DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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March 1, 2005

John R. Sladek, Jr., Ph.D.
Vice Chancellor for Research
University of Colorado Health Sciences Center
Office of the Chancellor
4200 East Ninth Avenue
Campus Box A095
Denver, Colorado 80262

RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 5070

Research Project:	**The Joint Outcomes Study**
Principal Investigator:	**Marilyn Manco-Johnson, M.D.**
Protocol #:	**95-011**
Research Project:	**Myocardial Energy Substrate Utilization in Patients with Dilated Cardiomyopathy**
Principal Investigator:	**Eugene E. Wolfel, M.D.**
Protocol #:	**01-017**

Dear Dr. Sladek:

The Office for Human Research Protections (OHRP) has reviewed the University of Colorado Health Sciences Center's (UCHSC) January 13, 2005 letter, which was submitted in response to OHRP's letter of December 15, 2004.

In its December 15, 2004 letter, OHRP made the following findings:

> (1) OHRP found that UCHSC applied exempt status to certain research activities that exceeded the specific categories of exempt human subjects research activities identified under Department of Health and Human Services (HHS) regulations at 45 CFR 46.101(b)
>
> **Corrective Action:** OHRP acknowledges that all studies previously determined to be

exempt by the UCHSC institutional review board (IRB) will be re-reviewed to ensure that they meet the exemption requirements under HHS regulations at 45 CFR 46.101(b). OHRP also acknowledges that the UCHSC IRB has contacted the investigators in the specific protocols noted in OHRP's December 15, 2004 letter to either revise the protocols so that they meet the exemption criteria or submit the studies for review by the IRB. In addition, OHRP notes that the UCHSC IRB has provided training for its co-chairs on the appropriate determination of exemptions.

(2) OHRP found that the UCHSC IRB failed to maintain adequate documentation of IRB activities, as required by HHS regulations at 45 CFR 46.115(a).

Corrective Action: The UCHSC IRB will amend its practices to require that any conversational information that an IRB decision is based upon must be written into the minutes. In addition, the IRB co-chairs and staff will be educated to ensure that appropriate documentation exists to support all IRB actions.

(3) OHRP found that the principal investigator for Protocol # 95-011 failed to ensure that the research had adequate provisions for monitoring the data collected to ensure the safety of subjects, as required by HHS regulations at 45 CFR 46.111(a)(6).

(4) **OHRP found that the principal investigator for Protocol # 02-257 conducted human subjects research without IRB review and approval,** as required by **HHS regulations at 45 CFR 46.103(b) and 46.109(a).**

Corrective Action: OHRP acknowledges that for items (3) and (4) above, UCHSC has suspended or designated a new principal investigator for all of the investigator's protocols.

In addition, OHRP acknowledges that UCHSC will implement a requirement for continuing education for all local investigators, as well as all research staff named on protocol applications. This training will include specifics on the investigator's responsibilities for obtaining IRB approval for research and appropriate data monitoring. UCHSC will also provide additional education to its faculty and staff, through a variety of mechanisms, on the importance of appropriate data safety and monitoring practices.

Furthermore, to ensure that its investigators understand their responsibility not to change research protocols without approval of the IRB, UCHSC will revise its continuing review form to include a statement from the investigator indicating that all changes to the research have been previously approved by the UCHSC IRB.

(5) OHRP found that UCHSC failed to report certain suspensions of research or unanticipated problems involving risks to subjects, as required by HHS regulations at 45

CFR 46.103(a) and (b)(5).

Corrective Action: OHRP acknowledges that the UCHSC IRB has revised its written procedures to ensure that all unanticipated problems involving risks to subjects or others, or any suspensions or terminations of research are promptly reported to OHRP. In addition, UCHSC will provide training for its co-chairs and staff on the revised procedure.

OHRP finds that the corrective actions noted above adequately address the findings (1) through (5) and are appropriate under the UCHSC FWA.

(6) OHRP found that the UCHSC IRB occasionally approves research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB.

Corrective Action: OHRP acknowledges that the UCHSC IRB has provided additional training to its co-chairs and regulatory compliance staff to ensure that substantive modifications to a protocol are subsequently reviewed by the convened IRB. In addition, the UCHSC IRB will update its written procedures to describe which protocol modifications require additional full board review.

(7) OHRP found that certain informed consent documents reviewed and approved by the UCHSC IRB failed to include an adequate description of the reasonably foreseeable risks and discomforts, as required by HHS regulations at 45 CFR 46.116 (a).

Corrective Action: OHRP acknowledges that, for the research noted in OHRP's December 15, 2004 letter, the UCHSC IRB has asked its investigators to revise their informed consent documents and submit them for re-review. The UCHSC IRB will review informed consent document issues with its co-chairs.

Required Action: UCHSC must provide a report on (i) the continued progress on the re-review of exempt protocols and (ii) the development and implementation of educational efforts for its IRB members, staff and investigators, and (iii) revisions being made to informed consent documents noted in the UCHSC letter dated January 13, 2005. In addition, OHRP requests that UCHSC provide a copy of any revised procedures which were described in the UCHSC letter, as well as copies of the minutes of three recent IRB meetings. Please provide your report no later than March 31, 2005.

At this time, OHRP makes the following additional determinations:

(8) HHS regulations at 45 CFR 46.111(a)(3) state that, in order to approve research covered by the regulations, the IRB shall determine that the selection of subjects is equitable. OHRP finds that for Protocol #04-0482, the UCHSC IRB failed to determine that the selection of subjects is equitable. In specific, the principal investigator excluded

Spanish-speaking subjects due to the fact that the investigator did not speak Spanish.

Corrective Action: OHRP acknowledges that the UCHSC IRB will require that the protocol be amended to include non-English speaking subjects and that a Spanish speaking research assistant be available during the course of the research. UCHSC will also require that interview questions and letters to participants be translated into Spanish.

(9) HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each *application* or proposal for research covered by the assurance has been reviewed and approved by the IRB. OHRP finds one instance in which the UCHSC IRB apparently failed to review the grant application for Protocol #01-517.

Corrective Action: OHRP acknowledges that the UCHSC IRB has requested that the principal investigator for this research submit the NIH grant for review by the IRB. The UCHSC IRB will evaluate its continuing review form to enhance the capture of new funding information for research already being conducted.

(10) 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 finds that the UCHSC IRB inappropriately reviewed Protocol # 04-0687 through an expedited review procedure.

Corrective Action: OHRP acknowledges that the UCHSC IRB has suspended this research and required that the investigator submit the protocol for review by the convened IRB. In addition, this case will be reviewed with the IRB co-chairs to reinforce the requirements for expedited review.

(11) HHS regulations at 45 CFR 46.117(a) require that informed consent be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative, unless the IRB waives this requirement. OHRP finds that informed consent process for Protocol #04-0522 was not documented by a written consent form signed by the subject and that documentation of informed consent was not waived.

Corrective Action: OHRP acknowledges that the UCHSC IRB has re-reviewed the research and determined that a waiver of the requirement for documentation of consent would be appropriate for only a portion of the research. The IRB has asked the principal investigator to submit an amendment to the protocol requesting a waiver of documentation of consent for the parent interview portion of the research only.

OHRP finds that the corrective actions noted above adequately address the findings (8) through

(11) and are appropriate under the UCHSC FWA.

(12) OHRP finds that UCHSC has adequately addressed the additional questions and concerns raised in OHRP's December 15, 2004 letter.

(13) OHRP finds that UCHSC has adequately addressed all determinations of noncompliance noted in OHRP's December 15, 2004 letter regarding Protocol # 01-017. As a result of this determination, there should be no need for further involvement of OHRP as it relates to this protocol.

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

Sincerely,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Ms. Lisa Jensen, Director, COMIRB
Mr. Ken Easterday, Chair, IRB Panel A, UCHSC
Dr. Norman Stoller, Chair, IRB Panel B, UCHSC
Dr. Doug Ford, Chair, IRB Panel C, UCHSC
Mr. Stephen Bartlett, Chair, IRB Panel D, UCHSC
Commissioner, FDA
Dr. David Lepay, FDA
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Dr. Bernard Schwetz, OHRP
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