DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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July 20, 2001

Kenneth G. Preston
Associate Vice President for Research
University of South Florida
4202 E. Fowler Avenue, ADM 200
Tampa, FL 33620-5950

J. Thomas Danzi, Sr., M.D.
Vice President and Chief Medical Officer
Tampa General Healthcare
P.O. Box 1289
Tampa, FL 33601

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1284

Research Project: An Ascending Dose Safety and Feasibility Study of OSSIGEL in the Management of Stable and Unstable Closed Diaphyseal Fractures of the Tibia
Principal Investigator: Roy W. Sanders, MD
Project Number: 5194

Dear Dr. Preston and Dr. Danzi:

The Office for Human Research Protections (OHRP) has reviewed your report of June 14, 2001, regarding the above referenced research conducted at Tampa General Healthcare, which has an inter-institutional amendment with University of South Florida (USF).

Based upon its review, OHRP makes the following determinations regarding the above-referenced research project.

(1) OHRP finds that when reviewing this protocol application, the IRB lacked sufficient information to make the determinations required for approval of research under HHS

regulations at 45 CFR 46.111. For example, USF's June 14, 2001 response to OHRP regarding the inclusion of additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence stated that "the IRB assumed that trauma victims would not be eligible to participate in the study....based upon the available information at the time of the IRB review...."

(2) OHRP finds that the informed consent documents reviewed and approved by the IRB for this project failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116(a)(1):

(a) An explanation of the purposes of the research (i.e., the protocol stated that a major purpose of the study was to evaluate the safety of OSSIGEL);

(b) A complete description of the procedures to be followed, and identification of any procedures which are experimental. The informed consent document that the USF IRB approved for this study failed to distinguish clearly those procedures being done as part of standard treatment versus those being done for research purposes.

Corrective Action: OHRP acknowledges that USF has taken several steps to enhance training programs and opportunities, expand staffing levels, improve services for the IRBs, and increase budgetary support for the Division of Research Compliance. OHRP has determined that these corrective actions adequately address findings (1) and (2) and are appropriate under the USF Multiple Project Assurance (MPA).

(3) HHS regulations at 45 CFR 46.116 require that the information provided in the informed consent documents be in language understandable to the subject. OHRP finds that the informed consent document approved by the IRB for this study included complex language that would not be understandable to all subjects.

Corrective Action: OHRP acknowledges that USF is making a concentrated effort to keep the complexity in informed consent document language as low as possible and has entered into a tentative agreement with an organization to revise and rewrite the USF Adult Informed Consent template to a reading level of fifth to sixth grade. In addition, USF will conduct an Informed Consent Workshop for USF investigators. OHRP has determined that these corrective actions adequately address finding (3) and are appropriate under the USF MPA.

(4) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes to previously approved research. OHRP finds that the IRB employed expedited procedures to review changes that exceed this limitation. In May of 1999 a new protocol for previously approved research was approved by expedited review. This new protocol had many changes including expanding treatment groups if a subject developed proteinuria, addition of a pre-treatment blood draw, and OSSIGEL

dosage changes, that appear to exceed minor changes. USF responded that "[i]n Dr. Bercu's opinion, the changes posed no increased risk to the participants, and therefore the request qualified for expedited review." OHRP finds that the IRB inappropriately confounds the concepts of minimal risk and expedited review.

Required Action: The USF IRB should make it clear that their policy for conducting expedited review on proposed changes to approved research follows the regulations at 45 CFR 46.110(b)(2) and provide OHRP with a corrective action plan to ensure that IRB members and staff understand this requirement.

OHRP has the following additional concerns and questions regarding the above-mentioned research.

(5) HHS regulations at 45 CFR 46.111(b) require that, in order to approve research, the IRB must ensure that additional safeguards have been included in the research to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence. OHRP is still concerned about vulnerable subjects being included in research (those under sedation) and that the IRB may be failing to ensure that adequate additional safeguards are included in research.

In particular, OHRP notes that a USF ad hoc committee developed scientific guidelines regarding "the acceptable level of sedation" for consent of a subject to occur.

(i) The guidelines state that "...if the consultants agree that the potential research subject lacks the capacity to make a willful and knowing decision to participate in the research study, a surrogate or proxy may be asked to give consent on behalf of the patient." HHS regulations at 45 CFR 46.116 state that no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. OHRP is concerned that these guidelines do not specify this nor what constitutes a "legally authorized representative" in the state of Florida.

(ii) OHRP is also concerned that these guidelines state that an "acceptable level of sedation for consent" includes a person who is "anxious, agitated, or restless."

Please respond.

Please submit to OHRP your response to the above required actions, questions and concerns no later than August 31, 2001. If upon further review of the concerns and questions, USF or Tampa General Healthcare identify additional instances of non-compliance with the HHS regulations for protection of human subjects, please include detailed corrective action plans to address the noncompliance.

OHRP appreciates your institution's continued commitment to the protection of human research subjects. Do not hesitate to contact me if you have any questions regarding this matter.

Sincerely,

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

cc: Dr. Barry B. Bercu, Chair, USF IRB 01, 01b, and 02
Dr. Martin Klemperer, Chair, USF IRB 03
Dr. Ramon Lopez del Valle, Chair, USF IRB 04
Dr. Roy Sanders, Tampa General Healthcare
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. John Mather, VA
Dr. Greg Koski, OHRP
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Mr. Barry Bowman, OHRP