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: 301-402-2136
FAX: 301-402-0527
E-mail:rhakimian@osophs.dhhs.gov

January 7, 2005

Fred Rothstein, M.D.
President and CEO
University Hospitals of Cleveland
11100 Euclid Avenue
Cleveland, OH 44106

RE: Human Research Subject Protections Under Federalwide Assurance FWA-3937 and Multiple Project Assurance MPA-1521

Research Project: Protection Against Adverse Effects of UV Radiation on Human Skin
Principal Investigator: Dr. Seth Stevens and Dr. Elma Baron
Project Number: 03-99-16

Dear Dr. Rothstein:

The Office for Human Research Protections (OHRP) has reviewed University Hospitals of Cleveland's (UHC) June 29, 2004 report in response to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) in the above-referenced research.

Based upon its review, OHRP makes the following determinations:

(1) OHRP finds that the informed consent documents reviewed and approved by the UHC Institutional Review Board (IRB) for the above-referenced research failed to address the following elements adequately, as required by HHS regulations at 45 CFR 46.116:

(a) A complete description of the procedures to be followed, as required by HHS regulations at 45 CFR 46.116(a)(1). The informed consent document reviewed and approved by the UHC IRB did not refer to either the use of allergens or the purpose(s) of such use.

(b) The expected duration of subjects' participation, as required by HHS regulations at 45 CFR 46.116(a)(1). The section of the informed consent document entitled "Sunburn/MED test" (page 1) stated that volunteers would be exposed to ultraviolet light for "a short period of time." It also said that subjects would undergo subsequent examination by researchers and then further exposure to ultraviolet light. However, no further information was given regarding the estimated duration of each period of exposure to ultraviolet light, nor was there information about the estimated time involved for subjects' participation *in toto*.

(c) An adequate description of the foreseeable risks or discomforts to subjects, as required by HHS regulations at 45 CFR 46.116(a)(2). OHRP finds that the informed consent document reviewed and approved by the UHC IRB did not adequately explain that a strong reaction to the allergen DNCB may be painful to some subjects.

(d) 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 finds that the informed consent document approved by the UHC IRB for the above-referenced protocol included complex language that would not be understandable to all subjects.

In specific, OHRP notes the use of such terms as "allergens," "immune response," "antioxidants," "patch test filter disks," "patch testing," "sunscreen-like vehicle," "vehicle cream," "liposome," and "T4 liposome," which are not explained and might not be understandable to all subjects.

Corrective Action: OHRP acknowledges that UHC has revised the informed consent document for the above-referenced research as follows:

(a) UHC has added a more complete description of the procedures to be followed.

(b) UHC has added information regarding the expected duration of the various procedures.

(c) UHC has added a description of reasonably foreseeable risks or discomforts to subjects.

(d) UHC has revised the informed consent document to eliminate the use of complex terms and to define the research activities in a manner that would be understandable to participants.

OHRP finds that these corrective actions adequately address the above finding and are appropriate under the UHC FWA.

(2) HHS regulations at 45 CFR 46.109(e) require that continuing review be conducted at intervals appropriate to the degree of risk, and not less than once per year. OHRP notes that the above-referenced research protocol was initially reviewed on March 28, 2000; the first continuing review and approval was finalized on May 1, 2001; and the next continuing review and approval was finalized on June 18, 2002. Further, OHRP notes that the UHC IRB policy described in the June 29, 2004 report permits research protocols to remain open up to sixty days beyond the date on which IRB approval expires.

HHS regulations make no provision for extending the conduct of the research beyond the date on which IRB approval expires. Further, in accordance with HHS regulations, if an investigator has failed to provide continuing review information to the IRB, or if the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop unless, according to OHRP's guidance on continuing review (see http://www.hhs.gov/ohrp/humansubjects/guidance/contrev2002.htm), the IRB finds that it is in the best interest of individual subjects already enrolled in the research to continue participating in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration of IRB approval.

Therefore, OHRP finds that the UHC IRB policy permitting research to continue for up to sixty days after IRB approval has expired, and before the next continuing review and approval has occurred, does not meet the requirements of HHS at 45 CFR 46.109(e).

Required Action: By February 21, 2005, please submit to OHRP a corrective action plan to ensure that continuing review of research is conducted not less than once per year, and that research is suspended that is not reviewed and approved by the IRB by the date on which IRB approval expires, in accordance with HHS regulations and OHRP guidance.

In addition, OHRP has the following questions and concerns:

(3) [Redacted]

(4) [Redacted]

Please submit your response to (2), (3) and (4) above no later than February 21, 2005.

OHRP appreciates UHC's commitment to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Rina Hakimian, J.D., M.P.H.
Compliance Coordinator
Division of Compliance Oversight

Enclosure

cc: Mr. Philip A. Cola, IRB Administrator, UHC
Dr. William Dahms, Chair, UHC IRB
Dr. Seth Stevens, UHC
Dr. Elma Baron, UHC
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Kristina Borror, OHRP
Ms. Shirley Hicks, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Janet Fant, OHRP