DEPARTMENT OF HEALTH & HUMAN SERVICES

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RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1431

Dear Drs. Tsuang and Grinspoon:

The Office for Human Research Protections (OHRP) has reviewed your report of July 5, 2001 regarding the research conducted at the Massachusetts Mental Health Center (MMHC). These reports contained information about the following research projects:

Research Project: Genetic Linkage Study of Schizophrenia
Principal Investigator: Dr. Ming T. Tsuang
HHS Project Number: R01 MH59624
B&WH Project Number: 099802

Research Project: Molecular Genetics of Heroin Dependence
Principal Investigator: Dr. Ming T. Tsuang
HHS Project Number: R01 DA12846

B&WH Project Number: 209901

Based upon its review, OHRP makes the following determinations regarding the above-referenced research projects.

A. OHRP Determinations Regarding Project Number R01 MH59624

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.111(b) require that in order to approve research the Institutional Review Board (IRB) ensure that additional safeguards have been included in research to protect the rights and welfare of vulnerable subjects. OHRP finds that MMHC IRB records reveal no evidence that the MMHC IRB considered such additional safeguards for this project, which appears to have involved vulnerable individuals who had potentially impaired capacity to consent and may have been economically and educationally disadvantaged.

B. OHRP Determinations Regarding Project Number R01 DA12846

(2) OHRP again finds that MMHC IRB records reveal no evidence that the MMHC IRB considered additional safeguards for this project, which likely involves vulnerable individuals with potentially impaired capacity to consent and may be economically and educationally disadvantaged.

Action 1-- Required: Please provide OHRP with a corrective action plan to ensure that considerations of additional safeguards to protect the rights and welfare of vulnerable subjects take place during MMHC IRB review and are documented in MMHC IRB records. OHRP acknowledges that MMHC has revised its policies and procedures to address one safeguard (review of capacity assessment plans).

Action 2-- Required: Please also provide specific documentation of the local investigators' procedure for determining subject competency, as requested by the MMHC IRB for R01 DA12846.

(3) OHRP finds that when reviewing this protocol application, the MMHC IRB lacked sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. In particular, OHRP notes the following:

(a) According to the IRB-approved protocol, information was to be collected from the subjects by a variety of methods, including a "structured interview." The MMHC IRB did not review and approve the content of the Temperament and Character Inventory.

(b) The consent document supplied by Dr. Tsuang in his July 17, 2000 response to NIDA (Appendix C) was different from the informed consent document approved by the MMHC IRB, and from the one submitted to OHRP with the Single Project

Assurance (SPA) for the Yunnan Institute for Drug Abuse (YIDA).

Furthermore, OHRP remains concerned that the MMHC IRB noted several major concerns with the project on March 18, 1999, such as concerns for newly identified heroin users and confusion regarding future commercial uses of samples, but approved the protocol "subject to the Primary Reviewer's approval of the above clarifications and modifications." This was apparently done by expedited approval, and there is no evidence that the findings were reported to the MMHC IRB.

Action 3– Required: OHRP acknowledges that the MMHC IRB is reviewing this instrument as part of its continuing review of this study and has reviewed the current informed consent document and has required additional changes. Please provide the revised informed consent document when it is approved by the MMHC and YIDA IRBs (Chinese and English translations). In addition, please provide OHRP with a satisfactory corrective action plan to ensure that the MMHC IRB receives and reviews sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111.

(4) OHRP finds that the informed consent document that was used for the research failed to adequately address the following element required by HHS regulations at 45 CFR 46.116(a)(1): a complete description of the procedures to be followed, and identification of any procedures which are experimental (i.e., the consent does not clearly reflect the study's current procedures, such as explicit permission to contact other family members, separate language for subjects only providing a blood sample, and a statement that information a subject may disclose about family members' substance use will not be recorded).

Action 4– Required: OHRP acknowledges that the committee has asked that new subjects not be enrolled until a revised informed consent document is approved by the committee. Please provide OHRP with a plan to reconsent those subjects who have already signed the old informed consent document. Enrollment of new subjects and research interactions or interventions with already enrolled subjects may not resume until OHRP verifies that a satisfactory corrective action plan has been development by the MMHC to address the above finding.

(5) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. OHRP finds that the MMHC IRB failed to conduct continuing review of research at least once per year for this project. The protocol was approved initially on 3/18/99. The first continuing review did not occur until 5/25/00.

Corrective Action: OHRP acknowledges that the MMHC IRB Procedure Manual will be

clarified to reflect that the date of the next periodic review is calculated from the date of the committee's initial review, or the most recent periodic review. This corrective action adequately addresses this finding and is appropriate under the MMHC Multiple Project Assurance (MPA).

C. OHRP Determinations Regarding General Human Subjects Protections at MMHC

(6) HHS regulations at 45 CFR 46.107(a) require that the IRB membership be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. OHRP finds that the MMHC IRB did not have the background and expertise to review the above-referenced research based on its failure to include members with sufficient understanding of the cultural conditions, including the social, economic, and political status, of the subject population.

Action 5– Required: OHRP acknowledges that the MMHC IRB has initiated a discussion of local conditions and research review procedures with the YIDA IRB. Nevertheless, OHRP requires that the MMHC provide additional corrective action plans to ensure that the MMHC IRB has sufficient experience and expertise to consider the cultural conditions of the subject population.

(7) Continuing IRB review of research must be substantive and meaningful. OHRP finds that continuing review of research by the MMHC IRB may not have been substantive and meaningful. In specific, the MMHC "Certificate of Continuing Surveillance" does not elicit sufficient information from investigators for making determinations under 45 CFR 46.111. For example, the "Certificate of Continuing Surveillance" does not include information on withdrawal of subjects, complaints regarding research, or summary of recent literature, nor does it appear to require inclusion of current informed consent documents.

Corrective Action: OHRP acknowledges that the Certificate of Continuing Surveillance has been modified to ensure this information is solicited and taken into account in every continuing review. This corrective action adequately addresses this finding and is appropriate under the MMHC MPA.

(8) OHRP finds that the institution does not have written IRB policies and procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

> (i) The procedures which the IRB will follow 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.

(ii) 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.

(iii) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and Department or Agency head 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. The Procedures Manual does not mention a requirement for reporting such events to OHRP.

(9) OHRP has the following guidance regarding the Procedure Manual of the MMHC Human Studies Committee:

(a) HHS regulations at 45 CFR 46.116(a)(8) require that the informed consent documents reviewed and approved by the IRB include, among other things, the following: A statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. The manual states that informed consent documents should include a "statement of the subject's right to withdraw from the study at any time, without jeopardizing future access to standard clinical care." There could be loss of other benefits besides "standard clinical care."

(b) The Manual states that "[c]hanges which, in the judgement of the committee chair, do not substantially affect subject safety or the balance of risk and benefit in a study may be approved by expedited review," but HHS regulations at 45 CFR 46.110(b)(2) state only that "minor changes" may be reviewed in an expedited manner. Some major changes may not "substantially affect safety or the balance of risk and benefit" and would not be eligible for expedited review.

(c) The Manual states "[i]n special situations, the committee may require periodic review and reapproval more frequently than once a year" but does not note what those situations are or how this is determined.

(d) The Manual does not include the consideration of additional protections for vulnerable subjects in listed "review criteria."

Corrective Action: OHRP acknowledges that the Procedure Manual of the MMHC Human Studies Committee has been revised to address many of these findings. OHRP notes that the additional protections mentioned in the Procedure Manual only refer to capacity assessment. OHRP recommends other protections be considered.

(10) HHS regulations at 45 CFR 46.108 require that, except when an expedited review procedure is used, the IRB review proposed research at convened meetings at which a majority of the members of the IRB are present. OHRP finds that the MMHC IRB failed to meet this requirement for its August 24, 2000 meeting. At that time the MMHC IRB had 13 members but only 5 attended this meeting.

Corrective Action: OHRP acknowledges that the MMHC IRB will re-review the protocols receiving continuing review approved at this meeting. This corrective action adequately addresses this finding and is appropriate under the MMHC MPA.

OHRP has the following additional concerns and questions.

(11) OHRP notes again that while a certificate of confidentiality was obtained for R01 MH59624, such a certificate cannot be legally enforced outside the U.S. OHRP is concerned that the receipt of a certificate of confidentiality for protocol R01 MH59624 is listed in the informed consent document for this project as strengthening the protection of subject's privacy. Subjects should be informed that this certificate is provided by the United States Federal government and cannot be legally enforced outside the U.S.

(12) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects.

(a) OHRP is still concerned that the following protocol change was implemented without MMHC IRB approval: although Millennium Pharmaceuticals was listed in the R01 MH59624-01 protocol as the entity performing the genome scan, the Center for Inherited Disease Research (CIDR) was the organization that was eventually chosen for this task. OHRP is unable to locate documentation that the MMHC IRB chair was informed of this use of CIDR instead of Millennium in 1999, as your July 5, 2001 response indicated. Please provide documentation of this communication.

(b) In his July 17, 2000 response to NIDA, Dr. Tsuang also suggested that concerns

regarding the identification of new addicts unknown to the registry could be addressed by modifying "...the [R01 DA12846] protocol to only collect blood samples from family members not in the registry." Your July 5, 2001 response indicated that this change was communicated to the MMHC IRB through letters exchanged with NIDA and periodic discussions. Please provide documentation of MMHC IRB approval of this change.

(c) In a September 1, 1999 letter to NIDA, Dr. Tsuang stated that subjects for protocol R01 DA12846 will be contacted for the study by the following procedures suggested by OPRR:

> "[P]sychiatrists or case managers will determine who among their case load might fulfill our criteria for inclusion, including the presence of a sibling who is an addict. They will then contact the potential volunteer and explain the facts of the research project. They will then ask the potential proband to either contact the ...PI or give written permission for the PI to contact him or her....we will ask the proband to talk with his or her family members and request that they either contact the PI or ....provide written permission to be contacted by the PI. The procedures described above will replace the contact procedures described in sections D.2.1 and D.2.2 of my grant proposal."

OHRP has still not been able to locate any evidence that the MMHC IRB was ever notified of these changes, or whether they were ever implemented.

Please respond. In your response, please provide documentation that these changes were reviewed and approved by the MMHC IRB and were implemented by the investigator.

Please submit to OHRP your response to the above determinations, questions and concerns no later than May 10, 2002. If upon further review of this matter you identify additional instances of non-compliance with the HHS regulations for protection of human subjects, please describe the corrective actions that have been or will be taken to address the noncompliance.

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

Sincerely,

Kristina C. Borror, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Ramon Greenberg, IRB Chair, MMHC
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Jonathan Pollock, NIDA
Dr. Michael A. Carome, OHRP
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Mr. George Gasparis, OHRP
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