DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

95168d

WARNING LETTER
Via Federal Express

JAN 10 2005

Lynn C. Orfgen
President and CEO
Crittenton Hospital Medical Center
1101 W. University Drive
Rochester, Michigan 48307-1831

Dear Mr. Orfgen:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection of your institutional review board (IRB) and to request immediate action. The inspection was conducted during the period of September 28 and 29, 2004, by Ms. Alanna Mussawwir-Bias, an investigator with FDA's Detroit District Office. The purpose of the inspection was to determine if the IRB had implemented corrective actions promised in response to a November 7, 2002, Warning Letter from FDA and if the IRB is presently functioning in compliance with applicable FDA regulations. IRBs that review FDA-regulated studies must comply with applicable regulations found in Title 21, Code of Federal Regulations (21 CFR) Part 56, Institutional Review Boards; Part 50, Protection of Human Subjects; Part 312, Investigational New Drug Applications, and Part 812, Investigational Device Exemptions.

Our review of the inspection report prepared by the district office revealed that serious violations of applicable regulations continue. At the close of the inspection, Ms. Mussawwir-Bias presented a Form FDA 483, "Inspectional Observations," to you for review and discussed the listed deviations. The deviations noted on the Form FDA 483 and our subsequent inspection report review are discussed below.

Failure to conduct continuing review of research at least annually (21 CFR 56.109(f))

Pursuant to 21 CFR 56.109(f), an IRB is required to conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. Review of study documents and related IRB minutes indicates that the IRB granted retroactive reapproval to two FDA-regulated studies, [redacted] sponsored study of the use of [redacted] and [redacted]. The [redacted] study was retroactively reapproved in both 2003 and 2004, after approximately two months of lapsed approval each time. The [redacted] sponsored study was retroactively reapproved in 2003, also after approximately two months of lapsed approval.

In addition, the IRB has no procedures regarding studies that experience a lapse in IRB approval. For FDA-regulated studies, with the exception of activities necessary to ensure the welfare of the study subjects, no study-related activities are to occur during an approval lapse. The inspectional report notes that an adverse effect occurred in the [redacted] study on [redacted], during a lapse in IRB approval of this study, indicating that the study remained in progress despite the lapse in approval.

Failure to follow written procedures regarding which projects require review more often than annually (21 CFR 56.108(a)(2))

Pursuant to 21 CFR 56.108(a)(2), an IRB must follow written procedures for determining which projects require review more often than annually. According to your IRB's procedures on page 8, Continuing Review, item B, "The IRB shall require that the Investigator submit progress reports to the IRB on a quarterly basis for studies involving significant risk devices..." The [redacted] is a significant risk device study hence requiring review quarterly, however, the study approval letter (copy enclosed) required only annual progress reports.

In addition, minutes for the meeting at which this device study was approved do not include evidence that the IRB discussed whether this study represented a significant risk or non-significant risk when deciding the timeframe for continuing review. Attachment VII to the IRB's procedures is entitled Significant Versus Non-Significant Risk Device and states "The IRB shall assess and determine the risk of all investigational devices."

Failure to maintain copies of all research proposals reviewed (21 CFR 56.115(a)(1))

Pursuant to 56.115(a)(1), an IRB is required to prepare and maintain adequate documentation of IRB activities including copies of all research proposal reviewed. The study protocol for the [redacted] approved by the IRB on [redacted] was not maintained in the IRB files. Apparently, the IRB maintained only the Request for Approval, the Protocol Summary, and correspondence for this study.

The deviations described above are not intended to be an all-inclusive list of deficiencies. The IRB is responsible for adhering to each requirement of the law and relevant regulations.

As a result of the IRB's continued non-compliance with FDA regulations, we are directing that no new subjects be added to on-going FDA-regulated studies until we have evidence of adequate corrective actions. Inspectional findings indicate that the only FDA-regulated studies presently on-going at your institution are the four (4) mentioned above, the [redacted] studies. Therefore, under 21 CFR 56.120(b)(2), we are directing that you immediately inform the clinical investigators for these studies that no new subjects may be added to their on-

going FDA-regulated studies. In addition, within fifteen (15) working days after receiving this letter, please provide written documentation of the specific steps you have taken or will take to assure that the violations noted will not be repeated.

Inspectional findings appear to indicate that the failure to conduct continuing review in a timely fashion results from the fact that the IRB meets infrequently. We therefore recommend that you adopt and implement procedures to ensure that IRB meetings are scheduled as needed to ensure that all on-going FDA-regulated studies are reviewed prior to the expiration of IRB approval. Guidance regarding the continuing review process is available in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators which can be found at http://www.fda.gov/oc/gcp/guidance.html. The section specific to continuing review is found at http://www.fda.gov/oc/ohrt/irbs/review.html and a copy of that section is enclosed.

Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. Please send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Viola Sellman, Chief, Program Enforcement Branch.

We are also sending a copy of this letter to FDA's Detroit District Office, 300 River Place, Suite 5900, Detroit, Michigan 48207, and request that you also send a copy of your response to that office. If you have any questions please contact Ms. Sellman at the address listed above or by telephone at (240) 276 - 0125.

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

Enclosures