DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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September 9, 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) M-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) reports of August 8, 2002; June 10, 2004; and August 19, 2004, 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 finds that the corrective actions summarized below adequately address the determinations and requests set forth in OHRP's August 2, 2004 letter to CUMC:

> (1) HHS regulations at 45 CFR 46.115(a) require that institutions prepare and maintain adequate documentation of institutional review board (IRB) activities. OHRP found 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.

**Corrective Action**: CUMC has developed an electronic system for IRB submissions and review, effective May 2003, which has improved the IRB's ability to track documents and follow through on requests and questions. The system maintains an electronic copy of every submission and a record of every IRB action, with frequent backups of all data and a high-level security design to ensure the integrity of all data files. CUMC has also modified the form letters for IRB approval of amendments, so that they now summarize the specific protocol changes being approved.

(2) 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 found that: (a) IRB approval of the above study expired on February 8, 2001; (b) CUMC IRB policy in effect in February 2001 appropriately held that if a study does not receive reapproval 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 rereviewed the study on February 28, 2001.

**Corrective Action**: CUMC's IRB operating system, in effect since May 2003, does not permit entry of retroactive approval dates. Furthermore, the IRB has revised its process for sending approval letters to investigators. All approval letters are currently reviewed by IRB staff and the IRB Chair.

As a result, there should be no need for further OHRP involvement in this matter. OHRP appreciates CUHS's continued commitment to the protection of human research subjects.

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
Dr. Kristina Borror, OHRP
Ms. Janice Walden, OHRP
Ms. Pat El-Hinnawy, OHRP
Ms. Shirley Hicks, OHRP
Ms. Melinda Hill, OHRP
Commissioner, FDA
Dr. David Lepay, FDA