**DEPARTMENT OF HEALTH & HUMAN SERVICES**

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**Office of Public Health and Science**

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May 2, 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) April 5, 2005 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 February 24, 2005 letter, OHRP made the following determinations regarding the above-referenced research:

> (1) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the institutional review board (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 found 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 obtaining prior IRB approval for this change.
>
> **Corrective Action:** OHRP acknowledges that the UMB IRB has distributed information to all investigators and research personnel to remind them that the UMB IRB must review all proposed changes in research activities prior to initiation of such changes. In

addition, the IRB written procedures now address this, and the IRB has implemented quality assurance auditing to verify prior IRB approval of all proposed changes.

(2) OHRP found that when reviewing the above-referenced protocol application, the UMB IRB lacked sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. In specific, OHRP noted 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 found that the IRB would need to have that information in order to determine that risks to subjects are minimized.

**Corrective Action:** OHRP acknowledges that the UMB IRB has modified its written procedures to include evidence of a thorough literature search and use of a full protocol template, which includes specific details pertaining to appropriate time frames for eligibility testing.

(3) 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 found that risks to subjects were not minimized and were not reasonable in relation to anticipated benefits to the complainant. OHRP noted 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 found that confirmation of the eligibility criteria for this protocol at the time of brachytherapy was not determined accurately for this subject.

**Corrective Action:** OHRP acknowledges that the UMB IRB requires use of a full protocol template, which includes specific details pertaining to appropriate time frames for eligibility testing. In addition, the IRB has reminded investigators of the importance of verifying subject eligibility and determining acceptable time frames for eligibility testing.

OHRP finds that the corrective actions described above adequately address the determinations in our February 24, 2005 letter and are appropriate under the UMB assurance. As a result of these determinations, OHRP anticipates no further involvement in this matter.

At this time, OHRP offers the following additional guidance:

(4) The UMB draft procedure 02b includes a description of "Administrative Hold." OHRP noted 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). UMB responded that the administrative hold is not a suspension or termination of IRB approval of the research, but rather a hold on research

activities until adequate information is obtained for the IRB to make a decision whether to suspend or terminate the approval. OHRP again notes that **any** suspension or hold by the IRB of any human subject research activities (enrollment, analysis, etc.) is a suspension of IRB approval and would need to be reported to OHRP.

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
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Ms. Janet Fant, OHRP
Ms. Patricia El-Hinnawy, OHRP