DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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CBER–00-003

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

OCT 27 1999

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Robert W. Rand, Ph.D., M.D.
Associate Medical Director
Neuro-Oncology/Stereo Radiosurgery
John Wayne Cancer Institute
2200 Santa Monica Boulevard
Santa Monica, California 90404

Dear Dr. Rand:

During an inspection ending on August 31, 1999, Mr. Ronald Koller, an investigator with the Los Angeles District Office of the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study using Pseudomonas toxin fusion protein (IL-4(38-37)-PE38KDEL) in human subjects with recurrent malignant astrocytoma. You are the sponsor-investigator of the study. 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. Subject — did not meet the study inclusion criteria; however, the subject was enrolled into the study. The subject underwent radiation therapy through August 27, 1997, and received the first infusion of the study drug on September 12, 1997. The protocol directs that subjects not undergo radiation therapy and/or chemotherapy, for at least 4 weeks before study enrollment.

b. Subjects — and — were infused with the study drug for - — — respectively. The protocol indicates that the maximum length of time for infusion be —

c. The total volume of the infusate containing the study drug exceeded the calculated tumor volume for 7 of 9 subjects. Examples include, but are not limited to the following:

Subject	Tumor Volume (ml)	Volume of Infusate (ml)
—	48.6	—
—	23.0	—
—	106.0	—
—	22	—
—	38.9	—

The protocol indicates that the total volume of the infusate containing the study drug at the specified concentration will —

d. A safety report for subjects — and — was not submitted to the IND in a timely manner for an adverse event requiring hospitalization of the subjects due to communicating hydrocephalus, and to rule out the possibility of neurotoxicity after treatment with the study drug. The protocol indicates that adverse events that require hospitalization be reported verbally within 24 hours of the event and followed within 48 hours by a written report to FDA.

e. Magnetic resonance imaging scan (MRI) was not performed for any subject, — after infusion of the study drug as required by the protocol. An MRI was to be performed to evaluate the distribution of the toxin within the neoplasm.

f. An MRI was not performed — post-infusion for 8 of 9 subjects. An MRI was to be performed — post-infusion for all subjects to determine their tumor status (progression, stability, or response).

g. Serum samples were not obtained ——— of treatment and —— following treatment for all subjects. Subjects' serum samples were to be saved and stored at ——for determination of the study drug levels.

h. Liver function tests were not performed —— post-infusion for any subject.

i. Pre-study HIV test, hepatitis ABC panel, and ——————— tests were not performed as required by the protocol.

j. ——————— post-infusion chemistry lab tests were not performed for 6 of 9 subjects.

k. Post-treatment evaluations were not performed for 6 of 9 subjects. —— —— after the completion of the subject's initial treatment, the subject was to return to the clinic for follow-up evaluation to include a complete physical examination, neurological examination, and brain MRI scan.

l. A pregnancy test was not performed for subject — The subject was of child-bearing age.

It is your responsibility as principal investigator to ensure that all tests and evaluations are conducted at the time points indicated in the protocol. Missing tests, tests performed outside of protocol-specified time windows, missed clinical visits (e.g., follow-up visits), and other missing clinical procedures can adversely affect data safety and efficacy analyses.

2. **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. There are no progress reports for dates of drug infusion for subject ——

b. Subject — was treated with Cehalexin (antibiotic), but it was not documented under "concomitant medications" in the case report form.

c. The case report forms that document neurological examination, complete lab panels, and MRI tumor evaluations for subject —— (first infusion) were not completed.

d. The case report form for subject —records the first infusion as 12/16/97; however, there is no record of the infusion given in the ——— intake flow chart and progress notes (source documents). The Physician's Order Sheet indicates that the study drug was ordered for subject — on 12/16/97.

e. Case report forms reporting infusions are not always complete in that the infusion rate and volume infused are not always recorded. Examples include, but are not limited to, the following:

Subject	Case Report Form
—	1/22/98 - volume infused is not recorded. 1/24/98 - infusion rate is not recorded.
—	12/16,17/97; 4/3/98 – infusion rate and volume infused are not recorded.
—	12/17/97 - infusion rate and volume infused are not recorded.

f. The case report forms for subject — for infusions and liver panels do not record any entries.

g. Case report forms contain several data entry changes, which have cross-outs and write-overs without initials and dates by the person making the correction.

Proper procedures for correcting records show the changes, indicate when the changes were made, and who made the changes. Errors should be crossed by a single line but not obliterated, the correction inserted, and the change initialed and dated by the individual making the change.

All case report forms should be completed in a neat, legible manner to ensure that data are accurately interpreted. Clinical investigators are responsible for assuring that the data contained in the case report forms are complete and accurate. Please assure us that study personnel are instructed in the proper procedures for making corrections to study records.

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 responsibilities.

3. **Failure to maintain adequate records for the receipt and disposition of the test article. [21 CFR 312.62(a)]**

a. There are no records documenting the receipt of test article from the manufacturer.

b. Dispensing records are incomplete and/or inaccurate. Examples include, but are not limited to, the following:

   i. Lack of dispensing records for subject ~ who was infused with ~ of the infusate.

   ii. Lack of dispensing records for subject ~ who was infused with ~of the infusate. The only record located is a physician's order sheet dated 3/31/98 for ~ syringes each of ~ (a total volume of ~); however, the case report form documents that subject ~ was infused with ~ of the infusate.

   iii. There is a dispensing record dated 7/13/98 for subject ~ however, there is neither documentation of infusion of the study drug on 7/13/98 nor record of the final disposition of the prepared dose.

   iv. Records do not document the dose of study drug that was administered to subjects ~ and ~on 3/31/98.

   v. Records do not document how many vials of the study drug were left or unused after the pharmacy prepared the doses for subjects ~, and ~

c. There is no documentation of the final disposition of the test article.

Although the site's personnel have been delegated the responsibility for test article accountability, it is the principal investigator who is ultimately responsible for the following related tasks:

- maintaining complete shipment and receipt records, inventory and dispensing logs, and drug reconciliation and return records; and
- ensuring the security and proper storage of the test article.

Even when a research pharmacist is involved in a study at a site, the clinical investigator retains responsibility for ensuring that the test article was appropriately prepared, dispensed, and administered.

4. **Failure to notify the Institutional Review Board (IRB) of changes in research activity. [21 CFR 312.66]**

The protocol approved by the IRB specifies that the total volume of the infusate containing the study drug at the specified concentration will ——— In addition, the protocol requires that the maximum length of time for infusion be —— The decision to administer higher volume of the infusate and extend the infusion time for several subjects was not submitted to or approved by the IRB. These changes constitute an increased risk to subjects and must be reviewed by the IRB prior to implementation.

5. **Failure to notify the Institutional Review Board (IRB) of serious adverse events and/or subject deaths. [21 CFR 312.66]**

The deaths of seven subjects were not reported to the IRB. The IRB requires immediate reporting of all fatal or life-threatening adverse events within 72 hours after discovery, all serious and/or unexpected adverse events within 7 calendar days after discovery, and all adverse events at continuing review (including all deaths, regardless of cause). In addition, the protocol requires reporting of death on study, regardless of cause.

Deviations in the conduct of this study appear to be the result of your lack of understanding of the procedures and requirements that govern the use of investigational new drugs. Good Clinical Practice (GCP) is essential to maintain the quality of data collection regarding the conduct of clinical trials.

You deviated from an authorized study plan, investigator statement, and other conditions imposed on the study by the IRB or federal regulations. 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.

This letter is not intended to be an all inclusive list of deficiencies with your clinical study of investigational IL-4(38-37)-PE38KDEL. 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.

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
Tel. (301) 827-6221

We request that you send a copy of your response to the Food and Drug Administration's Los Angeles District Office, Director, Compliance Branch, 19900 MacArthur Blvd., Suite 300, Irvine, California 92715. 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