DEPARTMENT OF HEALTH & HUMAN SERVICES

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October 27, 2000

John McDonald, M.D.
Acting Vice Chancellor and Dean
School of Medicine in Shreveport
Louisiana State University Medical Center
1501 Kings Highway
P.O. Box 33932
Shreveport, LA 71130-3932

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1131

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: 95-488

Dear Dr. McDonald:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed Dr. Ike Muslow's June 14, 1999 report regarding the above referenced research. OHRP apologizes for the delay in responding to Dr. Muslow's report.

Dr. Muslow'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. Muslow'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 Louisiana State University Medical Center Shreveport (LSUMC) 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.

OHRP acknowledges that no subjects were enrolled in the above referenced research at LSUMC. It is also OHRP's understanding that this research project has been completed. Therefore, OHRP is closing its compliance oversight investigation of this matter.

At this time, OHRP provides the following additional guidance:

(3) For all current and future nonexempt human subject research conducted by LSUMC, the IRB must ensure that informed consent is obtained from all subjects in accordance with the requirements of HHS regulations at 45 CFR 46.116, unless the IRB waives the requirement for informed consent in accordance with the requirements of one of the following: (a) HHS regulations at 45 CFR 46.116(d); (b) FDA regulations at 21 CFR 50.24 for research subject to regulations codified by the FDA; or (c) 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).

(4) The copy of the IRB file for the above referenced research that was provided with Dr. Muslow's report did not include a copy of the investigator's brochure for Fomepizole. Please note that in conducting the initial review of proposed research, IRBs must obtain information in sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111. Materials should include the full protocol, a proposed informed consent document, any relevant grant applications, the **investigator's brochure** (if one exists), and any advertising intended to be seen or heard by potential subjects. Unless a primary reviewer system is used, all members should receive a copy of the complete documentation. If a primary reviewer system is utilized, the investigator's brochure should be reviewed by the IRB member serving as primary reviewer.

(5) 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.

(6) 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.

(7) OHRP notes that IRBs frequently approve research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. 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 must 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 may 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.

(8) Regarding the IRB's Standard Operating Procedures, please note the following:

(a) The description of the procedures for initial and continuing review of research should be expanded to specify the documents and materials that are provided to primary reviewers and all other IRB members for review (please note the guidance provided above regarding continuing review).

(b) The Standard Operating Procedures 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):

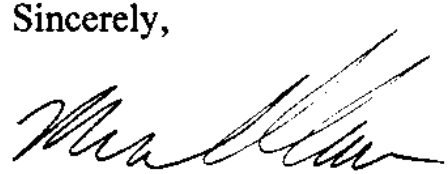
> The procedures which the IRB follows for determining which projects need verification from sources other than the investigator that no material changes have occurred since the previous IRB review.

(c) On page 2.01, the section entitled "IRB RESPONSIBILITIES"should be expanded to include all of the criteria for IRB approval of research stipulated by HHS regulations at 45 CFR 46.111.

(d) Appendix II entitled "Additional Protections for Activities Involving Prisoners as Subjects" should be expanded to include the requirements of HHS regulations at 45 CFR Part 46, Subpart C.

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. Nicholas E. Goeders, Chairperson, IRB, LSUMC
Dr. Kenneth McMartin, LSUMC
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
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