DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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August 23, 2000

Ralph D. Amado, Ph.D.
Vice Provost for Research
University of Pennsylvania
Room 212, College Hall
Between 34/36th Sts. And Locust
Philadelphia, PA 19104-6380

Mr. John K. T. Tran
Secretary-Treasurer
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 Numbers 1921-1
Principal Investigator: Charles J. Wysocki; HHS Project # RO1 DC-00298; P50 DC00214; F32 DC-00197

Dear Dr. Amado and Mr. Tran:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed the December 6, 1999 report from the University of Pennsylvania and Monell Chemical Senses Center concerning the above referenced matter.

Based upon its review of your report, OHRP makes the following determinations regarding this research project:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures by the Institutional Review Board (IRB) to research activities involving no more than minimal risk and in which the only involvement of human subjects is in one or more specific categories published in the Federal Register (the list of specific categories of research eligible for expedited review at the time this research underwent initial and continuing review was published in the Federal Register at 46 FR 8392).

OHRP finds that:

(a) The research project underwent expedited review by Dr. Karl Rickels, the IRB Executive Chair, during its initial review in December 1994, and by Ms. Ruth Clark, an IRB member, during its only continuing review in October 1995.

(b) This research was not eligible for expedited review. In specific, OHRP finds that the research (i) did not satisfy the criteria for any of the categories of research eligible for expedited review described in the Federal Register at 46 FR 8392; and (ii) appears to have involved greater than minimal risk to the subjects.

(c) Because of the inappropriate use of expedited review, this research did not receive adequate initial or continuing review by the IRB.

(2) HHS regulations at 45 CFR 46.111(a)(1) and 46.111(a)(2) stipulate that, in order to approve research, the IRB must determine that risks to subjects are minimized and reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge that may reasonably be expected to result.

Based upon the following observations, OHRP finds that the IRB failed to receive or request from the investigators sufficient information necessary to make the determinations required by HHS regulations at 45 CFR 46.111(a)(1) and 46.111(a)(2), and thus failed to ensure that risks to subjects were minimized and reasonable:

(a) While the IRB-approved protocol indicated the concentration of, and duration of exposure to, acetone (800 ppm for 20 minutes per exposure) and phenylethyl alcohol (800 ppm for 20 minutes per exposure) that subjects were to be exposed to when they were placed in an exposure chamber, the protocol did not provide any information regarding the concentration of, and duration of exposure to, acetone and butanol during the sniff tests for any of the studies described. Furthermore, the protocol indicated that the concentration of acetone released from the sniff bottles was one of the parameters being measured by the investigators as part of the IRB-approved protocol.

(b) The Material Safety Data Sheet (MSDS) provided to the IRB at the time of initial review described the following health effects for inhalation of acetone:

"Irritant/narcotic. 20,000 ppm immediately dangerous to life or health. Acute exposure - Vapor concentrations around 1000 ppm may cause slight transient irritation of the upper respiratory tract. Exposure to 12,000 ppm has caused throat irritation and central nervous system depression with weakness in the legs, headache, dizziness, drowsiness, nausea, and a general feeling of malaise. Other possible side effects from exposure to high concentrations include dryness of the mouth and throat, incoordination of motion and speech, restlessness, anorexia,

abdominal pain, vomiting, sometimes followed by hematemesis, hypothermia, dyspnea, slow, irregular respiration, slow, weak pulse, progressive collapse with stupor, and in severe cases, coma."

(c) The journal article entitled "Acetone Odor and Irritation Threshold Obtained from Acetone-Exposed Factory Workers and From Control (Occupational Unexposed) Subjects" (American Industrial Hygiene Association Journal 58:704-712; 1997) that described the results of part of this research indicated that during sniff test experiments, acetone-exposed and unexposed subjects were exposed to median acetone concentrations of 36,669 and 15,578 ppm, respectively, during lateralization experiments.

(3) OHRP finds that the informed consent documents reviewed and approved by the IRB between December 1994 and October 1995 for Study I ("Determining the Irritation Threshold for Acetone: Detection and Lateralization Study") failed to adequately address or include the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1): (i) an adequate explanation of the purpose of the research (i.e., to better understand the perceptual response to acetone at levels commonly found in the workplace and to determine sensitivity to acetone in people who work with acetone and in people who do not); and (ii) a complete and accurate description of the procedures to be followed (i.e., a description of the chemicals to which subjects were to be exposed, the level of chemical exposure expected, and the known maximal levels of safe exposure at that time). Furthermore, OHRP finds that the statement in the informed consent document that "[t]he odors that you will be smelling are regarded as harmless" was misleading and not consistent with the potential acute toxicities reported for acetone in the MSDS, given the level of exposure for the sniff test studies reported by the investigators in their above referenced journal article.

(b) Section 46.116(a)(2): An adequate description of the reasonably foreseeable risks and discomforts. In specific, other than the risk of experiencing a burning or stinging sensation and light-headedness because of rapid breathing, no other potential risks or discomforts from acetone exposure were described.

(c) Section 46.116(a)(3): An adequate description of any benefits to the subject or others that may reasonably be expected from the research.

(d) Section 46.116(a)(7): An explanation of whom to contact for answers to questions about research subjects' rights.

(4) OHRP finds that the informed consent documents reviewed and approved by the IRB between December 1994 and October 1995 for Study II ("Evaluating the Perceptual Response to Acetone: Judgements of Intensity and Irritation") failed to adequately address or include the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1): (i) an adequate explanation of the purpose of the research (i.e., to better understand the perceptual response to acetone at levels commonly found in the workplace and to determine sensitivity to acetone in people who work with acetone and in people who do not); and (ii) a complete and accurate description of the procedures to be followed (i.e., a description of the chemicals to which subjects were to be exposed, the level of chemical exposure expected, and the known maximal levels of safe exposure at that time). Furthermore, OHRP finds that the Study II informed consent for one group of non-exposed control subjects misrepresented the chemical to which subjects were to be exposed as "a natural extract from the balsam tree . . . . used in aromatherapy to produce positive effects on both physical and mental health."

(b) Section 46.116(a)(2): An adequate description of the reasonably foreseeable risks and discomforts. In specific, the informed consent documents included no description of any potential risks or discomforts.

(c) Section 46.116(a)(3): An adequate description of any benefits to the subject or others that may reasonably be expected from the research.

Action 1 - Required: By September 29, 2000, the University of Pennsylvania and Monell Chemical Senses Center must submit to OHRP satisfactory corrective action plans to address the above cited noncompliance and prevent recurrence of similar incidents.

Action 2 - Required: The University of Pennsylvania IRB, with input from the research investigators, must develop and forward to OHRP a plan, including both the means and the content, for contacting the subjects who participated in the above referenced research and adequately informing them of the nature of the research and its potential risks. Please submit a written report regarding the IRB's determinations and plan for this matter and the documentation underlying these determinations, including relevant IRB minutes and the proposed text for debriefing the subjects. Please forward your report so that OHRP receives it no later than September 29, 2000.

Action 3 - Required: By September 29, 2000, the University of Pennsylvania and Monell Chemical Senses Center must provide OHPR with a list of any similar research protocols currently being conducted at your institutions. For each protocol listed, please provide the following (a) protocol title, principal investigator name, IRB project number, any applicable HHS award number, the date of initial review, and the date of the most recent continuing review; (b) a detailed description of the research; and (c) a copy of the current IRB-approved informed consent documents.

Based upon its review of your report, OHRP makes the following determinations regarding the University of Pennsylvania's system for protecting human subjects:

(5) HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each *application* for research has been reviewed and approved by the IRB.

OHRP finds that the IRB Guidelines for the Preparation of Protocols for Review instruct investigators to "not provide complete copies of grant applications as much of the information is not required for review" is in contravention of the HHS regulatory requirement at 45 CFR 46.103(f).

Action 4 - Required: By September 29, 2000 the University of Pennsylvania must provide written assurance to OHRP that the IRB has received and reviewed a copy of the complete grant application for any active Federally supported research projects involving human subjects (enclosed for your reference is a copy of OHRP's guidance regarding review of grant applications).

(6) OHRP finds that the written IRB policies and procedures provided with your report fail to adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

(a) The procedures which the IRB will follow (i) for conducting its 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.

(b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, Department or Agency head, and OHRP 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.

Action 5 - Required: By September 29, 2000, the University of Pennsylvania must provide OHRP with revised written IRB policies and procedures that include an adequate description of all procedures required by HHS regulations at 45 CFR 46.103(b)(4) and (5).

OHRP has the following additional concerns and questions regarding the above referenced research project:

(7) The IRB records provided to OHRP indicate that (i) in October 1995, the research protocol underwent continuing review and was re-approved for another one year period; and (ii) in a memorandum dated January 5, 1998, Ms. Clark notified the principal investigator that the study was "administratively" terminated.

(a) What is the explanation for the delay between the expiration of IRB approval in October 1996 and the notification to the principle investigator that the research had been administratively terminated and no further research involving subjects could be conducted?

(b) Were any research activities involving human subjects conducted under this research protocol after October 1996? If so, please provide a complete description of these research activities, including the number of subjects enrolled, the date of enrollment, and any publications that resulted.

(c) What procedures are currently being utilized by the University of Pennsylvania IRBs to ensure that all nonexempt research involving human subjects undergoes substantive and meaningful continuing review at least annually?

(8) The IRB records provided to OHRP indicate that for Study II ("Evaluating the Perceptual Response to Acetone: Judgements of Intensity and Irritation") acetone-exposed factory worker subjects were not given any financial remuneration, whereas other subject groups were paid $12.00 for participating in the research. OHRP is concerned that this difference in compensating subjects may violate the principle of justice, one of the three basic ethical principles presented in the Belmont Report upon which the HHS regulations are premised, and embraced by the University of Pennsylvania in its MPA. Please respond.

(9) For HHS award number R01DC00298, please provide a copy of the applicable OPRR-approved Single Project Assurance document for the Monell Chemical Senses Center.

Please provide your response to items (7)-(9) above no later than September 29, 2000.

Please feel free to contact me if you have any questions regarding this matter.

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,

Sanford Leikin, M.D.
Compliance Oversight Coordinator
Division of Human Subject Protections

Enclosure: Memorandum on IRB Review of Applications for HHS Support.

cc: Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. J. Thomas Puglisi, OHRP
Dr. Cliff Scharke, OHRP
Dr. Katherine Duncan, OHRP
Ms. Freda Yoder, OHRP
Dr. Joseph Sherwin, Director of Regulatory Affairs, University of Pennsylvania
Dr. Nicholas Kefalides, IRB Chair, University of Pennsylvania
Commissioner, Food and Drug Administration, HF-1
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. John Mather, VA