DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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February 24, 2005

Donald E. Wilson, M.D., M.A.
Dean, School of Medicine
University of Maryland Baltimore Professional Schools
655 West Baltimore Street
Baltimore, MD 21201-1559

RE: Human Research Subject Protections Under Federalwide Assurance FWA-7145

Research Project: A Phase II Randomized Trial Comparing Iodine-125 Versus Palladium-103 for Low Risk Prostate Cancer
Principal Investigator: Dr. Steven DiBiase
Project Number: GCC 0002

Dear Dr. Wilson:

The Office for Human Research Protections (OHRP) has reviewed the University of Maryland Baltimore Professional School's (UMB) December 10, 2004 report responding to determinations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) involving the above-referenced research.

In its November 3, 2004 letter, OHRP made the following determinations regarding general human subjects protections at UMB:

> (1) OHRP found that UMB institutional review board (IRB) members were not advised of (a) research protocols approved at the time of initial or continuing review under an expedited review procedure, or (b) minor changes in research protocols approved under an expedited review procedure, as required by HHS regulations at 45 CFR 46.110(c).
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> (2) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the *Federal Register* at 63 FR 60364-60367. OHRP found that the UMB IRB inappropriately applied expedited review to continuing review of research that involved greater than minimal risk and does not appear in the categories of research published in the *Federal Register*. OHRP requested a copy of UMB IRB written procedures which implement continuing review of greater

than minimal risk studies by the convened IRB.

(3) OHRP found that the institution does not have written IRB procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

(a) The procedures which the IRB will follow for conducting its continuing review of research.

(b) The procedures which the IRB will follow for reporting its findings and actions to investigators and the institution.

(c) The procedures which the IRB will follow for determining which projects require review more often than annually.

(d) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(e) The procedures which the IRB will follow for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(f) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any Department or Agency head, and OHRP of: (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.

Corrective Action: OHRP acknowledges that UMB has developed draft written procedures to address these requirements. OHRP makes the following recommendations about the UMB draft written procedures:

(a) The UMB draft procedure 1b includes a table which identifies typical activities that may require IRB review. Under "Quality Assurance and Quality Improvement Activities," it states, "Where the primary intent (design) of the activity is for internal assessment or improvement," the activity does not require IRB review. OHRP notes that if **any** intent (primary, secondary, etc.) of the research is to develop or contribute to generalizable knowledge, then that activity is research under HHS regulations at 45 CFR 46.102(d).

(b) The UMB draft procedure 02b includes a description of "Administrative

Hold." OHRP notes that such a hold would appear to constitute a suspension of IRB approval and, as such, would need to be reported to appropriate institutional officials, any Department or Agency head, and OHRP, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

(c) UMB draft written procedure 3k.3 states that a study must meet certain criteria to be eligible for closure, including the criterion that the only research activity being conducted is data analysis. OHRP notes that data analysis of identifiable private information is human subjects research, and continuing review for such research must occur at least annually, although such review may be expedited.

Based upon its review of UMB's December 10 and April 28, 2004 reports, OHRP makes the following additional determinations regarding the above-referenced research:

(4) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the 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. OHRP finds that the investigator failed to conduct a digital rectal exam, a urinary function test and questionnaires within the time window prescribed by the protocol without prior IRB approval.

Required Action: By April 8, 2005, please provide OHRP with an appropriate corrective action to address this finding. Please include the steps UMB will take to ensure that the UMB IRB reviews all proposed changes in research activities prior to initiation of such changes.

(5) OHRP finds that when reviewing the above-referenced protocol application, the IRB lacked sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. In specific, OHRP notes that one eligibility criterion for the above-referenced research was histologically confirmed adenocarcinoma of the prostate with a Gleason score of 6 or less. The protocol does not specify the time frame prior to brachytherapy in which the prostate biopsy confirming the Gleason score must occur. OHRP finds that the IRB would need to have that information in order to determine that risks to subjects are minimized.

Required Action: By April 8, 2005, please provide OHRP with an appropriate corrective action to address this finding. Please include the steps UMB will take to ensure that the UMB IRB receives sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111 for all research reviewed by the IRB.

(6) HHS regulations at 45 CFR 46.111(a)(1) and (2) require that the IRB ensure that risks to subjects are minimized and are reasonable in relation to anticipated benefits to subjects. OHRP finds that risks to subjects were not minimized and were not reasonable

in relation to anticipated benefits to the complainant. OHRP notes that the complainant did not have a digital rectal exam (DRE) within 6 weeks of the brachytherapy, as required by the protocol, but the last DRE was conducted more than 6 months prior to brachytherapy. In addition, the complainant had a prostate biopsy 8 months prior to the brachytherapy. OHRP finds that confirmation of the eligibility criteria for this protocol at the time of brachytherapy was not determined accurately for this subject.

Required Action: By April 8, 2005, please provide OHRP with a corrective action to address this finding.

OHRP appreciates 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. Susan Buskirk, Program Manager, Human Research Protections, UMB
Dr. Robert Edelman, Chair, UMB IRBs
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
Ms. Janet Fant, OHRP
Ms. Patricia El-Hinnawy, OHRP