DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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January 8, 2002

Daniel R. Masys, M.D.
Institutional Official for Human Subjects
University of California, San Diego
9500 Gilman Drive
La Jolla, CA 92093-0052

RE: Human Research Protections Under Multiple Project Assurance (MPA) M-1274

Research Project: Safety and Tolerability of Rapidly Titrated Risperidone
Related Publication: Safety and Tolerability of Rapidly Escalating Dose-Loading Regimen for Risperidone, Feifel, D., et al, Journal of Clinical Psychiatry 2000; 61: 909-911.
Principal Investigator: David Feifel, M.D.
Protocol Number: 000827X

Dear Dr. Masys:

The Office for Human Research Protections (OHRP) has reviewed your November 8, 2001 report regarding the above referenced research conducted at the University of California, San Diego (UCSD) that was submitted in response to OHRP's October 4, 2001 letter.

Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(a) require that the Institutional Review Board (IRB) review and approve all human subject research, unless the research is exempt under HHS regulations at 45 CFR 46.101(b). OHRP had expressed a concern that subjects were prospectively enrolled in this research project without IRB approval.

OHRP acknowledges UCSD's statement that they have found no evidence that a systematic prospective clinical trail was performed, but that a retrospective chart review was conducted with IRB review and approval.

OHRP recognizes that the distinction between research and clinical practice is often blurred and the application of innovative therapy in the management of patients does not necessarily make such

activities research. Of note, the Belmont Report states the following regarding the boundaries between research and clinical practice:

> (1) "The distinction between research and practice is blurred partly because both often occur together."
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> (2) "Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects."

UCSD may wish to consider establishing a committee to review independently proposed innovative therapeutic interventions in order to determine in advance whether a particular intervention involves human subject research and should be conducted under an IRB- approved protocol.

OHRP also acknowledges that UCSD has asked the principle investigator to retract the article because the publication is written in the style of a prospective trial and may cause some confusion, and has launched an inquiry into this matter. OHRP looks forward to receiving the report of this inquiry when it becomes available.

Based on its review of UCSD's November 8, 2001 report, OHRP makes the following determinations:

> (1) HHS regulations at 45 CFR 46.116(d) require that the IRB find and document four specific criteria when approving waiver or alteration of some or all of the required elements of informed consent. OHRP finds that when the UCSD IRB approved the above-referenced research under an expedited review procedure, it approved a waiver of informed consent but failed to make and document the required findings under 45 CFR 46.116(d).
>
> (2) OHRP finds that the UCSD IRB frequently approves research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. The IRB appears to approve protocols pending receipt of revised applications, modifications in informed consent documents, and clarification of experimental procedures. Such documents are then reviewed by "the IRB chair or her/his designee(s)" rather than going to the full IRB. OHRP noted several instances in which major clarifications/revisions directly relevant to the determinations that the IRB must make under HHS regulations at 45 CFR 46.111 were requested without requiring subsequent review by the convened IRB (see, for example, projects #011072, #011083, #011085, #011087, #011089, and 011092 reviewed on October 4, 2001; projects #011021 reviewed on September 20, 2001; projects #010574, #010947, #010953, #010968, and #010972 reviewed on September 6, 2001).
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> OHRP recommends the following guidelines in such cases: (a) When the convened IRB requests **substantive clarifications, protocol modifications, or informed consent document revisions**, IRB approval of the proposed research should be **deferred**, pending

subsequent review by the convened IRB of responsive material. (b) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator should the IRB Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure.

Required Action: By February 11, 2002, please provide OHRP with corrective actions to address findings (1)and (2) above. In addition, please provide a copy of the completed form, if any, that the principle investigator used to obtain inpatient medical records for the restrospective chart review for the research described in the above-referenced journal article. OHRP previously requested this form in its October 4, 2001 letter, but was only provided with blank forms. Please clarify if the principle investigator requested the medical records through this mechanism, and if not, why not.

Please submit to OHRP your response to the above determinations no later than February 11, 2002. **Please note OHRP's new address.** If upon further review of the concerns and questions, UCSD identifies instances of non-compliance with the HHS regulations for protection of human subjects, please include detailed corrective action plans to address the noncompliance.

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,

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

cc: Ms. Lucille Pearson, UCSD
Mr. Gary Rossio, San Diego VA Medical Center
Dr. J. Allen McCutchan, UCSD IRB Chair
Dr. Richard Kornbluth, UCSD IRB Chair
Dr. John Mather, ORCA, Dept of Veterans Affairs
Dr.Greg Koski, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Jeff Cohen, OHRP
Mr. George Gasparis, OHRP
Dr. Kamal Mittal, OHRP