DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 301-435-8072
FAX: 301-402-2071
E-mail:kborror@osophs.dhhs.gov

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Ming T. Tsuang, M.D., Ph.D.
Stanley Cobb Professor of Psychiatry
Head, Harvard Department of Psychiatry
Massachusetts Mental Health Center
74 Fenwood Road
Boston, MA 02115

Lester Grinspoon, M.D.
Executive Director
Massachusetts Mental Health Research Corporation
74 Fenwood Road
Boston, MA 02115

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 May 6, 2002 regarding the research conducted at the Massachusetts Mental Health Center (MMHC). This report 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

In its March 28, 2002 letter, OHRP required that MMHC develop satisfactory corrective action plans to address the following determinations made by OHRP regarding the above-referenced research projects.

(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) must ensure that additional safeguards have been included in the research to protect the rights and welfare of vulnerable subjects. OHRP found that MMHC IRB records revealed no evidence that the MMHC IRB considered such additional safeguards for Project Number R01 MH59624 or Project Number R01 DA12846, both of which appear to have involved vulnerable individuals who had potentially impaired capacity to consent and may have been economically and educationally disadvantaged.

Corrective Action: OHRP acknowledges that the MMHC IRB has modified its procedures 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 records. These include referencing subjects with cognitive impairment and subjects who are economically and educationally disadvantaged as potentially vulnerable, and requiring that the IRB consider safeguards for vulnerable populations such as the use of independent consent monitors, subject advocates, special educational techniques such as consent summaries and questionnaires, and consent waiting periods. In addition, the MMHC IRB has asked the investigators to develop a consent summary and questionnaire for the subjects still participating in project # MH59624 in Taiwan. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the MMHC MPA.

(2) OHRP found that when reviewing project number R01 DA12846, 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 noted 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 used during structured interviews.

(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).

Corrective Action: OHRP acknowledges that the MMHC IRB has reviewed this instrument and the current informed consent document and has required additional changes. In addition,

the MMHC IRB has revised the Procedure Manual to specify that the primary reviewer for a study receives and reviews all study materials and to state that all these materials must be available to other IRB members during the IRB's convened review. The MMHC IRB also has revised the Guidelines for Submission of Research Protocols to clearly describe the information and materials required by the IRB in order to review research, and has developed a checklist of review materials. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the MMHC MPA.

(3) OHRP found that the informed consent document that was used for project number R01 DA12846 failed to adequately address the following element required by HHS regulations at 45 CFR 46.116(a)(1): a description of the procedures to be followed, and identification of any procedures which are experimental (i.e., the consent did 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).

Corrective Action: OHRP acknowledges that enrollment of new subjects has been suspended, and that the subjects who had been enrolled with the previous informed consent document have been reconsented with the revised, IRB-approved informed consent document. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the MMHC MPA. Enrollment of new subjects and research interactions or interventions with already enrolled subjects may now resume.

(4) 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 found 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.

Corrective Action: OHRP acknowledges that the MMHC IRB has initiated a discussion of local conditions and research review procedures with the YIDA IRB. In addition, the MMHC IRB has met with a consultant who is a Chinese-American physician who has studied human subject protections in China, and who helped the MMHC IRB refine its strategy for continuing to monitor project number R01 DA12846. In addition, the MMHC IRB has asked the principal investigator to provide a consent monitoring plan that includes direct contact with investigators and subjects at the YIDA study site. The Procedure Manual now includes a reminder regarding situations in which the IRB should consider consulting with other experts, including ascertaining the local research context of remote study sites. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the MMHC MPA.

(5) OHRP found that MMHC did 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): 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, as required by 45 CFR 46.103(a).

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 Procedure Manual apparently still lacks the procedures for ensuring prompt reporting to OHRP of any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB. The MMHC IRB Procedure Manual should be revised to include such procedures.

In its March 28, 2002 letter, OHRP had the following additional concerns and questions.

(6) OHRP noted that while a certificate of confidentiality was obtained for R01 MH59624, such a certificate cannot be legally enforced outside the United States. OHRP expressed concern 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 United States.

Corrective Action: OHRP acknowledges that the MMHC IRB has asked the investigators for this modification to the informed consent document for subjects in Taiwan. OHRP finds that this corrective action adequately addresses the above concern and is appropriate under the MMHC MPA.

(7) 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 already has been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP expressed concern that several protocol changes were implemented without MMHC IRB approval.

Corrective Action: OHRP acknowledges MMHC's statements that these changes were reviewed and approved by the MMHC IRB or by expedited review by the IRB chair and that all current procedures are now integrated in a revised protocol that was approved by the IRB during its April 25, 2002 continuing review. OHRP also acknowledges that the Procedure Manual now clearly states that the committee's approval of amendments, by convened or

expedited review, will be conveyed in writing. OHRP finds that this corrective action adequately addresses the above concern and is appropriate under the MMHC MPA.

As a result, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

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. Jonathan Pollock, NIDA
Dr. Michael A. Carome, OHRP
Dr. Melody H. Lin, OHRP
Mr. George Gasparis, OHRP
Ms. Yvonne Higgins, OHRP
Mr. Barry Bowman, OHRP