

**WARNING LETTER**

VIA FEDERAL EXPRESS

Steven L. Stroup, M.D.  
Centennial Medical Center  
Radiation Oncology Associates  
2410 Patterson Street  
Nashville, TN 37203-1605

APR 10 2007

Dear Dr. Stroup:

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 January 4 through January 31, 2007, by an investigator from the FDA New Orleans District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study, [redacted] and [redacted] of the [redacted] with the [redacted] IDE # [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 response dated [redacted] addressed to [redacted] [redacted]

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 Exemptions 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. The deviations noted on the Form FDA 483, our subsequent review of the inspection report, and your written response are discussed below:

In your response you state, although you believe that you always acted in the therapeutic best interests of the enrolled subjects, you did not provide sufficient oversight to ensure

that all participating investigators, including yourself, and staff members complied with the protocol and all applicable clinical research regulations. You state you bear full responsibility for this failure and now have a greater appreciation for the importance of not only protecting individuals as patients, but remaining mindful of these specific additional protections afforded to patients also serving as subjects. Additionally you state that you are planning to retire from the practice of medicine on [redacted] and that [redacted] and [redacted] will be principally responsible for this trial. Although you state you are retiring, it is essential that corrective actions be developed and implemented to address the FDA concerns. Please work with [redacted] and the IRB to develop and implement an effective corrective action plan.

You state the trial has been closed to enrollment since October 2006 and the IRB directed you and the co-investigators not to enroll subjects in any clinical research studies. You state you intend to engage an independent consultant, at the IRB's direction, to perform a complete review of the trial. In addition, you state that the IRB requires the investigators and staff to meet other conditions before approving further research involving your practice, including completing education regarding the use of inclusion/exclusion criteria and checklists, research record keeping and document record retention, and receiving in-person good clinical practice (GCP) training for all investigators. Your response is incomplete in that you did not provide any documentation of the independent consultant review and enrollment for training.

In your response you concur with the citations; however, your response is incomplete in that you did not include any corrective action plan to correct and prevent the noted deficiencies and any other issues discovered during the review of the trial by the independent consultant.

**Failure to properly document informed consent for 5 of 82 subjects and report to the sponsor and the reviewing IRB within 5 working days after the use of a device without obtaining informed consent. [21 CFR 812.100, 21 CFR 812.150(a)(5), and 21 CFR 50.27(a)]**

Informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legal representative at the time of the consent. In addition, if an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

- There was no documentation of informed consent for 5 of 82 subjects. In addition, there was no documentation of notification of the sponsor and the reviewing IRB. Examples include, but are not limited to, the following:
  - 1) Study subject [redacted]
  - 2) Study subject [redacted]
  - 3) Study subject [redacted] and [redacted]
  - 4) Study subject [redacted]

Please provide copies of policies and procedures, with expected completion dates that are being developed and implemented to ensure informed consent is obtained and documented prior to any study-related procedures. In addition, please submit a copy of the notification sent to the IRB and sponsor of the use of a device without obtaining informed consent for the aforementioned subjects and any additional applicable subjects. Please provide copies of policies and procedures, with expected completion dates that are being developed and implemented to ensure that the sponsor and the reviewing IRB are notified within 5 working days after the use of a device without obtaining informed consent.

**Failure to conduct the investigation according to the signed agreement, the investigational plan, and applicable FDA regulations. [21 CFR 812.100 and 21 CFR 812.110(b)]**

It is the responsibility of the investigator to conduct the investigation in accordance with the signed investigator agreement, investigational plan, and applicable FDA regulations. Examples of this failure include, but are not limited to, the following:

- A) Subject [redacted] Case Report Forms (CRFs) lack documentation of [redacted] in the [redacted] and [redacted] pre and post treatment. The following required pre treatment diagnostic tests: [redacted] [redacted] and [redacted] are checked as not performed as well as the required post treatment [redacted] is checked on the CRF as not performed.
- B) Subject [redacted] CRFs lack documentation of pre treatment [redacted] in the [redacted] pre treatment and post treatment assessments [redacted] overall patient tolerance, and adverse effects from [redacted]. Additionally, the following required pre treatment diagnostic tests; [redacted] and [redacted] are checked on the CRF as not performed.

Please provide copies of policies and procedures, with expected completion dates that are being developed and implemented to ensure the investigation is conducted in accordance with the investigational plan.

**Failure to obtain, in a non-emergency situation, prior approval by the sponsor of changes in or deviations from the investigational plan and failure to obtain such approval from FDA and the reviewing IRB, where the changes or deviations could have affected the rights, safety, or welfare of human subjects. [21 CFR 812.150(a)(4)]**

An investigator is responsible for notifying the sponsor and the reviewing IRB of any deviations from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan. If these changes or deviations may affect the scientific soundness of the plan or rights, safety, or

welfare of human subjects, FDA, and IRB approval is required in accordance with 812.35(a).

You failed to secure FDA, IRB, and sponsor approval of deviations in non-emergency situations prior to treating subjects. Examples of your failure to comply with the above stated requirement include, but are not limited to, the following:

- A) Patient eligibility [redacted] required histologically proven advance, persistent, or recurrent [redacted] of the [redacted] i.e. [redacted] or [redacted]. You treated 26 of 82 subjects with [redacted] outside the [redacted]. Examples of your failure include, but are not limited to, the following:

Subject Number	Initials	[redacted] Location
[redacted]	[redacted]	Left Axillary
[redacted]	[redacted]	Left Chest Wall
[redacted]	[redacted]	Liver
[redacted]	[redacted]	Adrenal Gland
[redacted]	[redacted]	Renal Cell
[redacted]	[redacted]	Breast
[redacted]	[redacted]	Liver
[redacted]	[redacted]	Para Spinal
[redacted]	[redacted]	Breast
[redacted]	[redacted]	Chest Wall
[redacted]	[redacted]	Neck
[redacted]	[redacted]	Para Spinal
[redacted]	[redacted]	Pancreas
[redacted]	[redacted]	Liver
[redacted]	[redacted]	Liver/Esophagus
[redacted]	[redacted]	Chest Wall
[redacted]	[redacted]	Right Flank
[redacted]	[redacted]	Esophagus
[redacted]	[redacted]	Breast
[redacted]	[redacted]	Pancreas
[redacted]	[redacted]	Buttock
[redacted]	[redacted]	Right Shoulder
[redacted]	[redacted]	Liver
[redacted]	[redacted]	Pancreas
[redacted]	[redacted]	Para Spinal
[redacted]	[redacted]	Liver

- B) Eligibility exclusion criteria [redacted] excludes subjects whose [redacted] is [redacted]. Your case histories lack documentation of subject's [redacted] and [redacted]. In addition, this measurement is a critical measurement for determining response to the therapy. Examples of your failure include, but are not limited to, the following:

- 1) Examples of subject's CRFs that lack any documentation of [redacted] in [redacted] include: [redacted]
- 2) Subject [redacted] CRF notes 'N/A' in [redacted] in [redacted]

Please provide copies of policies and procedures, with expected completion dates that are being developed and implemented to ensure subjects enrolled meet the eligibility criteria. In addition, please provide copies of policies and procedures, with expected completion dates that are being developed and implemented to ensure appropriate approvals are obtained.

**Failure to maintain accurate, complete, and current case histories. [21 CFR 812.140(a)(3)]**

An investigator is responsible for maintaining accurate, complete, and current records of each subject's case history and exposure to the device, which encompasses the case report forms (CRF), and supporting data including documentation of adverse device effects. You failed to maintain accurate, complete, and current records of each subject's case history and the study protocol, as required by 21 CFR 812.140(a)(3). Under 21 CFR 812.150, an investigator must submit, to the sponsor and the reviewing IRB, a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The comments below relate to documentation of adverse device effects. It is not clear whether these effects were "unanticipated" adverse device effects. Examples of these failures include, but are not limited to, the following:

A) You failed to document adverse device effects.

The comment area on the CRF contains a comment section to document adverse effects specifically. Examples of this failure include but, are not limited to, the following:

- 1) Subject [redacted] CRF comment section states the following: "developed significant [redacted] and a [redacted] condition. Treatments were held after [redacted] due to overall [redacted] of her condition. She has since begun to slowly improve," however, the adverse effects section from [redacted] section of the CRF is blank.
- 2) Subject [redacted] CRF comment section states the following: "with minimal [redacted] however, the adverse effects section from [redacted] [redacted] lacks notation of this event even though it is specifically documented in the comment section of the CRF.
- 3) Subject [redacted] CRF comment section states the following, [redacted] however, the adverse effects from [redacted] treatment section of the CRF is blank.

B) CRF's are incomplete and include inconsistent information. Examples include, but are not limited to, the following:

- 1) Subject [redacted] CRF indicates that treatment was received on [redacted] however, it also states that the course of therapy was discontinued prior to completion because "the patient [redacted] There is no documentation of the cause of the [redacted] and [redacted] and IRB and sponsor notification.
- 2) CRF's lack documentation of overall patient tolerance, examples include: subject [redacted] subject [redacted] subject [redacted] and subject [redacted]

Please provide copies of policies and procedures, with expected completion dates that are being developed and implemented to ensure case histories, including supporting data, are accurate, complete, and current.

It appears you may not fully understand your role and responsibilities as a clinical investigator using an investigational device. The regulations in 21 CFR Part 812 set forth requirements for investigational device exemptions, including investigator and sponsor responsibilities for the conduct of investigational device studies. The regulations in 21 CFR Part 50 set forth requirements for the protection of human subjects, including responsibilities of the investigator and IRB in the informed consent process. The regulations in 21 CFR Part 56, Institutional Review Boards set forth specific requirements for IRBs. These various requirements help to ensure appropriate conduct of clinical studies and the protection of the rights and welfare of participating subjects. Though a sponsor involved in a study may have been remiss in fulfilling its responsibilities, an investigator is still held responsible for knowing and following the regulations pertinent to the activities as a clinical investigator in FDA-regulated studies.

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.

Within fifteen (15) working days of receiving this letter, please provide written documentation of the 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. In addition, please provide a complete list of all clinical trials in which you have participated for the last five years, including the name of the study and test article, the name of the sponsor, the number of subjects enrolled, and the current status of the study. 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

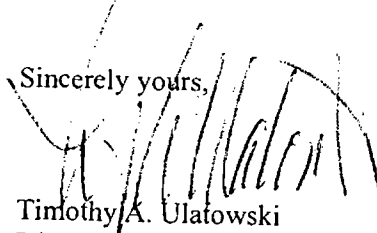
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<http://www.fda.gov/oc/ohrt/irbs/>. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Send your response to: Attention: Doreen Kezer, Food and Drug Administration, Center for Devices and 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 New Orleans District Office, 2410 Patterson Street, Nashville, TN, 37203-1605. Please send a copy of your response to that office.

If you have any questions, please contact Doreen Kezer, (240) 276-0125, or [doreen.kezer@fda.hhs.gov](mailto:doreen.kezer@fda.hhs.gov).

Sincerely yours,



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

cc (omitted)

[Redacted]

[Redacted]

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