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

CBER-00-032

SEP 19 2000

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

David M. Goldenberg, Sc.D., M.D.
President,
Garden State Cancer Center
520 Belleville Avenue
Belleville, NJ 07190-0023

Dear Dr. Goldenberg:

During the inspection that ended on May 25, 2000, Cheryl L. Curet and Lisa B. Hall, investigators with the Food and Drug Administration (FDA), reviewed the activities of your firm, Garden State Cancer Center, as the sponsor of research with investigational products. The inspection was conducted under the FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of clinical research involving investigational drugs.

At the close of the inspection, a Form FDA 483 (Enclosure A) was issued to you and discussed with you and members of your staff. Your letter (Enclosure B) in response to the Form FDA 483, dated August 1, 2000, has been reviewed. This inspection revealed deviations from applicable federal regulations as published in Title 21, Code of Federal Regulations, Parts 50 and 312 [21 CFR 50 and 312] including the following:

1. Failure to submit an Investigational New Drug Application (IND) to the FDA and failure to withhold administration of an investigational new drug until an IND is in effect. [21 CFR 312.20 and 312.50].

Your firm administered investigational products, including: _____, and _____ to human subjects without filing an IND. You are a co-author on 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. They are listed below by subject number:

Twelve of these subjects received more than one dose of the investigational product.

b. Six subjects were given radiolabeled doses of _____, without an IND in effect: [_____]

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

- 2. Failure to ensure proper monitoring of the investigation(s) and failure to ensure that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND. [21 CFR 312.50 and 312.56]**

Monitoring of Clinical Trials

This inspection revealed an absence of monitoring of clinical activities at the Garden State Cancer Center. In your letter to the FDA (Enclosure B), you stated that patients seen at Garden State Cancer are carefully monitored. However, during the inspection, there were multiple examples of the lack of monitoring activities resulting in a direct impact on the conduct of the clinical trials and the safety of human subjects. Furthermore, when asked about monitoring at your facility, Dr. Robert Sharkey, Director of Clinical Research Administration, said that there was none. He also said that your firm had hired a new clinical research associate specifically for this purpose.

In your letter (Enclosure B); you stated that a new staff member in the Regulatory Office will be responsible for conducting an independent review of the clinical program. You also stated that you have requested the hiring of an independent contractor to audit your firm's clinical and regulatory programs.

- a. Your firm failed to monitor the clinical trials conducted under Garden State Cancer Center protocols. The Principal Investigator for the majority of these studies was Dr. Malik Juweid, Director of Nuclear Medicine, Garden State Cancer Center. []

- i. Your firm failed monitor for completion of documentation of the eligibility of subjects, based on the results of the pre-therapy (diagnostic) radiolabeled antibody scans, prior to the administration of potentially toxic therapeutic doses of the same investigational products.

The Garden State Cancer Center patient informed consent documents, as well as the protocols, require that each subject must demonstrate visualization of uptake of the investigational product, a radiolabeled antibody, by at least one confirmed site of tumor on the pre-therapy scan in order to be eligible for a therapeutic dose of the same product. A confirmed site of tumor was defined as a site that has been proven to be tumor 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 therapy 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 were blank. Dr. Sharkey said that there was no documentation of the radiolabeled antibody scan results in the subject medical records, because data was entered directly on the CRFs. At the time of the inspection, there were no pre-therapy radiolabeled antibody scan results for multiple subjects. Your firm failed to insure that Dr. Juweid entered his interpretations of the pre-therapy radiolabeled antibody scans on the CRFs, the source documents, prior to administering the therapeutic doses.

Your letter (Enclosure B) said that Dr. Juweid and Dr. Sharkey attested during the inspection that Dr. Juweid always read the films prior to authorizing the injection of patients. Your firm does not have written documentation of the uptake of the investigational products by tumor sites prior to the administration of multiple doses of potentially toxic therapeutic doses of radiolabeled antibodies.

One example of the impact of the lack of monitoring of the documentation of eligibility on the safety of human subjects was seen in the case of subject _____, who had incomplete documentation of eligibility and suffered a severe adverse event that your firm designated as possibly related to therapy. This subject received a therapeutic dose of a radiolabeled antibody when the CRFs for the pre-therapy radiolabeled antibody scan and the _____ were blank, and the CRF for the baseline CT scan noted a moderate pericardial effusion. After therapy, this subject developed life-threatening cardiac tamponade and required surgery for drainage of a 1500 cc pericardial effusion.

A second example was the misadministration of a therapeutic dose ordered by Dr. Juweid for subject _____. While this subject was receiving the therapy dose, a Garden State Cancer Center consultant radiologist was unable to confirm uptake of the radiolabeled antibody by tumor on the pre-therapy radiolabeled antibody scan. As a result, the consultant radiologist stopped the intravenous infusion already in progress. Review of the CRFs for this subject showed that the CRF for the pre-therapy antibody scan results was blank. In addition, the CRF entitled _____ the form designed to compare the baseline CT scan with the pre-therapy radiolabeled antibody scan, was also blank.

ii. Your firm failed to monitor for the accuracy and timeliness of Dr. Juweid's entries on the CRFs. During the inspection, pre-therapy radiolabeled antibody imaging results were found in the CRFs of 31% (14/45) subject records reviewed. Specifically, there were pre-therapy radiolabeled antibody scan results in the CRFs of those subjects who were included in the IND annual reports.

Dr. Juweid said that he documented the scan results in the CRFs at the time of the IND annual reports. He said that he wrote the dates of the scans on the CRFs, and not the actual dates on which he entered his interpretations. This gives the impression that the CRFs are being filled out prior to the administration of the therapeutic doses. Furthermore, it affects the accuracy of the data, since evaluation of the pre-therapy scan in conjunction with a scan obtained after the administration of the therapeutic product enhances the imaging characteristics of the investigational product. Your firm failed to correct this practice.

iii. Your firm failed to monitor for documentation of the eligibility of subjects to receive therapeutic doses prior to their transfer, by Dr. Juweid, to another clinical facility, _____
_____. Dr. Juweid sent multiple subjects there without entries in the CRFs of the uptake of the investigational product by at least one confirmed site of tumor, when their therapeutic doses were too high to be administered in your clinic. Dr. Sharkey said that patients went to this other facility because the therapeutic doses of Iodine were at a level that required hospitalization in a special room separated from the public until the radioactivity of the patient decreased to a level where they could be released.

b. Your firm failed to monitor clinical trials conducted at _____
_____ to insure that the Garden State Cancer Center protocols were followed. According to Dr. Sharkey, your firm has been sending subjects to this facility since 1992 for therapeutic interventions that can not be done in your clinic, including the harvest and reinfusion of stem cells, as well as the administration of therapeutic doses of radiolabeled antibodies too high to be given in your clinic.

There were no written procedures to monitor this other site in 1996 when the FDA performed an inspection of the clinical investigator, _____,
Chief of Oncology, _____; a clinical investigator for your firm's protocols.

During the interval since the 1996 inspection, your firm has not performed any monitoring at this site. Your staff has not reviewed subject medical records at _____ to determine whether stem cell harvests and reinfusions, or the therapeutic infusions of radiolabeled antibodies, have been performed according to protocol. *In your letter (Enclosure B), you said that your firm made unsuccessful attempts, starting in July 1999, to conduct monitoring at this site.*

Although your firm was unable to monitor medical records for Garden State Cancer Center protocol subjects undergoing therapy at _____, transfer of subjects to this other clinical facility continued. *Your letter (Enclosure B) said that patient accrual to this site was stopped and that there was ongoing discussion.*

Monitoring of Clinical Records

c. Your firm failed to insure that the Garden State Cancer Center research coordinators use a consistent method for data entry in the CRFs, as well as for the review of CRFs already completed. The inspection revealed the following problems, with representative examples of each.

i. Garden State Cancer Center research coordinators failed to document the reason that data was not entered on CRFs, when CRF pages were left blank for subjects, including _____

ii. Garden State Cancer Center research coordinators signed CRF pages prior to the completion of data entry on those pages. CRF entries were made after the date of the research coordinator's signature for subjects _____

iii. Garden State Cancer Center research coordinators failed to sign and date CRFs that had already been completed for subjects _____

In your letter (Enclosure B), you said that, with respect to sign-off practices, part of the problem was the design of the CRFs that were being used at the time of the inspection. Your firm is preparing new CRF format that isolates individual entries according to the time the test is performed.

d. Garden State Cancer Center research coordinators coded abnormal urinalysis results as "Normal" on CRFs for subjects _____ For example, subject _____ had a urinalysis result of "Protein 3+, Blood Large, RBC 30-50/hpf" that was entered a "Normal" on a CRF..

Your letter (Enclosure B) said that the staff has been retrained concerning the completion of this CRF. You also said that, since the inspection, additional errors have been identified on CRF pages for the following subjects: _____

e. Your staff did not transcribe follow-up data provided by referring physicians onto the CRFs. The medical record for subject _____ had follow-up summaries from outside physicians, dated 6/21/99 and 8/23/99, containing data that had not been entered into the CRFs.

Your letter (Enclosure B) said that this was a topic for additional training of the clinical staff, and that they have been instructed that CRF pages must be completed in a timely manner.

f. Your firm does not have signature sheets designating the staff who are allowed to make entries on the CRFs. During the inspection, Dr. Sharkey said that this is something that your firm will implement.

g. Your firm failed to monitor for documentation of adverse events on the CRFs, as required by Garden State Cancer Center Standard Operating Procedures (SOPs). 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>
	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.)

Your letter (Enclosure B) said that despite not having CRFs completed for subject [redacted] toxicities were and are always reported to the FDA in annual reports. You said that this merely reflected the clinical coordinator's misunderstanding the need for completing the CRFs for expected toxicity, such as myelotoxicity, and not a failure to document and report these events. You did not provide an explanation of how adverse events are tracked when they are not recorded in the CRFs.

Your firm does not follow the Garden State Cancer Center SOP, entitled "Documenting and Reporting Adverse Experiences and Deaths", for summarizing adverse events. Research coordinators did not complete the forms entitled "Summary of Adverse Experiences for an Individual Patient". Neither are the forms entitled "Summary of Adverse Experiences for a Study" filled out. Dr. Sharkey agreed that the SOP should be updated to reflect the current practice of your firm.

h. Your firm failed to document that the Principal Investigator, Dr. Juweid, was aware of the occurrence of adverse events. On the CRF entitled "ADVERSE EXPERIENCE REPORT FORM", the box for "PHYSICIAN ACKNOWLEDGEMENT" was empty for several subjects, including [redacted] and [redacted]. Examples are given below:

ii. One Garden State Cancer Center research coordinator said that they relied on phone contact from _____ staff to find out about adverse events that occurred while subjects were undergoing therapeutic interventions there, but had never received any phone calls. Another research coordinator said that they called the other facility every day that subjects were hospitalized to find out how they were doing. In addition, your firm failed to obtain medical records regarding these adverse events.

j. Your firm sent subject follow-up letters that did not contain adequate information to referring physicians. These letters were prepared by Garden State Cancer Center clinical research coordinators, but were not reviewed by Dr. Juweld. The letters did not contain summaries of the protocols (including lists of protocol violations), the definition of serious adverse events, or information about the necessity of reporting of serious adverse events to your firm.

Your firm failed to monitor the content of the follow-up letters, and a letter containing incorrect information was sent out for two subjects, _____. As a result, neither of them received _____ medications that were required by a myeloablative protocol.

k. Your firm does not monitor the follow-up data provided by referring physicians. There is no procedure to verify data sent to your firm by the physicians who receive the subject follow-up letters.

Follow-up data for multiple subjects (including _____ is incomplete, without documentation to explain why items are missing. In addition, your firm failed to insure that all of the chemistry tests required by protocol for subjects _____ were done, or to provide documentation as to why they were not done.

l. Your firm does not monitor the follow-up data provided by subjects.

i. There is no verifiable documentation for the required daily contact with patients who receive _____ Garden State Cancer Center protocols require the administration of _____ for subjects receiving investigational products radiolabeled with ¹³¹Iodine. The CRF entitled "PROTOCOL-REQUIRED MEDICATION COMPLIANCE" has boxes to check "Yes" or "No" for each day of medication. There is no place on the CRF for the initials of the person making the entries.

ii. Information about adverse events is solicited directly from subjects, through phone contacts initiated by Garden State Cancer Center research coordinators. There is no procedure to verify this data.

3. Failure to maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug, and failure to assure the return of all unused supplies of the investigational drug, or to assure alternative disposition of unused supplies of the investigational drug.

[21 CFR 312.57 and 312.59]

Your firm cannot account for the disposition of any of the unused investigational products at Garden State Cancer Center. There are no records documenting date of disposal of radiolabeled test articles. Your firm cannot provide documentation for the disposition of unused investigational products at any other clinical sites, and does not accept returned test articles from these facilities.

4. Failure to obtain prior written approval of the FDA before charging for investigational drugs. [21CFR312.7(d)(1)]

Your firm charged subjects for "tumor imaging" in cases where the CRF pages for the radiolabeled antibody scan results, the source documents, were blank. Review of the billing records for two subjects, _____, revealed charges for "tumor imaging" when there was no record of Dr. Juweid's interpretation of the radiolabeled antibody scan images, or any other scan reports, in their CRFs, the source documents.

In addition to the items above, please comment on the following:

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

"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."

In the clinic at Garden State Cancer Center where radiolabeled antibodies are infused into human subjects, please describe the equipment and medications that were available for resuscitation prior to the inspection that ended on May 25, 2000. How many Garden State Cancer Center subjects have had allergic or anaphylactic reactions to radiolabeled antibodies? How many subjects have been transferred to another medical facility because their care could not be managed at your facility? Please provide documentation.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Federal Food, Drug, and Cosmetic Act, as well as the Public Health Service Act, and relevant regulations. All regulations cited in this letter are available via the Internet at <http://www.access.gpo.gov/nara/cfr/index.html>.

Please notify this office in writing, within 15 business days after receipt of this letter, of the specific steps you have taken to correct the noted violations, as well as any steps taken to prevent the occurrence of similar violations in future studies. If corrective action cannot be completed within 15 business days, please 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. This letter does not preclude the possibility of a corollary judicial proceeding or administrative action concerning these violations. Failure to achieve correction may result in regulatory action being initiated by the Food and Drug Administration without further notice.

Your written response should be sent 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

Sincerely,



Steven A. Masiello

Director

Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Enclosures:

Enclosure A: Form FDA 483, Inspectional Observations, dated May 25, 2000.
Enclosure B: Letter from David M. Goldenberg, Sc.D., M.D., President, GSCC,
to the FDA dated August 1, 2000

cc:

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