



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

920461

DEC 4 2001

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 – 004

Warning Letter

Janet Eary, M.D., Director
Division of Nuclear Medicine
Professor of Radiology
University of Washington School of Medicine
1959 N.E. Pacific Way
Seattle, Washington 98195-6113

Dear Dr. Eary:

During the period from September 17 through September 28, 2001, Carl A. Anderson, an investigator with the Food and Drug Administration (FDA) reviewed your conduct of clinical studies at the University of Washington Medical Center using the investigational product ¹³¹Iodine-BC8. The sponsor for the studies is Dr. Dana C. Matthews, Fred Hutchinson Cancer Research Center (FHCRC). The inspection was conducted as part of the FDA's Bioresearch Monitoring Program that includes inspections designed to review the conduct of clinical research involving investigational drugs.

At the close of the inspection, a Form FDA 483 (enclosed) was issued to you. Your letter, dated October 25, 2001, sent in response to the Form FDA 483, has been reviewed. 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), Part 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 was conducted according to the investigational plan (protocol). [21 CFR § 312.60].**

You failed to document the review of ¹³¹Iodine-BC8 diagnostic scans, as required by the protocols. The inspection revealed that there are no records that a physician evaluated the biodistribution of the investigational product on these images. Although you claim, in your letter dated October 25, 2001, that gamma camera images have always been reviewed by a nuclear medicine subinvestigator, there is no documentation to verify that a physician did this.

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. You failed to protect the safety of subjects under your care by not ensuring that a physician who was authorized to use the investigational product signed and dated the order for the therapeutic dose. For 13 of 25 subject records reviewed, there is no written documentation to show that a physician approved the administered dose. In addition, for all 25 records, there is no documentation of oversight during the infusion by a physician authorized to use the investigational product. In your letter dated October 25, 2001, you said that, in the future, dosing forms will have signature lines for all those involved in administration of the study agent.
- b. You failed to ensure the safety of subjects by not documenting the rationale for assumptions made during dosimetry calculations used to determine the milliCurie dose of the investigational product. For each of 15 subject records reviewed, there are no source documents to verify the radiation absorbed doses for the kidneys that you reported to the sponsor. In addition, for 7 of 15 records, there are no source documents to verify the radiation absorbed doses reported for the lungs. During the inspection, you provided the FDA investigator with a memorandum, dated September 25, 2001, in which you said that dosimetry estimates were derived from a standard formulation. However, there is no documentation 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 other organs. See 1. above.

3. You failed to maintain adequate case histories. [21 CFR § 312.62(b)].

The inspection revealed that there are numerous examples of markovers and obscuring of original data in subject charts. In your letter dated October 25, 2001, you said that staff will draw a single line through each error, initialing and dating the correction.

In addition to the above items, we note the following:

For one of your protocols, documentation provided during the inspection shows Radiation Safety Committee approval for doses of _____ milliCuries of the investigational product. However, several subjects received higher doses, up to milliCuries. In your letter dated October 25, 2001, you said that this protocol does not contain any restriction on the upper limit of radiation to be administered. Please explain the discrepancy.

This letter is not intended to be an all-inclusive list of deficiencies in your clinical study of investigational drugs. It is your responsibility to ensure adherence to each requirement of the law and relevant 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 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.

Failure to achieve correction may result in enforcement action without further notice. The actions could include initiation of investigator disqualification proceedings which may render a clinical investigator ineligible to receive investigational new drugs.

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
Telephone: (301) 827-6221

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