DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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October 17, 2001

Kenneth L. Dretchen, Ph.D.
Director of the IRB and Chairman of Pharmacology
Georgetown University Medical School
3900 Reservoir Road, N.W.
NW103 Medical-Dental Building
Washington, D.C. 20007

RE: Human Research Subject Protections Under FederalWide Assurance (FWA) 00001080
Research Project: T97-0033: "A Phase I/II Study of Sequential Vaccinations with ALVAC-CEA with the Addition of IL-2 and GM-CSF in Patients with CEA Expressing Tumors
Principal Investigator: John Marshall, M.D.

Dear Dr. Dretchen:

The Office for Human Research Protections (OHRP) has reviewed Georgetown University's (GU's) March 23, 2000 report responding to OHRP's February 23, 2000 letter concerning GU's dispensation of an investigational tumor vaccine prepared using an incorrect gene therapy vector to six study patients following a shipping error by the National Cancer Institute's (NCI's) clinical drug repository. Based on its review of your report, OHRP makes the following determinations:

(1) Under Department of Health and Human Services (HHS) regulations for the protection of research subjects at 45 CFR 46.103(b)(5), institutions conducting human subject research must have written procedures for ensuring the prompt reporting of: (i) unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with the HHS human subject protection regulations or IRB requirements and determinations, and (ii) any suspension or termination of IRB approval, to (a) the institutional review board (IRB), (b) appropriate institutional officials and (c) OHRP. OHRP questioned whether GU had complied with these regulatory requirements.

OHRP finds that the erroneous dispensation of an incorrect gene therapy vector to six enrolled patients constitutes an unanticipated problem involving risks to subjects which

was required to be reported to the IRB, appropriate GU officials, and OHRP. OHRP further finds that the incident appears to have been reported: (a) to the IRB by investigator John Marshall, M.D. on December 9, 1999; (b) to GU officials including the Dean of Research, Medical Director, and Hospital Chief Executive on or before January 21, 2000; and (c) to OHRP by NCI, but not by GU, as required by 45 CFR 46.103(b)(5).

Corrective Action: OHRP acknowledges that subsequent to GU's failure to report to OHRP the above-described unanticipated problem involving risks to subjects, GU modified its IRB Policies and Procedures to include reporting policies in compliance with the requirements of 45 CFR 46.103(b)(5).

(2) Research cannot be approved by the IRB unless it is determined that risks to subjects participating in the research are minimized, under HHS regulations at 45 CFR 46.111(a)(1). OHRP inquired whether GU had procedures in place that minimized risks to subjects in accordance with regulatory requirements.

OHRP finds that GU failed to ensure that risks to subjects were minimized as required by HHS regulations at 45 CFR 46.111(a)(1). Specifically, as noted in GU's January 26, 2000 report, the Pharmacy's audit and review procedures were not adequate to ensure the accuracy of dispensed medications in that: (a) irregularities in shipping such as lack of required signatures were not pursued by Pharmacy staff; (b) the investigator was not called for clarification when questions arose; (c) the Pharmacy audit did not include double checking of labels; (d) the Pharmacy staff did not have requisite knowledge of the drug; and (e) the drug, physician's order and computer generated label for dispensing were not all reviewed simultaneously.

Corrective Action: OHRP finds that GU's corrective actions in response to its January 26, 2000 findings adequately address the issues raised, including corrective policies for: a) checking drugs upon receipt of shipment by two individuals at least one of whom is a pharmacist, (b) reading and checking drug labels at a weekly audit, (c) comparing the physician's order, computer generated label, and drug label prior to application of the dispensing label; (d) requiring research nurses to compare the drug label to the physician's order and record administration of drugs in a timely manner; and (e) requiring consultation with the investigator when any questions arise.

(3) HHS regulations at 45 CFR 46.116(b)(5) require investigators to notify subjects, when appropriate, of findings developed during the course of research that may influence subjects' willingness to continue participation in the research. HHS regulations at 45 CFR 46.109(b) direct the IRB to consider whether subjects should receive information beyond the standard informed consent requirements that would meaningfully add to the protection of subjects' rights and welfare. OHRP expressed concern whether the IRB had considered if subjects erroneously given a tumor vaccine prepared using an incorrect gene therapy vector should have received notice and any additional information from GU.

Corrective Action: OHRP finds that GU complied with the above-described regulatory requirements. On December 17, 1999, the IRB requested that investigator John Marshall, MD verify whether or not any adverse effects resulted from administration of the drug, and whether there were any expected or potential side effects. On December 20, 1999, the IRB approved an informed consent document to be given to the six study subjects who received the incorrect drug, which explained the known and potential side effects of the improperly administered drug and requested that subjects report any side effects noticed since receiving the incorrect agent.

As GU has taken appropriate corrective action to address the findings set forth above, OHRP is now closing this matter. At this time, OHRP provides the following additional guidance to GU.

(4) OHRP notes that the continuing review forms used for the research captioned above do not seek sufficient information for the IRB to make the determinations required for continuing approval under 45 CFR 46.111. In order for continuing review of research by the full IRB to be substantive and meaningful, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

When conducting research under an expedited review procedure, the IRB Chair (or designated IRB member(s)) should receive and review all of the above referenced documentation.

OHRP appreciates GU's continued commitment to the protection of human research subjects. Feel free to contact me should you have any questions.

Sincerely,

Carol J. Weil, J.D.
Division of Compliance Oversight

cc: Elisabeth Crigler, Georgetown
Dr. Willard Barnes, Georgetown
Dr. Harry Preuss, Georgetown
Dr. John Marshall, Georgetown
Dr. Kristina Borror, OHRP
Mr. George Gasparis, OHRP
Dr. Greg Koski, OHRP
Dr. Melody Lin, OHRP
Mr. Barry Bowman, OHRP
Dr. Jeffrey Cohen, OHRP
Dr. Joan Mauer, CTEP/NCI