DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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August 9, 2007

Peter J. Deckers, M.D.
Executive Vice President for Heath Affairs
University of Connecticut Health Center
263 Farmington Avenue
Farmington, CT 06030-3826

RE: Human Research Subject Protections Under Federalwide Assurance FWA-6064

Research Project:	Effects of Aripiprazole on Subjective and Physiological Responses to Alcohol
Principal Investigator:	Henry Kranzler, M.D.
Project Number:	GCRC #536 (MO1 RR06192); IRB # 04-108
Research Project:	Targeted Naltrexone for Problem Drinkers
Principal Investigator:	Henry Kranzler, M.D.
Project Number:	GCRC #495; IRB 03-107
Research Project:	Sertraline Pharmacotherapy for Alcoholism Subtypes
Principal Investigator:	Henry Kranzler, M.D.
Project Number:	GCRC #531; IRB 03-225

Dear Dr. Deckers:

The Office for Human Research Protections (OHRP) has reviewed University of Connecticut Health Center's (UCHC) June 1, 2006 letter, June 8, 2006 email, and August 25, 2006 letter in response to OHRP's May 3, 2006 letter regarding research conducted under the above-referenced research projects.

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

(1) It was alleged that the UCHC institutional review board (IRB) failed to ensure that risks to subjects were minimized as required by Department of Health and Human Service (HHS) regulations at 45 CFR 46.111(a)(1). In particular, it was alleged that

the principal investigator and research staff for the study, Effects of Aripiprazole on Subjective and Physiological Responses to Alcohol (IRB 04-108), were improperly trained to conduct the research. According to the complaint, the principal investigator for IRB 04-108 is a post-doctoral fellow with no medical training. (Notwithstanding the complainant's belief that the principal investigator was a post-doctoral fellow, OHRP acknowledges that Dr. Kranzler has served as principal investigator on this project since the time of initial study approval.) In addition, the complainant alleged that a research staff member involved with IRB 04-108 conducted medical procedures that she was not qualified to conduct, e.g., physical examinations, interpretation of lab results, evaluating subjects after study sessions, and discharging subjects when they are "safe" to go home after the alcohol challenge.

In response to this allegation, UCHC provided the following:

> "Our investigation found no evidence to support this allegation. … To date, there have been 37 subjects enrolled in the study. Based on a discussion with Dr. Kranzler, Dr. Pierucci-Lagha's involvement in the study consists of having participated in the writing of the protocol and in submitting the regulatory work to the IRB. A review of each of the 37 subject charts provided no evidence that Dr. Pierucci-Lagha's involvement represents work in any medical capacity or that Ms. Nellissery had any involvement whatsoever in the study."

Based on the information received by OHRP, OHRP makes no finding regarding the above allegation.

(2) It was alleged that a research staff member performed procedures that she is not qualified to conduct in the following research projects in which Dr. Henry Kranzler is the principal investigator: Targeted Naltrexone for Problem Drinkers (IRB 03-107) and Sertraline Pharmacotherapy for Alcoholism Subtypes (IRB 03-225).

UCHC provided the following in response to this allegation:

> "Our investigation, which consisted of a review of every subject chart for both studies and interviews with the PI, has substantiated this allegation as related to study #495 [IRB 03-107], but not for study #531 [IRB 03-225]. Our investigation also revealed that corrective measures were implemented when the problem was recognized in the Fall of 2003. … Nearly all of Ms. Neillissery's involvement occurred within GCRC study #495 [IRB 03-107], as summarized in Appendix A

Based on the information received by OHRP, OHRP finds that the UCHC IRB failed to ensure that risks to subjects were minimized as required by HHS regulations at 45 CFR 46.111(a)(1) when it approved research that involved

research team members who were unqualified to conduct the research-related clinical procedures outlined in the protocol.

Corrective Action: OHRP acknowledges that one of the corrective measures UCHC implemented in the Fall of 2003 consisted of stopping postdoctoral fellows from conducting clinical procedures in a research context across all studies. OHRP also acknowledges that UCHC has revised its IRB review process to correct this problem. Specifically, "the UCHC IRB **now** (emphasis added) receives a monthly report from the Medical Staff Office that reflects all individuals credentialed at UCHC. Names listed on the IRB application are cross referenced with this list, as appropriate to the role listed on the application. The IRB application **now** (emphasis added) solicits information pertaining to the earned degrees, licensures, and functions within a study for each of the co-investigators named on the application." OHRP finds this corrective action to be adequate and appropriate under UCHC's FWA.

(3) HHS regulations at 45 CFR 46.116(a) delineate specific elements required for informed consent. OHRP reviewed the UCHC IRB-approved consent forms containing DNA testing language for IRB 03-107 and finds that all of the IRB-approved consent forms failed to include the following informed consent elements specific to DNA testing as required by 45 CFR 46.116(a):

(a) Section 46.116(a)(1): an explanation of the purposes of the DNA testing aspects of the research and a complete description of the DNA tests to be run on the collected blood.

(b) Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts to the subjects regarding DNA testing.

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

(d) Section 46.116(a)(5): A statement describing the extent, if any, to which confidentiality of records/samples identifying the subject will be maintained.

Required Action: Please provide OHRP with a corrective action plan outlining how UCHC will ensure that the UCHC IRB only approves consent forms that contain the elements outlined in HHS regulations at 45 CFR 46.116.

OHRP has the following questions and concerns regarding the above-referenced research, as well as UCHC's human subject protection program:

(3) [Redacted]

[Redacted]

(4) [Redacted]

[Redacted]

[Redacted]

(5) [Redacted]

[Redacted]

(6) [Redacted]

[Redacted]

[Redacted]

(8) [Redacted]

[Redacted]

OHRP has the following questions and concerns regarding the study, Effects of Aripiprazole on Subjective and Physiological Responses to Alcohol (IRB 04-108):

(9) [Redacted]

(10) [Redacted]

OHRP has the following questions and concerns regarding the study, Targeted Naltrexone for Problem Drinkers (IRB 03-107):

(11) [Redacted]

(12) [Redacted]

[Redacted]

(13) [Redacted]

(14) [Redacted]

[Redacted]

(15) [Redacted]

[Redacted]

OHRP has the following questions and concerns regarding the study Sertraline Pharmacotherapy for Alcoholism Subtypes (IRB 03-225):

(16) [Redacted]

[Redacted]

(17) [Redacted]

(18) [Redacted]

(19) [Redacted]

(20) [Redacted]

OHRP has the following questions and concerns regarding UCHC's Human Subjects Protection Office *IRB General Information and Standard Operating Procedures Document*, which was last revised on March 31, 2006[1]:

(21) [Redacted]

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(22) [Redacted]

(23) [Redacted]

[1] OHRP did not review UCHC's Investigators Guide for Human Subject Research because it appears as if all the information contained in that document, which was last revised November 23, 2004, has been addressed in the Human Subjects Protection Office IRB General Information and Standard Operating Procedures Document, which is a more recent document than the Investigator's Guide.

[Redacted]

(24) [Redacted]

At this time, OHRP provides the following guidance regarding UCHC's Human Subjects Protection Office *IRB General Information and Standard Operating Procedures Document*:

(25) *Minutes* Section. It is not clear that UCHC IRB meeting minutes are required to contain a written summary of the discussion of controverted issues and their resolution, as required by HHS regulations at 45 CFR 46.115(a)(2). OHRP notes that the minutes appear to only require "findings of the Board (basis for contingencies for approval or reasons for denial of approval)," but not a summary of the discussion of any controverted issues.

(26) *All Submissions Reviewed by the Convened IRB* Section. OHRP notes that UCHC introduces the term "secondary reviewer" in the forth full paragraph of this sub-section. OHRP suggests defining the term and the responsibilities of the secondary reviewer.

(27) *Prisoners* Section. OHRP notes that the definition of a minor modification under this section differs from the definition of a minor modification under *Review of Modifications to Previously Approved Research by Expedited Procedures*, pg. 15.

At this time, OHRP provides the following guidance on UCHC's human subjects protections program:

(28) OHRP notes that the IRB approval memorandum is not complete in that it does not require the investigator to report all that is outlined in 45 CFR 46.103(a) and (b)(5).

(29) OHRP notes that many of the protocols or consent forms that were approved by UCHC for IRB 03-107 did not contain version dates or other identifying information. As a result, it was difficult for OHRP to identify which protocols and/or consent forms were associated with a particular UCHC approval memorandum. Given this

difficulty, and in an attempt to avoid confusion by IRB members, IRB staff, and investigators regarding which version of a document had been approved by the UCHC IRB, OHRP recommends that the UCHC IRB require that investigators include version dates (or other identifying information) on all protocols, consent forms, or other documents requiring IRB approval. Implementation of this practice will help avoid such confusion in the future.

Please submit your response to the findings, questions and concerns noted above so that OHRP receives them no later than October 5, 2007. If during your review you identify additional areas of noncompliance with HHS regulations for the protection of human subjects, please provide corrective action plans that have been or will be implemented to address the noncompliance.

OHRP appreciates your institution's continued commitment to the protection of human research subjects. Do not hesitate to contact OHRP if you should have any questions regarding this matter.

Sincerely,

Lisa A. Rooney, J.D.
Compliance Oversight Coordinator

cc: Dr. Richard H. Simon, Director, Human Subjects Protection Office, UCHC
Ms. Judi Kulko, IRB Chair, UCHC IRB #1
Dr. Ronald M. Kadden, IRB Chair, UCHC IRB #2
Dr. Mahlon Hale, IRB Chair, UCHC IRB#1 - Panel 03
Dr. Nancy R. Rodrigues, IRB Chair, University of Connecticut, Storrs IRB #1
Dr. Amira Pierucci-Lagha, UCHC
Dr. Henry Kranzler, UCHC
Dr. Sam Shekar, OER, NIH
Dr. Andrew C. von Eschenbach, Commissioner, FDA
RADM Linda Tollefson, FDA
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP
Dr. Kristina Borror, OHRP
Ms. Cathy Slatinshek, OHRP
Ms. Kelley Booher, OHRP
Mr. Barry Bowman, OHRP