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CBER -99-025

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

WARNING LETTER

SEP 21 1999

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

David H. Livingston, M.D.
New Jersey Trauma Center
University Hospital, Room E-245
150 Bergen Street
Newark, New Jersey 07103

Dear Dr. Livingston:

During an inspection ending on May 20, 1999, Ms. Cheryl LeGrand, an investigator with the New Jersey District Office of the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study using _____

The clinical study is sponsored _____ The inspection was conducted under FDA's Bioresearch Monitoring Program that includes inspections designed to monitor the conduct of clinical research involving investigational drugs.

Based on information obtained during the inspection, we have determined that you have violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations, Part 312 [21 CFR 312] (copy enclosed). Our investigation revealed that you did not fulfill your obligations as a clinical investigator in the use of unlicensed investigational new drugs for the reasons listed below. The applicable provisions of the CFR are cited for each violation.

1. Failure to ensure that the investigation is conducted according to the investigational plan (protocol). [21 CFR 312.60]

Our inspection revealed that several important protocol directives were not followed, resulting in significant deviations from the protocol.

- a. The protocol requires commencement of study drug administration within 12 hours from time of traumatic incident. The following subjects were randomized after the 12-hour recruitment window of eligibility:

Subject No.	Reason Inclusion Criteria not met
	Study drug commenced outside of 12 hours window.
	Study drug commenced 4 hours outside of 12 hours window.
	Study drug commenced ½ hour outside of 12 hours window.
	Study drug commenced 4 ½ hours outside of 12 hours window.
	Study drug commenced 1 ½ hours outside of 12 hours window.
	Study drug commenced outside of 12 hours window.
	Study drug commenced 2 hours and 40 minutes outside of 12 hours window.

- b. According to the protocol, each subject was to receive either _____ or placebo by continuous intravenous infusion at a dose of 8 mg/kg over 48 hours (4 mg/kg/day x 2 days). The amount of study drug administered to the subjects was determined based on the subject's weight. Twelve of twenty subjects received an incorrect dose of the study drug.

Subject No.	Study Drug Infusion Irregularities/Deviations
	Study drug was infused 3 hours past 48 hours; therefore a total volume of 255 ml were infused instead of required 240 ml for this subject.
	Study drug was infused at 10 ml/hour instead of 9 ml/hour as per protocol appendix III (Drug Dosing Chart). Drug infusion stopped at 38 hrs; therefore, the subject received 52 ml less of the total study drug.
	Study drug was infused 1 hour past 48 hours.
	Study drug was infused 1 ½ hours past 48 hours.
	Drug infusion is 46 1/3 hours short of 48 hours. Subject went to the operating room for 1 hour and 40 minutes; however, there is no documentation that the study drug was being continuously infused while the subject was in the operating room.
	Study drug was discontinued 3 ½ hours prior to 48 hours.
	Study drug was discontinued 14 ¾ hours prior to 48 hours.
	Study drug was infused only 17 ¾ hours. Drug infusion is 30 ¼ hours short of 48 hours.
	Study drug infusion rate was set at 15 ml/hour instead of 6 ml/hour.
	Drug infusion is 3 ½ hours short of 48 hours. There is no documentation of study drug infusion while the subject was in the operating room for 3 ½ hours.
	Study drug discontinued 1 hour prior to 48 hours.
	Study drug infused at 12 ml/hr. instead of 10 ml/hr.

There is no documentation that you actively reviewed that the test article was administered as the protocol required.

- c. Two out of three female subjects enrolled in the study were not tested for pregnancy as required in the protocol.

We view these protocol deviations (items a, b, and c) to be serious violations. Treatment of subjects outside the approved protocol may affect the final safety and/or efficacy results of the study. Moreover, entry/eligibility criteria must be critically reviewed to protect the safety and welfare of study subjects.

- d. All of the 20 subjects dosed with study drug (100%) did not have complete laboratory tests performed as per protocol number _____. These laboratory results are an important part of the overall safety assessment of the study drug. The following is a table for all hematology, chemistry, urinalysis, or coagulation tests that were either not done (ND) or were only partially done (X):

Subject No.	Hem Pre.	Hem Day 3	Hem Day 15/ Dis.	Chem Pre.	Chem Day 3	Chem Day 15/Dis	Urin Pre.	Urin Day 3	Urin Day 15/ Dis.	Coag Pre.	Coag Day 3	Coag Day 15/ Dis.
X				X	ND	X	ND		ND		ND	ND
X		ND	ND	X	ND	ND	ND	ND	ND		ND	ND
X		ND	ND	X	ND	ND		ND	ND		ND	ND
X		X	X	X	ND	X	ND		ND		ND	ND
X			ND	X	X	ND	ND	ND	ND		ND	ND
X	X	ND		X	ND	X			ND		ND	ND
X		X		X	X	X	ND	ND	ND			
X	X	ND	ND	X	ND	ND	ND	ND	ND		ND	ND
X		ND	ND	X	X	ND	ND		ND		ND	ND
X		ND	ND	X	ND	ND		ND	ND		ND	ND
X		X	ND	X	ND	ND	ND		ND	ND	ND	ND
X				X	X	X	ND	ND	ND		ND	ND
X			ND	X	X	ND	ND	ND	ND	X	ND	ND
X		X		X	X	X	ND	ND	ND			ND
X				X	X	X	ND	ND	ND		ND	ND
X	X		ND	X	X	ND	ND	ND	ND		ND	ND
X				X	X	X	ND					
X			X	X	X	X	ND	ND	ND		ND	ND

Legend

- Hem.**= hematology tests
- Chem.**= chemistry tests
- Urin.**= urinalysis
- Coag.**= coagulation tests
- Dis.**=discharge
- Pre.**= pretreatment (screening/baseline)

- e. Vital signs (blood pressure, temperature, respiration rate, and heart rate) for day 15 were not performed for subject _____

It is your responsibility as principal investigator to ensure that all tests and evaluations are conducted at the time points indicated in the protocol. It is your responsibility to ensure that blood samples are taken for hematology tests, blood chemistries, pregnancy tests, and other tests described in the protocol. Review of laboratory values is an essential component of the study to assess the safety and efficacy of the investigational product.

2. Failure to obtain informed consent in accordance with the provisions of 21 CFR Parts 50 and 56. [21 CFR 312.60]

The inspection revealed that verbal informed consent was obtained from next of kin or a relative by telephone for two subjects enrolled in the study. An oral approval does not satisfy the requirement for a signed consent document, as outlined in 21 CFR 50.27(a). However, it is acceptable to send the informed consent document to the legally authorized representative (LAR) by facsimile and conduct the consent interview by telephone when the LAR can read the consent as it is discussed. If the LAR agrees, he/she can sign the consent form and return the signed document to the clinical investigator by facsimile.

3. Failure to fulfill requirements for informed consent. [21 CFR 50.20]

The inspection disclosed that several subjects who signed the study consent form in English required a translator. In order to meet the requirements of 21 CFR 50.20, the consent document must be in language understandable to the subject. When non-English speaking subjects are expected to be entered into a study, the IRB must approve the consent document written in the language in which the information is to be presented to the subjects. A consultant may be utilized to assure that the translation is correct. A copy of the translated consent document must be given to each appropriate subject. While a translator may be used to facilitate conversation with the subject, routine ad hoc translation of the consent document may not be substituted for a written translation.

4. Failure to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation. [21 CFR 312.62(b)]

- a. The inspection disclosed many discrepancies between information documented in the case report forms (CRFs) and source documents (raw data). Examples include, but are not limited to the following:
 - i. The case report form for subject _____ documents that the subject did not develop bacteremia anytime after start of study drug through study day 15; however, the subject's medical record documents a positive blood culture in both aerobic and anaerobic bottles for Staphylococcus epidermidis and a fever of 102°F on June 25, 1998.

- ii. The case report form for subject _____ documents that the subject was never in the intensive care unit (ICU); however, the *Critical Care Flow Sheet* documents that the subject was in the ICU from 1:00 a.m. through 12:00 p.m. (11 hours) on September 27, 1998.
- iii. The case report form for subject _____ documents the discharge date from the intensive care unit as 3/5/98 at 12 p.m.; however, study source documents indicate that the subject was discharged from the ICU on 3/6/98 at 6:00 p.m.
- iv. The medical records for subjects _____ each document hematology and chemistry lab results for day 3 (post treatment), but each respective CRF indicates the tests were not done.
- v. The medical record for subject _____ documents that the subject was _____ medication, but it was not documented under “medications” in the case report form.
- vi. The case report form for subject _____ documents that vital signs at 48 hours were taken on June 4, 1998, at 10:00 a.m.; however, study source documents indicate that the vital signs were taken on June 4, 1998, at 4:00 p.m.
- vii. There are instances in which the laboratory tests were recorded as “not done” in the case report form; however, medical records document them as “being done,” but not necessarily complete.
- viii. The case report form for subject _____ documents that chemistry tests were not performed for day 3; however, study source documents indicate that chemistry tests were performed for day 3 on 6/12/98.
- ix. The case report form for subject _____ documents under “Pretreatment Findings, Radiologic Section” small sacral fractures; however, the radiologic report documents additional findings such as tibia and fibula fracture, and right growing hematoma extending into the scrotal sac.

Case report form entries should be checked against source documents, medical charts and laboratory results by the principal investigator. Inaccuracies found in CRFs are the investigator's responsibility.

- b. The protocol requires that chemistry, hematology/coagulation, and urinalysis panels be performed at day 3 following the administration of study drug. The case report forms for subjects _____ document the laboratory results from day 4 instead of day 3. Examples include, but are not limited to the following:
- i. Subject _____ started drug infusion on 8/29/98 (day 1). The case report form for this subject documents hematology results taken from a test performed on 9/1/98 at 1:30 a.m. (day 4); however, study source documents indicate that a hematology test was performed on 8/31/98 at 1:15 a.m. which is actually day 3. The case report form documents chemistry results for day 3 taken from a test performed on 9/1/98 (day 4) at 1:15 a.m.; however, source documents indicate chemistry tests performed on 8/31/98 at 1:15 a.m., which is actually day 3.
 - ii. Subject _____ started drug infusion on 12/2/98 (day 1). The case report form for this subject documents chemistry results for day 3 taken from a test performed on 12/5/98 (day 4) at 13:03 p.m.; however, study source documents indicate that a chemistry test was performed on 12/4/98, which is day 3.
 - iii. Subject _____ started drug infusion on 6/10/98 (day 1). The case report form for this subject documents hematology results for day 3 taken from a test performed on 6/13/98 (day 4) at 1:41 a.m.; however, study source documents indicate that a hematology test was performed on 6/12/98 at 7:41 a.m., which is day 3.
- c. Source documents were not adequately maintained for all subjects participating in study protocol _____. The inspection revealed that several source documents did not exist to support some of the case report form entries. Examples include, but are not limited to the following:
- i. Source records could not be located for time (initial and final stop time) of study drug infusions, vital signs and chest-X ray (baseline/screening), and the number of units of blood given prior to administration of study drug for subject _____. A part of the subject's medical records was missing.
 - ii. Study source documents for subject _____ did not include records for _____ Coma Score, admission physical examination, last 10 hours of study drug infusion, and vital signs for 48 hours after infusion starts. The inspection disclosed that these records were missing or lost.
 - iii. The entry in the case report form of vital signs at 24 hours after starting infusion of study drug could not be verified in study source documents for subject _____.

- iv. The case report form for subject _____ documents that the subject was administered tetanus toxoid, but there is no source document to substantiate this entry in the case report form.
- v. There is no documentation in source records to assure that the infusion bag/tubing administration set was completely changed after each 24 hour time period for each subject.

Source data are all information in original records or certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents allow verification of the existence of the subject and substantiate the integrity of data that are collected during a trial. Source documents are crucial not only because they show that data have been accurately reported, but also that the study has been carried out in accordance with the protocol. The clinical investigator is responsible for ensuring the adequacy of the clinical site's source documentation.

5. Failure to report adverse events to the sponsor. [21 CFR 312.64(b)]

Case report forms submitted to the sponsor do not report all adverse and serious clinical events that occurred during the study. The protocol requires that all adverse clinical events be reported in the case report forms, and serious clinical events be reported within 24 hours _____ (Contract Research Organization), whether or not related to the investigational drug. Review of adverse events is an essential component of the study to assess the safety of the investigational product.

The following adverse events and/or serious adverse events were either not reported in the case report forms or not reported in a timely manner _____

Subject No.	Adverse events not reported in the case report form (CRF)	Serious adverse events not reported in the CRF
X		Pulmonary insufficiency; necrotizing fasciitis (including right above the knee amputation)
		Pneumonia; necrosis & ischemia of left lower extremity
	Pleural effusion	Respiratory failure; sepsis; fasciitis with abdominal infection
	Acidosis; pneumonia	Sepsis; respiratory failure
	Wound dehiscence; high liver function test values	Pneumonia; respiratory failure
	Rectal bleeding; pleural effusion; urinary tract infection; abdominal hematoma	
		Sepsis

Subject No.	Serious adverse events and date of onset	Date reported to
	Pulmonary insufficiency, 12/5/98	2/2/99
	Septic shock, 12/5/98	2/2/99
	Renal insufficiency, 12/5/98	2/2/99
	Cardiac arrest, 12/5/98	12/9/98; follow-up report was sent 3/18/99
	Renal failure, 7/17/98	7/23/98; follow-up report was sent 3/8/99
	Bacteremia, 7/22/98	8/8/98; follow-up report was sent 3/9/99
	Compartment syndrome of left lower extremity, 7/17/98	3/18/99
	Pulmonary embolus, 6/25/98	2/2/99
	Multiple organ failure, 6/26/98	7/01/98
	Cardiac pause, 6/16/98	6/24/98
	Active hemorrhage left chest wall, 6/12/98	6/24/98
	Bacteremia, 8/6/98	8/18/98; follow-up report was sent 3/8/99
	Pelvic wound infection, 7/31/98	3/8/99
	Multiple system organ failure, 8/24/98	8/27/98; follow-up report was sent 3/8/99
	Cardiac arrest, 9/11/98	3/18/99
	Subgaleal bleed, 8/31/98	3/18/99
	Pneumonia, 8/22/98	2/2/99
	Intracranial bleed, 9/10/98	2/2/99

6. Failure to notify the Institutional Review Board of serious adverse reactions. [21 CFR 312.66]

The Institutional Review Board (IRB) requires immediate reporting of any adverse events or unexpected events. All serious adverse events were not immediately reported to the Institutional Review Board. Several serious adverse events were reported two-seven months after the onset. Examples include, but are not limited to the following:

Subject No.	Serious Adverse Events and date of onset	Date Reported to the IRB
	Pulmonary insufficiency; 12/5/98	2/4/99
	Septic shock; 12/5/98	2/4/99
	Renal insufficiency; 12/5/98	2/4/99
	Pulmonary embolus; 6/25/98	2/4/99
	Pelvic wound infection; 7/31/98	2/4/99
	Pneumonia; 8/22/98	2/4/99
	Intracranial bleed; 9/10/98	2/4/99
	Bacteremia; 9/3/98	2/4/99

It is your responsibility as principal investigator to report all adverse experiences of a serious or unexpected nature, whether or not related to the investigational drug, to the responsible Institutional Review Board and the sponsor. It is the investigator's responsibility to ensure that an adverse event is recorded accurately and completely on the case report form and is followed up to determine its outcome or resolution. Failure to record or report adverse events is a serious violation of good clinical practice standards and guidelines.

Deviations in this study appear to be the result of a serious lack of supervision of personnel involved in conducting this study. Staff who were delegated the authority to perform certain functions were not adequately trained and monitored. You should recognize that although authority may be delegated, it is the principal investigator who is ultimately responsible. Proper oversight or supervision of medical personnel is necessary to ensure the investigation is conducted according to the protocol. There is no documentation to assure that associates, research fellows, residents, and employees assisting in the conduct of the study were trained in good clinical practice (GCP).

Principal investigators may delegate clinical responsibility to other physicians, usually colleagues within their specialty, to residents and fellows, and to nurse practitioners. This downward delegation increases the need for careful supervision of these practitioners. The principal investigator must review their work, particularly their clinical decisions, and must make certain that they are following the study investigational plan (protocol). The principal investigator should meet periodically with the team of clinicians and non-clinicians participating in the study to discuss study progress and problems. Minutes of these meetings demonstrate that the principal investigator is effectively managing the study and its participants.

The lack of supporting raw data for several case report form entries, and the numerous inaccuracies found in the case report forms indicate a lack of attention to effective record keeping practices. All of the information pertinent to the investigation, such as necessary observations and tests, is required to be recorded on the case report forms provided by the sponsor. As the clinical investigator responsible for this and other trials, you must actively review the subject files including case report forms. Clinical investigators are responsible for assuring that the data contained in the case report form and submitted to the sponsor are complete and accurate. Investigators are also responsible for supervising the Study Coordinator and other assistants who complete the case report forms and process queries.

We remind you that you are responsible and may be held accountable for the conduct of your Study Coordinator and sub-investigator regarding the performance of clinical trials. Training and supervision of study personnel are essential to maintain the quality of data collection regarding the conduct of clinical trials.

Problems with the study staff were apparent early on in the conduct of the trial; however, you failed to take corrective actions. The FDA investigator found telephone conversation notes inquiring about irregularities/protocol violations, but no corrective actions were taken. The documentation on the telephone communication notes indicates that you were aware of irregularities early on in the study. For example, a telephone conversation note dated September 2, 1998, documents that subject _____ was enrolled in the study out of the recruitment window by more than 5 hours. The same note reports that these problems have been discussed with both you and Ms. Carol Scura in the past.

You deviated from an authorized study plan, investigator statement, or other conditions imposed on the study by the sponsor, IRB, or FDA. Your signature on Form FDA 1572, Statement of Investigator, indicates your agreement to comply with all requirements regarding the obligations of clinical investigators conducting human clinical trials and all other pertinent requirements in 21 CFR Part 312. An investigator is responsible for ensuring that an investigation is conducted according to the signed investigational statement, the investigational plan (protocol), and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

FDA relies on clinical trial data to make decisions about the safety and efficacy of new drug products. It is essential that FDA has confidence that data are valid and properly obtained. Significance of clinical trial findings is contingent upon adherence to a prospectively defined protocol. Study _____ contains serious deficiencies, which is not consistent with appropriate data collection for clinical studies.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of investigational _____. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations. We request that you inform us, in writing, within fifteen (15) business days after receipt of this letter, of the steps you have taken or will take to correct these violations to prevent the recurrence of similar violations in current and future studies. If corrective action cannot be completed within 15 business days, state the reason for the delay and the time within which the corrections will be completed.

The FDA's New Jersey District Office forwarded to CBER your letter dated June 25, 1999, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate.

Failure to achieve prompt correction may result in enforcement action without further notice. These actions could include initiation of clinical investigator disqualification proceedings which may render a clinical investigator ineligible to receive investigational new drugs, a clinical hold, or termination of an investigational new drug application (IND).

Please send your written response to:

Jose Javier Tavarez, M.S.
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Bioresearch Monitoring Team (HFM-650)
1401 Rockville Pike
Rockville, Maryland 20852-1448
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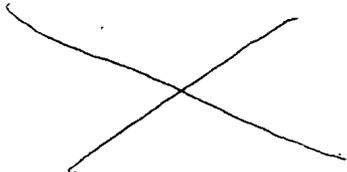
We request that you send a copy of your response to the Food and Drug Administration's New Jersey District Office, Director, Compliance Branch, 10 Waterview Boulevard, 3rd Floor, Parsippany, New Jersey 92612. If you require additional time to respond, or have any questions concerning this matter, please contact Mr. Tavarez at the telephone number above.

Sincerely,



Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

Enclosure
21 CFR Part 312



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