DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Office of Public Health and Science

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September 21, 2000

William R. Rice, J.D.
Vice President for Health Affairs
University of Tennessee, Memphis
62 South Dunlop Street
Memphis, Tennessee 38163

RE: Human Research Subject Protections Under Multiple Project Assurance M-1056

Research Project: Apomorphine in the Treatment of Female Sexual Disorder: Effect of Dosage Route on Pharmacokinetics and Safety
Principal Investigator: Candace Brown, Pharm.D., FNP

Dear Mr. Rice:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your April 17, 2000 report regarding the above referenced research projects, as well as your follow-up letters of August 16 and August 18, 2000.

Based upon its review of your report and letters, OHRP makes the following determinations regarding the above referenced research:

(1) Department of Health and Human Services regulations at 45 CFR 46.103(a) and 46.103(b)(5), as well as the University of Tennessee, Memphis (UTM) MPA (see Part 2, Section II.G) require that all unanticipated problems involving risks to subjects or others be promptly reported to the Institutional Review Board (IRB), appropriate institutional officials, and OHRP.

(a) OHRP finds that the medication errors in which a research nurse coordinator administered to two subjects subcutaneous doses of apomorphine that were ten-fold higher than dose stipulated in the IRB-approved protocol, resulting in a severe acute reaction in one of these subjects, represented unanticipated problems involving risk to the subjects.

(b) OHRP acknowledges that these events were promptly reported to the IRB Chair, the IRB, and the study sponsor.

(c) OHRP finds that these events were not promptly reported to OHRP.

(d) OHRP acknowledges your report that the one subject who experienced severe acute symptoms following the overdose of apomorphine was evaluated by appropriate medical personnel during the event and was determined not to have a life-threatening reaction.

(2) HHS regulations at 45 CFR 46.111(a)(1) require that risks to subjects be minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.

OHRP finds that the following events indicate a failure of the investigators to ensure that risks to subjects were minimized:

(a) On one or more occasions, blood was drawn from subjects via an intravenous line without the research staff following standard sterile techniques and universal precautions.

(b) The IRB-approved protocol stipulated that subjects would undergo a screening physical examinations prior to undergoing study interventions with apomorphine. Some of these physical examinations were performed by individuals (i.e., Pharm.D. fellows) who were not qualified to perform such examinations.

(3) Regarding the allegation that, despite the severity of a subject's acute adverse reaction to the overdose of apomorphine, the principal investigator discouraged the subject from receiving treatment because such treatment would have jeopardized the research, OHRP acknowledges your report that Dr. Brown told the subject that (i) if an antiemetic were administered to the subject, then it would likely invalidate the subject's results for the study and the subject's involvement would end; and (ii) it was the subject's decision whether or not to continue in the study without antiemetic medication. OHRP is concerned that given the amount of compensation that was to be given to the subject for her participation in the research, Dr. Brown's statements to the subject may have resulted in subtle coercion or undue influence and prevented the subject from making a truly voluntary decision regarding withdrawal from the study.

Corrective Actions: OHRP acknowledges that UTM has taken the following corrective actions in response to the above findings:

(1) UTM suspended the above referenced research protocol on March 10, 2000 following receipt of OPRR's March 10, 2000 letter requesting an investigation of this matter. OHRP acknowledges your report that this protocol has been permanently closed at UTM.

(2) The following limitations have been placed on Dr. Brown's research activities:

(a) For 18 months beginning July 1, 2000, Dr. Brown may not serve concurrently as a principal investigator on more than four human subject research projects involving (i) investigational new drug studies; (ii) studies of approved drugs for unapproved indications; and (iii) non-drug studies involving more than minimal risk to subjects.

(b) Dr. Brown will provide to the IRB a quarterly progress report for all ongoing studies for which she is the principal investigator. This IRB monitoring will continue for at least 18 months.

(c) Dr. Brown will provide assurance that, in no instances, will physical examinations or other medical interventions be performed, in the research context, by individuals not licensed to do so in the State of Tennessee.

(d) Collaborating physician investigators will be readily available for all interventions associated with significant risk and will be available to assess and appropriately respond to all adverse events occurring in the course of studies in which Dr. Brown is the principal investigator.

(3) The personnel who failed to follow standard sterile techniques and universal precautions when drawing blood samples were reprimanded. Furthermore, in-service education was provided to GCRC staff regarding the handling and disposal of blood, body fluids, and other biological specimens as dictated by OSHA.

OHRP has determined that these corrective actions adequately address the above findings and concerns, and as a result, there should be no need for further OHRP involvement in this matter. Furthermore, OHRP expects UTM to promptly report to OHRP any future unanticipated problems involving risks to subjects or others.

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

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Dr. Raymond H. Colson, Vice Chancellor, UTM
Dr. Clair E. Cox, Chair, IRB, UTM
Dr. Candace Brown, Principal Investigator, UTM
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. J. Thomas Puglisi, OHRP
Dr. Jeffrey Cohen, OHRP
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Mr. George Gasparis, OHRP