DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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June 18, 2002

Steven Knapp
Provost and Vice President for Academic Affairs
The Johns Hopkins University
Office of the Provost
265 Garland Hall
3400 N. Charles Street
Baltimore, MD 21218-2692

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1091

Research Activity: **Study of Tetramethyl (M_4N) and Glycinyl (G_4N) Derivatives of Nor-Dihydroguiarectic Acid for Oral Cancer Treatment in India**
Principal Investigator: Dr. Ru Chih Huang

Dear Dr. Knapp:

The Office for Human Research Protections (OHRP) has received The Johns Hopkins University's (JHU) January 30, 2002 report that was submitted in response to OHRP's December 10, 2001 letter regarding the above-referenced research.

Based upon its review of JHU's MPA (Homewood Schools) and JHU's January 30 2002 and November 12, 2001 reports, OHRP notes the following:

(1) The JHU MPA states the following:

(a) "This institution is guided by the ethical principles regarding all research involving humans as subjects, as set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (entitled: Ethical Principles and Guidelines for the Protection of Human Subjects of Research [the Belmont Report]), regardless of whether the research is subject to Federal regulation or with whom conducted or source of support (i.e., sponsorship)."

(b) "All requirements of Title 45, Part 46, of the Code of Federal Regulations (45 CFR 46) will be met for all federally-sponsored research, and all other human subject research regardless of sponsorship, except as otherwise noted in this Assurance."

(c) "The [Homewood Research Administration] will report promptly to the [Institutional Review Board (IRB)], appropriate institutional officials, the Office for Protection from Research Risks (OPRR), and any other sponsoring Federal department or agency head:....2. any serious or continuing noncompliance with the regulations or the requirements of the IRB...."

(2) JHU's January 30, 2002 report stated the following:

(a) "First, at the time in early 2001 that it became known that Dr. Huang had been involved in research in India involving human subjects, there was no indication of a need to report to ORI [Office of Research Integrity] or OHRP since administrative officials had no information showing that her activities in India were supported by the U.S. Public Health Service."

(b) "Our focus and first priority at the time was to make sure that Dr. Huang would be in compliance with University regulations as she went forward with her clinical research in India which she was urgently preparing to do on the strength of her belief that she was on the verge of a breakthrough in cancer research."

(c) "Dr. Huang insisted that the Regional Cancer Centre ('R.C.C.') [in India] had properly designed and approved these clinical trials through its own institutional review board. Indeed, until July 2001 when media reports coming out of India raised serious questions about the clinical trials, the limited information about these trials that was shared with University officials came only from Dr. Huang herself."

(3) A March 30, 2001 memorandum from Mr. Frederick G. Savage to Dr. Huang regarding a meeting held on March 23, 2001 stated "We also discussed the fact that you do not understand why you were required to get IRB approval since all you were doing was carrying the drug to India. The answer is that under our own rules, we consider such involvement to trigger the requirement for our own IRB approval. In addition, your agreement with them listed you as the principle [sic] investigator."

(4) On April 10, 2001, the U.S. Patent and Trademark Office approved patent number 6,214,874 for two nordihydrogiaretic acid derivatives (M4N and G4N) which were the drugs used in Dr. Huang's human subjects research in India.

(5) On July 14, 2001, an article appeared in the Times of India raising allegations of problems with the above-referenced research.

(6) A July 27, 2001 letter from Mrs. Estelle Fishbein to OHRP stated "The University has become aware of the possibility that a Johns Hopkins University scientist at the University's School of Arts and Sciences may have participated in or in some way have been associated with a foreign clinical study without the University's prior knowledge and approval."

(7) A September 4, 2001 memorandum from Mr. Theodore Poehler to Professors Ann Hubbard, Harris Silverstone, and Steven Yantis stated the following:

> (a) "After some documents related to the clinical trial in India had been provided to us by Professor Huang, I met with Mrs. Fishbein who has responsibility in the university administration on actions related to legal and regulatory matters. We discussed the desirability of recommending an inquiry into the matter. Her judgement in the matter was that our immediate priority was to identify possible infractions in professor Huang's current planned program, and thus it was advisable to briefly delay actions leading to an inquiry of the past work."
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> (b) "The primary rationale for this course of action was that Professor Huang was engaged in an ongoing program that involved future human subjects experiments, so that precedence should be given to a detailed review of the current program to assure that no irregularities were present, and that there was or would be full compliance with all applicable policies and regulations."
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> (c) "I concurred with Mrs. Fishbein's decision because there had been considerable difficulty establishing proper administrative oversight of this project since its inception."

(8) In response to a question in an interview on September 5, 2001, with the JHU internal investigation committee regarding what transpired during a March 23, 2001 meeting regarding the above-referenced research, Mr. Frederick Savage stated:

> "Well, I raised the issue of whether or not this had to be reported to somebody in Homewood for possible scientific misconduct or research misconduct or professional misconduct and the discussion that took place was essentially that that was an issue of concern but this was probably not the right time to do that ..."

(9) A September 11, 2001 memorandum from Mrs. Estelle Fishbein to Professors Ann Hubbard, Harris Silverstone, and Steven Yantis stated the following:

> (a) "A dely in initiating an inquiry and in notifying the federal agencies [from the period of April 2001 when documentation was first gathered indicating possible procedural infractions] did occur for which I assume full responsibility."
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> (b) "Nevertheless, when allegations of more serious violations related to experiments on human subjects in India reached the University from reports in the Indian press, an inquiry was started as expeditiously as possible, and notification of the federal agencies followed."

(10) The October 24, 2001 report of the JHU internal investigative committee provided with JHU's November 12, 2001 report stated the following:

> (a) "No systematic investigation of the effects of either drug on physiological function was carried out, and no pharmacokinetic study was conducted ..."
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> (b) "Professor Huang and her collaborators assumed that M_4N, because it was not water soluble, would not spread to other parts of the body and was therefore safe, but this assumption was not put to rigorous empirical test. They also assumed that although G_4N is water soluble, it would not spread far from the point of injection because it was not administered systemically. This assumption was not confirmed empirically, and because of the water solubility of G_4N, the risk of harm is greater."
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> (c) "The consent forms used in the study (Attachment 22) failed to warn patients of any risk at all of the M_4N or G_4N; instead the consent forms only mentions [sic] generic risks associated with injection regardless of the drug being injected (e.g., soreness at the injection site). Neither form states that these drugs are being administered to humans for the first time."
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> (d) "A meeting was held on March 23, 2001, attended by Professor Huang, Theodore Poehler, Vice Provost for Research, and Estelle Fishbein and Frederick Savage of the General Counsel's Office (see Attachment 28). At this meeting, Dr. Poehler, Ms. Fishbein, and Mr. Savage became aware that Professor Huang had conducted clinical trials at the RCC [Regional Cancer Centre] in India in 1999 and 2000 without first obtaining JHU IRB approval. According to all three, they recognized immediately that an inquiry was warranted (Attachment 29). However, the Vice President and General Counsel advised delaying any action. In particular, the KSAS [Kreiger School of Arts and Sciences] Dean's office was not notified, as provided by the KSAS Policy on Integrity in Research."

(e) "The Committee is disturbed that Officers of the University failed to initiate an investigation into this matter in March 2001. Breach of rules governing human subject protection in research is serious because it can affect not only the subjects in question, but all JHU studies involving human subjects."

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

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(a) and the JHU MPA require that the JHU IRB review and have authority to approve, require modifications in (to secure approval), or disapprove all non-exempt human subject research activities. OHRP finds that the above-referenced human subject research, which did not satisfy the criteria for exemption under HHS regulations at 45 CFR 46.101(b), was conducted without the review and approval of the JHU IRB.

(2) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) and the JHU MPA require prompt reporting to the IRB, appropriate institutional officials, Department or Agency heads, and OHRP of, among other things, any serious or continuing noncompliance with the regulations for the protection of human subjects or the requirements or determinations of the IRB. OHRP finds that:

(a) The conduct of the above-referenced research by a JHU investigator without the review and approval of the IRB designated under the JHU MPA represented serious noncompliance with the requirements of the HHS regulations for the protection of human subjects and the JHU MPA.

(b) As early as March 23, 2001, senior officials at JHU, including the JHU Vice President and General Counsel and the Vice Provost for Research, the Authorized Institutional Official who endorsed the JHU MPA, knew or should have known that the conduct of the above-referenced research by a JHU investigator without the review and approval of the IRB represented serious noncompliance with the requirements of the HHS regulations for the protection of human subjects and the JHU MPA.

(c) Senior officials of JHU, including the Vice President and General Counsel and the Vice Provost for Research, failed to ensure that procedures were followed for prompt reporting of this serious noncompliance in accordance with the above requirements, including prompt reporting to OHRP. Furthermore, these same senior officials failed to promptly initiate a formal inquiry into the matter, but initiated such an inquiry only after concerns about the research were raised in a media report in late July 2001.

(3) HHS regulations at 45 CFR 46.103(c) require that an institution's assurance of compliance with the regulations for the protection of human subjects shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations

imposed by the regulations. In view of the above findings and observations, OHRP finds that the JHU Vice Provost for Research has failed to fulfill his obligations imposed by the HHS regulations for the protection of human subjects and the JHU MPA.

Action 1 - Required: By July 26, 2002 JHU must submit to OHRP a revised Part 3 of its MPA for the Homewood Schools signed by a new Authorized Institutional Official. This official should reside at an administrative level above the Vice Provost for Research.

Action 2 - Required: By July 26, 2002, JHU must submit to OHRP a satisfactory corrective action plan which addresses findings (1) and (2) stated in this letter.

Based upon its review of JHU's reports, OHRP makes the following additional determinations regarding JHU's system for protecting human subjects:

(4) OHRP finds that the Homewood Schools of JHU do not have written IRB policies and 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 (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) 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.
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> (b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, OHRP and Department or Agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.

(5) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings be in sufficient detail to show, among other things, the vote on all IRB actions including the number of members voting for, against, and abstaining. OHRP finds that minutes of the Homewood Schools IRB meetings fail to meet this requirement. Please note that recording votes as unanimous does not satisfy this requirement.

In order to document the continued existence of a quorum, OHRP recommends that votes be recorded in the minutes using the following format: Total = 15; Vote: For-14, Opposed-0, Abstained-1 (NAME).

Action 3 - Required: By July 26, 2002, JHU must submit to OHRP a satisfactory corrective action plan which addresses findings (4) and (5), as stated above.

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,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Richard E. McCarty, Krieger School of Arts and Sciences
Mr. Marc D. Donohue, Associate Dean for Research, Whiting School of Engineering
Dr. Robert Sirota, Director, Peabody Institute
Mr. Stephen Szabo, Interim Dean, School of Advanced International Studies
Dr. Theodore Poehler, Vice Provost for Research
Mrs. Estelle Fishbein, JHU
Mr. Frederick Savage, JHU
Dr. Howard Egeth, JHU
Dr. Ru Chih C. Huang, JHU
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Greg Koski, OHRP
Dr. Melody Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. George Gasparis, OHRP
Dr. Harold Blatt, OHRP
Mr. Barry Bowman, OHRP