in current or future studies. For assistance in preparing your response, please refer to “FDA Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators,” which is available on the agency's Internet web site at <http://www.fda.gov/oc/ohrt/irbs/default.htm>. You may also contact Ms. Linda Godfrey at (301) 594-4722 with any questions you may have concerning this letter.

Please address your response to:

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
Attn: Ms. Linda Godfrey, Consumer Safety Officer.

A copy of this letter has been sent to FDA's San Francisco District Office, Food and Drug Administration, 1431 Harbor Bay Parkway, Alameda, CA 94502. We request that you copy the District Office on your response.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Timothy A. Ulatowski for". The signature is fluid and cursive.

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