DEPARTMENT OF HEALTH & HUMAN SERVICES

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June 29, 2004

Leonard Zwelling, M.D., M.P.H.
Vice President, Research Administration
University of Texas
M. D. Anderson Cancer Center
1515 Holcomb Blvd., Box 307
Houston, TX 77030

VIA FEDERAL EXPRESS

RE: Human Research Subject Protections Under Federalwide Assurance FWA-363

Research Project: A Phase II Study of High-Dose Intravenous Busulfan, and Cyclophosphamide with Allogeneic Marrow Progenitor Cell Transplantation for Chronic Myelogenous Leukemia (CML)
Principal Investigator: Richard Champlin, M.D.
Project Number: DM97-206

Dear Dr. Zwelling:

The Office for Human Research Protections (OHRP) has reviewed the M. D. Anderson Cancer Center's (MDACC) reports dated March 21, 2003 and April 29, 2004, in response to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) in the above-referenced research.

Based upon its review, OHRP makes the following determinations:

(1) HHS regulations at 45 CFR 46.111(a)(1) and (2) require that in order to approve research, the institutional review board (IRB) must determine that, among other things, risks to subjects are minimized and are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of knowledge that may reasonably be expected to result. OHRP's letter of February 21, 2003 requested a response to the allegation that the MDACC IRB failed to ensure that risks to subjects enrolled in Protocol DM97-206 were

minimized, and raised the specific concern that the protocol involved the administration of a dangerously high dose of intravenous Busulfan.

OHRP finds that the allegation that risks to subjects were not minimized in accordance with HHS regulations was not substantiated.

(2) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP was concerned that MDACC's IRB did not review or approve changes in the doses of Busulfan administered to the complainant's wife to account for tubing loss prior to implementation.

OHRP finds that the adjustment for tubing loss was not a change in the protocol that required IRB approval prior to implementation.

(3) HHS regulations at 45 CFR 45.116 state that, except as provided elsewhere in the regulations, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. HHS regulations at 45 CFR 46.116(a) delineate specific elements of informed consent that must be provided to the subject or the subject's legally authorized representative.

OHRP finds that the informed consent document reviewed and approved by the MDACC IRB for the above-referenced research failed to adequately address the following elements:

(a) An explanation of the purpose of the research, as required by HHS regulations at 45 CFR 46.116(a)(1). OHRP previously expressed concern that the paragraph entitled "Purpose of Study" of the informed consent document signed by the complainant's wife on October 30, 2000 did not provide sufficient information to subjects. In specific, OHRP notes that the informed consent document stated only the following as the study purpose: "*This is a clinical research study of how well Busulfan (BU) and cyclophosphamide (CY) work to control CML when given through a vein before an allogeneic bone marrow transplant*."

OHRP finds that the informed consent document did not explain to subjects that the purpose of the research was to test the efficacy and toxicity of intravenous Busulfan provided as a conditioning regimen for a bone marrow transplant in the treatment of CML, using an experimental design to deliver the drug(s) using pharmacologically monitored dosing based on individual differences in metabolic drug handling.

(b) A description of any reasonably foreseeable risks or discomforts to the subject, as required by HHS regulations at 45 CFR 46.116(a)(2).

OHRP finds that the informed consent document failed to adequately address the following reasonably foreseeable risks:

(i) The risk of hepatic toxicity associated with intravenous Busulfan.

(ii) The distinction between the risks of the bone marrow transplant and the risks of the conditioning regimen which involved taking the study drug Busulfan.

(iii) The risk of death. In particular, the informed consent document did not include a statement that the subject could have a higher risk of death, in comparison to not entering the trial, and receiving individualized care based upon the best clinical judgement of the subject's physicians. Furthermore, there was no statement that death could result from complications related to the use of Busulfan.

(c) A description of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject, as required by HHS regulations at 45 CFR 46.116(a)(4). OHRP finds that the informed consent document failed to include an adequate description of alternatives to participating in the trial. In particular, it would have been appropriate to explain to prospective subjects or their legally authorized representatives that in consultation with their physicians, they could have chosen a conditioning regimen for the bone marrow transplant that did not involve taking intravenous Busulfan.

Corrective Action: By August 13, 2004, please provide OHRP with a satisfactory corrective action plan to address findings (3) (a), (b), and (c).

OHRP appreciates MDACC's commitment to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Rina Hakimian, J.D., M.P.H.
Compliance Oversight Coordinator

cc: Dr. Carleen Brunelli, Chief Research and Regulatory Affairs Officer, MDACC
Dr. Aman Buzdar, IRB Chair, MDACC
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