DEPARTMENT OF HEALTH & HUMAN SERVICES

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June 6, 2001

Neal Nathanson, M.D.
Vice Provost for Research
110 College Hall
University of Pennsylvania
Philadelphia, PA 19104

Mary Chatterton, J.D.
Secretary
Monell Chemical Senses Center
3500 Market Street
Philadelphia, PA 19104-3308

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M1025

Research Project: Perception of Acetone; IRB #192101
Principal Investigator: Charles J. Wysocki;
HHS Project Numbers: RO1 DC-00298; P50 DC00214; F32 DC-00197

Dear Dr. Nathanson and Ms. Chatterton:

The Office for Human Research Protections (OHRP) has reviewed your February 15, 2001 report regarding the above referenced research that was submitted in response to OHRP's January 22, 2001 letter.

OHRP notes that the University of Pennsylvania (UP) Institutional Review Board (IRB) requested clarification about OHRP's rationale for the proposed debriefing of participants enrolled in the above referenced research. OHRP responds as follows:

(1) In its August 23, 2000 letter to UP, OHRP made the following determinations regarding the above referenced research:

(a) When it reviewed and approved the above referenced research, the UP IRB inappropriately used an expedited review procedure, in contravention of the requirements of Department of Health and Human Services (HHS) regulations for

the protection of human subjects at 45 CFR 46.108(b). As a result, the UP IRB's initial and continuing review of the research was inadequate.

(b) The UP IRB failed to receive or request from the investigators sufficient information to make the determinations required by HHS regulations at 45 CFR 46.111(a)(1) and (2), and thus failed to ensure that risks to subjects were minimized and reasonable in relation to anticipated benefits to the subjects and the importance of the knowledge that was expected to result.

(c) Informed consent documents reviewed and approved by the UP IRB for the research failed to adequately address or include all basic elements of informed consent required by HHS regulations at 45 CFR 46.116(a). Furthermore, for some subjects, the informed consent document was deceptive because it misrepresented both the purpose of the research and the nature of the chemical to which subjects were to be exposed.

(2) An institution that accept HHS funds for research involving human subjects is obligated to comply with all requirements of HHS regulations for the protection of human subjects, including the provisions at 45 CFR 46.111 and 46.116, for research projects covered by the regulations and the institution's assurance of compliance with these regulations.

(3) The HHS regulations are premised upon the 1978 report from the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research entitled "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." This report, embraced by the UP under MPA M-1025 (see Part 1, Section I.A) set forth three basic ethical principles related to the conduct of research involving human subjects: (a) respect for persons; (b) beneficence; and (c) justice. While the UP IRB's analysis of the proposed debriefing procedure appears to take into consideration the principle of beneficence, it fails to address the principle of respect for persons which is relevant to this matter.

The principle of respect for persons involves a recognition of the personal dignity and autonomy of individuals. Recognition of personal autonomy requires truthful disclosure of important information to a person, even if such information may have unpleasant or negative implications.

(4) While recognizing the importance of the principle of respect for persons, OHRP does not discount the UP IRB's application of the principle of beneficence in their analysis of this matter. OHRP acknowledges the sentiment expressed by the UP IRB that the presentation of information might create some anxiety among the participants of the above referenced research. However, the principle of respect for persons must still be addressed.

OHRP recommends that the IRB, in conjunction with the investigators, develop a plan for helping the subjects cope with, and recover from, any anxiety that might be engendered by the debriefing process.

Furthermore, based on its review, OHRP finds UP's proposed debriefing to be in need of further revision. To carry out UP's responsibilities under the human subject protection regulations and its MPA, please note that OHRP expects the debriefing text to include, at a minimum, the following information for subjects who participated in either Study I ("Determining the Irritation Threshold for Acetone: Detection and Lateralization Study") or Study II ("Evaluating the Perceptual Response to Acetone: Judgements of Intensity and Irritation") of the above referenced protocol:

(1) An accurate explanation of the purpose of the research.

(2) A simple, complete, and accurate description of all research procedures that the subjects underwent.

(3) The names and approximate levels of all chemicals to which the subjects were exposed, and the known exposure safety limits for each chemical.

(4) A description of the reasonably foreseeable risks and discomforts of the research.

(5) A description of any benefits to the subjects or others that may have resulted from the research.

(6) An explanation of whom to contact if the subjects have any questions about their rights as research subjects.

In order to provide an explanation to the subjects about why the debriefing is taking place at this time and to minimize possible anxiety, it may also be appropriate for the debriefing text to also include the following:

(1) A statement that OHRP reviewed this research after receiving a complaint that the research violated Federal regulations for the protection of human subjects.

(2) A statement that OHRP concluded that (a) the UP IRB did not adequately review this research; and (b) the informed consent documents failed to address or include all of the information required by Federal regulations.

By July 13, 2001, please provide OHRP with copies of appropriately revised debriefing letters or written documents that have been approved by the UP IRB and are to be provided to the research subjects enrolled in either Study I or Study II of the above referenced protocol.

Regarding **Action 2** required by OHRP in its January 22, 2001 letter, OHRP finds that UP has developed detailed written IRB policies and procedures that incorporate the major elements required by HHS regulations at 45 CFR 46.103(b)(4) and (5). At this time OHRP provides the following additional guidance regarding UP's written IRB policies and procedures:

(1) Page 41, POLICY F0 301, RESEARCH SUBMISSIONS REQUIREMENTS, section 3.1.1 - The list of required documents to be submitted to the IRB should be modified to include a copy of any relevant Federal grant application.

(2) Page 43, POLICY F0 302, IRB MEETING ADMINISTRATION - OHRP recommends that this section be modified to include a description of the documents received by the primary reviewer and non-primary reviewer members for protocols undergoing continuing review, and the procedure for conducting continuing review at convened meetings.

(3) The IRB policies and procedures should be modified to include additional operational details of the procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, the Department or Agency head, if appropriate, and OHRP of (a) any unanticipated problems involving risks to subjects or others; or (b) any suspension or termination of IRB approval.

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

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Dr. Greg Koski, OHRP
Dr. Melody Lin, OHRP
Mr. George Gasparis, OHRP
Ms. Roslyn A. Edson, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. Barry Bowman, OHRP
Dr. Joseph Sherwin, Director of Regulatory Affairs, UP
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