DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for HumanResearch Protections
The Tower Building
1100 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 301-402-3006
FAX: 301-402-2071
E-mail: rmeyer@osophs.dhhs.gov

May 13, 2002

Eugene S. Wiener, M.D.
Medical Director
Children's Hospital of Pittsburgh
3705 Fifth Avenue
Pittsburgh, PA 15213

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1230 and FederalWide Assurance (FWA) 00000600
Research Project: Infantile Esophagitis: Natural History and Optimal Therapy
Principal Investigator: Susan R. Orenstein, M.D.

Dear Dr. Weiner:

The Office for Human Research Protections (OHRP) has reviewed the Children's Hospital of Pittsburgh's (CHP's) September 15, 2000 report in response to OHRP's August 3, 2000 letter regarding the allegations of possible noncompliance with the Department of Health and Human Services (HHS) regulations for protection of human subjects (45 CFR Part 46) involving the above-referenced research. OHRP apologizes for the delay in its response.

Based upon its review, OHRP makes the following determinations regarding the above-referenced research protocol:

(1) HHS regulations at 45 CFR 46.116(a)(2) and 45 CFR 46.117(b)(1) require that a description of any reasonably foreseeable risks or discomforts to the subject be included in the

informed consent document.

(a) OHRP finds that the informed consent document approved by the CHP Institutional Review Board (IRB) appropriately disclosed the known, potentially life-threatening heart rhythm problems associated with the use of Propulsid® (cisapride) in infants.

(b) OHRP notes that the Undesirable effects section of the investigator's brochure for cisapride states the following:

(i) "In line with the pharmacological activity of Prepulsid (sic), transient abdominal cramping, borborygmi and diarrhoea may occur."

(ii) "Cases of hypersensitivity including rash, pruritus and urticaria, bronchospasm, mild and transient headache or lightheadedness and dose-related increase in urinary frequency have been reported occasionally."

OHRP notes that the CHP's Reflux Medication Study Instructions related to both cisapride and cimetidine for the above-referenced research given to the subject's parents state the following:

"Possible side effects include irritability, cramping, or diarrhea."

OHRP finds that many of the above stated risks or discomforts of cisapride or cimetidine stated in the investigator's brochure and the study instructions were not specifically disclosed in the IRB-approved informed consent document.

Corrective action: OHRP acknowledges that the research has been completed. OHRP also acknowledges CHP's commitment to ensure that any reasonably foreseeable risks and discomforts to the subject are specifically included in future informed consent documents.

(2) HHS regulations at 45 CFR 46.116(a)(1) require that the informed consent document provide a description of the procedures to be followed and identification of any procedures which are experimental. OHRP finds that the CHP IRB-approved informed consent document misrepresented Propulsid® (cisapride) as being approved by the Food and Drug Administration (FDA) to treat esophagitis in infants.

Corrective action: OHRP notes CHP's recognition of the inappropriate reference to FDA approval stated in the informed consent document for the above-referenced research. OHRP acknowledges CHP has conducted a comprehensive audit of informed consent documents relating to inaccurate representations of FDA approval for all current research activities. OHRP also acknowledges that the current CHP IRB procedures now require that for research submitted for initial and continuing review, a designated IRB member investigate and confirm representations relating to FDA approval of drugs or devices stated in informed consent documents.

(3) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) require that any unanticipated problems involving risks to subjects or others be promptly reported to the IRB, appropriate institution officials, the Department or Agency head, and OHRP. OHRP notes that the death of a subject enrolled in the subject research was promptly reported to the CHP IRB, the study sponsor and the FDA. With regard to the allegation presented in OHRP's August 3, 2000 letter, OHRP finds that the death of a subject enrolled in the research could reasonably be judged not to meet the criteria for a reportable event to OHRP under HHS regulations at 45 CFR 46.103(b)(5).

(4) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. OHRP found instances in which the IRB failed to conduct continuing review of the above-referenced research at least once per year. In specific, the continuing review of the above-referenced research was conducted 19 days late in 1993, 6 months and 12 days late in 1995, 4 months late in 1996, and 2 months late in 1997.

Corrective action: OHRP acknowledges that the continuing review of the above-referenced research was conducted on an annual basis in 1998 and 1999. OHRP also acknowledges that under current CHP IRB policies and procedures, failure to obtain IRB renewal of ongoing research constitutes serious noncompliance with Federal regulations and CHP IRB requirements which can result in the suspension or termination of the research.

OHRP finds that the above corrective actions adequately address the issues raised in OHRP's August 3, 2000 letter. 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.

At this time, OHRP has the following additional guidance:

(5) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. 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.

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,

Robert J. Meyer
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Mr. Ronald L. Violi, President and CEO, CHP
Dr. Eva Vogeley, IRB Chairperson, CHP
Ms. Patricia T. Saloga, IRB Coordinator, CHP
Commissioner, FDA
Dr. David A. Lepay, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. Jeffrey M. Cohen, OHRP
Mr. George Gasparis, OHRP

Dr. Harold Blatt, OHRP
Mr. Barry Bowman, OHRP