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**WARNING LETTER**

VIA FEDERAL EXPRESS

Robert P. Hickey  
President and Chief Executive Officer  
SyntheMed Inc.  
200 Middlesex Essex Turnpike  
Suite 210  
Iselin, NJ 08830

FEB 19 2008

Dear Mr. Hickey:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at SyntheMed Inc. from October 9 to October 26, 2007, by an investigator from the FDA New Jersey District Office. The purpose of this inspection was to determine whether your activities as the sponsor of the clinical study, [redacted]

[redacted] complied with applicable federal regulations. [redacted] 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 Dr. Eli Pine's written response dated October 31, 2007, 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 (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 C.F.R.) Part 812 -- Investigational Device Exemption. 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, Dr. Eli Pine's written response, and our subsequent review of the inspection report are discussed below:

**Failure to secure the investigator's compliance with the signed investigator 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)]**

Sponsors are responsible for ensuring that all clinical investigators participating in the investigation adhere to the signed agreement, the investigational plan, applicable FDA regulations, and any other conditions of approval imposed by the reviewing IRB or FDA. A sponsor that discovers an investigator who is not complying shall promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigation.

You failed to secure investigator compliance and ensure documentation and reporting of the protocol deviations that occurred, in accordance with FDA regulations. [redacted] of the protocol states, [redacted]

[redacted] During the FDA inspection it was noted that [redacted] assessments were performed by the same [redacted] who performed the [redacted] and randomization. Therefore, these physicians performing the [redacted] assessment were not masked from the randomization assignment. In addition, during the FDA inspection there was no documentation of sponsor approval, IRB notification, or notation in the monitoring documentation of these deviations. Examples of these failures include but are not limited to the following:

- A) Site [redacted] performed both the [redacted] and [redacted] assessment for [redacted] subjects enrolled, [redacted] therefore was not masked to the randomization. In addition, there was no documentation of sponsor approval, IRB notification, or notation in the monitoring documentation of these deviations.
- B) Site [redacted], the same physician performed both the [redacted] and [redacted] assessment on [redacted] subjects. Specifically, Dr. Lodge on subject [redacted] and [redacted] on subjects [redacted]. In addition, there was no documentation of sponsor approval, IRB notification, or notation in the monitoring documentation of these deviations.

Dr. Eli Pine's written response states "the investigator at site 16 was reminded at the November 29, 2005, monitoring visit that according to the protocol the surgeon performing the surgery could not also perform the assessment. It was recognized from the beginning of the program that this would be a novel, complex, and challenging study in a difficult patient population. Therefore, the Statistical Analysis plan that was finalized prior to locking the database and unmasking the randomization included an analysis to assess the impact of unmasking." Dr. Eli Pine's written response also states "in the future, monitors will be retrained to ensure that when protocol violations occur an appropriate corrective action will be instituted to prevent further violations." This response is inadequate in that it does not include a written corrective plan for securing investigator compliance and documentation and reporting of protocol deviations. Also, in the response it states monitors will be trained, please provide a copy of the training and

documentation of completion of the training for all applicable personnel. Please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to secure investigator compliance and documentation and reporting of protocol deviations. In addition, please provide copies of policies and procedures, with expected completion dates that are being developed and implemented to manage investigators from whom you are unable to secure compliance.

**Failure to ensure adequate monitoring of the investigation [21 CFR 812.40] and to include written procedures for monitoring in the investigational plan [21 CFR 812.25(e)]**

Sponsors are responsible for ensuring proper monitoring of the investigation. An investigational plan shall include written procedures for monitoring of the investigation and include the name and address of monitors.

[redacted]  
[redacted] monitoring Standard Operating Procedure (SOP), [redacted]  
[redacted] states, [redacted]  
[redacted], You failed to consistently [redacted] after monitoring visits to the sites. In addition, when you [redacted] they did not identify the protocol deviations. Examples of your failure include but are not limited to the following:

- A) Site [redacted], there was no documentation of a [redacted] to the site including documentation of any issues that need to be addressed after the [redacted] and [redacted] monitoring visits. This site had documented protocol deviations of the same physician performed both the [redacted] [redacted] and [redacted] assessment therefore, he was not masked from the randomization assignment.
- B) Site [redacted], subject [redacted] assessment was not performed by a masked surgeon. [redacted] performed both the randomization assignment and the assessment. The monitoring reports do not identify this protocol deviation.

Dr. Eli Pine's written response states "all monitors will be retrained on all relevant monitoring SOPs. In addition, all Project Managers will be trained to assure that follow-up letters are being sent." This response is inadequate. Please provide copies of the training and documentation of completion of the training for all applicable personnel. The response does not include documentation of corrective actions to ensure communication to the clinical sites to document, correct and, prevent protocol deviations. Please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to ensure adequate communication with the clinical sites. In addition, please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to ensure prior sponsor approval for protocol deviations and reporting of protocol deviation to the IRB and FDA occurs in accordance with local IRB policies and the federal regulations.

**Failure to accurately document device shipment records. [21 CFR 812.140(b)(2)]**

It is a sponsor's responsibility to maintain accurate, complete, and current records relating to the shipment and disposition of the devices. Records shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of disposition shall describe the batch number or code marks of any device returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reason for and method of disposal. Examples of your failure include but are not limited to the following:

- A) Your shipment records do not include the following accurate information:
  - 1) Records of disposition did not include shipment date.
  - 2) Information on transmittal record was not accurate. Specifically, the shipment transmittal record for [redacted] dated April 20, 2005, states shipped items were samples [redacted], however the sites comments are, "we already had sample #'s [redacted] Note: lot #'s are different!"
  - 3) Your records do not contain a batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal are incomplete.
- B) Section 4 Institutional Review Board of the investigational plan states, "A copy of the letter signed by the Chairman of the IRB to the Principal Investigator indicating IRB approval of the protocol must be received by the sponsor and maintained in the study file prior to study initiation. Device supply will not be shipped to study site until this documentation is received by the sponsor." [redacted]  
[redacted] SOP also states, [redacted]  
[redacted]  
[redacted]" You shipped devices to [redacted] prior to IRB approval.

Dr. Eli Pine's written response states in the future, detailed study specific procedures will be put in place to fully monitor investigational device shipments to and from the investigational sites. This response is incomplete in that it does not include a copy of aforementioned procedures and a written corrective action to ensure accurate and complete device distributions records are maintained. Please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to ensure these records are accurate and maintained.

**Failure to prepare and submit progress reports at regular intervals and at least yearly to FDA and reviewing IRBs. [21 CFR 812.150(b)(5)]**

For a significant risk device investigation a sponsor is responsible for submitting progress reports of the investigation to the FDA and all reviewing IRBs at regular intervals, and at

least yearly. These reports shall be complete and accurate. Examples of this failure include but are not limited to the following:

- A) There is only documentation of one progress report being submitted to the FDA in January 2005 since the initial approval of the IDE in March 1998.
- B) There is only documentation of one report containing current lists of the names and addresses of all investigators participating in an investigation being submitted to FDA.

Dr. Eli Pine's written response states for all future IDE studies the FDA will be informed every 6 months of the current names and addresses of all investigators. This response is incomplete in that it does not include a written corrective action to ensure this occurs. Please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to ensure progress reports are submitted to the FDA at regular intervals and at least yearly and investigator lists are submitted to the FDA every six months.

**Failure to obtain adequate signed investigator agreements for each participating investigator. [21 CFR 812.43(c)(5)]**

It is a sponsor's responsibility to obtain from each participating investigator a signed agreement that shall include sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement to the FDA. The agreement also must contain a commitment from the investigator to promptly update this information if any relevant changes occur during the course of investigation and for 1 year following the completion of the study. You failed to obtain the aforementioned information from participating investigators. Examples of your failure include but are not limited to the following:

Financial disclosure information was not obtained from investigators at any of the  clinical sites reviewed during the FDA inspection. You, as the sponsor signed a Form FDA 3454 for each investigator however, there is no documentation of financial disclosure information from the investigators. In addition, the Form FDA 3454 was not completed for  until the FDA inspection on October 9, 2007.

Dr. Eli Pine's written response states financial disclosure forms were either signed directly by the Principle Investigator (PI), key sub-investigators or by SyntheMed at the time of the qualification/initiation visit. However, during the FDA inspection there was no documentation from the principle investigators related to financial disclosure available, the documentation provided was Form FDA 3454s signed by Dr Pine. Dr. Eli Pine's corrective action states all sites will be contacted to obtain Financial Disclosure for investigators not on file in the study book and for future studies the information will be obtained from all investigators and included a commitment from the investigators to report any changes in financial conflict of interest for up to one year after study closure. This response is inadequate in that it does not include a written corrective action plan to

ensure this information is obtained and maintained from all IDE investigations. Please provide copies of policies, procedures, and training with expected completion dates that are being developed and implemented to ensure financial disclosure information is obtained and maintained from all investigators.

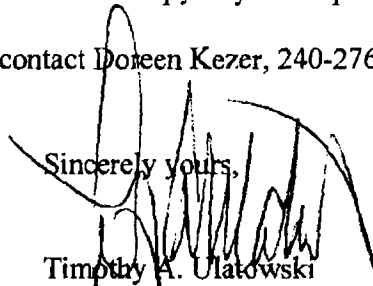
The violations described above are not intended to be an all inclusive list of problems that may exist with your clinical study. It is your responsibility as a study sponsor to ensure compliance with the Act and applicable regulations.

Within fifteen (15) working days of receiving this letter, please provide written documentation of the 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: Doreen Kezer, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 9200 Corporate Boulevard, HFZ-310, Rockville, Maryland 20850.

A copy of this letter has been sent to New Jersey District Office, 10 Waterview Blvd., 3<sup>rd</sup> Floor, Parsippany, NJ, 07054. Please send a copy of your response to that office.

If you have any questions, please contact Doreen Kezer, 240-276-0125, & [Doreen.kezer@fda.hhs.gov](mailto:Doreen.kezer@fda.hhs.gov).

Sincerely yours,



Timothy A. Ulatowski  
Director  
Office of Compliance  
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