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

December 31, 2001

By Certified Mail – Return Receipt Requested

CBER 02 – 006

Warning Letter

Dana C. Matthews, M.D.  
Clinical Research Division  
Fred Hutchinson Cancer Research Center  
1100 Fairview Avenue North  
Seattle, Washington 98109

Dear Dr. Matthews

During the period between June 5 through October 26, 2001, Carl A. Anderson, Linda S. Leja, and Connie P. Rezendes, investigators with the Food and Drug Administration (FDA), reviewed your activities as the sponsor-investigator at the Fred Hutchinson Cancer Research Center (FHCRC) and the University of Washington Medical Center (UWMC). Three inspections were conducted under the FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of clinical research involving investigational drugs.

At the close each inspection, a Form FDA 483 (enclosed) was issued on the following dates: June 15, September 28, and October 26, 2001. We reviewed the two letters, dated July 9 and October 25, 2001, that you submitted to the FDA in response to the first two Forms FDA 483. 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.

- 1 You failed to ensure that the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND. [21 CFR § 312.50].**

You failed to ensure documentation of the review of the <sup>131</sup>I-BC8 diagnostic scans at UWMC, as required by the protocols. The inspection at UWMC revealed that there are no records that a physician evaluated the biodistribution of the investigational product on these scans.

**2. You failed to protect the safety of subjects under your care by failing to maintain adequate case histories. [21 CFR §§ 312.60 and 312.62(b)].**

- a. There is no documentation that a physician authorized to use the investigational product signed and dated orders for doses of test article. For 13 of (b)(7) UWMC subject records reviewed, there is no written documentation to show that a physician approved the therapeutic doses given to subjects. Furthermore, there is no record that you, as the sponsor-investigator, approved the prescribed doses.
- b. There is no documentation that a physician authorized to use the investigational product supervised the infusion of the test article for any of the (b)(7) UWMC subjects whose records were reviewed during the inspection.
- c. There is no documentation of the rationale for assumptions made during dosimetry calculations at UWMC. These calculations are used to determine the milliCurie dose of the investigational product. There are no source documents to verify the radiation doses to the kidneys for each of (b)(7) subject records reviewed. In addition, for 7 of (b)(7) records, there are no source documents to verify the radiation doses to the lungs.

During the inspection at UWMC, Dr. Janet Eary, Director, Division of Nuclear Medicine, University of Washington School of Medicine, said that dosimetry estimates were derived from a standard method, but there is no documentation to explain this. Furthermore, there is no record that a physician participated in the dosimetric calculations by reviewing the diagnostic scans to look at the biodistribution of the investigational product in the kidneys, lungs, or any other organs. See (1.) above.

**3. You failed to properly monitor the progress of the clinical investigations. [21 CFR §§ 312.50 and 312.56(a)]**

- a. You failed to verify the reliability of subject data entered into three different databases for your subjects: your personal database, the database maintained by your study coordinator, and a FHCRC database. In the letter dated 7/9/01, you said that you will enhance your current processes to consolidate data collection and provide for formal cross-checking for the purpose of data verification.
- b. You failed to document your monitoring of quality control for manufacture of the investigational product at the FHCRC Biologics Production Facility and at UWMC.

There are no records to verify that you reviewed all of the documentation accompanying the test article transferred from the Biologics Production Facility to your laboratory, as you asserted during the inspection. In addition, you failed to ensure documentation at UWMC of review of microbiology tests that are part of the batch production records for the investigational product.

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

The investigation at FHCRC revealed inadequate documentation of case histories:

- a. For the majority of the subject charts reviewed, you failed to sign the cover sheet CRF after data entry. There is no other documentation to verify your review of these CRFs. In your letter dated 7/9/01, you said that you will implement a process to ensure review of the CRFs.
- b. The inspection revealed that entries on CRFs were obscured by correction fluid. In your letter dated 7/9/01, you said that any change in records at FHCRC will be made by a single line that is initialed, and a log sheet will list the date and nature of the corrections.

The inspection at UWMC also revealed numerous examples of markovers and obscuring of original data.

- c. Prior to April 1999, there is no documentation at UWMC to confirm the eligibility of subjects to receive the investigational product. A form was used for this purpose after that date. However, the majority of forms were signed by the study coordinator, without documentation of review by a physician.
- d. You failed to ensure documentation of the review and approval of the protocol for the radiolabeling of BC8 at UWMC. This protocol was revised in 1989 and contained hand written changes. During the inspection Dr. Eary's staff provided a copy of a new protocol, dated 9/10/01, that had not been reviewed or approved either by you or by Dr. Eary.

**5. You failed to provide basic elements of informed consent. [21 CFR §§ 50.25(a)(1) and (a) (2)].**

You failed to advise subjects enrolled in Protocol (b)(4) that there is no upper limit to the milliCurie dose of the investigational product and to provide an accurate assessment of foreseeable risks of the procedures to be followed. Although the subject informed consent document, approved by the Institutional Review Board, gives a dose range of (b)(4) milliCuries, (b)(4) subjects were given higher doses. In the letter dated 10/25/01, Dr. Eary said that there is no upper limit for the radiation dose on this protocol. When there is no limit to the milliCurie dose of the investigational product, this provision, along with the associated risks, should be stated in the consent form.

**6. You failed to report to the FDA regarding information relevant to the safety of the drug. [21 CFR § 312.56(c)].**

The inspection revealed that there were no procedures for the prompt reporting of serious adverse events and deaths to the FDA. For several subjects, serious adverse events and deaths were included in annual reports to the FDA, but not reported in an expedited manner.

During the inspection, you said that adverse events had not been reported appropriately to the FDA. In your letter dated 7/9/01, you said that you will amend the protocols to specify guidelines for expedited reporting.

**7. You failed to provide a complete list of the subinvestigators who assisted you in the conduct of the investigations. [21 CFR § 312.53(c)(1)(viii)].**

You failed to ensure that Dr. Eary was listed on a Form FDA 1572 until 9/25/01. During the inspection at UWMC, Dr. Eary said that she participated in the studies since their beginning, and helped to originate the idea for the investigational product. It is your responsibility, as the sponsor-investigator, to list the names of your subinvestigators on a Form FDA 1572.

This letter is not intended to be an all-inclusive list of deficiencies. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in enforcement action without further notice. These actions could include initiation of investigator disqualification proceedings which may render a clinical investigator ineligible to receive investigational new drugs, termination of Investigational New Drug Applications, and/or injunction.

You should notify this office in writing, within fifteen (15) business days after receipt of this letter, of the specific actions you have taken to correct the noted violations. If corrective action cannot be completed within fifteen (15) business days, state the reason for the delay and the time within which the corrections will be completed. Your response should include any documentation necessary to show that correction has been achieved.

Please send your written response to

Mary Andrich, M.D.  
Office of Compliance and Biologics Quality, HFM-664  
Center for Biologics Evaluation and Research  
1401 Rockville Pike  
Rockville, Maryland, 20852

We request that you send a copy of your response to the Food and Drug Administration's Seattle District Office at the address below.

Sincerely,



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

Enclosures:

Form FDA 483, Inspectional Observations, dated June 15, 2001.  
Form FDA 483, Inspectional Observations, dated September 28, 2001.  
Form FDA 483, Inspectional Observations, dated October 26, 2001.

CC:

Karen Hansen, Director  
Institutional Review Office  
Fred Hutchinson Cancer Research Center  
1100 Fairview Avenue North  
Seattle, Washington 98109

Charles M. Breen, Director  
Food and Drug Administration  
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