DEPARTMENT OF HEALTH & HUMAN SERVICES

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April 28, 2008

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:

Thank you for your March 28, 2008 letter in response to our March 3, 2008 letter regarding research conducted under the research project entitled "Targeted Naltrexone for Problem Drinkers."

In our letter dated December 17, 2007, we raised a question and concern regarding the use of a single informed consent document for IRB 03-107 without an "opt out" option for subjects, which may have failed to minimize the possibility of coercion or undue influence. In a letter dated January 28, 2008, UCHC provided the following response to this question and concern:

> "Prior to the initiation of these studies, the study protocols have specified that the genetic analysis is one of the primary study aims and therefore does not constitute

> a sub-study (Attachments 3 & 4). In each case, when the IRB requested a separate consent form, the PI made this argument and the IRB agreed with this assessment. Because the genetic analysis is considered part of the main study, the IRB did not request a separate consent form or an "opt out" option."

In our letter dated March 3, 2008, we informed UCHC that we reviewed the above-referenced attachments and noted that Attachment 3 contained excerpts from the protocol for study IRB 03-107, dated January 5, 2003; excerpts that were limited to the exploration of genetic predictors of Naltrexone (NTX) treatment response. In that March 3, 2008 letter we noted that none of the excerpts discuss the use of collected DNA for unspecified population genetic studies and studies of unspecified non-pathological traits - uses that were first proposed by the investigator on June 23, 2005 via a modification request. In specific, we noted that the June 23, 2005 modification proposed to expand the IRB approved analysis of DNA to cover other potential genetic moderators of the response to naltrexone and use the DNA collected in this study to examine the risk of alcohol dependence and related disorders, as well as population genetic studies and studies of non-pathological traits. This modification expanded the initial IRB approved use of collected DNA beyond the exploration of genetic predictors of NTX treatment to cover unspecified population genetic studies and studies of non-pathological traits response – studies which may or may not be related to one of the specified aims of the study.

With this as background, in our letter dated March 3, 2008, we remained concerned as to whether the use of a single informed consent document for IRB 03-107, without an "opt out" option for subjects, is consistent with the regulatory requirement of 45 CFR 46.116 to ensure that consent is sought only under circumstances that minimize the possibility of coercion or undue influence. As such, we asked UCHC to explain how the failure to allow subjects to "opt out" of the unspecified population genetic and non-pathological traits response sub-studies, even if they wish to participate in the intervention study, is in compliance with this regulatory provision.

In your letter dated March 28, 2008, UCHC provided the following information:

> "OHRP correctly states that the aim of 03-107 related to genetics was limited to the pharmacogenetic analyses. The substudies (use of samples for "other purposes") were not aims of the intervention study initially, but were added midway through its completion. At that time (June 2005), the PI and the IRB did not adequately consider as coercive or as creating undue influence the failure to allow subjects to "opt out" of prospectively providing DNA for analysis of the risk of alcohol dependence, or of population genetics or non-pathological traits. The IRB did not approve the use of existing samples for analysis of the risk of alcohol dependence, or of population genetics or non-pathological traits, which was also proposed in the June modification. In November of 2005 the IRB approved a modification to allow for the use of existing samples in the expanded analysis provided that the samples were stripped of all links to the donor prior to the analysis occurring.
>
> In February 2008 the IRB approved a modification request to de-identify all

> samples (including those that had been prospectively obtained after approval of the June 2005 modification) to allow them to be used in the expanded analysis. In summary, enrollment in the study has been completed, IRB approval has been obtained for a specific plan to de-identify the samples and associated data, and implementation of the plan is currently underway. Thus, all samples obtained during the study will be rendered anonymous before they will be included in additional studies of the risk of alcohol dependence, or of population genetics or non-pathological traits."

We acknowledge that UCHS has taken the following actions in response to the concern expressed in our March 3, 2008 letter:

(1) The topic of minimizing the possibility of undue influence and/or coercion during the consent process was discussed at the UCHC Human Subjects Protection Office (HSPO) Executive Council meeting held on March 26, 2008.

(2) IRB Chairs and IRB coordinators were instructed to pay attention to optional study components (i.e., sub-studies) and the need for an "opt-out" provision.

(3) Effective April 10, 2008, the IRB will require a separate consent form for sub-studies associated with new applications. The IRB may continue to accept opt-out provisions incorporated into a main consent form for studies that are already approved. However, if the IRB determines that the sub-study is not adequately addressed within the main consent the IRB will require that a separate consent form be developed and that subjects be re-consented.

(4) IRB Chairs will discuss the topic with their IRB panels at the IRB meetings convened in April 2008.

(5) The research community will be reminded about the need for providing opt-out options for optional sub-studies.

(6) The informed consent template and checklist have been revised to aid the research community and reviewers in ensuring that sub-study opt-out requirements are fulfilled.

These actions adequately address our concern. As a result, there should be no need for our further involvement in this matter.

We appreciate your institution's continued commitment to the protection of human research subjects. Please contact me 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 chairperson, UCHC IRB #1
Dr. Ronald M. Kadden, IRB chairperson, UCHC IRB #2
Dr. Mahlon Hale, IRB chairperson, UCHC IRB#1 - Panel 03
Dr. Nancy R. Rodrigues, IRB chairperson, University of Connecticut, Storrs IRB #1
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Dr. Andrew C. von Eschenbach, Commissioner, FDA
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