DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

FOR US POSTAL SERVICE DELIVERY:
Office for Human Research Protections
6100 Executive Boulevard, Suite 3B01
National Institutes of Health (MSC 7507)
Rockville, Maryland 20892-7507

FOR HAND DELIVERY OR EXPRESS MAIL:
Office for Human Research Protections
6100 Executive Boulevard, Suite 3B01
Rockville, Maryland 20852

Telephone: 301-402-5567
FAX: 301-402-2071
E-mail: mc2a@nih.gov

October 27, 2000

Darrell G. Kirch, M.D.
Dean, College of Medicine
Senior Vice President for Health Affairs
The Pennsylvania State University
500 University Drive
Hershey, Pennsylvania 17033-0850

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1027

Research Project: Brent J, McMartin K, Phillips S, *et al.* Fomepizole for the Treatment of Ethylene Glycol Poisoning. N Engl J Med 1999;340:832-8.
Related HHS Project number: FDR-001256-01
IRB-Approved Protocol Title: An Open-Label, Phase III Pivotal Trial of the Antidotal Efficacy and Pharmacokinetic Profile of Antizol (Fomepizole) for the Treatment of Ethylene Glycol Poisoning
IRB Protocol Number: 95-116

Dear Dr. Kirch:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed Dr. Kevin Gleeson's June 28, 1999 report regarding the above referenced research. OHRP apologizes for the delay in responding to Dr. Gleeson's report.

Dr. Gleeson's report was submitted in response to OPRR's May 10, 1999 letter which expressed concern that the informed consent procedures used to enroll subjects in the above referenced research failed to comply with the requirements of Department of Health and Human Service (HHS) regulations at 45 CFR 46.116.

Based upon its review of Dr. Gleeson's report, as well as relevant documents provided by other institutions involved in the conduct of the research, OHRP makes the following determinations regarding the above referenced research project:

(1) In accordance with the requirements of HHS regulations at 45 CFR 46.116, no investigator may involve a human subject in research unless one of the following conditions is met:

(a) The investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

(b) The institutional review board (IRB) has waived the requirement for informed consent in accordance with the requirements of (i) HHS regulations at 45 CFR 46.116(d); (ii) the Food and Drug Administration (FDA) regulations at 21 CFR 50.24 (copy enclosed) for research subject to regulations codified by the FDA; or (iii) the October 2, 1996 waiver of the applicability of the 45 CFR Part 46 requirement for obtaining and documenting informed consent that was approved by the Secretary, HHS, under HHS regulations at 45 CFR 46.101(i)(see enclosed OPRR Reports 97-01).

(c) The research only involves one or more of the exempt categories of research stipulated by HHS regulations at 45 CFR 46.101(b).

(2) OHRP finds that the Pennsylvania State University College of Medicine (PSUCM) IRB approved an informed consent procedure (i.e., the procedure under which "consent" could be obtained from two physicians uninvolved in the trial for subjects who were not lucid and for whom legally authorized representatives) that failed to comply with the above cited regulatory requirements. In specific, OHRP finds that:

(a) The research was not exempt under HHS regulations at 45 CFR 46.101(b).

(b) The research involved greater than minimal risk to the subjects and therefore would not have satisfied the requirement for waiver of informed consent at 45 CFR 46.116(d)(1).

(c) The research was subject to regulations codified by the FDA, but there is no evidence that the requirements for exception from informed consent for emergency research stipulated by FDA regulations at 21 CFR 50.24 were satisfied.

(3) Legally effective informed consent was not obtained for five subjects enrolled in this research by investigators at PSUCM.

(4) HHS regulations at 45 CFR 46.116 require that the information provided in the informed consent documents be in language understandable to the subject. OHRP is concerned that the informed consent document approved by the IRB for this study appeared to include complex language that would not be understandable to all subjects.

It is OHRP's understanding that this research project has been completed. Furthermore, OHRP acknowledges that since the above referenced research was initially approved by the IRB, PSUCM has implemented a number of corrective actions to ensure that the informed consent requirements stipulated by HHS regulations at 45 CFR 46.116 are satisfied for all research conducted by PSUCM, unless appropriately waived by the IRB. As a result, OHRP is closing its compliance oversight investigation of this matter.

At this time, OHRP provides the following additional guidance:

(5) OHRP recommends that PSUCM expand its IRB application form to ensure that the IRB receives sufficient information to make all of the determinations required for approval of research under HHS regulations at 45 CFR 46.111, as well as the additional determination required under 45 CFR Part 46, Subpart B, C, and D. For example, the IRB application should solicit additional information regarding (a) minimization of research risks; (b) subject recruitment and enrollment procedures; (c) provisions to protect the privacy of subjects and maintain the confidentiality of data; and (d) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable. Furthermore, for research proposing involvement of prisoners or children, investigators should be prompted to provide specific information justifying the inclusion of such subjects in order to satisfy the requirements of Subparts C and D, respectively.

(6) Continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see enclosed OPRR Reports 95-01). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

When conducting research under an expedited review procedure, the IRB Chair (or designated IRB member(s)) should receive and review all of the above referenced documentation.

(7) HHS regulations at 45 CFR 46.115(a)(2) require that the minutes of IRB meetings document the vote on all IRB actions including the number of members voting for, against, and abstaining. In order to document the continued existence of a quorum, OHRP strongly recommends that votes be recorded in the minutes using the following format: Total = 15; Vote: For-14, Opposed-0, Abstained-1 (NAME). Please note that recording votes as "unanimous" is not sufficient.

(8) Where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which alters or waives the requirements for informed consent [see 45 CFR 46.116(d)]; (b) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP strongly recommends that all required findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding.

(9) The IRB Policy and Procedures Manual should be expanded to include additional operational details for the following procedure, as required by HHS regulations at 45 CFR 46.103(b)(4)(ii):

> The procedures which the IRB follows for determining which projects require review more often than annually.

(10) Regarding the IRB Policy and Procedures Manual, page 28, the section entitled "Voting requirements," it appears that the IRB's Administrative Staff, which may include individuals who are not voting members of the IRB, may review and approve non-substantive changes to protocol informed consent documents that are stipulated by the IRB. Please note that any changes to the protocol or informed consent document required by the IRB as a condition for approval must be reviewed and approved either by the convened IRB when changes are substantive, or by the IRB Chair (or another voting member designated by the Chair) when the changes are specific and require simple concurrence by the principal investigator.

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,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

Enclosures: (1) 21 CFR 50.24
(2) OPRR Reports 97-01
(3) OPRR Reports 95-01

cc: Dr. Kevin Gleeson, Chairperson, IRB, PSUCM
Ms. Jean Elizabeth Vary, Research Compliance Coordinator, PSUCM
Dr. Keith K. Burkhart, PSUCM
Dr. J. Ward Donovan, PSUCM
Dr. Dayton T. Reardan, Vice President for Regulatory Affairs, Orphan Medical, Inc.
Dr. John Mather, Director, ORCA, Department of Veterans Affairs
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Ms. Mary Jo Zollo, FDA
Ms. Patricia Robuck, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. J. Thomas Puglisi, OHRP
Dr. Clifford C. Scharke, OHRP
Dr. Jeffrey M. Cohen, OHRP
Dr. Katherine Duncan, OHRP
Ms. Roslyn Edson, OHRP
Mr. Barry Bowman, OHRP