DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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October 26, 2000

Jeffrey Brent, M.D.
Toxicology Associates
2555 South Downing Street
Suite 260
Denver, CO 80210

Dayton T. Reardan, Ph.D., RAC
Vice President for Regulatory Affairs
Orphan Medical, Inc.
13911 Ridgedale Drive, Suite 475
Minnetonka, Minnesota 55305

RE: Human Research Subject Protections under Department of Health and Human Services Regulations at 45 CFR Part 46

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

Dear Dr. Brent and Dr. Reardan:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed the Toxicology Associates' July 7, 1999 report and Orphan Medical's June 2 and June 23, 1999 letters regarding the above referenced research. OHRP apologizes for the delay in its response to your report and letters.

Based upon its review of your report and letters, as well as relevant documents provided by other institutions involved in the conduct of this research, OHRP makes the following determinations:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.116 stipulate that no investigator may involve a human subject in research unless (a) the investigator has obtained the legally effective informed consent of the subject or the

subject's legally authorized representative; or (b) the institutional review board (IRB) has waived the requirement for informed consent in accordance with the requirements of either HHS regulations at 45 CFR 46.116(d) or FDA regulations at 21 CFR 50.24 (requirements for exception from informed consent for emergency research for FDA-regulated research).

(a) OHRP finds that (i) the above referenced 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); and (ii) some subjects were enrolled in the above referenced research without the investigators obtaining the legally effective informed consent of the subjects or the subjects' legally authorized representative. In specific, the IRB-approved procedure where "consent" was obtained from two physicians uninvolved in the trial for subjects who were not lucid and for whom a legally authorized representative was not available failed to satisfy the requirements of HHS regulations at 45 CFR 46.116.

(b) OHRP acknowledges that OPRR received and reviewed a copy of the grant application for this research that described the above referenced "informed consent" procedure prior to its review and approval of Single Project Assurances for this project. However, OHRP notes the following:

(i) In facsimile correspondence sent prior to issuing such approvals, OHRP informed Dr. Bertram Spilker, the President of Orphan Medical, that the requirements for exception from informed consent for emergency research stipulated by FDA regulations at 21 CFR 50.24 (copy enclosed) would have to be satisfied.

(ii) In a March 24,1997 letter to Dr. Spilker that was forwarded to OPRR by Orphan Medical, Dr. Martin Lee, Chairman of the IRB at the Institute for Research and Education (the IRB designated under the OPRR-approved Single Project Assurance S-13579-03 for Orphan Medical that applied to the above referenced research project), stated the following:

> "The requirements for exception from informed consent for emergency research detailed in 21 CFR section 50.24 have been met relative to these protocols"

(iii) OHRP finds no evidence that the requirements for exception from informed consent for emergency research stipulated by FDA regulations at 21 CFR 50.24 were satisfied by any of the IRBs that reviewed and approved the above referenced research.

(2) HHS regulations at 45 CFR 46.103(a) require that each institution "engaged" in human subjects research provide OHRP with a satisfactory Assurance to comply with the regulations, unless the research is exempt under 45 CFR 46.101(b).

OHRP finds that Toxicology Associates (a) was engaged in the conduct of the above referenced research project, and (b) did not provide OPRR with any Assurance to comply with the regulations. OHRP acknowledges that all performance sites engaged in enrolling subjects in this research appear to have had an applicable OPRR-approved Assurance.

It is OHRP's understanding that the human subject research supported by HHS award number FDR-001256 has been completed. Therefore, OHRP is closing its compliance oversight investigation of this matter.

Please note that OHRP expects your institutions to adhere to the following requirements of HHS regulations for the protection of human subjects for any HHS-supported human subject research that your institutions are engaged in:

(1) The IRBs acting on behalf of your institutions 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 IRBs waive the requirement for informed consent in accordance with the requirements of (i) HHS regulations at 45 CFR 46.116(d); (ii) FDA regulations at 21 CFR 50.24 for research involving FDA-regulated investigational products; 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).

(2) Your institutions must obtain OHRP approval of an applicable Assurance of Compliance in accordance with the requirements of HHS regulations at 45 CFR 46.103(a).

Please contact Mr. George Gasparis, the Assurance Coordinator for your region of the country, at 301-402-5164 if you are engaged in any active HHS-supported research that still requires an OHRP-approved Assurance.

Please note that failure to comply with these requirements may result in sanctions by the awarding HHS agency.

OHRP appreciates the commitment of your institutions to the protection of human subjects. Please feel free to contact me if you have any questions regarding this matter.

Sincerely,

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

Enclosures: (1) 21 CFR 50.24
(2) OPRR Report 97-01

cc: Dr. Bertram A. Spilker, President, Orphan Medical, Inc.
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
Mr. George Gasparis, OHRP
Dr. Kamal Mittal, OHRP
Dr. Katherine Duncan, OHRP
Dr. Clifford C. Scharke, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. Barry Bowman, OHRP