DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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August 2, 2004

Dr. Harvey Colten
Vice President and Associate Dean
Columbia University Health Sciences
630 West 168th Street, P&S 2-2041
New York, NY 10032

RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 2636
and Multiple Project Assurance (MPA) 1356
Research Project: Daily versus thrice weekly interferon alpha-2b in combination with ribavirin for patients with chronic hepatitis C infection who have relapsed or failed prior interferon therapy
IRB Project Number: 8897
Principal Investigator: Dr. Robert S. Brown, Jr.

Dear Dr. Colten:

The Office for Human Research Protections (OHRP) has reviewed Columbia University Medical Center's (CUMC) August 8, 2002 and June 10, 2004 reports evaluating allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) involving the above-referenced research.

Based upon its review, OHRP makes the following determinations regarding the protection of human subjects in this research:

(1) HHS regulations at 45 CFR 46.111(a)(1) require that in order to approve research covered by the regulations, an institutional review board (IRB) shall determine that risks to subjects are minimized, in part, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risks.

(a) OHRP finds that the IRB-approved protocol for the research included the following safeguards to minimize the risk of depression and suicidal ideation in subjects: (i) exclusion for diagnoses of severe depression, manic-depressive disease, and suicidal ideation; (ii) therapeutic management of enrolled subjects identified as depressed (mild to moderate) at screening; (iii) monitoring of depression developed during the study through office visits or telephone contact; (iv) reduced dosing of study medications for moderately depressed subjects; and

(v) discontinuation of study medications and psychiatric referral for severely depressed subjects.

(b) OHRP received allegations that risks may not have been minimized with respect to a research subject who attempted suicide on May 23, 2000. Specifically, it was alleged that the subject developed depression and suicidal ideation, known rare side effects of the research interventions, while participating in the research, and that the subject reported these side effects to the research team, but no action was taken by the researchers in response. In its December 1, 2003 letter to CUMC, OHRP questioned whether the subject was given a questionnaire for monitoring depression which the IRB approved as an amendment to the protocol. OHRP further questioned whether the investigators responded to a January 20, 2000 inquiry from the IRB regarding how patients identified as depressed after completing the questionnaire would be treated.

OHRP notes CUMC's June 10, 2004 report states that: (i) clinical questioning was the medically accepted method for assessing depression in the research subjects; (ii) the subject who attempted suicide on May 23, 2000 was questioned about depression upon enrollment and throughout his participation in the research; (ii) medical records indicate that the subject's mother called the research study coordinator on May 22, 2000 to report concern that the subject was depressed, and that the study coordinator suggested the subject be medically evaluated for depression; (iii) the principal investigator viewed the questionnaire as a research tool to establish baseline data rather than a procedure to monitor depression in the research subjects; (iv) the subject signed his consent to participate in the research on December 22, 1999, and the questionnaire was only administered to subjects who enrolled in the research after January 2000, when the principal investigator understood that the amendment was finally approved; (v) the principal investigator addressed the IRB's January 20, 2000 inquiry as to how subjects identified as depressed after completing the questionnaire would be treated, in a February 11, 2000 letter stating that such subjects would speak with the staff psychiatrist at the Center for Liver Disease and Transplantation. Based upon statements provided by the complainant and CUMC, OHRP is unable to make a determination regarding allegations that research risks were not minimized with respect to the subject who attempted suicide on May 23, 2000.

(2) HHS regulations at 45 CFR 46.115(a) require that institutions prepare and maintain adequate documentation of IRB activities. OHRP finds that the IRB file for the above research study lacked adequate documentation of the following: (a) review and approval of an amendment to administer a depression questionnaire and (b) February 26, 2001 correspondence from the principal investigator addressing questions raised by the IRB about exclusion criteria and the monitoring of depressed subjects.

(3) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be

conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. OHRP finds that: (a) IRB approval of the above study expired on February 8, 2001; (b) CUMC IRB policy in effect in February of 2001 appropriately held that if a study does not receive re-approval by its expiration date, no new subjects may be enrolled and previously enrolled subjects must be notified that the study has been terminated; and (c) the IRB, in violation of HHS regulations and its own policy, extended approval of the above study from its expiration date on February 8, 2001 until the IRB re-reviewed the study on February 28, 2001.

Required Corrective Action: Please submit to OHRP no later than August 20, 2004 a corrective action plan to address findings (2) and (3) above.

OHRP appreciates CUHS'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.
Compliance Oversight Coordinator
Office for Human Research Protections

cc: Mr. George Gasparis, CUHS
Dr. Robert Brown, Jr. CUHS
Dr. Andrew Wit, CUHS IRB #1 Chair
Dr. Elaine Larson, CUHS IRB #2 Chair
Dr. Andrew Davidson, IRB #3 Chair
Dr. Bernard Schwetz, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
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Ms. Janice Walden, OHRP
Ms. Pat El-Hinnawy, OHRP
Ms. Shirley Hicks, OHRP
Ms. Melinda Hill, OHRP
Commissioner, FDA
Dr. David Lepay, FDA