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:Kristina.borror@hhs.gov

March 30, 2009

Mark A. Slater, PhD
Vice President, Research
Scottsdale Healthcare
10510 N. 92nd Street, Ste. 300
Scottsdale, AZ 85258

RE: Human Research Protections Under Federalwide Assurance FWA-1751

Research Project: Molecular and Genomic Rationale for Adjunctive Hyperbaric Oxygen Therapy of Selected Crush Injuries Using DNA Microarray Analysis (CRUSH Study)
Principal Investigator: Dr. Dennis Weiland

Research Project: HOLLT study
Principal Investigator: Dr. Dennis Weiland

Dear Dr. Slater:

Thank you for your October 31, 2008 report in response to our September 9, 2008 request that Scottsdale Healthcare (SH) evaluate allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46). While the above-referenced research projects are not conducted or supported by HHS, we note that SH has voluntarily extended its Federalwide Assurance (FWA) to cover all human subjects research at SH, regardless of the source of support for the particular research activity. Based on review of your response, we make the following determinations:

A. Determinations regarding the above-referenced research

(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. We determine that certain protocol changes were initiated without

IRB review and approval, in circumstances where the changes were not necessary to eliminate apparent immediate hazards to the subjects. In specific, we note the following:

(a) The application submitted to the SH IRB indicated that the HOLLT Study was to be a retrospective chart review and that de-identified data would be collected from the CRUSH study. However, the principal investigator (PI) enrolled subjects into the "full" HOLLT study (a randomized controlled trial of hyperbaric oxygen in lower limb trauma) by using an altered CRUSH study consent form.

(b) The study coordinator did not complete study logs to identify the patients and she did not complete proper follow up according to the study protocol for the CRUSH study.

(2) In accordance with HHS regulations at 45 CFR 46.103(b) and 46.109(a), the IRB must review and approve all non-exempt human subject research covered by an assurance before the research can be conducted. We determine that certain non-exempt human subjects research was conducted without IRB review and/or approval. We determine that the SH IRB did not review and approve the "full" HOLLT study (a randomized controlled trial of hyperbaric oxygen in lower limb trauma) but instead reviewed and approved the retrospective chart review described in the IRB application.

(3) 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 that is signed by the subject, or the subject's legally authorized representative, unless the IRB waives this requirement in accordance with 45 CFR 46.117(c). We determine that informed consent was not appropriately documented by a written consent form reviewed and approved by the IRB and signed by the subject(s) for this research and there was no appropriate IRB waiver of this requirement. In specific, we note that the subjects in the HOLLT study were enrolled using the informed consent document for the CRUSH study and areas were crossed out.

Corrective Action: We acknowledge that SH has taken or proposed the following corrective actions to address these determinations: suspended Dr. Weiland's conduct of human subjects research until he completes educational requirements; conduct a comprehensive audit of all studies in which Dr. Weiland is the PI; retain a third party to monitor any future human subjects research conducted by Dr. Weiland; subject any future studies for which Dr. Weiland is the PI to continuing review intervals of 6 months for two years; and revise all IRB applications to include a Certification whereby the PI agrees to adhere to the protocol, except when necessary to eliminate apparent immediate hazards to subjects, and to notify the IRB of any protocol deviations or serious adverse event, and to not alter or amend the IRB-approved informed consent form when presenting it to study subjects. These corrective actions

adequately address the above determinations and are appropriate under the SH FWA.

Required Action: Please indicate whether or not the HOLTT study has been or will be continued at SH. If the HOLTT study will be continued, please note that the SH IRB would have to review and approve the full HOLTT protocol.

B. Questions and Concerns

(1) [Redacted]

(2) [Redacted]

(3) [Redacted]

(4) [Redacted]

(5) [Redacted]

C. Recommendations

We make the following recommendations regarding SH's human subject protection program:

(1) We recommend that written IRB procedures provide a step-by-step description with key operational details for each of the procedures required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5). Important operational details for the required procedures should include:

(a) a specific procedure for how the IRB determines which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review, including specific criteria used to make these determinations; for example, such criteria could include some or all of the following:

(i) randomly selected projects;
(ii) complex projects involving unusual levels or types of risk to subjects;
(iii) projects conducted by investigators who previously have failed to comply with the requirements of the HHS regulations or the requirements or determinations of the IRB; and
(iv) projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources;

(b) a description of which office(s) or institutional official(s) is responsible for promptly reporting to the IRB, appropriate institutional officials, any supporting agency or department heads, and OHRP any:

(i) unanticipated problems;
(ii) any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and
(iii) any suspension or termination of IRB approval;

(c) a description of the required time frame for accomplishing the reporting requirements; and

(d) the range of possible actions taken by the IRB in response to reports of unanticipated problems or of serious or continuing noncompliance.

(2) We note that several of your written procedures state that "Changes may not be implemented prior to IRB review and approval per Federal regulations." We recommend that these procedures be revised to add "except when necessary to eliminate apparent immediate hazards to subjects."

(3) We note that several of your written procedures drafted after we opened our evaluation into this matter contain errors and extraneous characters, e.g. "#STAB#$TAB#$TAB#$TAB"

Please provide us with responses to the above required action and our concerns by May 11, 2009. Feel free to contact me if you would like guidance in developing a corrective action plan.

We appreciate 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,

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

cc: Ms. Liz Brouchoud, IRB Coordinator, Scottsdale Healthcare
Dr. Robert A. Marlow, IRB Chair, Scottsdale Healthcare
Dr. Dennis Weiland, Scottsdale Healthcare
Commissioner, FDA
Dr. Joanne Less, FDA