DEPARTMENT OF HEALTH & HUMAN SERVICES

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April 19, 2001

Kenneth G. Preston
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J. Thomas Danzi, Sr., M.D.
Vice President and Chief Medical Officer
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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), formerly the Office for Protection From Research Risks (OPRR), has reviewed your report of January 12, 2000, 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 determination regarding the above-referenced research project.

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.116 require that an investigator seek informed consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or

not to participate and that minimize the possibility of coercion or undue influence. OHRP finds that a prospective subject was approached in a manner inconsistent with this requirement.

**Corrective Action:** OHRP acknowledges that USF has taken several steps to reduce the possibility of coercion or undue influence in this study. These include designating the research nurse as the sole person to interview potential participants, and requiring that the investigator provide the Institutional Review Board (IRB) with the signed informed consent documents and phone numbers of the next 10 enrollees so the IRB may contact these subjects if they choose. OHRP also acknowledges that USF has taken several actions to increase compliance with this and other human subjects protections such as enhanced educational outreach. OHRP has determined that these corrective actions are appropriate under the USF Multiple Project Assurance.

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

(2) 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.

(a) OHRP is concerned that vulnerable subjects could be included in this research (trauma victims and those under sedation) and that the IRB failed to ensure that adequate additional safeguards were included in the research. Please respond. OHRP notes that an ad hoc committee will be formed by USF to develop scientific guidelines regarding "the acceptable level of sedation" for consent of a subject to occur. Please provide OHRP with a copy of any guidelines that have been developed.

(b) The protocol included as an exclusion criterion that "the subject is physically or mentally compromised and unable to perform functional examinations." It is not clear what "functional examinations" were to be conducted to determine if subjects were "mentally compromised." Please clarify.

(3) OHRP is concerned that the informed consent documents reviewed and approved by the IRB for this project may have failed to include 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. In particular, OHRP notes the following: (i) the "Plan of Treatment" section stated that "[y]our regular medical treatment..." will include, among other things, taking a medical history to be used "to determine if you are able to take part in this study" and blood and urine analysis and pregnancy tests "to help determine if it is safe for you to participate in the study." The second paragraph of this section stated that the "experimental treatment" is reduction of the fracture. (ii) The "Alternatives of Being Part of This Research Study" section noted that "standard treatment" is reduction of the fracture. (iii) A November 5, 1998 memo from the IRB to the principal investigator stated "...the whole surgery and everything involved with that is experimental...."

In addition, the protocol stated that "a 48 hour [blood] collection time point will be added when studying patients treated with larger volumes of OSSIGEL," and that "use of NSAIDS should be avoided." These procedures were not mentioned in the informed consent document.

Please respond.

(4) 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 is concerned that the informed consent document approved by the IRB for this study appeared to include complex language that would not be understandable to all subjects. In addition, the informed consent document had multiple typographical errors. Please respond.

(5) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. On November 1, 1999 the IRB reviewed an amendment that proposed the inclusion of children in this research. OHRP can find no evidence that IRB made the required findings under 45 CFR 46.404-407 when reviewing this research involving children. Please respond.

(6) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes to previously approved research. OHRP is concerned that the IRB may have 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. Please respond.

(7) It appears that several changes to the informed consent documents that were suggested or required by the USF IRB were never made by the investigator. These included (a)

changes to the dosing schedule to make them easier to understand; (b) stating that the patient will not receive any reimbursement until qualified for the study; (c) clarifying the last sentence under "payments"-- "you must attend all follow-up visits." Please respond.

(8) At one point the enrollment ceiling changed from 56 to 32. It is not clear when this change was made, the reasons for the changes, and whether the IRB reviewed and approved this change. Please clarify.

Please submit to OHRP your response to the above questions and concerns no later than June 15, 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
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