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Inspections, Compliance, Enforcement, and Criminal Investigations

Pattanam D. Srinivasan, MD 3/14/14



Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

MARCH 14, 2014

WARNING LETTER

VIA UNITED PARCEL SERVICE

Pattanam D. Srinivasan, MD
Clinical Director
Advanced Interventional Pain Center
613 West Lincoln Road, Suite A
Kokomo, IN 46902

Dear Dr. Srinivasan:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection of your clinical site from September 16, 2013, to September 27, 2013, by investigators from the FDA Detroit District Office. This correspondence addresses your role as both sponsor and Clinical Investigator (CI). In addition, we note that you are the head official of the Advanced Interventional Pain Center Institutional Review Board (IRB) that oversaw your investigation. A separate correspondence addresses the inspection findings of the IRB. Please note that we have concerns about you serving in these distinct roles simultaneously.

This inspection was conducted to determine whether activities as both sponsor and CI of the clinical study entitled "**(b)(4)**," **(b)(4)** request **(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), because it is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or to affect the structure or function of the body. This letter also requests prompt corrective action to address the violations cited and discusses your written responses dated October 18, 2013, and November 18, 2013, to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval applications (PMA), and Premarket Notification (510(k)) submissions 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 several violations of Title 21, Code of Federal Regulations (CFR) Part 812 - Investigational Device Exemptions and Part 50 - Protection of Human Subjects, which concerns requirements prescribed under section 520(g) of the Act 21 U.S.C. § 360j(g). 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. The deviations noted on the Form FDA 483, your written responses, and our subsequent review of the inspection report, are discussed below:

1. Failure to submit an IDE application to the FDA and obtain approval of the IDE prior to allowing subjects to participate in the investigation [21 CFR 812.20(a)(1), 21 CFR 812.42, and 21 CFR 812.110(a)].

A sponsor must submit an IDE application to the FDA and obtain FDA approval of the application before allowing subjects to participate in a clinical investigation of a significant risk device. You failed to adhere to the above-stated regulations and treated nine subjects without an approved IDE from FDA.

On April 18, 2013, FDA notified you as the sponsor that the **(b)(4)** device is a significant risk (SR) device, as defined in 21 CFR 812.3(m). Therefore, an IDE application approved by FDA is required before subjects are enrolled and an investigation can begin.

You treated the following subjects after receiving the April 18, 2013, FDA correspondence:

	Subject Initials	Treatment Date(s)
1	(b)(4); (b)(6)	(b)(4); (b)(6)
2	(b)(4); (b)(6)	(b)(4); (b)(6)
3	(b)(4); (b)(6)	(b)(4); (b)(6)
4	(b)(4); (b)(6)	(b)(4); (b)(6)
5	(b)(4); (b)(6)	(b)(4); (b)(6)
6	(b)(4); (b)(6)	(b)(4); (b)(6)
7	(b)(4); (b)(6)	(b)(4); (b)(6)
8	(b)(4); (b)(6)	(b)(4); (b)(6)
9	(b)(4); (b)(6)	(b)(4); (b)(6)

Failure to obtain FDA approval of an IDE prior to subject enrollment and treatment may place study subjects at increased risk of harm and serious illness. FDA approval of an IDE application helps to ensure subject safety and that the risks associated with the device and study procedures are minimized.

Your written responses state that you initiated the study without FDA approval because you believed that the study was exempt from "any requirement to obtain IDE approval." You also stated that you have taken corrective action to suspend use of the **(b)(4)** device, and that you will not resume until you have obtained FDA approval or clearance.

We note that, to date, there is no record of you submitting an IDE application to FDA. Any future clinical studies with your SR device must receive both FDA approval of an IDE and IRB approval prior to enrolling subjects. You have not provided documentation that you have informed the study subjects who received the device that the study did not have FDA approval and has been suspended. You should provide to FDA a copy of the letter sent to the subjects, the IRB approval of that letter, and documentation that all subjects were notified in your response to this letter.

On April 18, 2013, FDA communicated to your firm that the use of the **(b)(4)** device without applicable approval or clearance by FDA would be a violation of the Act. See section 501(f)(1)(B) of the Act (21 U.S.C. § 351(f)(1)(B)), section 502(o) of the Act (21 U.S.C. § 352(o)), and section 510(k) of the Act (21 U.S.C. § 360(k)).

The kind of information that your firm needs to submit in order to obtain approval or clearance for the device is described on the Internet at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/default.htm>¹. The FDA will evaluate the information that your firm submits and decide whether the product may be legally marketed. For additional information about IDE regulations, please refer to <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm>².

2. Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50 [21 CFR 812.100, 21 CFR 50.20, 21 CFR 50.25, and 21 CFR 50.27].

A CI is responsible for obtaining and documenting informed consent from a subject using an IRB approved consent form prior to involving the subject in the clinical investigation. In seeking informed consent, basic elements, and additional elements when appropriate, must be provided to each subject as described in 21 CFR 50.25. Examples of your failure to adhere to FDA regulations relating to informed consent are as follows:

- Your study informed consent forms (ICF) were not approved by an IRB, as required by 21 CFR 50.27.
- Your study ICF included the following statement: "In the event of an adverse effect **I agree to hold members** of the Institutional Review Board, Advanced Interventional Pain Center, Dr. Srinivasan and his associates **harmless**, as each of the members collectively or individually had acted in good faith in the best interest of me as a patient." This statement is an example of exculpatory language which is a violation of FDA regulations. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence. As the study sponsor-investigator, you are responsible for respecting and protecting the rights and welfare of study subjects, including their legal rights.
- Your consent documentation does not include all the essential elements listed in 21 CFR 50.25. Examples of missing essential elements in your study ICF include statements that the study involved research, the research is voluntary, and description of reasonable foreseeable risks or discomforts to the subjects. In order to make an informed decision to participate, research subjects must be given all required information to decide whether to enroll in the study.

The corrective actions noted in your written responses include a modified ICF, dated October 17, 2013, which was approved by the IRB on October 30, 2013. You also planned to re-consent all participants enrolled in the clinical study and to provide FDA copies of the signed informed consent documents by December 30, 2013. In addition, you stated that you implemented a new standard operating procedure (SOP) to provide an original copy of a signed ICF to the subject at the time of consent.

Although you provided documentation of training on the new SOP, your responses are inadequate because you have not submitted complete documentation of your attempts to re-consent all subjects enrolled in the study with the modified consent form, and you did not provide documentation of training from all research staff involved in the conduct of these studies.

3. Failure to maintain accurate, complete, and current records related to the investigation [21 CFR 812.140(a)(2), 21 CFR 812.140(b)(3), and 21 CFR 812.140(d)].

CIs are responsible for maintaining accurate, complete, and current records of study-related matters, including receipt and use of a device. Sponsors are responsible for maintaining financial disclosure information. CIs and sponsors must maintain these records during the investigation and for two years after the latter of the following two dates: the date the investigation is terminated or completed, or the date that the records are no longer required to support a PMA application. Examples of your violations include the following:

- Original ICFs and subjects' source documents, including PRI-assessment results, were not maintained for a period of 2 years after the date on which the investigation was completed.
- Device use and disposition documentation was not maintained to indicate which device or lot code were used for each subject. This is a serious violation, as accurate device accountability records are important for the control of devices and adequate follow-up should any device related adverse events occur. Accurate device records also help to confirm that the investigational device is used

only by qualified investigators on subjects appropriately enrolled in the study.

- As the sponsor, you did not maintain financial disclosure forms for each sub-investigator or other physicians who performed study procedures. Examples include **(b)(4)**.

Your written responses state that you implemented a new electronic patient record (EPR) system to prevent treatment and included a patient records SOP to maintain original source documents and device accountability records.

Your response is not adequate because you did not provide complete financial disclosure forms for all sub-investigators and you also did not provide documentation of training for all research staff. We recommend that you implement time-stamped audit trail of your EPR system to independently record the date and time of operator entries and actions that create, modify, or delete electronic records.

Please refer to FDA's Guidance for Industry: Part 11, Electronic Records; Electronic Signatures — Scope and Application, which is available online at <http://www.fda.gov/regulatoryinformation/guidances/ucm125067.htm>³.

4. Failure to conduct the investigation according to the investigational plan and failure to report deviations from the investigational plan [21 CFR 812.110(b)].

A CI must conduct an investigation according to the investigational plan, which includes the protocol and any conditions of approval imposed by the IRB or FDA. You failed to adequately conduct study subjects' follow-up evaluation, as required by the study protocol.

- The investigational plan requires study visits at **(b)(4)**, **(b)(4)**, **(b)(4)**, and **(b)(4)** following treatment with the study device. The original study protocol lists secondary effectiveness endpoints for pain relief and improvement in function at **(b)(4)** post-treatment. However, **(b)(4)**, **(b)(4)**, **(b)(4)** follow-up visits were not performed as required by protocol for the following subjects:

Subject	Treatment	Follow-Up Visits		
		(b)(4); (b)(6)	(b)(4); (b)(6)	(b)(4); (b)(6)
(b)(4); (b)(6)	(b)(4); (b)(6)			(b)(4); (b)(6)
(b)(4); (b)(6)	(b)(4); (b)(6)			(b)(4); (b)(6)
(b)(4); (b)(6)	(b)(4); (b)(6)			(b)(4); (b)(6)
(b)(4); (b)(6)	(b)(4); (b)(6)			(b)(4); (b)(6)
(b)(4); (b)(6)	(b)(4); (b)(6)			(b)(4); (b)(6)
(b)(4); (b)(6)	(b)(4); (b)(6)			(b)(4); (b)(6)
(b)(4); (b)(6)	(b)(4); (b)(6)	(b)(4); (b)(6)	(b)(4); (b)(6)	(b)(4); (b)(6)
(b)(4); (b)(6)	(b)(4); (b)(6)	(b)(4); (b)(6)	(b)(4); (b)(6)	(b)(4); (b)(6)

Your failure to perform follow up physical examinations according to the protocol increased the risks to subjects because of the potential delay in recognizing and treating any study related complications. This also affects the integrity of the clinical data you submitted to FDA.

Your written responses state the study protocol does not require a **(b)(4)** follow-up visit. You provided a revised study protocol with follow-up windows, which was approved by the IRB on **(b)(4)**. However, this revised study protocol also lists secondary effectiveness endpoints for pain relief and improvement

in function at **(b)(4)** post-treatment. Therefore, it appears that a **(b)(4)** follow-up is required to collect for these secondary effectiveness endpoints. Your responses are inadequate since you also failed to describe how you will ensure that protocol deviations are reported as required by the FDA regulations.

In your response to this letter, please provide the following:

- the corrective action that you have taken to prevent the recurrence of these violations,
- copies of correspondence submitted to the IRB,
- copies of policies, procedures, and training that are being developed and implemented to ensure that IRB approval of deviations are obtained prior to treating subjects in non-emergency situations, and
- the expected completion dates for all trainings that you have developed or implemented.

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 clinical investigator and sponsor to ensure compliance with the Act and applicable regulations.

Within 15 working days of receiving this letter, please provide documentation of the additional actions that you have taken or will take to correct these violations and to prevent the recurrence of similar violations in current or future studies for which you are the study sponsor and clinical investigator. Any submitted corrective action plan must include projected completion dates for each action to be accomplished as well as a plan for monitoring the effectiveness of your corrective actions. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 CFR 812.119.

Your response should reference "CTS # GEN1200847/E001" and be sent to:

Attention: Veronica J. Calvin, M.A.
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room 3508
Silver Spring, Maryland 20993-0002.

A copy of this letter has been sent to FDA's Detroit District Office, 300 River Place, Suite #5900, Detroit, MI 48207. Please send a copy of your response to that office.

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>⁴.

If you have any questions, please contact Veronica Calvin at (301) 796-5647 or Veronica.Calvin@fda.hhs.gov.

Sincerely yours,
/S/
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