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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

WARNING LETTER
VIA FEDERAL EXPRESS

Sanjay S. Yadav, M.D.
9500 Euclid Ave. F25
Cleveland OH 44195

APR 11 2005

Dear Dr. Sanjay Yadav:

The purpose of this Warning Letter is to inform you of the objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site from January 6-18, 2005, by [redacted], an investigator from the FDA Cincinnati District Office. This letter also discusses your written response dated February 25, 2005, to the violations on the FDA Form 483 and requests that you implement prompt corrective actions to these violations.

The purpose of the inspection was to determine if your activities and procedures relating to your participation in the clinical study entitled "[redacted]" complied with applicable federal regulations. The products under investigation are devices 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).

The FDA conducted the inspection under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and Premarket Notifications [510(k)] are scientifically valid and accurate. The program also ensures 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 investigator revealed problems in the conduct of the trial and your role as a "Clinical Investigator". The regulations governing clinical trials are found in Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions, and Part 50 - Protection of Human Subjects. These deviations were listed on the Form FDA 483, "Inspectional Observations," that was presented to and discussed with you. These deviations and our subsequent review of the inspection report are discussed below:

Failure to conduct the investigation according to the signed agreement, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by the IRB or FDA.
[21 CFR 812.100 and 812.110(b)]

Clinical investigators are required to ensure that investigations are conducted according to the signed agreement, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by the IRB or FDA. Please note that the study protocol is part of the investigational plan as defined in 21 CFR 812.25(b). Our investigation revealed several deviations from the signed agreement and investigational plan. including, but not limited to, the following:

1. You failed to report the use of non-investigational [redacted] in 12 of the [redacted] subjects as required by FDA regulations and the guidelines set forth by your IRB. Non-investigational [redacted] were used during the index procedure for 15 of the [redacted] subjects enrolled in the study. As of January 6, 2005, the IRB had been notified of the use of non-investigational stents in only 3 of these [redacted] subjects ([redacted]).

   The protocol deviation procedure of your IRB states that deviations from the investigational plan by the investigator or support personnel should be reported promptly to the IRB. The use of non-investigational stents is a deviation from the investigational plan; this deviation was not reported promptly to the IRB. The IRB was not informed of the use of all of the non-investigational stents in this study until the FDA inspection took place. Examples include the following:

   A. [redacted] received commercial/non-investigational [redacted]) in conjunction with the [redacted] during their index procedure. The use of these non-investigational [redacted] is a protocol deviation that was not reported promptly to the IRB and sponsor.

   B. [redacted] was treated with an investigational [redacted] in the [redacted] during the index procedure on [redacted]. On [redacted] the subject then received a non-investigational [redacted] in the [redacted] 28 days after the index procedure. This subject was treated despite meeting an exclusion criterion which excludes those subjects where "there is a planned combination procedure involving either the contra lateral carotid artery, a coronary artery, or peripheral artery 30 days before or after the index procedure". These protocol deviations were not reported to the IRB and sponsor as required by your IRB policy and FDA regulations [21 C.F.R. 812.150(a)(4)].

   Your written response states that the study coordinator misunderstood the IRB policy. and that the use of these non-investigational [redacted] was reported to the IRB prior to the completion of the FDA inspection. While this task may be delegated. it is the

responsibility of the clinical investigator to ensure proper reporting of protocol deviations. Both FDA regulations and your IRB policy require the reporting of protocol deviations. Please submit copies of the policies and procedures (including documentation of training with expected completion dates) which are being developed and implemented to ensure that deviations from the investigational plan are reported in accordance with the FDA regulations and IRB policy.

2. You failed to ensure that subjects met inclusion/exclusion criteria prior to study enrollment. Examples include, but are not limited to, the following:

   A. [redacted] had an investigational [redacted] The Barthel stroke scale on [redacted] was 12/20. This subject should have been excluded from the study since the exclusion criterion states the stroke scale value must be greater than 60.

   In addition, the subject's baseline coagulation blood work of March 15, 2004, indicated a protime result of 16.4 seconds (normal: 9.9-13.0 seconds) and an International Normalized Ratio (INR) of 1.52 (normal: 0.9-1.2). There was no source documentation indicating that this subject's abnormal laboratory value was not clinically significant; therefore, this subject met exclusion criteria and should not have been enrolled.

   In your written response you state that the neurologist interpreted a baseline Barthel score of less than 60 -- rather than less than or equal to 60 -- as exclusionary. The neurologist stated that this "patient was functionally independent and would benefit from the carotid re-vascularization." Though this duty may be delegated, it is the responsibility of the clinical investigator to ensure the study eligibility of potential study subjects. In addition, your response did not address the abnormal coagulation profile. Please submit copies of the policies, procedures, and training (with expected completion dates) being developed and implemented to ensure subject eligibility prior to enrollment.

3. You failed to conduct diagnostic evaluations in accordance with the investigational plan. Examples include, but are not limited to, the following:

   A. The protocol required that PT/PTT times be determined prior to study enrollment. There was no source documentation indicating that [redacted] had a PT/PTT time evaluated prior to study enrollment.

   B. [redacted] did not have documented protocol-required pre-procedure coagulation tests (PT/PTT). This subject was enrolled on [redacted], and the first coagulation test was on July 6, 2004. Also, source documents for the protocol-required post-procedure ultrasound examination were unavailable.

   C. [redacted] did not have documented protocol-required pre-procedure coagulation tests (PT/PTT).

D. [redacted] did not have documented protocol-required pre-procedure neurological examination stroke scales. These stroke scales were to be performed and evaluated within one week prior to study enrollment.

E. [redacted] did not have documented protocol-required six-month follow-up neurological examination stroke scales. The protocol requires neurological examination stroke scales to be performed at the six-month follow-up visit.

F. [redacted] did not have documented protocol-required post procedure neurological examination stroke scales. The protocol requires neurological examination stroke scales to be performed post-procedure prior to discharge from hospital.

G. [redacted] did not have documented protocol-required post-procedure neurological examination stroke scales. The protocol requires neurological examination stroke scales to be performed post-procedure prior to discharge from hospital. In addition, the protocol-required pre-procedure coagulations tests (PT/INR) were not performed for this subject.

1. In addition, the pre-procedure PTT drawn in the catheterization lab was extremely elevated (130.6 seconds). There was no source documentation noting that this was not a clinically significant abnormal clotting profile result. Therefore this subject met the exclusion criteria and should not have been enrolled.

H. [redacted] did not have a documented stroke scales assessment one week prior to enrollment or an ultrasound examination 30 days prior to enrollment as required by protocol. In addition, there was no source documentation of the subject's protocol-required pre-procedure PT.

I. [redacted] did not have a documented stroke scales assessment one week prior to enrollment as required by protocol.

J [redacted] had pre-procedure source documentation noting "[redacted] On J [redacted] was treated with a commercial [redacted]. The subject was enrolled 21 days later on August 18, 2004, and an investigation [redacted] was placed into the subject's [redacted] This subject was treated despite meeting an exclusion criterion which excludes those subjects where "there is a planned combination procedure involving either the [redacted] co [redacted] 30 days before or after the index procedure".

Please submit copies of the policies, procedures, and training (with expected completion dates) being developed and implemented to ensure that diagnostic evaluations are conducted in accordance with the investigational plan.

4. You failed to administer concurrent medications in accordance with the investigational plan. For example: Source documentation for [redacted] indicates that [redacted] was used during the implantation procedure instead of the protocol-required heparin.

   In your written response you state that this is the only subject who did not receive heparin during the procedure. Your response also stated that it was emphasized to all investigators that only heparin be used during the carotid stent procedure. Please submit copies of the policies, procedures and training (with expected completion dates) being developed and implemented to ensure that concurrent medications are administered in accordance with the investigational plan.

5. You failed to submit complete, accurate and current reports to the sponsor for unanticipated/major adverse device effects that occurred during the investigation within the time constraints set forth by the reviewing IRB and stated in the investigational plan.

   The case report forms in the investigational plan state that "major adverse events" are to be reported to [redacted] within 24 hours of knowledge of the events. The list of "major adverse events" includes but is not limited to death, myocardial infraction (MI), neurological events, and unanticipated adverse device effects. Some major adverse device events were reported up to a year after their occurrence. Examples of your failure to report major events in accordance with investigational plan include but are not limited to:

   A. The index procedure for [redacted] was performed on March 3, 2004. The subject experienced a seizure during post-dilation lasting <30 seconds. The CRF was completed on September 2, 2004. This adverse event was not reported to [redacted] until September 27, 2004.

   B. [redacted] experienced a non-Q-wave MI on February 2, 2004. This adverse event was not reported to [redacted] until September 8, 2004.

   C. [redacted] experienced an embolic stroke with mild left facial droop on February 5, 2004. This adverse event was not reported to [redacted] until October 7, 2004.

   D[redacted]xperienced a neurological event on November 26, 2003. This adverse event was not reported to [redacted] until May 4, 2004.

Please provide copies of policies and procedures, with expected completion dates, that are being developed and implemented to ensure case histories are complete, accurate and current. In addition, provide copies of policies and procedures, with expected completion

dates, which are being developed and implemented to ensure that the reporting of major adverse device effects are in accordance with the investigational plan.

The deviations cited above are not intended to be an all-inclusive list of deficiencies at your site. As a clinical investigator, it is your responsibility to ensure that investigations that you participate in are conducted in accordance with applicable FDA regulations. **Within 15 working days** after receiving this letter, please provide written documentation of the specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. In addition, please provide a list of your current investigational studies and include the name of the study sponsor and the date of IRB approval. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action, including initiation of disqualification procedures pursuant to 21 C.F.R. 812.119, without further notice.

Please respond in writing to:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
Program Enforcement Branch I (HFZ-311)
2094 Gaither Road
Rockville, Maryland 20850
Attention: Michael Marcarelli, Pharm.D.

We are also sending a copy of this letter to FDA's Cincinnati District Office. We request that a copy of your response also be sent to that office. If you have any questions, please contact Michael Marcarelli, Pharm.D. by phone at (240) 276-0125.

For further information concerning the Bioresearch Monitoring program, please visit our Internet homepage at http://www.fda.gov/cdrh/comp/bimo.html. Valuable links to related information are included at this site.

Sincerely yours,

Larry D. Sparks for

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