DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 240-453-8132
FAX: 240-453-6909
E-mail:kborror@osophs.dhhs.gov

February 17, 2006

Myron Rosenthal, Ph.D.
Senior Associate Dean and Director, Human Subjects Research Office
Faculty/Professional Affairs
University of Miami
Park Plaza East, Suite M
Miami, FL 33136

RE: Human Research Subject Protections Under Federalwide Assurance FWA-2247

Research Project: A 4-Year, Double Blind, Randomized, Placebo-Controlled Study of Atorvastatin as Preventative of CHD End Points in Patients with (Type II) Noninsulin-Dependent Diabetes Mellitus
Principal Investigator: Dr. Ronald Goldberg
Project Number: 981-71-27

Dear Dr. Rosenthal:

The Office for Human Research Protections (OHRP) has reviewed the University of Miami's (UM) September 27, 2005 report responding to determinations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46).

In its August 9, 2005 letter, OHRP made the following determinations:

> (1) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the institutional review board (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. OHRP found that several protocol changes were implemented in the atorvastatin protocol before IRB approval was obtained.
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> **Corrective Action:** OHRP acknowledges that current written UM IRB procedures state that the principal investigator must not initiate any changes in the protocol prior to IRB approval. In addition, the UM IRB now requires that all principal investigators and other

study personnel pass a human subjects protection certification program and remain certified. All letters defining IRB approvals now include an "investigator's responsibility sheet," which includes the requirement that the IRB review and approve proposed changes in a research activity prior to their implementation. OHRP finds that these corrective actions adequately address the finding and are appropriate under the UM FWA.

(2) HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject's legally authorized representative. OHRP found that the informed consent document approved by the IRB for the retinopathy substudy included complex language that would not be understandable to all subjects.

(3) OHRP found that the informed consent documents reviewed and approved by the IRB for the retinopathy substudy failed to include and/or adequately address numerous elements required by HHS regulations at 45 CFR 46.116(a).

(4) OHRP found that the informed consent document reviewed and approved by the IRB for the atorvastatin protocol failed to adequately address a complete description of the procedures to be followed, and identification of any procedures which are experimental, as required by HHS regulations at 45 CFR 46.116(a)(1).

Corrective Action: OHRP acknowledges that the draft written UM IRB procedures more clearly define that it is the principal investigator's responsibility to submit understandable informed consent documents and that it is the IRB's responsibility to review the document and approve only those that meet the outlined regulatory requirements, including comprehensibility. In addition, the Human Subjects Research Office directors and administrators are to examine informed consent documents to ensure that they contain key elements and are understandable to subjects, and that a guide for the simplification of medical terms, as well as an informed consent checklist, will be implemented.

Required Action: Please submit to OHRP a copy of the complete draft revised UM IRB written procedures.

(5) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the Federal Register at 63 FR 60364-60367. OHRP found that continuing review in the atorvastatin protocol on September 10, 2001 was conducted in an expedited manner even though it was not eligible for expedited review.

Corrective Action: OHRP acknowledges that the draft UM IRB written procedures outline the procedures for determining when a study is appropriate for review in an expedited manner, and the IRB directors, staff, and chair utilize the OHRP decision chart in making those determinations. IRB staff, administrators, members, and chairs have been educated about the process, which includes documenting the category of expedited

review.

(6) 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. OHRP found that the IRB failed to conduct continuing review of research at least once per year for numerous studies.

Corrective Action: OHRP acknowledges that, while the UM IRBs are being reconstructed, a commercial IRB is reviewing all UM human subjects research, except research that is reviewed in an expedited manner. OHRP acknowledges UM's statement that letters are being sent to investigators informing them that they must stop all human subjects research activity in protocols that have expired, unless it is in the best interests of the subjects to continue, and that notices are being sent to investigators warning them of the expiration date of their protocols before the protocols expire. Your letter also stated that, as of September 27, 2005, some investigators have still not been notified that their protocols have expired.

Your June 9 and September 27, 2005 reports stated that you are surveying department chairs and individual investigators to assure completeness of your database. OHRP is concerned that if UM has been unable to notify all investigators in a timely manner that their protocols have expired, the investigator-by-investigator survey may also be very far behind.

Required Action: Please provide OHRP with an update on the status of this survey and the notification of investigators that their protocols have expired. In your response, please outline the details of how the investigator survey is being conducted and what percentage of investigators have been contacted for this survey.

(7) Continuing review must be substantive and meaningful. HHS regulations at 45 CFR 46.111 specify the criteria that must be satisfied before the IRB can approve research at the time of both initial and continuing review. These criteria include determinations by the IRB regarding risks, potential benefits, informed consent, and safeguards for human subjects. OHRP expressed concerned that continuing review is not being conducted as required by HHS regulations.

Corrective Action: OHRP acknowledges that, at this time, the only continuing reviews that are being conducted by the UM IRB are those conducted in an expedited manner. IRB staff are responsible for pre-review of research protocols, and their recommendations are forwarded to the IRB chair or designee on a checklist which includes a section for comments. The expedited reviewer then conducts the reviews and makes a final decision. In addition, training has been provided to the IRB chairs and designees regarding thorough and meaningful expedited review.

Required Action: Please provide OHRP with a list of all protocols that have undergone expedited review by the UM IRB in the last 3 months.

OHRP has the following additional concern:

(8) [Redacted]

By March 31, 2006, please provide responses to the required actions and concerns above.

OHRP appreciates the continued commitment of the University of Miami to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight

cc: Dr. Steven Ullman, Vice Provost for Faculty Affairs, UM
Dr. Leo Twiggs, Assistant Vice Provost, Human Subjects Research Office, UM
Ms. Kelly Insignares, Exec Dir for HSRO, UM
Ms. Judith Aguirre, Dir for Regul Affairs and Educ Initiatives, UM
Dr. Andrew M. Brickman, chair, UM IRB #1
Dr. Erik Barquist, chair, UM IRB B
Dr. Stephen Sapp, IRB chair, UM Social and Behavioral Sci Committee
Ronald A. Gadde, chair, Western Institutional Review Board-IRB/Panels 1-8 & 11-12
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Lana Skirboll, Director, Office of Science Policy, NIH
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP
Ms. Janet Fant, OHRP
Ms. Patricia El-Hinnawy