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

By Certified Mail - Return Receipt Requested

CBER - 02 - 007

Warning Letter

Juan Chediak, M.D.  
Angelo Creticos Cancer Center  
901 West Wellington Avenue  
Chicago, Illinois 60657-6708

JAN 2 2002

Dear Dr. Chediak:

During the inspection that ended on August 21, 2001, investigators with the Food and Drug Administration (FDA) reviewed your conduct of clinical studies of two investigational blood products. The inspection was conducted under the FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of clinical research involving investigational drugs. The inspection focused on the following study protocols:

1. ATC 93-01 – "A Multicenter, Open Label Study to Evaluate the Safety and Efficacy of [REDACTED] in the Treatment of [REDACTED] (hereafter, referred to as Protocol 1).
2. ATC 93-01 – "A Multicenter, Open Label Study to Evaluate the Safety and Efficacy of [REDACTED] in the Treatment of [REDACTED] (hereafter, referred to as Protocol 2).

The deficiencies noted during the inspection are listed on the Form FDA 483 (enclosed) that was issued to and discussed with you at the conclusion of the inspection. We reviewed your response letter dated November 7, 2001, with the attachments.

We determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 312 (available at <http://www.access.gpo.gov/nara/cfr/index.html>).

The applicable provisions of the CFR are cited for each violation listed below. These deviations include, but are not limited to the following items:

1. **You failed to fulfill the general responsibilities of investigators.**  
[ 21 CFR § 312.60 and Part 50 ].

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigational statement, the investigational plan, 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. Our investigation revealed that you did not fulfill your obligations as a clinical investigator in the use of investigational new drugs in that you failed to follow the investigational plan and adequately protect the safety and welfare of subjects.

2. **You failed to ensure that an investigation is conducted according to the investigational plan (protocol).** [ 21 CFR § 312.60 ].

FDA documented numerous protocol violations in the review of subject records for Protocols 1 and 2. The violations include, but are not limited to the following

- A. You failed to perform tests to establish that prospective subjects are eligible to be enrolled into the studies.

You failed to perform the required pregnancy test for all nine female subjects enrolled under Protocols 1 and 2.

In your response letter dated November 7, 2001, you explain that, in your judgment, several of these female subjects did not require a pregnancy test and, hence, you did not perform this test. You state that in the future you will follow the protocol and obtain prospective written approval from the sponsor prior to any protocol deviation.

- ii. You failed to perform or document the Karnofsky score for all 12 subjects enrolled in the studies. Protocols 1 and 2 require that potential study subjects have a Karnofsky performance score of at least ■ to be included in the studies.

In your response letter you state that you will maintain the source documentation for all entry criteria in future clinical trials

- B. You failed to administer the correct dosage of investigational product to eight of twelve subjects as shown in the examples below:

You did not document the volume of ■ administered to subject 0103 between 10/14/98 and 10/15/98 for infusions ■ as a result of an undetermined ■ dose to this subject.

- ii. Subject 0107 was administered an incorrect volume of [REDACTED] as a result of inaccurate weight calculations for each of the [REDACTED] infusions for surgery number 4 under Protocol 2 Part IIb between 5/20/98 and 5/23/98. Your response letter acknowledges this violation.
- iii. Subject 0112 was administered [REDACTED] instead of [REDACTED] on 6/9/98, for the first infusion under Part IIb. You acknowledge this deficiency in your response letter.

- C. You administered a second infusion of the investigational product to subject 0111 on 10/23/96, even though the subject failed to achieve levels of [REDACTED] activity at or above [REDACTED] of normal [REDACTED] after the initial infusion prior to surgery. The infusion log indicates that the subject's [REDACTED] level was [REDACTED] after the first infusion and, therefore, the subject was ineligible to receive additional investigational product.

Your response letter acknowledges that the administration of the second infusion of investigational product on 10/23/96 is a protocol violation.

- D. You failed to perform the screening evaluation as required by the protocol. For subject 0106, under Part Ia of Protocol 1, the pre-infusion blood chemistry sample was obtained several hours after the infusion was completed on 8/10/93.

Your response letter explains that the sample was obtained prior to the infusion, but there is no documentation to support your claim that the sample was collected before the infusion was begun.

- E. You failed to measure the bleeding time at [REDACTED] post-infusion for subjects 0101 (Part Ia and Ib) and 0102 (Part Ia) under Protocol 1.

In your response letter, you indicate that you contacted the sponsor regarding this protocol directive. However, there is no documentation to confirm that the sponsor authorized this protocol deviation.

- F. You failed to save a sample of the [REDACTED] as required by the protocols under Part Ia for subjects 0101, 0102, 0103, 0106, and 0108 and under Part IIa for subject 0107.

You acknowledge this deficiency in your response letter, and indicate that you will ensure that study personnel understand the protocol requirements.

- G. You failed to draw blood to determine the hemostatic response at baseline and [REDACTED] post-infusion, or obtained the sample at inappropriate times for the following subjects:

Subject	Treatment	Samples not drawn or drawn incorrectly
0101	Part Ib	Not drawn on 11/16/93
0103	Part IIb	Not drawn on 10/2/98
	Part IIa	Not drawn for bleeding episode 8 for infusions [REDACTED] to [REDACTED]
0111	Part Ib	Baseline samples were drawn after the infusion had started
	Part IIb	[REDACTED] post-infusion sample was drawn late, for surgery 1

In your response letter, you explain that in future clinical trials your research staff will be more diligent in adhering to the protocol requirements.

- H You failed to obtain vital signs as required by the protocols. This is not a complete list, but is provided for illustration.

Part Ia of the protocols required vital signs to be recorded at [REDACTED] [REDACTED] post-infusion of the study drug. You failed to follow this protocol directive for subjects 0101, 0104, 0105, 0106, 0107, 0108, 0109.

- ii. For subject 0103 you failed to obtain vital signs for numerous infusions. Examples include, but are not limited to, the infusions under Part IIa, bleeding episode 7 (infusions [REDACTED] and [REDACTED] and Part IIb, surgery 9 (infusions [REDACTED]).

In your response letter, you acknowledge these violations, and commit to train your staff in future studies.

You failed to report all serious adverse experiences (SAEs) to the sponsor as required by protocol 2.

Subject	SAE	Onset date of SAE	Protocol requirement
0111	[REDACTED]	10/23/96	Within [REDACTED] working days under version 3.0
0107	Hematuria	1/22/97	Within [REDACTED] working days under version 3.0
0103	Adenocarcinoma of the cervix	4/9/98	Within [REDACTED] working days under amendment 3 dated 8/27/97
	Pnumonia and pulmonary effusion	8/10/98	
	Hematochezia	9/2/98	
	Melena, anemia	10/12/98	
	Pulmonary embolism	10/22/98	
	Deep vein thrombosis	10/23/98	
	Diarrhea	10/27/98	

In your response letter, you acknowledge your deficiency in reporting of SAEs to the sponsor in a timely manner and will implement better oversight of study personnel for proper documentation and reporting of SAEs to the sponsor.

- J Protocols 1 and 2 require that case report form (CRF) "corrections will be made by a single line stroke through the entry to be corrected, and the correct entry will be made above the deleted entry, initialed and dated." You routinely failed to follow these protocol directives in the following subjects' records, as illustrated in the following examples: 0101 (CRF page 3.4, dose calculation), 0103 (CRF page 3.1, dated 6/8/93, CRF page 17.1, 9/12/98, infusion [REDACTED]), 0104 (CRF page 3.3, dose calculation), and 0107 (CRF page 24.1, 5/20/98, infusion [REDACTED]).

In your response letter, you acknowledge the inappropriate corrections made by the study staff, and state that you will retrain your staff regarding the proper procedures for correcting errors.

- K Protocols 1 and 2 require the investigator or sub-investigators named on the Form FDA 1572 to review and sign the CRFs, thereby ensuring the completeness, correctness, and timely entry of data relating to the clinical trial. Several CRFs were corrected by an individual not listed on the Form FDA 1572. This is not a complete list, but is provided for illustration.

Subject	CRF page	Date of infusion - infusion number - data entry	Correction by an individual not listed on Form FDA 1572
0102	3.2, Part 1a	Calculation of dose	Item 3f, volume needed
0104	3.3, Part 1a	Calculation of dose	Item 7, end of infusion time
0105	3.3, Part 1a	Calculation of dose	Item 6b, question regarding same volume as entered in item 3f
0107	24.1, Part IIb addendum	5/20/98-5/23/98, infusions to [REDACTED]	Infusion dosage information
0109	3.0, Part 1a	7/18/94	Infusion of actual volume
0111	24.0, Part IIb	10/23/96, infusions [REDACTED]	Total [REDACTED] units entry in the infusion log
	24.1, Part IIb	10/16/96, infusions [REDACTED]	[REDACTED] dose entry under infusion dosage information

3. **You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50. [ 21 CFR § 312.60 ].**

You failed to obtain the written informed consent from the subject or their legally authorized representative before you initiated study-related procedures. You performed study-related blood tests for subject 0110 on 7/11/95 before the subject signed the informed consent document (ICD) on 7/18/95. In your response letter, you acknowledge this protocol deviation. However, you did not provide documentation that the sponsor prospectively agreed to permit this testing without a signed informed consent document.

4. **You failed to maintain adequate and accurate case histories. [ 21 CFR § 312.62(b) ]**

- A. Case report forms contain numerous data entry changes resulting in documentation discrepancies. These changes involve critical data information, such as dates, identification of the subject by number and initials, drug dosage information, drug lot number, concomitant medications, and adverse experiences. The following examples illustrate the type and number of data entry changes found in other records:

*Incorrect subject identifiers.* The dosing calculation work sheet dated 5/20/97 for subject 0101, the shipping tracking form dated 7/26/95 for subject 0106, and the dosing calculation worksheet under Part Ia for subject 0107 have incorrect subject numbers or initials.

- ii. *Incorrect dosage information.* There are discrepancies in the volume of investigational product administered to subject 0104 on 10/26/93, under Part Ia of Protocol 1, between CRF pages 3.2, 3.3 and the doctor's note dated 6/13/94 on CRF page 3.2.

*Inconsistent documentation of concomitant medications.* Multiple CRFs are discrepant in the listing of concomitant medications. For example, for the infusion on 7/18/94 for subject 0109, CRF page 3.3 did not list any concomitant medications whereas CRF page 3.0 listed the administration of [REDACTED]. In addition, discrepancies were noted for subject 0111 in the two CRF pages marked 3.0, dated 8/19/96, for the concomitant medications listing.

- iv. *Inconsistent error corrections in adverse experiences.* For subject 0103, for the infusions [REDACTED] between 4/9/98 and 4/12/98, there were multiple discrepant corrections in reporting adverse experiences.

- B You failed to maintain all supporting source documents for the subjects' study-related CRF entries. Source documents could not be verified for the CRF entries regarding administration of concomitant medications for the subjects listed:

CRF page 3.3 for subject 0102 reports the administration of Solu-Cortef on 5/19/93. Source documents could not be located during the inspection in the subject's case history for this medication.

CRF page 3.5 for subject 0108 reports the administration of Benadryl and Hydrocortisone to treat hives on 9/15/93. During the inspection neither written order could be located.

You provided copies of these source documents in your response letter, but you did not explain why these documents were not available during the inspection.

- C. You failed to document all pertinent data relating to the study in the subject's CRF.

The progress notes dated 10/16/96 state that subject 0111 developed nausea and chills as a reaction to the administration of the investigational product, requiring the administration of Hydrocortisone. You failed to record these adverse experiences (AEs) and the administration of Hydrocortisone on the subject's CRF.

In your response letter, you explain that the adverse experiences occurred on 10/23/96, not on 10/16/96. You entered the date, 10/23/96, in your progress note for the above-mentioned AEs, subsequently. We note that you entered the AE "chills" in the CRF 24.3, on a later date.

- ii. For subject 0103 you failed to document the duration of infusion on the following infusion dates: 9/6/98, 10/4/98, 10/6/98, 10/7/98, 10/16/98, 10/17/98, 10/20/98, 10/21/98, 10/22/98, 10/26/98, and 10/27/98.

In your response, you explain that in future studies you will use an infusion pump to correct this deficiency.

- D. You failed to maintain complete and relevant case histories for the subjects enrolled in the study.

For subject 0106, who was administered investigational product on 8/10/93, you were unable to locate the consent form, signed by the subject or subject's legally authorized representative, during the inspection.

In your correspondence dated November 7, 2001, you enclosed an ICD signed and dated 8/10/93, by the subject's representative for subject 0106.

- ii. You did not have documentation during the inspection to confirm that the sponsor prospectively granted approval to allow you to enroll subject 0109 who was [REDACTED] of age, under protocol 1.

In your correspondence dated November 7, 2001, you enclosed sponsor's approval letter dated April 25, 1994, agreeing to enroll subject 0109.

**5. You failed to maintain adequate records of the disposition of the drug. [ 21 CFR § 312.62(a) ].**

You failed to maintain adequate records of the disposition of the investigational products including the dates, quantity, and use by subjects. You failed to complete the investigational drug utilization record (IDUR) for the drug lots received by the pharmacy, and could not account for discrepancies in the inventory of the investigational products. Examples include, but are not limited to the following:

- A. Lot [REDACTED]: You did not record the receipt date, distribution, and the stock verification date in the IDUR. Furthermore, you could not account for distribution of five vials of this lot for recipient [REDACTED]; no subject with these initials was enrolled in Protocols 1 or 2.
- B. Lot [REDACTED] The distribution time and stock verification date are not recorded in the IDUR, and there is an inventory discrepancy of one vial on 9/30/98.
- C. Lot [REDACTED] The distribution time, received by, disposition of units, and stock verification are not recorded in the distribution log of the IDUR. The total number of remaining units could not be calculated based on the IDUR.
- D. Lot [REDACTED] You failed to record the receipt date in the receipt log, the date and time of the distribution, and the stock verification date in the distribution log of the IDUR. There is an inventory discrepancy of two vials.

In your response letter, you state that you will conduct more extensive training for study personnel associated with drug distribution and accountability.

**6. You failed to promptly report to the Institutional Review Board (IRB) all unanticipated problems involving risk to human subjects. [ 21 CFR § 312.66 ].**

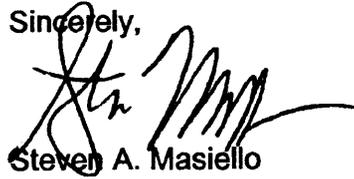
In its approval letter dated 2/25/93, the Illinois Masonic Medical Center IRB required that you immediately report adverse experiences. You failed to report eight of nine serious adverse experiences (SAEs) listed in item 2I above to the IRB. In your response letter, you acknowledge that you neglected to report the SAEs to the IRB.



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We request that you send a copy of your response to the FDA Chicago District Office at the address listed below.

Sincerely,



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

**Enclosure:** Form FDA 483, Inspectional Observations, dated August 21, 2001

**CC:**

Joann Givens, Acting District Director  
Food and Drug Administration  
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Rimgaudas Nemickas, M.D., Chairman  
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