



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

• CBER-01-015

FEB 23 2001

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Malik Juweid, M.D.
Department of Nuclear Medicine
University of Iowa Hospitals and Clinics
200 Hawkins Drive
Iowa City, Iowa 52242

Dear Dr. Juweid

During the inspection that ended on May 25, 2000, investigators with the Food and Drug Administration (FDA) reviewed your conduct of clinical studies at the Garden State Cancer Center, Belleville, New Jersey. At that time, you were the Director of Nuclear Medicine at the Garden State Cancer Center, and the clinical investigator on the investigational protocols that were reviewed. 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.

Based on information obtained as a result of the inspection, we have 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. Failure to withhold administration of an investigational new drug until an Investigational New Drug Application (IND) is in effect. [21 CFR § 312.40(d)].

You administered investigational products, including _____ to multiple subjects without filing an IND with the FDA. In addition, you are a co-author of articles published in medical journals with data from these studies, which were supported by government grants.

a. Seventy-two subjects were given radiolabeled doses of _____, without an IND in effect. Twelve received more than one dose. They are listed below by subject number:

639	1076	1152	1303	1368	1434
794	1091	1185	1310	1370	1435
842	1093	1227	1313	1372	1436
881	1101	1246	1337	1373	1447
882	1105	1253	1342	1375	1451
908	1108	1258	1343	1377	1457
909	1118	1260	1345	1414	1463
933	1127	1270	1347	1418	1467
995	1128	1272	1349	1422	1574
1021	1139	1280	1357	1427	1575
1046	1146	1293	1360	1429	1576
1064	1148	1300	1365	1433	1585

b. Six subjects were given radiolabeled doses of _____ without an IND in effect: 1490, 1508, 1544, 1552, 1567, and 1569.

c. Seventeen subjects were given _____ labeled antibodies, without an IND in effect:

1324	1365	1416	1463
1325	1373	1433	1467
1330	1378	1436	
1339	1387	1447	
1364	1410	1457	

2. Failure to ensure that the investigation is conducted according to the investigational plan (protocol) and failure to protect the rights, safety, and welfare of subjects under your care. [21 CFR Part 50 and § 312.60].

You failed to follow the investigational plan and to protect the rights, safety, and welfare of subjects enrolled under Garden State Cancer Center clinical protocols by not documenting eligibility to receive potentially toxic therapeutic doses of radiolabeled antibodies prior to the administration of therapy. Both the Garden State Cancer Center clinical protocols and the informed consent documents require visualization of uptake of the radiolabeled investigational product on a pre-therapy (diagnostic) scan by a confirmed site of tumor before administration of the therapeutic dose. A confirmed site of tumor is defined as a site that has been proven by biopsy, or one for which progressive growth, based on radiographic studies, had been observed. All subjects agree to the condition that they are eligible for therapeutic doses of investigational radiolabeled antibodies only if this criterion is met.

For 69% (31/45) of subject records reviewed, the Case Report Form (CRF) pages for the pre-therapy scan results, the source documents designated for this purpose, were blank. Furthermore, Dr. Robert Sharkey, Director of Clinical Research Administration, Garden State Cancer Center, said that there was no documentation of the radiolabeled antibody scan results in the subject medical records because the scan data was entered directly on the CRFs. You stated that you were the only Nuclear Medicine physician at Garden State Cancer Center and the only person who interpreted the radiolabeled antibody scans. At the time of the inspection, you did not have any scan reports for multiple subjects.

After therapeutic doses of the investigational products had been administered, you reviewed the pre-therapy radiolabeled antibody scans in a retrospective manner. During the inspection, pre-therapy radiolabeled antibody imaging results were found in the CRFs for 31% (14/45) of subject records reviewed. Specifically, there were radiolabeled antibody scan results in the CRFs of subjects who were included in the Investigational New Drug Application (IND) annual reports. You said that you wrote your interpretations of the images in the CRFs at the time of the IND annual reports. For multiple subjects, you wrote the initial dates of the scans on the CRFs and not the actual dates on which you recorded your interpretations. This practice gives the impression that the CRFs are being filled out prior to the administration of the therapeutic doses of the test articles. Furthermore, we consider your interpretation of the pre-therapy scans to be compromised because you recorded your interpretations following the therapeutic doses of the investigational products, and could use the post-therapy scans to confirm tumor targeting in the pre-therapy scans. The pre-therapy scans are intended to confirm tumor targeting without exposing subjects to the higher therapeutic doses.

Examples of how your lack of documentation of eligibility had an impact on the safety of subjects are given below:

a. For subject 1861, your failure to document the pre-therapy radiolabeled antibody scan results contributed to the misadministration of the therapeutic dose that you ordered. While this subject was receiving the therapy dose, a Garden State Cancer Center consultant radiologist was unable to confirm uptake of the investigational product by tumor on the pre-therapy radiolabeled antibody scan. As a result the consultant radiologist stopped the intravenous infusion already in progress.

You did not fill out either the CRF for the pre-therapy radiolabeled antibody scan results or the CRF entitled ~~_____~~ the form designed to compare baseline CT scan results with pre-therapy radiolabeled antibody scan findings. Documentation of the eligibility of this subject for therapy was incomplete at the time of the therapeutic infusion that was discontinued by the consultant radiologist.

b. You failed to fill out the CRFs for the pre-therapy radiolabeled antibody scan and the ~~_____~~ for subject 1853, who suffered a severe adverse event that was designated as "possibly related" to therapy. The baseline CT scan for this subject showed a moderate pericardial effusion. After therapy, this subject developed life-threatening cardiac tamponade and required surgery for the drainage of a 1500 cc pericardial effusion. Documentation of eligibility for therapy was incomplete.

c. You failed to document the eligibility of multiple subjects to receive therapeutic doses of radiolabeled antibodies prior to their transfer to another clinical facility to receive therapeutic doses of radioactive Iodine at a level that required hospitalization in a special room separated from the public until the radioactivity of the subject decreased to a level where they could be released. You sent subjects to this other facility without documenting the uptake of the investigational product by tumor when therapeutic doses were too high to be administered in your clinic, as demonstrated by the lack of entries in the CRFs

3. Failure to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug. [21 CFR § 312.62(b)].

a. You failed to document that you were aware of the enrollment of a subject with a white blood cell count that was lower than permitted by protocol. Subject 1780 was enrolled with a low white blood cell count, with documentation by the sponsor's research coordinator. There were no notes in the subject's record signed by you regarding this protocol deviation. Furthermore, this subject went on to develop a Grade 3 neutropenia that was not documented on the CRFs.

b. You failed to document that you were aware of abnormal laboratory results that were coded as "Normal" in the CRFs. These abnormal results included urinalysis results for subjects 1825 and 1829. For example, subject 1829 had a urinalysis result of "Protein 3+, Blood Large, RBC 30-50/hpf" that was entered as "Normal" on the CRF. After the inspection, in response to the Form FDA 483, the sponsor submitted data to the FDA with additional abnormal urinalysis results that were coded as "Normal" on the CRFs, requiring correction for the following subjects: 1866, 1867, 1868, 1871, 1875, 1880, 1884, 1885, 1888, 1889, 1890, 1892, 1894, 1896, 1897, 1899, 1908, 1909, and 1911.

c. After you transferred subjects to another facility for therapeutic interventions that could not be performed at the Garden State Cancer Center, you failed to review the medical records for these subjects from the other facility to determine whether the therapeutic interventions were performed according to protocol. Although you did not review these records, you continued to transfer Garden State Cancer Center protocol subjects to the other facility for several years.

d. You failed to review the content of letters sent to referring physicians delineating the clinical parameters to be followed for subjects enrolled at Garden State Cancer Center. These letters were prepared and sent out by the sponsor's research coordinators without your supervision. As a result of errors in these letters, referring physicians did not prescribe medications required by myeloablative protocols to subjects 1791 and 1796. The erroneous letters indicate that _____ should not be given, even though the administration of _____ was designated by the protocol. In addition, two other required medications, _____ were not prescribed.

e. You failed to document adverse events on the CRFs, as required by Garden State Cancer Center Standard Operating Procedures. Examples of adverse events that were not documented in the CRFs are given below:

<u>Subject Number</u>	<u>Adverse Event</u>	<u>Grade of Adverse Event</u>
1780	thrombocytopenia	3
	neutropenia	3
	thrombocytopenia	3
	leukopenia	3
	granulocytopenia	3
	liver function tests	3
	hypercalcemia	3
	leukopenia	3
	anemia	2
	thrombocytopenia	2
	abdominal pain with nausea	2
	difficulty breathing	Not recorded
	abdominal pain	Not recorded

f. You failed to document that you were aware of the occurrence of adverse events. You did not co-sign the CRFs entitled "Adverse Events Form" for multiple subjects, including 1825 and 1853. Examples are given below:

<u>Subject</u>	<u>Adverse Event</u>	<u>Severity</u>
1825	Diarrhea with mucous	Severe
	Abdominal pain	Severe
1853	Dysphagia	Not recorded
	Hospitalization for dizziness and light-headedness	Grade 3 (anemia)
	Thrombocytopenia	Grade 4
	Dyspnea	Not recorded
	Fever	Not recorded
	Sinus tachycardia	Not recorded
	Cardiac tamponade	Not recorded

After the inspection, in response to the Form FDA 483, the sponsor submitted to the FDA additional adverse event CRFs requiring your signature that had not been signed by you for the following subjects: 1745, 1747, 1753, 1760, 1763, 1765, 1774, 1777, 1787, 1791, 1798, 1799, 1819, 1824, 1830, 1834, 1846, 1849, 1850, 1871, 1875, 1880, 1888, 1890, 1892, 1896, and 1899.

4 Request for information

Garden State Cancer Center patient informed consent documents list the possible risks to subjects from the radiolabeled antibody infusions. For example, the consent form for Protocol C029A states,

¹³¹I-antibody: You risk developing an allergic reaction to the antibody or iodine solution, resulting in developing fever and rash. In case of an allergic reaction that could manifest itself by itching, skin rash, difficulty breathing, or hypotension (low blood pressure), treatment of this adverse reaction may require the administration of anti-allergic medications. Sometimes muscle and bone pain may be experienced during the injection and the rate of infusion needs to be slowed. If any allergic symptom cannot be adequately treated, and the condition is deemed life-threatening, the injection of the radiolabeled antibody must be stopped, and you will be ineligible to receive further treatments under this protocol.

Please describe the equipment and medications that you had available for resuscitation prior to the inspection that ended on May 25, 2000. In addition, please explain how you treated reactions to investigational products at Garden State Cancer Center.

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.

It is strongly recommended that you undergo training in the responsibilities of investigators, 21 CFR Part 312, Subpart D, and the protection of human subjects regulations, 21 CFR Part 50.

Please notify 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, and to prevent the recurrence of similar violations in future studies. 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 me at the following address

Office of Compliance and Biologics Quality, HFM-600
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 400S
Rockville, Maryland, 20852-1448

We request that you send a copy of your response to the Food and Drug Administration's New Jersey District Office, Waterview Corporate Center, 10 Waterview Boulevard, 3rd Floor, Parsippany, NJ 07054.

Sincerely,



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

Enclosure: Form FDA 483, Inspectional Observations, dated May 25, 2000

cc:

Douglas Ellsworth
Director
FDA/New Jersey District Office
Waterview Corporate Center
10 Waterview Boulevard, 3rd Floor
Parsippany, New Jersey 07054