DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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April 30, 2001

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Thomas P. Pishioneri
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Glenn D. Warden, M.D.
Chief of Staff
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3229 Burnet Avenue
Cincinnati, OH 45229

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1138

Research Project: Olanzapine vs. Placebo in the Treatment of Bipolor Disorder, Manic or Mixed
Principal Investigator: Susan McElroy, MD
UC Study Number: 97-12-9-3

Dear Dr. Harrison, Mr. Cohen, Mr. Pishioneri and Dr. Warden:

The Office for Human Research Protections (OHRP) has reviewed your report of March 27, 2001, as well as all previously submitted reports, regarding the above referenced research conducted at the University of Cincinnati (UC).

Based upon its review, OHRP makes the following determinations.

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.116 require that the investigator seek consent only under circumstances that provide the prospective subject with sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. Given the complainant's self-report of her mental state at the time of admission to the UC University Hospital, as well as the description of her mental status in the records provided with UC's May 27, 1999 report, OHRP finds that the informed consent of the subject for the research was not sought under conditions that provided her with sufficient opportunity to consider whether or not to participate and that minimized the possibility of coercion or undue influence, as required by HHS regulations at 45 CFR 46.116.

(2) 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 subjects who are likely to be vulnerable to coercion or undue influence. Based upon its review of the IRB records provided with UC's May 27, 1999 report, OHRP finds that (i) the subjects of the proposed research included individuals who were likely to be vulnerable; and (ii) the IRB failed to ensure that adequate additional safeguards were included in the research.

(3) HHS regulations at 45 CFR 46.116(a)(4) require description of appropriate alternative procedures or courses of treatment that might be advantageous to the subject. OHRP finds that the informed consent documents reviewed and approved by the IRB for this project failed to include this element. Other treatments listed in the Alternatives do not make it clear that subjects can get the study drug, olanzapine, outside of the trial. Since olanzapine can be prescribed for bipolar disorder "off-label" it would have been appropriate to note in the informed consent document that subjects could receive the study drug, olanzapine, outside of this clinical trial. Including such a statement would not be unethical, nor would it imply that olanzapine is standard of care for bipolar disorder, as your March 27, 2001 letter stated it would.

Corrective Actions: OHRP acknowledges that this project is closed to enrollment. OHRP also acknowledges that since the IRB initially approved this research, UC implemented a number of corrective actions to ensure that additional safeguards are included for research involving vulnerable subjects. These include designating a physician not affiliated with the research to oversee the treatment of inpatients enrolled in psychiatric research protocols, establishment of a Community Advisory Committee to review all psychiatry studies involving more than minimal risk, and including on the IRB a close family member of an individual who has a severe psychiatric illness.

Recommended Action: OHRP recommends that the Community Advisory Committee review all psychiatry studies involving more than minimal risk as they come up for continuing review.

OHRP finds that the preceding corrective actions adequately address these findings and are appropriate under the UC Multiple Project Assurance. 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: Mr. Michael Walton, Medical Center Director, Chillicothe VAMC
Dr. Peter Frame, IRB Co-Chair, UC IRB-01/A
Dr. Frederick J. Samaha, MD, Chair, UC IRB-01/B
Dr. Margaret Miller, Chair, UC IRB-02XM
Ms. Carolyn West, UC IRB Administrator
Dr. Susan McElroy, UC
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