DEPARTMENT OF HEALTH & HUMAN SERVICES

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December 7, 2004

Leonard Zwelling, M.D., M.B.A.
Vice President, Research Administration
University of Texas
M. D. Anderson Cancer Center
1515 Holcombe Blvd., Box 307
Houston, TX 77030-4095

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) July 26, 2004 report 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 46.116 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. In its June 29, 2004 letter to MDACC, OHRP found that several required elements were not addressed adequately in the informed consent document used for this research.

Corrective Action: OHRP acknowledges that MDACC has revised the informed consent document for the above-referenced research as follows:

(a) MDACC has added an explanation of the purpose of the research, as required by HHS regulations at 45 CFR 46.116(a)(1).

(b) MDACC has added a description of reasonably foreseeable risks or possible discomfort to subjects, as required by HHS regulations at 45 CFR 46.116(a)(2).

(c) MDACC has revised the section describing 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).

In addition to the changes identified by MDACC in its July 26, 2004 letter, OHRP recommends the following additional changes to the informed consent document (approved 7/22/2004):

(a) In the section entitled "Alternative Procedures or Treatments," the first sentence is printed twice, and the third sentence (apparently optional text) should be deleted.

(b) The section entitled "Description of the Research" refers to an injection of "Mesna." The term "Mesna" should be defined.

(c) In the section entitled "Purpose of Study," OHRP recommends that MDACC add the statement "one purpose of the study is to study the relative toxicity of intravenous Busulfan."

(d) The acronym "CML" is not defined and should be explained.

(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. The protocol approved by the MDACC IRB stated that blood samples were to be obtained during and after the ninth and thirteenth doses of Busulfan, to assay the pharmacokinetic outcome of the adjusted drug dose.

OHRP's February 23, 2003 letter to MDACC requested further information regarding the change in the protocol that resulted in the complainant's wife being tested after receiving Dose 5 of intravenous Busulfan, rather than after Dose 9. MDACC's March 31, 2003 report states that the results of the pharmacokinetic tests performed on the complainant's wife before and after Dose 1 indicated that a dose reduction of Busulfan was required. The report further states: "In the interest of patient safety, a decision was made to test after Dose 5 instead of waiting until Dose 9 to ensure that the dose reduction based on the first set of test results was adequate to keep the patient's drug levels in the desired range."

OHRP finds that performing the pharmacokinetic test on the complainant's wife after Dose 5 instead of after Dose 9 was done to eliminate an apparent immediate hazard to the subject. Therefore, prior IRB review and approval was not required in accordance with HHS regulations. OHRP notes that MDACC has implemented a new Protocol Deviation Notification Form and Guidelines, and has communicated information on this procedure to faculty, research nurses, and principal investigators since 2002. OHRP also acknowledges MDACC's statement that it performed an audit of all other protocol revisions and found them to have received approval from the MDACC IRB.

OHRP notes that MDACC has informed OHRP that the following additional steps have been taken to improve the system of protection of human research subjects at MDACC:

(a) Implementation of a ten-hour mandatory clinical research training program for all clinical research faculty and trainees, with special emphasis on the informed consent process.

(b) Implementation of an electronic protocol-authoring tool, which contains specific language that must be included in all consent documents.

(c) Hiring an additional medical editor to supplement the review of informed consent documents by the MDACC Office of Protocol Research.

(d) Reminding members of the MDACC IRB of the need for informed consent documents to indicate the purpose(s) and risk(s) of the research clearly as well as the need for adequate information regarding alternative therapies.

In addition to the above findings, OHRP makes the following recommendation:

(3) While examining the MDACC IRB records, OHRP found it difficult to reconstruct a complete history and sequence of all IRB actions related to review, approval, and continuing review of this research protocol.

Specifically, when reviewing the steps that the MDACC IRB took to suspend enrollment on the study on September 25, 2001 (pending receipt and review of efficacy and safety data), followed by resumption of subject accrual in November 2001, OHRP found that the IRB records submitted to OHRP included only minimal information. HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings be in sufficient detail to show the basis for requiring changes in or disapproving research, and that they include a written summary of the discussion of controverted issues and their resolution. Therefore, OHRP recommends that MDACC take steps to ensure that the records kept by the MDACC IRB reflect the discussions of the IRB in sufficient detail, particularly when suspending a research activity or allowing it to resume.

OHRP finds that the above corrective actions adequately address OHRP's concerns and findings, and that they are appropriate under the MDACC FWA. As a result of these determinations, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified that might alter this determination.

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. Aman Buzdar, IRB Chair, MDACC
Dr. Richard Champlin, Principal Investigator, MDACC
Acting Commissioner, FDA
Dr. David Lepay, FDA
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