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Food and Drug Administration  
9200 Corporate Boulevard  
Rockville, Maryland 20850

**WARNING LETTER**

Anthony R. Ignagni  
President and CEO  
Synapse Biomedical Inc.  
300 Artino Street  
Oberlin, OH 44074

JUN 20 2008

Dear Mr. Anthony Ignagni:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection at Synapse Biomedical Inc. from February 25 to March 18, 2008, by investigators from the FDA Cincinnati District Office. The purpose of this inspection was to determine whether your activities as the sponsor of the following clinical studies complied with applicable federal regulations:

- IDE [redacted]
  - Multi-Center Pivotal Study [redacted]
- IDE [redacted]
  - Pilot Study: [redacted]
  - [redacted] and
  - Pivotal Study o [redacted]

[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 your written response, dated April 8, 2008, 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 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. The deviations noted on the Form FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

**Failure to obtain FDA approval prior to allowing subjects to participate in an investigation. [21 CFR 812.42]**

A sponsor shall not begin an investigation or part of an investigation until an IRB and FDA have both approved the application or supplemental application relating to the investigation or part of an investigation. You began the investigation prior to FDA approval by enrolling subjects in the study.

Specifically, you expanded the [redacted] to four additional clinical sites without prior FDA approval.

| Site       | First subject enrolled | FDA approval |
|------------|------------------------|--------------|
| [redacted] |                        |              |

Your response is inadequate in that you did not describe a corrective and preventive action plan for ensuring appropriate approvals will be obtained in future studies. Please provide copies of policies and procedures, with expected completion dates, that are being developed and implemented to ensure all appropriate approvals are obtained prior to implementation.

**Failure to ensure adequate monitoring of the investigation. [21 CFR 812.40]**

Sponsors are responsible for ensuring proper monitoring of the investigation. Your monitoring was inadequate and you failed to monitor in accordance with your written monitoring procedure. Examples of this failure include, but are not limited to the following:

- A) Standard Operating Procedure (SOP), Clinical Study Monitoring Procedure, section [redacted] states the following: [redacted]

[redacted]” However, during the FDA inspection you

could not provide documentation of monitoring for the [redacted] involving 16 subjects after you acquired sponsorship of the IDE on [redacted]  
B) SOP, Clinical Study Monitoring Procedure section [redacted] states, "[redacted]

[redacted]

- 1) The monitoring visit report for site 01 dated [redacted], noted numerous omissions, such as missing laboratory tests, missing pulmonary or neurological evaluations, missing EKGs, missing chest X-rays, and missing conditioning logs; however, there is no documentation for corrections and/or clarifications of these omissions.
- 2) The monitoring visit report for site 05 dated [redacted] noted the IDE # as [redacted] however, the study monitored was actually [redacted] based on Subject ID numbers. In addition, the [redacted] had [redacted] [redacted]?" checked as "[redacted];" however, on the CRF, it is not checked as completed. The monitoring report lacks any corrections and/or clarifications of these discrepancies.
- 3) The monitoring visit report for site 08 dated [redacted] for subject [redacted] notes, copy of [redacted] results as "[redacted]" and [redacted] evaluations completed as "[redacted]" however, the CRF notes [redacted] [redacted]" and "[redacted]" The monitoring report lacks any corrections and/or clarifications of these discrepancies.

In your response you state you are cognizant of the need to improve your overall study monitoring procedures in order to better prevent the types of issues that the FDA identified in its inspection. You provided a copy of your SOP "Clinical Study Monitoring Procedure." However, your response is incomplete in that you did not provide documentation of implementation or training on this SOP. Please clarify your expected completion dates for training and implementation of the procedure and provide documentation of training of all monitoring personnel. In addition, please provide the name, address, and qualifications of the monitors. Additionally, a critical component of monitoring is securing investigator compliance and identification of protocol deviations. Your monitoring SOP does not address approving, documenting, and reporting of protocol deviations. Please add protocol deviations to your SOP.

Also, in your response you state following transfer of sponsorship on [redacted] you have "prioritized the monitoring of the active studies over historical data because of the opportunity to identify and remedy protocol nonconformance" (pg. 5). You have developed a corrective and preventative action plan (CAPA) for the transfer of the data for the [redacted] however, during the FDA inspection you had no documentation of a plan for the transfer of the [redacted] This response is inadequate in that you did not provide a plan to ensure the historical data is verified and reported. Please provide a plan including a time-line for the verification and reporting of the historical data.

**Failure to obtain from each participating investigator a signed agreement that includes sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement. [21 CFR 812.43(c)(5)]**

A sponsor shall obtain from each participating investigator a signed agreement that includes sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement. You failed to obtain a signed agreement that includes sufficient accurate financial disclosure information from each participating investigator. Specifically, during the FDA inspection you could only provide documentation of financial disclosure information obtained from one of the [redacted] investigators.

We understand that you did not obtain signed agreements regarding financial disclosure, because you "do not interpret the regulation as requiring a signed agreement with relation to financial interest" (page 9 of your response). We noted that you cited to 21 CFR 54.4 for authority; however, please understand that 21 CFR 812.43(c)(5) requires a sponsor to obtain signed agreements that includes sufficient accurate financial disclosure information.

In your response you state you are updating your investigator agreement to include financial disclosure requirements. This response is incomplete in that it does not contain documentation of financial disclosure information from the current investigators involved in these studies. Please provide written documentation of financial disclosure from all investigators involved in the studies involving [redacted]

**Failure to ship investigational devices only to qualified investigators participating in the investigation. [21 CFR 812.43(b)]**

A sponsor shall ship investigational devices only to qualified investigators participating in the investigation. You failed to adhere to this regulation in that, you shipped replacement parts for your investigational device, [redacted] to persons other than qualified clinical investigators, namely the subjects. Your device shipping log shows replacement parts such as, stimulators, external wires, and batteries have been sent to subjects' homes.

Please provide copies of policies and procedures with expected completion dates that are being developed and implemented to ensure investigational devices are shipped only to qualified 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.

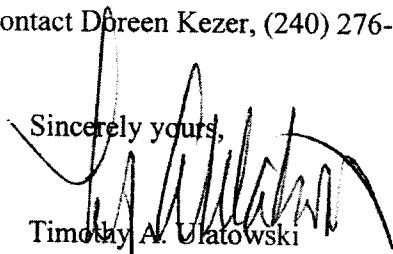
Within fifteen (15) working days of receiving this letter, please provide written documentation of the additional actions you have taken or will take to correct these

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: 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 the Cincinnati District Office, 6751 Steger Drive, Cincinnati, OH 44074. 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,



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Director  
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cc.  
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