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Inspections, Compliance, Enforcement, and Criminal Investigations

Genetics & IVF Institute, 11/10/09



Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

WARNING LETTER

VIA FEDERAL EXPRESS

NOV 20 2009

David S. Karabinus, Ph.D.
Scientific Director
Genetics & IVF Institute
3015 Williams Drive, Suite 110
Fairfax, VA 22031-4623

Dear Dr. Karabinus:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at Genetics & IVF Institute from June 23 to 30, 2009 by an investigator from the FDA Baltimore District Office. The purpose of this inspection was to determine whether activities as sponsor of the clinical study **(b)(4)**, complied with applicable federal regulations **(b)(4)** is a device as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h). This letter also requests prompt corrective action to address the violations cited and discusses your written response dated July 17, 2009, to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in requests for IDEs, PMA applications, and Premarket Notification submissions (510(k)) are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR) Part 812-Investigational Device Exemptions. At the close of the inspection, the FDA investigator presented an inspectional observations form FDA 483 for your review and discussed the observations listed on the form with you, **(b)(4)** clinical investigator, and **(b)(4)**, contract research organization representative from **(b)(4)**. The deviations noted on the FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

1. Failure to ensure adequate monitoring of the investigation and failure to secure the investigator's compliance with the signed agreement, the investigational plan, applicable FDA regulations, and any other conditions of approval imposed by the reviewing Institutional Review Board or FDA. [21 CFR 812.40, 21 CFR 812.46(a)].

Sponsors are responsible for ensuring proper monitoring of the investigation (21 CFR 812.40). You failed to monitor in accordance with your written monitoring procedures in your investigational plan (21 CFR 812.25(e)). Sponsors are also responsible for securing the investigator's compliance with the signed agreement, the investigational plan, applicable FDA regulations, and any other conditions of approval imposed by the reviewing IRB or FDA (21 CFR 812.46(a)). If, through monitoring reports or otherwise, a sponsor discovers that an investigator is not in compliance with any of the above, the sponsor shall promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigation. You failed to secure the

compliance of **(b)(4)**, the principal investigator of the clinical site located in **(b)(4)** after repeated notification of his noncompliance with applicable FDA regulations.

Examples of these failures include, but are not limited to, the following:

- Section 4.3 of the original and undated **(b)(4)** specifies that monitoring visits will be conducted at least every **(b)(4)**. These procedures were amended in 2007 to require monitoring visits at least every **(b)(4)**. Monitoring was not performed in accordance with these procedures.
 - i. The clinical site located in **(b)(4)**
 1. There were no monitoring visits for the years 2000, 2001, and 2008.

FDA approved the IDE in **(b)(4)**. However, the first monitoring visit was not conducted until November 2002; there was no monitoring conducted at the site for the first two and a half years of study activity.
 2. There was only **(b)(4)** monitoring visit conducted per year for 2004, 2005, 2006, and 2007.
 - ii. The clinical site located in **(b)(4)**.
 1. There were no monitoring visits for the years 2004 and 2005, though subjects were enrolled beginning in March 2004.
 2. There was only one monitoring visit per year for 2006, 2007 and 2008.
- You were repeatedly notified, through monitoring reports dated as early as December 31, 2007, of problems with **(b)(6)** use and documentation of IRB approved informed consent forms, which would indicate **(b)(6)** noncompliance with applicable FDA regulations (21 CFR 812.100 and 21 CFR 50.27(a)). Yet you failed to secure his compliance or terminate the investigation.

Your response acknowledges that monitoring of the study was not conducted at the frequency specified in the investigational plan. It also states that you have retained two Contract Research Organizations (CROs) to perform monitoring and project management services, and that OIVF has developed a new monitoring procedure (dated December 24, 2008) and has conducted training sessions on the new procedures. This response is inadequate because it is insufficiently detailed and does not identify any corrective and preventive actions you have taken, or will take, to ensure that this violation does not recur. Please provide copies of training materials for your staff and clinical sites, dates of training, a list of staff trained, and how you plan to ensure that corrective and preventive measures are taken. In addition, please note that your investigational plan states that monitoring visits will occur every **(b)(4)** but your monitoring procedure dated December 24, 2008 (section 6.2) does not address or otherwise reference this frequency. Please ensure that the new monitoring procedure is consistent with the investigational plan.

Your response further acknowledges that the study was not always conducted in compliance with the regulations. You contend in the response that you were not made aware of this noncompliance until November 2008; however, as stated above, you were in possession of monitoring reports dated as early as December 31, 2007 that documented noncompliance with the applicable regulations. In your response, you identify corrective actions you have implemented, including intensive OCP training, retention of an additional CRO for project management services, and revision of the monitoring procedures to include a procedure for follow-up to findings from monitoring visits. These corrective actions appear to be adequate. At the next inspection we will ensure these corrective actions have been properly implemented and maintained.

2. Failure to maintain accurate, complete, and current records of all correspondence with a monitor, an investigator, an IRB, or FDA. [21 CFR 812.140(b)(1)]-

Sponsors are responsible for maintaining accurate, complete, and current records of all correspondence with a monitor, an investigator, an or FDA.

- There is no written documentation that protocol version numbers 2, 3, or 4 were approved by the Genetics & IVF Institute IRB (IRB) prior to the retroactive letter issued on June 18, 2009 by the IRB chairperson indicating the respective approval dates.
- There was no written documentation from the IRB that specifically identifies **(b)(4)** and his clinical site located in **(b)(4)** as being approved by the IRB to conduct the study from the initiation of study enrollment until the retroactive letter issued on June 18, 2009 by the IRB chairperson.

Please identify any corrective and preventive actions you have taken or will take, to ensure that this violation does not recur. Please include copies of training materials and new or revised written procedures if applicable.

The violations described above are not intended to be an all inclusive list of problems that may exist with your clinical study. It is your responsibility as a study sponsor to ensure compliance with the Act and applicable regulations.

Failure to adequately respond to this letter and take appropriate corrective action could result in further action without additional notice.

Within fifteen (15) working days of receiving this letter please provide written documentation of the additional actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future studies for which you are the study sponsor. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. Send your response to: Attention: Linda Godfrey, Food and Drug Administration 10903 New Hampshire Ave. W066-3462 Silver Spring, MD 20993-0002.

The Division of Bioresearch Monitoring has developed introductory training modules in FDA regulated device clinical research practices, which are available on the FDA website. The modules are for persons involved in FDA regulated device clinical research activities. These modules are located at the following website address: <http://www.fda.gov/Training/CDRHLearn/ucm162015.htm>.

A copy of this letter has been sent to Evelyn Bonnin District Director, FDA Baltimore District Office HFR-CE200 6000 Metro Drive, Suite 101 Baltimore, MD 21215. Please send a copy of your response to that office.

If you have any questions please contact Linda Godfrey (301) 796-5490, Linda.Godfrey@fda.hhs.gov.

Sincerely yours,

/s/

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

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