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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
9200 Corporate Blvd
Rockville, MD 20850

WARNING LETTER JUN 23 2005
Via Federal Express

Mark R. Taylor
President
St. John Hospital and Medical Center
22101 Moross Road
Detroit, MI 48236-2148

Re: St. John Hospital IRB

Dear Mr. Taylor:

The purpose of this letter is to inform you of objectionable conditions revealed during a Food and Drug Administration (FDA) inspection of the St. John Hospital Institutional Review Board (IRB), and to request your prompt reply. During the period of January 10 through 13, 2005, Alanna L. Mussawwir-Bias, an investigator from FDA's Detroit District Office inspected your site. The purpose of the inspection was to determine whether your IRB's activities and procedures relating to investigational studies of FDA-regulated products complied with applicable FDA regulations. The products used in the [redacted] Trial (Studies [redacted] and [redacted]), the [redacted] for Treatment of [redacted] Study [redacted] the [redacted] Study [redacted]), Trial to [redacted] as the [redacted] ([redacted]), [redacted] ([redacted]), [redacted] Study ([redacted]), [redacted] ([redacted]), [redacted] Study ([redacted]), [redacted] Study ([redacted]), and [redacted] Study ([redacted]), are devices as the term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S. C. 321(h).

We have completed our review of the inspection report prepared by the Detroit District Office which described and documented deviations from the requirements of Title 21, Code of Federal Regulations (21 CFR), Part 50 – Protection of Human Subjects, Part 56 – Institutional Review Boards, and Part 812 Investigational Device Exemptions. These deviations were listed on the Form FDA 483, "Inspectional Observations," that was presented to and discussed with you and the following other St. John personnel at the conclusion of the inspection:

Julie Gorczyca, R.N., Director of Clinical Safety & Risk Management,
Peter A. Nickles, M.D., IRB Chairman,
Noel Lawson, M.D., Vice President for Medical Affairs,

Ronald F. LaPensee, Executive Vice President/Chief Operating Officer,
Ruth Moore, Ph.D., Director of Biomedical Investigation & Research
Medical Education,
Mary Bernhart, IRB Coordinator, and
Janice Pinchak, R.Ph., M.S., IRB Coordinator

The inspection was conducted under a program designed, in part, to ensure that data and information contained in applications for Investigational Device Exemptions (IDEs) are scientifically valid and accurate. Another objective of this program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

A description of deviations from FDA regulations follows:

1. Failure to follow written procedures for ensuring prompt reporting to the IRB and the FDA. [21 CFR 56.108(b)(2)]

Pursuant to FDA Regulations at 21 CFR 56.108(b)(2), an IRB must follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of any instance of serious or continuing noncompliance with FDA regulations or the requirements or determinations of the IRB. Materials reviewed by the FDA investigator during the inspection indicate that, during the period of 2001 through 2004, the clinical investigator and sponsor of the [redacted] Trial wrote to the IRB manager various times concerning the approval status of the study. Some of these letters reveal that the clinical investigator continued to enroll patients in the study and implant them with the study device during periods in which IRB approval had expired. Other correspondence sent to the IRB manager indicates that the clinical investigator implanted the study device in a patient (subject 9095-[redacted]) on 3/1/02 despite the fact that the enrollment of additional subjects was suspended in December 2000 following review of information from the sponsor and FDA suggesting that the device posed a more significant risk to human subjects than previously documented. As a result of your IRB's failure to establish and follow written procedures to ensure prompt reporting of serious or continuing noncompliances with FDA regulations or IRB requirements or determinations, these instances of serious and continuing noncompliance by the clinical investigator were not promptly reported to the full IRB and to FDA as mandated in the IRB procedures and operating guidelines.

2. Failure to follow written procedures for conducting continuing review of research. [21 CFR 56.108(a)(1)]

Pursuant to 21 CFR 56.108(a)(1), the IRB shall follow written procedures for conducting its continuing review of research and for reporting its findings and actions to the investigator and the institution. The St. John Hospital and Medical Center IRB Procedures and Operations Guidelines state that the IRB will establish the continuing review intervals appropriate to the degree of risk, but not less than every 12 months. For continuing review, the guideline states that the "...investigators will be asked to submit a

written annual report on studies one month prior to the actual annual date of the initial or previous approval of the study...e.g. For studies with initial approval in April, the continuing review report would be submitted in time for the March agenda." Your IRB failed to follow these guidelines as written. Examples of this failure include, but are not limited to, the following:

A. The IRB approved all six arms of the [redacted] Trial ([redacted]) by 1999. There is no documentation of a full board review of any continuing (annual) review report or follow-up report submitted concerning the study since December 2000, at which time enrollment of additional patients was suspended.

B. The IRB initially reviewed and approved the [redacted] Study ([redacted]) on 6/18/01, with annual review and re-approval on 7/18/02. As stated above, the St. John Hospital and Medical Center IRB Procedures and Operations Guidelines state for continuing review, investigators will be asked to submit a written annual report on studies one month prior to the actual annual date of the initial or previous approval of the study. There is no record in that the IRB sent a reminder to Dr. [redacted] requesting a report on progress on the study in 2003; nor is there documentation in the 2003 meeting minutes of IRB continuing review for this study.

C. The IRB initially reviewed and approved the [redacted] ([redacted]) on 6/20/02. Although the June 2004, IRB meeting minutes include a review of adverse event reports received from the clinical investigator for this study, there is no documentation in the meeting minutes of annual review in 2003 or 2004 as mandated by the IRB Procedures and Operations Guidelines governing continuing review of research.

3. Failure to follow written procedures for determining which projects require review more often than annually. [21 CFR 56.108(a)(2)]

Pursuant to 21 CFR 56.108(a)(2) an IRB shall follow written procedures for determining which projects require review more often than annually. The St. John Hospital and Medical Center Institutional Review Board Procedures and Operations Guidelines state that your IRB will determine which projects require review more frequently than once every 12 months, and will establish the continuing review at intervals appropriate to the degree of risk, but not less than once per year. The guidelines further state that the frequency of review will be indicated in the IRB meeting minutes. During the inspection, the FDA investigator examined your IRB's meeting minutes for the period of 2002 through 2004. The minutes do not document any discussion by the IRB concerning the risk to human subjects or the frequency of continuing review of any clinical or non-clinical study involving FDA-regulated products.

4. Failure to prepare and maintain adequate documentation of IRB activities. [21 CFR 56.115]

Pursuant to 21 CFR 56.115(a)(2), an IRB shall prepare and maintain adequate documentation of IRB activities, including the following: minutes of IRB meetings which shall be in sufficient detail to show attendance at all meetings; actions taken by the IRB; the vote of these actions; the basis for requiring changes in or disapproving research; and a written summary of the discussion and the resolution. The inspection revealed several instances in which your IRB failed to prepare and maintain adequate documentation of its activities, including the following:

A. The [redacted] Trial (Studies [redacted] and [redacted]) was closed to enrollment by the St. John Hospital IRB in December 2000 following review of correspondence from the sponsor that stated FDA had suspended the [redacted] IDE study enrollment due to Serious Adverse Events (SAEs) and increased risk of the device on human subjects. The IRB manager received numerous letters from the clinical investigator and study sponsor regarding approval status during the period of 2001 through 2004. Some of this correspondence showed that the clinical investigator implanted the study device in a patient (Subject 9095-[redacted] on 3/1/02 under the Emergency Use/Compassionate Use protocol two years after the study enrollment was suspended due to concerns regarding an increased risk to human subjects. There is no documentation in the IRB meeting minutes regarding any action taken by the IRB as a result of this noncompliance.

B. The clinical investigator for the [redacted] Trial (Studies [redacted] and [redacted]) sent a letter to the IRB dated 4/17/03 with a list of Significant Adverse Events (SAEs) covering the period from 1998 to 2001 that had not been previously reported. FDA regulations require investigators to report unanticipated adverse events as soon as possible but in no event later than 10 working days after the investigator learns of the event. 21 CFR 812.150(a)(1). In addition, the protocols for these studies state that "Any unanticipated device related AE must be reported by telephone or FAX to the sponsor within 24 hours of detection or reporting by the subject. Any serious adverse event, regardless of whether it is related to the device or procedure, or whether it is unanticipated, must be reported by telephone or FAX to the sponsor within 5 days of occurrence." There is no documentation in the IRB meeting minutes regarding any discussion of these adverse events or any action taken by the IRB in response to the clinical investigator's failure to timely report the SAEs.

C. Review of the investigator's 4/17/03 letter to the IRB concerning the [redacted] (Studies [redacted] and [redacted]) also revealed that 15 subjects were implanted during the period in which IRB approval had expired for the High Risk (HR) and Low Profile System (LPS) arms of the study. There is no documentation in meeting minutes or elsewhere that the IRB reviewed this correspondence or took any action regarding the implantation of investigational devices during this period.

D. On 11/1/04, the sponsor sent information to the IRB regarding possible implantation of investigational devices during the period in which IRB approval had expired, including information from the clinical investigator regarding the subjects enrolled and dates of device implantation. There is no documentation in meeting minutes or elsewhere that this information was reviewed by the IRB or that any action was taken by the IRB in response to the sponsor's letter.

5. Failure to prepare and maintain adequate documentation of written procedures for the IRB as required by 21 CFR 56.108(a) and (b). [21 CFR 56.115(a)(6)]

Pursuant to 21 CFR 56.115(a)(6), an IRB must prepare and maintain adequate documentation of written procedures for the IRB as required by 56.108(a) and (b). Section 56.108(a) and (b) requires an IRB to have and follow written procedures for conducting its activities, including its initial and continuing review activities. You failed to have written procedures for approving Emergency Use of an investigational device, making significant versus non-significant risk device determinations, and for approving and conducting continuing review of the use of a Humanitarian Use Device (HUD) under an approved Humanitarian Device Exemption (HDE). For example, the IRB Procedures and Operating Guidelines state that your IRB will determine the appropriate frequency of IRB review of projects based on the degree of risk. In addition, clinical studies that are proposed by the sponsor as involving a non-significant risk device but which actually involve a significant risk device must receive FDA approval of an application for an investigational device exemption (IDE) before the study can go forward. (21 CFR §§ 812.2(b)(1) and 812.20). Your IRB lacks written procedures for determining which projects involve significant risk (SR) devices and which involve non-significant risk (NSR) devices. The IRB has approved a number of device studies, including: [redacted]. The IRB meeting minutes for these studies do not document any determination of SR/NSR, nor of the required frequency of review for any of these device studies based on risk.

The deviations discussed above are not intended to be an all-inclusive list of deficiencies at your site. As an IRB, it is your responsibility to ensure that investigations that you participate in are conducted in accordance with applicable FDA regulations.

FDA acknowledges your written response of January 26, 2005. In your response you state that new and revised policies will be drafted, reviewed, and implemented, including policies covering the following topics: Noncompliance, Continuing Review, Assessment of Risk, Emergency Use, Humanitarian Use Devices, Expedited Review, and Significant/Non-significant Risk Device Determinations. According to your response, the new and revised policies were scheduled to be presented to the IRB for review and approval in a special meeting held on February 3, 2005. You also agreed to forward copies of these policies, once approved by your IRB, to FDA. Please be advised that we have not yet received this information.

Within 15 working days, you must respond to this letter in writing. You should be aware that FDA considers your actions to be serious violations of the law which may result in FDA taking regulatory action without further notice to you.

You should direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Special Investigations Branch, HFZ-311, 2094 Gaither Road, Rockville, Maryland 20850. Attention: Janet Cooper, Consumer Safety Officer.

A copy of this letter has been sent to the FDA's Detroit District Office., 300 River Place, Suite 5900, Detroit, MI 48207. We request that a copy of your response also be sent to the Detroit District Office.

Please direct all questions concerning this matter to Janet Cooper at (240) 276- 0125.

Sincerely yours,

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

cc:
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