DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for HumanResearch Protections
The Tower Building
1100 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 301-402-3006
FAX: 301-402-2071
E-mail: rmeyer@osophs.dhhs.gov

September 24, 2002

Nancy C. Martin, Ph.D.
Vice President for Research
Office of Graduate Programs and Research
University of Louisville
Jouett Hall, Room 202B
Louisville, Kentucky 40292

Carol Z. Garrison, Ph.D.
Provost
University of Louisville
209 Gawemeyer Hall, MS 05-07
Louisville, Kentucky 40292

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1189 and FederalWide Assurance (FWA) 00002211

Research Project: Use of Photofrin® and Photodynamic Therapy (PDT) for Malignancies Which Have Either Failed Conventional Therapy or for Patients Who Have Refused Conventional Therapy [HSC 180-96]
Principal Investigators: T. Jeffery Wieman, M.D. and Scott W. Taber, M.D.
UL Protocol Number: HSC 180-96

Dear Drs. Martin and Garrison:

The Office for Human Research Protections (OHRP) has reviewed University of Louisville's (UL's)

November 15 and December 18, 2001 reports that were submitted in response to OHRP's October 24, 2001 letter to UL regarding the allegations of possible noncompliance with the

Department of Health and Human Services (HHS) regulations for protection of human subjects (45 CFR Part 46) involving the above-referenced research.

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

(1) In its October 24, 2001 letter, OHRP presented the allegation that the investigators may have conducted research on all of their patients by using "pooled data" to evaluate the use of PDT. In its December 18, 2001 report, UL stated the following:

> "The HSC [UL Institutional Review Board (IRB)] found that the investigators failed to clearly distinguish 'enrolled research subjects' from 'off-label treated clinical patients' when using PDT laser therapy and recording data from PDT treatment. The investigators research records for 180-96 were incomplete and inaccurate. Reports to the HSC regarding 180-96 included data obtained from patients not enrolled as subjects, as well as subjects who were properly enrolled. One subsequent publication (J Surg Onc) included data obtained from both enrolled subjects and from patients not enrolled in the study who were treated off-label with PDT. The investigators were found to be in non-compliance based on inaccurate record keeping and use of pooled data when reporting research results."

HHS regulations at 45 CFR 46.116 stipulate that, except as provided elsewhere in the regulations, no investigator may involve a human being as a subject in research covered by regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. OHRP finds that the principal investigators failed to obtain the legally effective informed consent of certain individuals reported as research subjects.

Corrective Action: OHRP finds that UL has implemented a number of corrective actions that adequately address the above finding of noncompliance. In particular, OHRP notes the following:

> (a) All research projects conducted by Drs. Wieman, Fingar and Taber were terminated by UL effective December 13, 2001.

(b) UL notified the editor of the Journal of Surgical Oncology of the specific human subject protection violations associated with Protocol HSC 180-96.

(c) Prior to approval of new studies, the above investigators must (i) notify each study sponsor of the above terminations; (ii) show evidence of attending a national course in human subject protections; and (iii) develop acceptable procedures to assure adequate record keeping, subject enrollment procedures, and reports to the UL IRB. In addition, any new studies approved for the above investigators by the UL IRB will be subject to a three month continuing review cycle and quarterly auditing. Auditing procedures will include (i) observation of the consent process; (ii) interviews with enrolled subjects; (iii) on-site inspection of research records; and (iv) observation of study procedures.

(d) UL has implemented (i) continuous education programs for institutional officials, IRB members, investigators, and research staff; and (ii) mandatory requirements for certification of participation in human subject protection training for all investigators and research staff.

(2) In its October 24, 2001 letter, OHRP presented the allegation that the research may have failed to minimize the risks to subjects, as required by HHS regulations at 45 CFR 46.111(a)(1), by allowing untrained laser company personnel to operate equipment on subjects during the study. UL's December 18, 2001 report stated the following:

> "The HSC found no evidence that untrained laser company personnel operated equipment on research subjects or in the off-label use of the equipment or drug for clinical treatment. Laser company personnel were involved in advice and consultation and were present for the laser treatment phase of four or five subject/patients. The physicians (Wieman and Taber), investigator Ph.D. (Fingar) and study nurses performed treatment in compliance with the protocol and good clinical practice. There is no evidence of increased risks to research subjects based on the presence of laser company personnel."

OHRP acknowledges UL's report that laser company personnel were not involved in the operation of equipment during the performance of PDT for clinical treatment. OHRP finds that this allegation was not substantiated.

(3) In its October 24, 2001 letter, OHRP presented the allegation that the informed consent may have failed to include a description of all the reasonably foreseeable risks or discomforts to the subjects, as required by HHS regulations at 45 CFR 46.116(a)(2). In specific, the complainant alleged that risks of severe dermal wounds were not discussed with subject LOR even though such risks were considered an "anticipated outcome" by the investigator. UL's December 18, 2001 report stated the following:

> "The HSC approved informed consent (version 1996) reflected the major risks and discomforts known at the time of treatment (1997) to potential subjects as stated in the protocol, Investigator's Drug Brochure, and package insert. The major anticipated or foreseeable side effects of the treatment were related to light exposure and were listed in the informed consent and in the PDT treatment release. 'Severe dermal wounds' were not anticipated or considered as anticipated outcomes by either the investigator or the sponsor and were not stated in the protocol for HSC 180-96 or the Investigator's Drug Brochure. The [subject LOR]'s medical record does not speak to 'severe dermal wounds'. The severity and duration of wounds were considered 'superficial' and 'as anticipated'."

OHRP notes that the documentation included in UL's December 18, 2001 reports included the following:

> (a) The October 28, 1999 Deposition of Jeffrey T. Wieman, M.D. regarding the involvement of subject LOR in the research project referenced above, as taken in the law offices of Amshoff & Amshoff, Louisville, Kentucky, stated the following:
>
> > (i) "Q. [Mr. Amshoff] Following Photodynamic Therapy administered to [subject LOR] as a result of the conditions that developed, would you agree that she required wound therapy?
> > A. [Dr. Wieman] All patients required wound therapy."
> >
> > (ii) "Q. [Mr. Amshoff] Do you believe that the wounds that [subject LOR] sustained were related in any way to the Photodynamic Therapy that was administered to her?
> > A. [Dr. Wieman] The destruction of her tumor was a product of Photodynamic Therapy."
> >
> > (iii) "Q. [Mr. Amshoff] Had you ever provided Photodynamic laser therapy for

any patients prior to [subject LOR] with as large of an affected area?
A. [Dr. Wieman] I'm sure we have, but I couldn't give you a specific instance."

(b) The minutes of the UL IRB convened meeting of November 26, 2001 stated the following:

"Dr. Wieman explained that patients undergoing PDT treatment have tumors that can be treated with Photofrin and exposed to non-thermal laser light that causes the tumors to die out. Where the tumor and its' (sic) supply die out, a wound will appear. Some of the wounds may be involuted and may restore quickly. Other wounds may take months to fill in. The degree of [subject LOR]'s wounds were well within the normal range expected with PDT."

(c) The University Surgical Associates, PSC chart notes for subject LOR stated, in part, the following:

(i) "October 2, 1997 Chart Note: ...Has had a rather dramatic tumor destruction of the areas treated ...Our PLAN [emphasis included] is to continue to encourage fluids and nutrition; local wound care;..."

(ii) "October 9, 1997 Chart Note: ...Superficial skin loss and tumor loss is gradually being replaced by good quality skin..."

(iii) "October 16, 1997 Chart Note: ...tumor eschar is now desquamating. Overall the response continues to be as we would anticipate."

(iv) "October 30, 1997 Chart Note: ...She is in photodynamic therapy trial...She does have *full thickness skin loss of the right face, neck and chest area* [emphasis added]...It is starting to epithelialize underneath the desiccated skin."

(v) November 5, 1997 Chart note: ...continues to shed her eschar. Her wounds are doing well..."

(d) The Risks section in the informed consent document initially approved by the UL IRB on June 28, 1996, did not include a statement regarding the risks and discomforts of dermal wounding resulting from tumor necrosis.

(e) The Explanation of the study section in the informed consent document initially

approved by the UL IRB on June 28, 1996, stated:

> "I have been invited to participate in a clinical research study consisting of the injection of the drug PHOTOFRIN® into one of my veins. One to three days after this injection, I will receive light treatment of my tumors. The light treatment will involve the placement of a fiberoptic device (which is the light source) in proximity to my tumor site. If my tumor is on the outside of my body, I will have to holding (sic) still for approximately 10-30 minutes per tumor site while the light shines on my skin. If my tumor is very thick, I will have to have a light source implanted within my tumor for the light treatment period. If the tumor is on the inside of my body, I will have to undergo an endoscopy procedure in order to get the light to that site, I will have that procedure at the time of light treatment and the fiberoptic will be passed through the endoscope for the light treatment. The exact time that will be needed will be calculated as is suitable for my condition."

(f) A June 27, 1996 letter from Solly S. Mizrahi, M.D., UL IRB member, to Richard L. Miller, D.D.S., Ph.D., Chair, UL IRB, regarding the research project referenced above stated the following:

> "I reviewed the above-named study of Dr. Jeff Wieman and I have no changes in the investigator outline. I found that the checklist description is not enclosed with the consent form. The only change in the consent form is to clarify if we need to add the risks from the endoscopy procedure that the patient has to undergo according to paragraph 2, page 2, in case the tumor is inside the body."

Based on the information stated in (a), (b), (c) and (d) above, OHRP finds that Dr. Wieman was aware of clinical information regarding the potential for dermal wounding as a result of the PDT procedure using Photofrin® when the UL IRB initially approved the research study on June 28, 1996. Based on this determination, OHRP finds that in accordance with HHS regulations at 45 CFR 46.116(a)(2), the informed consent document initially approved by the IRB should have included a description of the reasonably foreseeable risks and discomforts of tissue necrosis of the tumor-infiltrated area with subsequent dermal wounding directly associated with the use of the PDT procedure using Photofrin®. Based on the statements in (e) and (f) above, OHRP also finds that the informed consent document initially approved by the IRB also should have included a description of the reasonably foreseeable risks and discomforts of the implantation of a fiberoptic device and the endoscopy procedure.

Required Action: OHRP notes that, although the informed consent document was amended to include the risks of dermal wounding and the implantation of fiberoptic devices in 1998, no description of the risks of the endoscopy procedure was provided. This research-associated procedure and its reasonably foreseeable risks and discomforts should have been described in the informed consent document as required by HHS regulations at 45 CFR 46.116(a)(1) and (2). By October 22, 2002, UL must submit to OHRP a detailed corrective action plan to address the above finding. The plan should address steps taken by the UL IRB to ensure that all informed consent documents approved by the UL IRB include a complete description of reasonably foreseeable risks and discomforts.

(4) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. OHRP finds that the UL IRB failed to conduct continuing review of the research at least once per year. In particular, OHRP notes the following:

(a) The UL IRB initially approved Protocol HSC 180-96 on June 28, 1996.

(b) The UL IRB's initial continuing review and approval of Protocol HSC 180-96 occurred on July 16, 1998.

Corrective Action: OHRP acknowledges that the UL IRB currently has in place written policies and procedures and continuing review forms to ensure that continuing review of all ongoing research will comply with the requirements of HHS regulations at 45 CFR 46.109(e).

Please submit UL's response to item (3) above so that OHRP receives it no later than October 22, 2002.

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

Sincerely,

Robert J. Meyer
Compliance Oversight Coordinator

Division of Compliance Oversight

cc: Mr. Michael Barr, Vencor, Inc.
Dr. Richard L. Miller, Chair, IRB 1-A, UL
Dr. Edward R. Leist, Chair, IRB 2-B, UL
Dr. Lynn L. Ogden, Chair, IRB 1-A, Jewish Hospital Healthcare Services
Dr. Frank T. Serratoni, IRB 2-B, Jewish Hospital Healthcare Services
Dr. T. Jeffery Wieman, UL
Dr. John Mather, Director, Office of Research Compliance and Assurance, Veterans Health Administration
Commissioner, FDA
Dr. David A. Lepay, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. Jeffrey M. Cohen, OHRP
Mr. George Gasparis, OHRP
Dr. Harold Blatt, OHRP
Mr. Barry Bowman, OHRP