DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

95486

SEP 16 2005

WARNING LETTER
VIA FEDERAL EXPRESS

John F. Dichiara
Senior Vice President
Clinical, Regulatory, and Quality
ReGen Biologics
509 Commerce Street, East Wing
Franklin Lakes, NJ 07417-1374

Dear Mr. Dichiara:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a recent Food and Drug Administration (FDA) inspection of your firm. During the period of April 21 through May 18, 2005, an investigator from FDA's New Jersey District Office inspected your site. The purpose of the inspection was to determine whether your sponsor activities and procedures relating to investigational studies of FDA-regulated products complied with applicable FDA regulations. The product used in the [redacted] Study [redacted] is a device as the term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 321(h)].

We have completed our review of the report prepared by the New Jersey District Office which described and documented deviations from the requirements of Title 21, Code of Federal Regulations (21 CFR), Part 812-Investigational Device Exemptions. These deviations were listed on the Form FDA 483, "Inspectional Observations," that was presented to and discussed with you and Margaret Crowe, Senior Clinical Affairs Manager, on site, and with Dr. Gerald Bisbee, Ph.D., President and CEO, via telephone, at the conclusion of the inspection. This letter also discusses your written response dated June 7, 2005, to the noted violations and requests that you implement prompt corrective actions to the violations cited.

The inspection was conducted under a program designed, in part, to ensure that data and information contained in applications for Investigational Device Exemptions (IDEs) are scientifically valid and accurate. Another objective of this program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

A description of deviations follows:

1. You failed to provide investigators with information they needed to conduct an investigation properly, to ensure proper monitoring, and to ensure IRB review and approval. [21 CFR 812.40]

Pursuant to 21 CFR 812.40, sponsors are responsible for providing investigators with the information they need to conduct the investigation properly, for ensuring proper monitoring, and for ensuring IRB review and approval. Sponsors are also required to supply all investigators with copies of the investigational plan, which includes the protocol. [21 CFR 812.45, 812.25] You failed to fulfill these requirements. Examples of these failures include, but are not limited to, the following:

- You failed to provide investigators with the information that they need to conduct the investigation, specifically, with the investigational plan, in that the correct version of the protocol was not provided to clinical investigators at all sites, specifically, IDE supplements [redacted] and [redacted]
- There were lapses in IRB approval, during which time subjects were randomized and/or had surgeries at three sites, and data were collected at five sites.
    - Four sites had lapses in IRB approval that were less than one year
    - One site had a lapse in IRB approval that was approximately three years
- In addition, IDE supplements [redacted] and [redacted] did not have IRB approval for use at all sites.

Your response acknowledges that (1) not all approved protocol amendments were transmitted in writing to the investigational sites; (2) that some investigators may not have transmitted and received IRB approval for certain protocol amendments; and (3) that some investigators may have allowed their IRB approvals to lapse. Your response states that you will (1) produce a current version of the protocol which incorporates all approved protocol amendments; (2) revise the "Clinical Study Monitoring" procedure; and (3) revise your "Organization and Administration of Clinical Studies procedure.

Your response is inadequate in at least the following respects: You do not address training on new procedures. In addition, your response does not address follow-up or monitoring to ensure that your corrective actions are effective. We recommend that you consider adding these elements to your corrective actions.

2. You failed to obtain IRB and FDA approval prior to the initiation of an investigation. [21 CFR 812.42]

Pursuant to 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. Five subjects were randomized and implanted at Site [redacted] prior to receiving IRB approval.

Your response acknowledges that enrollment of subjects should not have taken place prior to IRB approval and, in order to address this situation, you have revised the "Clinical Study Site Initiation" and the "Inventory Control of Investigational Devices" procedures.

Your response is inadequate in at least the following respects: You do not address training on new procedures. In addition, your response does not address follow-up or monitoring to ensure that your corrective actions are effective. We recommend that you consider adding these elements to your corrective actions.

3. You failed to prepare and submit complete, accurate, and timely reports regarding withdrawal of IRB approval. [21 CFR 812.150(b)(2)]

Pursuant to 21 CFR 812.150(b)(2), a sponsor shall notify FDA and all reviewing IRBs and participating investigators of any withdrawal of approval of an investigation within 5 working days after receipt of the withdrawal of approval. The IRB closed enrollment on 7/25/01 and terminated the study at site [redacted] on 8/28/01. There is no documentation that notification was prepared or submitted to FDA, all IRBs, and investigators, as required.

Your response states that the lack of notification occurred due to a misunderstanding of terminology, in that [redacted] thought "inactivation" meant enrollment was closed but that the study continued for patient follow-up and that further attempts should have been made to obtain copies of documentation submitted by the investigator to his IRB. Your response also states that you are revising the "Clinical Study Monitoring" procedures, are in the process of instituting an internal tracking of IRB renewals, and that future investigator agreements will include wording that the investigators are to provide the sponsor with copies of all IRB communications.

Your response is inadequate in at least the following respects: You do not address training on the new procedures. In addition, it is unclear what method(s) you intend to institute for internal tracking of IRB renewals. Your response does not address follow-up or monitoring to ensure that your corrective actions are effective. We recommend that you consider adding these elements to your corrective actions.

4. You failed to secure the compliance of an investigator who was not complying with the investigational plan. [21 CFR 812.46(a)]

Pursuant to 21 CFR 812.46(a), a sponsor who discovers that an investigator is not complying with the investigational plan shall promptly secure compliance, or discontinue

shipments of the device to the investigator and terminate the investigator's participation in the investigations. In each of five Site Monitoring Reports from 1997 through 1999, there was documentation of clinical investigator non-compliance at site [redacted]. There is no documentation that the firm took any action to bring the clinical investigator into compliance.

Your response acknowledges that you were unable to secure the compliance of this investigator and comments on your activities regarding this investigator's noncompliance. Your response also states that you have modified the "Clinical Study Monitoring" procedures to include actions to take in the event an investigator is not complying with FDA or IRB requirements, and that you have revised your "Clinical Site Close-Out" procedure to address dealing with a non-compliant investigator.

Your response is inadequate in at least the following respects: You do not address training on new procedures. In addition, your response does not address follow-up or monitoring to ensure that your corrective actions are effective. We recommend that you consider adding these elements to your corrective actions. In addition, your discussion of your activities regarding this investigator suggests that you would consider having an investigator continue with follow-up of previously enrolled subjects even if shipments of investigational devices to him had been halted and new enrollment stopped because of noncompliance. We note that under the regulation, a noncompliant investigator whose compliance cannot be obtained must be terminated from the investigation, and therefore, he should have no further participation in the investigation with regard to follow-up. In those circumstances, we would encourage you to find a new investigator to continue subject follow-up.

5. You failed to maintain complete records of the shipments of investigational devices. [21 CFR 812.140(b)(2)]

Pursuant to 21 CFR 812.140(b)(2), a sponsor is required to maintain accurate, complete and current records of shipment and disposition of investigational devices. There are discrepancies between sponsor and site records regarding number of units shipped to site [redacted] and dates of shipments. Inventory Control Log for site [redacted] indicates that four units of lot [redacted] were received on 9/1/98, and four of the same lot received on 10/20/98. All of these units were implanted. In addition, the same record shows that an additional three units of that lot were returned to the sponsor on 6/22/99. The sponsor records indicate that there were two shipments of four units each of this lot to site [redacted] on 10/6/98 and 11/16/99. Sponsor records do not document the date that the three units were returned from this site.

Your response acknowledges that records of shipment of an investigational device are not complete. Your response also states that you have conducted an internal audit of all device accountability records for all [redacted] investigational devices, and that you have also revised the "Inventory Control of Investigational Devices" procedure to include a more thorough monitoring and control of investigational devices.

Your response is inadequate in at least the following respects: You do not address training on new procedures. In addition, your response does not address follow-up or monitoring to ensure that your corrective actions are effective. We recommend that you consider adding these elements to your corrective actions.

6. You failed to obtain a signed investigator agreement from each participating investigator. [21 CFR 812.43(c)]

Pursuant to 21 CFR 812.43(c), a sponsor is required to obtain from each participating investigator a signed agreement and that agreement must include a statement of the investigator's commitment to conduct the investigation in accordance with the agreement, the investigational plan, part 812 and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA. Examples of this failure include, but are not limited to:

- None of [redacted] clinical investigator agreements reviewed during the inspection included a statement that the investigator agreed to conduct the investigation in accordance with applicable FDA regulations and conditions of approval.

- Three clinical investigators enrolled subjects and/or implanted devices prior to signing an investigator agreement:

    - Two clinical investigators at site [redacted] enrolled and/or implanted approximately 24 subjects prior to signing an investigator agreement.

    - One investigator at site [redacted] enrolled and/or implanted approximately 38 subjects prior to signing an investigator agreement.

Your response acknowledges that an investigator agreement should reference all applicable FDA regulations, and should instruct the investigator to comply with the conditions of approval imposed by FDA and the IRB. In addition, you acknowledge that several investigators randomized and/or performed surgeries prior to signing an investigator agreement. Your response states that you have constructed a new investigator agreement which contains references to all of the current requirements of 21 CFR 812, 50, 54, and 56, and that you have revised the "Clinical Study Site Initiation" procedure and the "Clinical Study Monitoring" procedure, and modified the "Inventory Control of Investigational Devices" procedure.

Your response is inadequate in at least the following respects: You do not address training on new procedures. In addition, your response does not address follow-up or monitoring to ensure that your corrective actions are effective. We recommend that you consider adding these elements to your corrective actions.

The deviations cited above are not intended to be an all-inclusive list of deficiencies at your site. As a sponsor, 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 a written response that includes the additional, specific steps you have taken or will take to correct these violations and to prevent the recurrence of similar violations in current and future studies which may be submitted in the form of a corrective action plan. Any submitted corrective action plan must include projected completion dates for each action to be accomplished.

[redacted] Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you.

You should direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, HFZ-310, 9200 Corporate Boulevard, Rockville, Maryland 20850. Attention: Doreen Kezer, Chief, Special Investigations Branch.

A copy of this letter has been sent to the Food and Drug Administration, New Jersey District Office, 10 Waterview Boulevard, Third Floor, Waterview Corporate Center, Parsippany, New Jersey, 07054. We request that a copy of your response also be sent to the New Jersey District Office.

Please direct all questions concerning this matter to Ms. Kezer at (240) 276-0125.

Sincerely yours,

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

cc:

Dr. Gerald Bisbee, Ph.D.
President and CEO
ReGen Biologics, Inc.
545 Penobscot Drive
Redwood City, CA