



b6290d

DEPARTMENT OF HEALTH & HUMAN SERVICES

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Public Health Service
Rockville MD 20857

Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

MAR 5 2007

WARNING LETTER

VIA FEDERAL EXPRESS

Hyrum A. Mead
President BSD Medical Corporation
2188 W. 2200 South
Salt Lake City, UT 84119-1326

Dear Mr. Hyrum Mead:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at BSD Medical Corporation (BSD) from November 13 through November 22, 2006, by an investigator from the FDA Denver District Office. The purpose of this inspection was to determine whether your activities as the sponsor of the clinical study, [redacted] and [redacted]

[redacted] complied with applicable federal regulations [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 written responses to the noted violations dated December 11, 2006, and January 17, 2007.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval (PMA) applications, and Premarket Notification submissions (510(k)) 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 serious violations of Title 21, Code of Federal Regulations (21 C.F.R.) Part 812 -- Investigational Device Exemption and Part 50 -- Protection of Human Subjects. 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. In your written responses, you state BSD takes very seriously the issues raised in the Agency's November 22, 2006, Form FDA 483. You note BSD is in the process of implementing a number of specific corrective actions to address the FDA's observations and to further strengthen procedures, including intensifying monitoring procedures, increasing the frequency of monitoring visits, and adding a separate work instruction for management of protocol deviations. In your January 17, 2007, response you included work instructions for monitoring, managing protocol deviations, and compassionate and emergency use that

you have modified or created. Also in your response, you state that in June 2006 prior to the FDA's inspection, you had already engaged a third party contract research organization (CRO) [redacted] to provide additional monitoring support for the ongoing study and supplementing the in-house monitoring already being performed by BSD personnel. In addition, you have now expanded the scope of [redacted] activities to include assistance with revision of the company's standard operating procedures (SOPs) for clinical research, as well as the other corrective actions. Obtaining assistance with monitoring and development of policies and procedures is an excellent initial step however, your response is incomplete in that it does not address all the items identified during the FDA inspection. The deviations noted on the Form FDA 483, your written responses, and our subsequent review of the inspection report are discussed below:

Failure to secure the investigator's compliance with the signed investigator agreement, the investigational plan, applicable FDA regulations, and any other conditions of approval imposed by the reviewing IRB or FDA. [21 CFR 812.46(a)]

Sponsors are responsible for ensuring that all clinical investigators participating in the investigation adhere to the signed agreement and the investigational plan. A sponsor that discovers an investigator who is not complying shall promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigation. In your response you state you were aware of the noncompliance of an investigator and made repeated unsuccessful attempts to achieve compliance consequently, you failed to secure investigator compliance with the investigation plan and applicable FDA regulations.

[redacted] failed to conduct the investigation in accordance with the signed agreement, the investigational plan, applicable federal regulations, and any other conditions of approval imposed by the reviewing IRB and FDA. He enrolled subjects that did not meet eligibility criteria and did not perform diagnostic tests in accordance with the investigational plan. Examples [redacted] failures include but are not limited to:

- A) [redacted] enrolled subjects that did not meet eligibility criteria #1, "Histologically proven advance, persistent, or recurrent deep tumors of the pelvis." Subjects were enrolled that have tumors outside the pelvis, for that reason they were not candidates for the protocol.
- 1) Subject [redacted] primary tumor site is the breast and she received hyperthermia treatment to the breast.
 - 2) Subject [redacted] has a diagnosis of Sarcoma and the primary tumor site is the left posterior chest, the treatment site was the left chest.
 - 3) Subject [redacted] primary tumor site is the breast, the treatment site was the chest wall.
 - 4) Subject [redacted] primary tumor site is the esophagus and the treatment site was the esophagus.

- B) The protocol requires pre-treatment and post-treatment evaluations to include Physical Exam, Chest X-Ray, Complete Blood Count (CBC) White Blood Cell Count/(WBC)/Platelets, Serum Chemistries, and Urinalysis (U/A). Examples of [redacted] failure to perform diagnostic tests in accordance with the investigational plan include but are not limited to:
- 1) Pre-treatment Chest X-Ray and post treatment Chest X-Ray, CBC/WBC/Platelets, Serum Chemistries, and U/A, are documented as not being performed for subject [redacted] on the case report form (CRF).
 - 2) Pre-treatment Chest X-Ray, CBC/WBC/Platelets, Serum Chemistries, and U/A, are documented as not being performed for subject [redacted] on the CRF.
 - 3) Pre-treatment Chest X-Ray and U/A and post-treatment Chest X-Ray are documented as not being performed for subject [redacted] on the CRF.
 - 4) Pre-treatment Chest X-Ray, CBC/WBC/Platelets, and Serum Chemistries are documented as not being performed for subject [redacted] on the CRF. In addition, the Patient Tumor Status- Follow-Up CRF is incomplete.

In your response you state BSD investigated the lack of documentation of pre and post-treatment tests and determined, from the patient files, that they were completed however, your response is incomplete in that you did not provide any documentation that these tests were performed. You stated the CRF errors were due to a misunderstanding on the part of the study coordinator therefore, the site received additional training on CRF completion. After this training the site did provide some of the missing information, showing progress, but did not completely address the issue. On February 9, 2005, you conducted another site monitoring visit and at that visit provided additional training to the study coordinator and staff with particular emphasis on completion of CRFs. The study coordinator was terminated in August 2005 and a replacement was not appointed until March 2006. Training was conducted again in May 2006. These interventions appear unsuccessful due to the continued documentation of noncompliance. For example: subject [redacted] was treated in August 2006, the CRF's note there was no pre-treatment Physical Exam, Chest X-Ray, CBC/WBC/Platelets, or Serum Chemistries performed. This violation was documented after the additional training was received by the staff. In your January 17, 2007, response you have included Work Instructions for Monitoring Clinical Trial Sites which describes your procedure for conducting monitoring however, it does not address continued noncompliance of investigators. You also included a Work Instruction for Protocol Deviation Management, this work instruction appears to focus on discovery of deviations after they have occurred instead of prevention. The interventions you have taken appear unsuccessful and you have not provided an adequate plan therefore, your response is inadequate. Please provide copies of policies, procedures, and additional plans, with expected completion dates that are being developed and implemented to ensure the investigation is conducted in accordance with the investigational plan. In addition, please provide copies of policies and procedures, with expected completion dates that are being developed and implemented to manage investigators from whom you are unable to secure compliance. In addition, please provide a copy of your plan to ensure documentation and reporting of deviations that have previously occurred.

Failure to ensure adequate monitoring of the investigation. [21 CFR 812.40]

Sponsors are responsible for ensuring proper monitoring of the investigation. An investigational plan shall include written procedures for monitoring of the investigation and include the name and address of monitors. Examples of inadequate monitoring include but are not limited to:

- A) Monitoring reports noted ongoing noncompliance with completion, review, and submission of CRFs to BSD however, the reports were inconsistent in that they also noted "Yes" to the following questions:
 - Is the investigator adhering to the Investigational Plan and in particular to the following: patient eligibility criteria, patient evaluations and examinations, and maintenance of patient records?This information is incorrect therefore, your monitoring reports are inaccurate.
- B) Documentation discrepancies were not noted, documented, or corrected during monitoring. For example: Subject date of death was documented as April 28, 2004, however, the dates of treatment are documented as April 30, 2005, May 4, 2004, May 7, 2004, May 11, 2004, and May 14, 2004. The monitoring reports lack any discussion of this discrepancy or an intervention to clarify.

In your January 17, 2007, response you submitted a copy of Work Instructions for Monitoring of Clinical Trial Sites. Your response does not include documentation of implementation or training on this document. In addition, your response does not address the inconsistencies in the monitoring reports. This inaccurate information could lead to confusion at the investigative site and misunderstanding. Also, in your response you state the aforementioned case history and CRF documentation was a clerical error and it has been corrected. This response is incomplete in that it does not address the lack of identification, clarification, and correction of data discrepancies during your monitoring process. Please provide copies of policies and procedures, with expected completion dates that are being developed and implemented to ensure adequate monitoring of the investigation.

Failure to prepare and submit progress reports at regular intervals and at least yearly to FDA and reviewing IRBs. [21 CFR 812.150(b)(5)]

For a significant risk device investigation a sponsor is responsible for submitting progress reports of the investigation to the FDA and all reviewing IRBs at regular intervals, and at least yearly. These reports shall be complete and accurate. Examples of this failure include but are not limited to:

- A) The progress reports that were submitted to the FDA are dated: October 3, 2003, June 2, 2005, and March 3, 2006. Accordingly, progress reports were not submitted to the agency at least yearly.
- B) Due to the unresolved incomplete and inaccurate case report forms from the clinical sites the progress reports submitted to the FDA were incomplete.

Your response is incomplete in that it does not address the assurance of submitting accurate, complete, and timely reports to the FDA. Please provide copies of policies and procedures, with expected completion dates that are being developed and implemented to ensure reports to the FDA and reviewing IRBs are complete, accurate, and submitted in a timely manner.

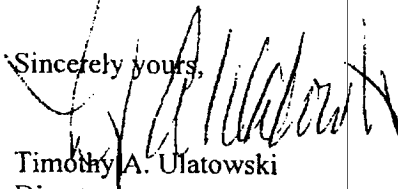
The violations described above are not intended to be an all inclusive list of problems that may exist with your clinical study. It is your responsibility as a study sponsor to ensure compliance with the Act and applicable regulations.

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 study sponsor. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. Send your response to: Attention: Doreen Kezer Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 9200 Corporate Boulevard, HFZ-310, Rockville, Maryland 20850.

A copy of this letter has been sent to the Denver District Office, 6th and Kipling Street, P.O. Box 25087, Denver CO, 80225-0087. Please send a copy of your response to that office also.

If you have any questions, please contact Doreen Kezer, 240-276-0125, or e-mail Doreen.kezer@fda.hhs.gov.

Sincerely yours,



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