DEPARTMENT OF HEALTH & HUMAN SERVICES

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May 31, 2001

John Mendelsohn, M.D.
President
The University of Texas M.D. Anderson Cancer Center
1515 Holcombe Boulevard
Houston, TX 77030

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1098

Research Project A: Phase II Study of Allogeneic/Syngeneic Blood Stem Cell Transplantation in Patients with High Risk Lymphoma (DM 95-182)

Research Project B: Compassionate Use of AmBisome for the Treatment of Invasive Fungal Infections in Patients Intolerant to or with Disease Unresponsive to Standard Antifungal Therapy (DM 96-274)

Dear Dr. Mendelsohn:

The Office for Human Research Protection (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your August 25, 1999 report responding to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR Part 46) that were presented in OPRR's July 22, 1999 letter.

The allegations involved the following:

(1) Failure of the investigators to follow the Institutional Review Board (IRB)-approved protocol by enrolling subject JK who did not meet eligibility criteria for the research protocols.

(2) Failure of the investigators to minimize risks to subject JK as required by HHS regulations at 45 CRF 46.111(a)(1). In specific, failure of the investigators to withdraw the

subject from the research protocols and allow his transfer to another hospital after serious adverse events occurred.

(3) Failure of the investigators to administer appropriate treatment to JK for adverse events that resulted from research interventions, as stipulated in section 10 of the informed consent documents for both protocols.

(4) Failure of the investigators to minimize the possibility of undue influence when obtaining the informed consent of subject JK, as required by HHS regulations at 45 CRF 46.116.

(5) Failure of the investigators to abide by the request of JK and/or JK's legally authorized representative to voluntarily withdraw from the research protocols, as required by HHS regulations at 45 CFR 46.116(a)(8).

(6) Failure of the informed consent documents to adequately describe all reasonably foreseeable risks and discomforts to the subject, as required by HHS regulations at 45 CFR 46. 116(a)(2). In specific, failure to describe the risk of various adverse events that may result from interactions between numerous drugs administered both under the research protocol and as part of routine clinical care.

Based upon OHRP's review of your August 25, 1999 report, OHRP finds no evidence to substantiate the above allegations.

As a result of the above findings, OHRP anticipates no further involvement in the above matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

OHRP has the following additional questions and concerns regarding the University of Texas M.D. Anderson Cancer Center (M.D. Anderson) system for the protection of human subjects:

(1) OHRP notes that the minutes of IRB meeting provided with your report suggested that the M.D. Anderson IRB routinely reviews large numbers of protocols at each meeting. For example, the minutes of the July 7, 1999 IRB meeting (the latest set of minutes supplied with your report) indicated that 10 new protocols were reviewed and that more than 200 protocols underwent continuing review. OHRP is concerned that the large volume of research for which the IRB has oversight responsibility may be indicative of an overburdened IRB. Please respond.

It is OHRP's observation that such a large volume of human subjects research warrants more than one fully functional IRB. OHRP acknowledges the recent efforts on the part of M.D. Anderson in the development of a second IRB, as evidenced by its April 17, 2001 letter from Leonard A. Zwelling, Vice President for Research Administration, requesting a new IRB as part of an application for a Federalwide Assurance (FWA). With your

response, please provide an explanation as to how the newly formed IRB will be utilized in addressing this apparent large volume of research conducted at M.D. Anderson.

(2) HHS regulations at 45 CFR 46.109(e) require that the IRB conduct continuing review or research involving human subjects at intervals appropriate to the degree of risk but not less than once per year. The minutes of the July 7, 1999 IRB meeting indicate that 44 protocols requiring continuing review were designated as "Deferred/Not Received." The minutes further indicate that some protocols had not been reviewed by the IRB for a number of years. OHRP is concerned that a substantial amount of research involving human subjects is ongoing at M.D. Anderson without proper IRB continuing review as required at 45 CFR 46.109(e). Please respond.

Please note, HHS regulations at 45 CFR Part 46 make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. If the IRB does not re-approve the research by the specified expiration date, subject accrual should be suspended pending re-approval of the research by the IRB. (Enrollment of new subjects cannot ordinarily occur after the expiration of IRB approval. Continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB finds that it is in the best interests of individual subjects to do so. OHRP and IRBs must address on a case-by-case basis those rare instances where failure to enroll would seriously jeopardize the safety or well-being of an individual **prospective** subject.)

(3) HHS regulations at 45 CFR 46.115(a)(2), as well as M.D. Anderson's IRB policies and procedures, require that the minutes of the IRB meetings be in sufficient detail to show the basis for requiring changes in or disapproving research and a written summary of the di0scussion of controverted issues and their resolution. Minutes of M.D. Anderson IRB meetings show little in the way of detail regarding the discussions which take place at the meetings. OHRP is concerned that the minutes of the M.D. Anderson IRB meetings fail to meet the requirements of 45 CFR 46.115(a)(2). Please respond.

Please respond to the above concerns and questions above no later than June 29, 2001.

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

Sincerely,

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

cc: Mr. R. Dan Fonatine, Chief Legal Officer, M.D. Anderson Cancer Center
Dr. Aman Budzar, IRB Chairperson, M.D. Anderson Cancer Center
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James McCormack, FDA
Dr. Greg Koski, OHRP
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