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January 24, 2001

David M. Goldenberg, Sc.D., M.D.
President
Garden State Cancer Center
520 Belleville Avenue
Belleville, New Jersey 07109-0023

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1490

FDA Warning Letter Dated September 19, 2000

Dear Dr. Goldenberg:

The Office for Human Research Protections (OHRP) has reviewed the Garden State Cancer Center's (GSCC) report dated November 16, 2000 regarding possible noncompliance with Department of Health and Human Services (HHS) regulations for protection of human subjects (45 CFR Part 46) involving the above referenced FDA warning letter.

Based on the documents provided with your report, OHRP notes the following:

(1) With respect to FDA's finding that GSCC failed to ensure proper monitoring of investigations and failed to ensure that investigations are conducted in accordance with general investigational plan and protocols, your October 10, 2000 letter in response to the FDA stated:

(a) "GSCC recognizes deficiencies in monitoring and adherence to investigational plans and protocols."

(b) "Thus, GSCC has taken immediate and definitive steps to correct all deficiencies that were noted in the April/May 2000 inspection."

(2) Regarding the actions taken by the GSCC Institutional Review Board (IRB) related to the deficiencies described in the FDA warning letter, your report stated that, "The IRB committee reviewed the corrective action plan, which was discussed and unanimously approved at the November 15, 2000 meeting. The IRB committee will review follow up monitoring reports issued by clinic staff on an on-going basis to ensure compliance with regulatory requirements for the protection of human subjects."

(3) As indicated in the IRB minutes submitted with your report, the GSCC IRB was notified that all GSCC IND's were placed on clinical hold at the September 13, 2000 meeting. OHRP also notes that no questions were raised by the IRB on this issue.

(4) GSCC's August 2, 2000 response to Form FDA 483 issued May 25, 2000, under item 9., relating to IRB quorum not being met, states, "The IRB Chairwoman stated that although there may have been some confusion at that time of what constituted a quorum under the specific circumstances when a member had to be excused from voting, this situation had been recognized and corrected and there have been no further occurrences.

(5) The GSCC IRB policies and procedures state:

(a) "A majority/quorum shall be defined as a number greater than one-half of the total."

(b) "If the IRB consists of 10 members, 6 must be present for a majority. Should the quorum fail during a meeting, the meeting is terminated from further votes unless the quorum can be restored."

OHRP makes the following determinations:

(1) HHS regulations at 45 CFR 46.111(a)(1) require that, in order to approve research, the IRB shall determine that risks to subjects are minimized by using procedures which are consistent with sound research design. Based on review of the documents submitted with your November 16, 2000 report, OHRP finds that the GSCC IRB failed to ensure that investigators minimized risks to subjects through proper monitoring of subjects and adherence to IRB-approved protocols.

OHRP notes the efforts GSCC has made in addressing the issues raised in the FDA warning letter relating to monitoring of subjects and adherence to IRB-approved protocols. These efforts include:

(a) Contracting with a contract research organization to review programs, policies and standard operating procedures.

(b) Providing training in GLP and GCP to all GSCC staff involved in its clinical research program.

(c) Establishing a standard operating procedure for routine on-site monitoring of all clinical sites.

(d) Implementation of research monitoring plans which include (i) audit of clinical study reports; (ii) clinical investigator site audits; (iii) audits of protocols, amendments, informed consent documents and case report forms; and (iv) audits of study master files.

OHRP is concerned that your report includes no documentation that the GSCC IRB has participated in the development of these corrective actions, other than review and approval at the November 15, 2000 IRB meeting. OHRP notes that the corrective action plans which were presented with your report do not require results of monitoring and audits of research to be forwarded to the IRB. Furthermore, the newly developed standard operating procedures for Monitoring of Clinical Studies and Internal Auditing of Completed/Terminated Clinical Studies do not reference 45 CFR Part 46, the responsibilities of the IRB, or the need for investigators to report unanticipated problems or any serious or continuing noncompliance as required under 45 CFR 46.103(b)(5) to the IRB. OHRP is concerned that results of audits and monitoring procedures may not be reviewed by the IRB which has responsibility for assuring that risks to human subjects are minimized.

(2) HHS regulations at 45 CFR 46.108 require that, except when an expedited review procedure is used, the IRB review proposed research at convened meetings at which a majority of the members of the IRB are present. OHRP finds that the IRB failed to meet this requirement for the September 13, 2000 IRB meeting when members were excused due to conflicts of interest. Thus, any actions taken at this meeting when a quorum was not acting must be considered invalid. OHRP emphasizes that should the quorum fail during a meeting (e.g., those with conflicts being excused, early departures, loss of a nonscientist), the meeting is terminated from further votes unless the quorum can be restored.

Action 1 - Required : GSCC must submit to OHRP a revised corrective action plan including all standard operating procedures, monitoring and audit plans, and training programs which ensures that such plans adhere to the requirements for the protection of human subjects under 45 CFR Part 46.

Action 2 - Required: GSCC must audit and identify all ongoing research projects involving human subjects that are not exempt under HHS regulations at 45 CFR 46.101(b) and confirm that all such research has been reviewed and approved at a meeting of the GSCC IRB where a quorum was achieved. The GSCC IRB must re-review and approve any research which was approved at a meeting where a quorum was not acting. GSCC must submit to OHRP a list of all research which was re-reviewed as a result of this audit.

OHRP has the following additional concerns and guidance:

(1) Regarding collaborating institutions for GSCC protocols, OHRP notes the following:

(a) Appendix 1 of the October 2, 2000 GSCC letter to Lyn Bacon of the National Cancer Institute indicated that Protocol Number C-041A included the Hospital of the University of Pennsylvania as a collaborating site. The GSCC's letter of August 1, 2000 to Ray Abrahams of the FDA indicated that St. Barnabas Medical Center was following a subject under protocol Number C-041A-98. St. Barnabas Medical Center does not appear to be listed as a collaborative site on for this protocol.

(b) The minutes of the April 12, 2000 GSCC IRB meeting indicated that a request to use the Staten Island University Hospital and the Hematology Association of NJ for two patients enrolled under protocol number C-037C-97 was approved via expedited review.

(c) The minutes of the May 31, 2000 GSCC IRB meeting indicated that the peripheral blood stem cell rescue (PBSCR) procedure for patient number 1892 was being performed at Hackensack University Hospital under protocol number C-033A.

OHRP is concerned that involvement of the above mentioned sites may require a modification of the protocol and approval of the GSCC IRB. Please respond. In your response please indicate whether changes to the protocol were made, when the IRB reviewed these changes, how these sites were being monitored for adherence to the protocol, and if these protocols were reviewed by any other IRB.

(2) Minutes of the May 12, 2000 IRB meeting indicated that under item 5. "New Protocol and Informed Consent **C-041Z-99**: Phase I/II Trial of a Combined Regimen of High Dose Chemotherapy (HCD) Plus ^{90}Y-Humanized MN-14 Anti-Carcinoembryonic Antigen (CEA) Antibody After Induction Chemotherapy for the Treartment of Stage IV Breast Cancer (**Dr. Burton PI, Dr. Goldenberg and Dr. Juweid, Co-PI**)" [emphasis in original], the IRB requested a number of items from the investigators and asked Drs. Saleh and Hybersten to provide written reports on the protocol and informed consent, respectively. The minutes also stated that approval of the protocol and informed consent would be given by expedited review once revisions were made. OHRP is concerned that expedited review may not have been appropriate for approval in this case, especially in light of the fact that written reports from IRB members were required. Please respond.

Where the IRB approves research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. OHRP recommends the following guidelines: (a) When the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research must be **deferred**, pending subsequent review by the

convened IRB of responsive material. (b) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure.

(3) With respect to the reporting to the IRB of the adverse event of cardiac tamponade in subject number 1853, GSCC's letter of August 1, 2000 to Ray Abrahams of the FDA stated that:

> (a) "The IRB Chair received notification of this event as specified, but the minutes failed to indicate that this event was presented to the full committee."
>
> (b) "It should be noted that this adverse event prompted a protocol amendment which was presented to the IRB Chair in March and discussed in the full committee on April 12th."

Minutes of the April 12, 2000 IRB meeting indicate that an amendment to protocol C-040A-98, for which subject number 1853 was enrolled, was approved under expedited review on March 20, 2000. No discussion of this amendment is noted and no vote was taken. Since the full committee did not receive the notification of this adverse event and the amendment was approved under expedited review, OHRP is concerned about the extent to which the full IRB could make an informed decision on this amendment. Please respond.

(4) In conducting the initial review of proposed research, IRBs must obtain information in sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111. Materials should include the full protocol, a proposed informed consent document, any relevant grant applications, the investigator's brochure (if one exists), and any advertising intended to be seen or heard by potential subjects. Unless a primary reviewer system is used, all members should receive a copy of the complete documentation. These materials should be received by members sufficiently in advance of the meeting date to allow review of this material.

If the IRB uses a primary reviewer system, the primary reviewer(s) should do an in-depth review of all pertinent documentation. All other IRB members should at least receive and review a protocol summary (of sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111), the proposed informed consent document, and any advertising material. In addition, the complete documentation should be available to all members for review.

OHRP notes that, according to GSCC IRB policies and procedures, the IRB receives only the protocol for initial review and that the Director of Clinical Research Administration reviews advertisements listing the title of the protocol. It is unclear from the documents provided with your report whether IRB members receive sufficient documentation to make the determinations required at 45 CFR 46.111. Please respond. OHRP emphasizes

that the IRB members should receive the documentation as described in the above guidance with sufficient time to review the material.

(5) It appears that GSCC does not have written IRB policies and procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

(a) The procedures which the IRB will follow (i) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (ii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and Department or Agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.

Please respond.

(6) GSCC's IRB policies and procedures include a list of research activities which may be reviewed through expedited review. An updated list of activities was published in the Federal Register on November 9, 1998 (see OPRR Reports at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc99-01.htm).

(7) The definition of quorum in the GSCC IRB policies and procedures should be revised to indicate that at least one nonscientist must be present.

Please provide to OHRP a response to the required actions and the above questions and concerns no later than March 16, 2001.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. R.H. Menard, Vice President of Administration, GSCC
Dr. Rhona Stein, Chair, IRB, GSCC
Commissioner, FDA
Dr. David Lepay, FDA
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