DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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June 25, 2007

Chiyome L. Fukino, MD
Director of Health
Hawaii State Department of Health
1250 Punchbowl Street
Honolulu, HI 96813

James R. Gaines, Ph.D.
Vice President for Research
University of Hawaii
2444 Dole Street
Honolulu, HI 96822

RE: Human Research Protections Under Federalwide Assurance FWA-3526 and FWA-118

Research Project: Effects of Upcountry Maui Water Additives on Health
Principal Investigator: Amber Rohner; Kenton Kramer, Ph.D., supervising professor

Dear Drs. Fukino and Gaines:

The Office for Human Research Protections (OHRP) has reviewed the Hawaii State Department of Health's (HSDOH) April 9, 2007 and the University of Hawaii's (UH) March 29, 2007 responses to OHRP's March 2, 2007 letter regarding compliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46).

OHRP makes the following determinations:

(1) OHRP described the following allegations in our March 2, 2007 letter:

(a) Failure of the institutional review board (IRB) to notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity, as required by HHS regulations at 45 CFR 46.109(d). In specific, it was alleged that the IRB disapproved the above-referenced research protocol, but did not notify the investigator in writing.

> (b) Failure of the IRB, if the IRB decides to disapprove a research activity, to include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing, as required by HHS regulations at 45 CFR 46.109(d). In specific, it was alleged that the IRB did not allow the investigator an opportunity to respond in person or in writing to the decision of the IRB to disapprove the above-referenced research activity.

OHRP notes that the UH IRB notified the principal investigator (who was a medical student) and her faculty supervisor in letters dated October 25, 2004 that the project was suspended as it appeared that it had been conducted before IRB review and approval were sought. They were also informed in these letters that "a preliminary inquiry has been instituted based on apparent non-compliance with federal regulations…." The letters also stated "We invite you to respond to the above concern."

In a March 23, 2005 letter the principal investigator was notified by the IRB that "[d]uring this time there has been no formal action taken on the unsigned application that you (or Dr. Kramer) submitted on the Maui project. We cannot accept nor grant retrospective review of a project that meets the federal definition of human subject research." Therefore the principal investigator was notified of the status of the research proposal and given an opportunity to respond and was notified that the proposal was not disapproved per se, but was instead not accepted or reviewed by the IRB.

As a result, OHRP finds that the above allegations cannot be substantiated. OHRP further notes that the complainant was not the principal investigator and therefore was not required to be notified of these events.

(2) OHRP finds that the HSDOH IRBs do 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 determining which projects require review more often than annually.
>
> (b) 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.
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> (c) 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.
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> (d) The procedures for ensuring prompt reporting to the IRB, appropriate institutional

officials, any department or agency head, and OHRP of: (i) 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.

Required Action: By July 6, 2007, please provide OHRP with a corrective action to address this finding. In your response please provide any revised written IRB procedures. Please note that while the HSDOH has written procedures to address reporting to the IRB of any unanticipated problems involving risks to subjects or others, the procedures may not ensure prompt reporting because they state that such events that are not serious should be reported no later than at the time of continuing review. Please respond.

OHRP has the following questions and concerns:

(3) [Redacted]

(4) [Redacted]

(5) [Redacted]

OHRP has the following additional recommendations:

(6) OHRP notes that the HSDOH education of IRB members and of investigators consists of

being provided with a copy of the "Hawaii Department of Health Policies and Procedures Governing Research Involving Human Subjects." OHRP recommends that more extensive education and training be provided to IRB members and staff on human subjects protections. OHRP also notes that the Director of Health and the IRB chair complete the on-line Assurance Training at the OHRP website. OHRP notes that this is not a comprehensive human subjects protections training program but only a module designed to train signatory officials, IRB administrators and IRB chairs about their responsibilities under the Federalwide Assurance.

(7) OHRP has the following guidance regarding the HSDOH "Hawaii Department of Health Policies and Procedures Governing Research Involving Human Subjects": Section II.A.2. indicates that ad hoc members with knowledge of special populations may also be appointed and used as needed and that such members are non-voting. OHRP notes that HHS regulations at 45 CFR 46.107(a) require that an IRB which regularly reviews research involving a vulnerable category of subjects consider inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects. Such individuals should be voting members. OHRP further notes that all individuals who are recognized as IRB members must be considered voting members.

(8) OHRP has the following guidance regarding the UH Committee on Human Studies Policies and Procedures Manual:

(a) On page 14 the manual states that IRB members can obtain necessary training by completing the on-line Assurance Training at the OHRP website. OHRP notes that this is not a comprehensive human subjects protections training program but only a module designed to train signatory officials, IRB administrators and IRB chairs about their responsibilities under the Federalwide Assurance.

(b) Pages 43-44 of the manual state that a grace period can be approved by the IRB chair for studies that have not undergone review at least annually "when closure may cause risk to the human subject(s), if there is an extenuating circumstance, or to allow for the submission and receipt of required documentation for the CHS review process." Please note that the only circumstances that would permit research to continue the date of approval expiration are when it is in the best interest of the subject(s) to continue.

(c) Page 45 of the manual states that when "non-compliance is found to be serious in nature, the IRB may….report to the sponsor, administrative officials, and government agencies (e.g., OHPR [sic], FDA, etc.)" Similarly, on page 46 of the manual it states "The Institutional Official may send written notice on behalf of the CHS to the following entities, as required under Federal regulations: the OHRP; the FDA if the suspension of research approval involves an investigational drug or device; the OHRP and FDA as applicable, if the matter involves the non-submission of a project which should have been reviewed by the CHS, and the researcher's failure to do so has resulted in unanticipated risks to human subjects or

serious or continuing Non-Compliance with CHS requirements; external and internal sponsors funding a study under suspension." Please note that these are regulatory requirements and therefore the "may" should be changed to "must."

(d) Page 49 of the manual states "PIs should terminate a protocol when human subjects are no longer being followed or studied. As long as subjects (patients or otherwise) are still being followed, even if the protocol is closed to subject accrual, a protocol is considered active and Continuing review must be completed." Please note that as long as investigators are analyzing identifiable private information for research purposes, they are conducting human subjects research and must have continuing review of that research.

(e) Please note that subpart B of 45 CFR part 46 has been revised; OHRP recommends that you update pages 59-62 accordingly.

(f) Page 70 of the manual states "If a subject becomes a prisoner after enrollment in research, the investigator is responsible for reporting in writing this situation to the IRB immediately. Upon its review, the IRB can either (i) approve the involvement of the prisoner-subject in the research in accordance with this policy or (ii) determine that this subject must be withdrawn from the research." Please note that if a human subject involved in ongoing research becomes a prisoner during the course of the study, and the relevant research proposal was not reviewed and approved by the IRB in accordance with the requirements for research involving prisoners under subpart C of 45 CFR part 46, the investigator must promptly notify the IRB. All research interactions and interventions with, and obtaining identifiable private information about, the now- incarcerated prisoner-subject **must be suspended immediately**, unless it is in the best interests of the subject to remain in the research study while incarcerated.

Please forward your response to the above findings, questions and concerns so that OHRP receives it no later than August 6, 2007.

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:

Dr. Betty J. Wood, Human Subjects Administrator, Hawaii State Department of Health
Dr. Catherine A. Sorensen, IRB Chairperson, Hawaii State Department of Health
Mr. William H. Dendle, Executive Secretary/Compliance Officer, University of Hawaii Committee on Human Studies
Dr. Peter V. Garrod, IRB Chairperson, University of Hawaii IRB #1
Dr. Dennis McDougall, IRB Chairperson, University of Hawaii IRB #2
Dr. Kenton Kramer, University of Hawaii
Dr. Lorrin Pang, Hawaii State Department of Health
Ms. Pam Galusha, Centers for Disease Control and Prevention
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Carla Brown, OHRP