DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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February 27, 2002

Michael M. Gottesman, M.D.
Deputy Director for Intramural Research
National Institutes of Health
Building 1, Room 114
Bethesda, MD 20982

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1000

Research Project: Combination of Cyclophosphamide and Fludarabine for Lupus Nephritis: Tolerance, Toxicity, Efficacy and Effects on B and T Lymphocyte Regeneration
IRB Protocol Number: 98-AR-0055
Principal Investigator: Dimitrios T. Boumpas, M.D.

Dear Dr. Gottesman:

The Office for Human Research Protections (OHRP) has reviewed your May 1 and 31, 2000 reports responding to concerns about possible noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR Part 46) that were presented in OHRP's March 30, 2000 letter regarding the above-referenced research.

Based upon its review, OHRP makes the following determinations regarding the above-referenced research:

(1) OHRP finds no evidence to substantiate the concern that the investigators and the National Institute of Allergy and Infectious Diseases (NIAID) Institutional Review Board (IRB) failed to ensure that risks to subjects were minimized as required by HHS regulations at 45 CFR 46.111(a)(1). In particular, OHRP acknowledges that (a) at the time of initial IRB approval of

the research, there were no known reports of transfusion associated graft-versus-host disease in patients treated with fludarabine other than those with leukemia; and (b) no cases of transfusion associated graft-versus-host disease had been reported in any patient with systemic lupus erythematosus despite therapy with numerous cytotoxic and immunosuppressive chemotherapy drugs.
(2) OHRP finds no evidence to substantiate the concern that the IRB-approved informed consent document for the research failed to provide a description of all reasonably foreseeable risks and discomforts to the subjects (i.e, the risk of graft-versus-host disease) as required by HHS regulations at 45 CFR 46.116(a)(2).

(3) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) require that institutions have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, the Department or Agency head, and OHRP of any unanticipated problems involving risks to subjects or others.

OHRP finds that development of transfusion associated graft-versus-host disease and subsequent death of subject #4 in the research in 1999 represented an unanticipated problem involving risk to the subject and that this problem was not promptly reported to OHRP. OHRP acknowledges that this problem was promptly reported to the NIAID IRB, appropriate officials at the National Institutes of Health (NIH), and the Food and Drug Administration. Furthermore, OHRP acknowledges that all other subject enrolled in the research were informed promptly of this newly identified risk of the research and were provided with medical bracelets alerting healthcare providers that these subjects should receive only irradiated blood cells if the subjects needed transfusions.

Corrective Action: OHRP acknowledges that in May 2000 NIH developed and implemented a policy to ensure that unanticipated adverse events are promptly reported to OHRP. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the NIH MPA.

As a result, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

In your May 31, 2000 letter, you requested OHRP advice regarding the Interim Guidelines for NIH Intramural Principal Investigators and for NIH Institutional Review Boards on Reporting Adverse Events. OHRP recommends that the policy be modified to include (i) specific additional references to "unanticipated problems involving risks to subjects or others;" and (ii) a description of events, other than adverse events, that may represent unanticipated problems involving risks to subjects or others (e.g., study drug dosing errors might be considered unanticipated problems involving risks to subjects even if the dosing error does not result in a specific detectable adverse event).

OHRP appreciates the commitment of NIH to the protection of human subjects. Please feel free to contact me if you have any questions regarding this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Dr. Ruth Kirschstein, Acting Director, NIH
Dr. Alan Sandler, NIH
Dr. Carol Langford, Chairperson, IRB, NIAID
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Mr. George Gasparis, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. Hal Blatt, OHRP
Mr. Barry Bowman, OHRP