WARNING LETTER

Steiner Biotechnology, LLC

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Medical Devices

Recipient:

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Chief Executive Officer

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February 3, 2020

WARNING LETTER

Dear Dr. Steiner:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at Steiner Biotechnology from June 24, 2019 to June 28, 2019, by an investigator from the FDA's Office of Bioresearch Monitoring Operations (OBIMO). This inspection was conducted to determine whether activities and procedures related to your participation in nonclinical Good Laboratory Practice (GLP) studies concerning the Skeletal Graft and Ridge Graft complied with applicable regulations. Specifically, the investigator reviewed the following GLP studies conducted at your facility:

- "The use of Steiner Biotechnology Skeletal Graft putties in the treatment of skeletal bone defects"
- "Evaluation of Ridge Graft in a rabbit mandibular condylar critical size defect"

The Skeletal Graft and Ridge Graft used in these nonclinical studies 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), because they are 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 response dated July 16, 2019 to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemption, Premarket Approval applications, and Premarket Notification 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 OBIMO revealed serious violations of Title 21, Code of Federal Regulations (CFR) Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies (FDA GLP Regulations), 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 response, and our subsequent review of the inspection report are discussed below:

1. Failure to conduct nonclinical laboratory studies in accordance with the protocols [21 CFR 58.130(a)]

Nonclinical GLP studies shall be conducted in accordance with the study protocol(s). Your failures to adhere to this requirement include, but are not limited to, the following examples:

a. You performed repeated, multiple surgeries on the same animals over time in both of your nonclinical studies. Neither the study protocol for studying Skeletal Graft nor the study protocol for studying Ridge Graft stipulates that the animals may be used in this manner. Also, you used some of the same animals in both of your rabbit nonclinical studies despite both study protocols not stating that animals will be used in multiple studies.

In your written response dated July 16, 2019, you explained that repeated surgeries on animals within a study and use of animals across multiple studies minimized the number of animals needed for the studies. Also, in your response, you stated that because the bone grafting material was the same in both the tibia and maxillofacial regions, use of the animals across multiple studies should not have resulted in any confounding issue.

Your response is not adequate. Performing multiple bone defects in the same animals over time was not stipulated in either of your protocols. Because rabbit bones are fragile and the tibia bones are in weight-bearing limbs, creating four, simultaneous, critical-sized defects repeatedly in the tibias puts the animal at risk of unwanted bone fractures. The increased risk of bone breaks on the weight-bearing limbs is both an animal welfare concern and a confounder for both studies. It is also possible that confounders could have been introduced to both studies by creating bone defects in different sites in the animal anatomy due both to the fact that bilateral limb defects would necessitate that the animal put significant weight on each limb, possibly affecting the healing response, and that the immune system may be overwhelmed by multiple bone defects in different phases of healing. This could result in study data with a high level of variability that challenges FDA's ability to interpret whether the subject device is safe and effective. Regardless, using the same animals in multiple studies was not stipulated in either of your protocols.

Please provide updated protocols for these studies as well as any ongoing or planned studies that include accurate and complete descriptions of how animals will be used in your studies. Please also provide documentation of completed GLP training for you and your study staff.

b. Both of your animal study protocols specify both **(b)(4)** for anesthesia. However, for rabbits on which you performed bone surgery on October 16, 2016, your procedure notes indicate that you used only **(b)(4)** for anesthesia.

In your written response dated July 16, 2019, you stated that your research veterinarian deemed that **(b)(4)** alone was adequate for anesthesia.

Your response is not adequate. Failure to follow the protocol impacts the quality and reliability of data contained within the final study report. In addition to this being a protocol deviation, the animals that received only **(b)(4)** did not receive adequate anesthesia and analgesia for major orthopedic surgeries as **(b)(4)** should be used in combination with other agents to provide moderate anesthesia/analgesia. Thus, not only is the use of **(b)(4)** alone as an anesthetic agent to achieve a surgical plane of anesthesia a protocol deviation, it compromised animal welfare for the study. This also could affect the outcomes of

the study as animals that are not sufficiently anesthetized and/or have insufficient pain control during surgeries may move during the procedure (potentially impacting the implantation of the device) or self-mutilate the surgical site during the peri-operative phases of the study (potentially affecting the healing of the device).

Please provide documentation demonstrating how you will ensure staff will follow your nonclinical study protocols and ensure proper use of anesthetics. If you create or revise Standard Operating Procedures (SOPs) to address this, please also provide documentation of staff training on the new procedures.

2. Failure of your quality assurance unit (QAU) to inspect each nonclinical laboratory study at intervals adequate to assure the study's integrity and maintain written and properly signed records of each inspection and failure to document in writing the responsibilities and procedures of the QAU along with the method for indexing such records [21 CFR 58.35(b)(3) and 58.35(c)]

A testing facility shall have a QAU that shall be responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the FDA GLP Regulations. Moreover, the QAU shall, among other things, inspect each nonclinical laboratory study at intervals adequate to ensure the integrity of the study and determine that no deviations from approved protocol or standard operating procedures were made without proper authorization and documentation. The QAU inspections also must be appropriately documented. Additionally, the QAU must be entirely separate from and independent of the personnel who are directing and conducting the nonclinical study.

Your QAU failed to meet these requirements. These failures include, but are not limited to, the following examples:

a. You created inspection sheets for your site that consisted of checklists of items that your site inspected periodically. However, these checklists did not have the necessary elements of documentation for the QAU inspections as set forth in 21 CFR 58.35(b)(3).

In your response dated July 16, 2019, you explained that you did not have formal documentation of the QAU for either of your nonclinical studies. You also stated that in the future, your QAU will perform and document all required inspections.

Your response is not adequate. The lack of proper documentation for your QAU and its inspection activities does not allow for appropriate assurance that the facilities, equipment, personnel, methods, practices, records, and controls are in accord with FDA GLP Regulations. A reliable QAU is integral to the successful completion of any GLP study. Without appropriate QAU oversight, there is no assurance that what is reported in the final study report is accurate. Failure to perform QAU functions calls into question the validity of the entire study.

Please provide documentation demonstrating how you will ensure appropriate documentation of QAU inspections. If you create or revise SOPs to address this issue, please also provide documentation of staff training on the new procedures. The QAU inspection documentation will need to clearly identify the following for each study, as required by 21 CFR 58.35(b)(3):

- study being inspected
- the segments or phases of the study that are being inspected
- the person or persons performing the inspection
- the inspection findings, problems, action recommended and taken to resolve existing problems
- any scheduled date for reinspection

b. You did not have written documentation relating to the responsibilities and procedures of the QAU.

In your response dated July 16, 2019, you stated that you plan to produce SOPs for the roles and responsibilities of the QAU prior to any planned nonclinical studies. These new SOPs were not included in your response. As a result, your response is not adequate.

As stated above, the QAU is a critical component of any GLP study. Without appropriate QAU documentation, the individuals in the QAU may not adequately understand their roles and responsibilities. A lack of appropriate documentation of the procedures and function of the QAU makes it difficult for a QAU to perform the proper oversight to ensure accuracy of the data

in your final report. Also, poor documentation of the records that must be maintained by the QAU may result in confusion over which study and what components of the study were inspected. Thus, the validity of a nonclinical study is jeopardized by an ineffective, poorly documented QAU.

Please provide copies of the new SOPs that describe the responsibilities and procedures of the QAU for any completed, ongoing, or planned studies. Please also provide documentation of training of you and your staff on these new SOPs. The items that must be included in this written documentation of the responsibilities and procedures of the QAU are the following, as required by 21 CFR 58.35(c):

- responsibilities and procedures applicable to the quality assurance unit
- records maintained by the quality assurance unit
- method of indexing records

3. Failure to ensure that specimens are properly identified by test system, study, nature, and date of collection [21 CFR 58.130(c)]

Nonclinical study specimens must be properly identified by test system, study, nature, and date of collection. This information must be located on the specimen container or must accompany the specimens in a manner that precludes error in the recording and storage of study data. You failed to satisfy these requirements. Examples of your failure to comply with these requirements include, but are not limited to, the following:

At least two containers of specimens were identified only with an animal number written in ink either on the side of the container or on the container lid. Additionally, multiple specimens were located together in the same container without adequate identification. Your SOP entitled “Collection and Identification of Specimens” specified the appropriate identification of specimens, but you did not follow your SOP.

In your response dated July 16, 2019, you explained that all specimens will be identified by test system, study nature, and date of collection. You did not provide a plan for preventing this violation from recurring in the future.

Your response is not adequate. Without proper labeling and identification of specimens, errors can easily be made in the recording and storage of data and, thus, the quality of the entire study is jeopardized.

Please provide a corrective action plan addressing how you will ensure proper identification of specimens. If you create or revise SOPs to address this issue, please also provide documentation of staff training on the new procedures.

4. Failure to ensure that the testing facility maintains a current summary of training and experience for each individual engaged in or supervising the conduct of a nonclinical laboratory study [21 CFR 58.29(b)]

Each testing facility shall maintain a current summary of training and experience and a job description for each individual engaged in or supervising the conduct of a nonclinical laboratory study. Examples of your failure to satisfy this requirement include, but are not limited to, the following:

The employees of your GLP facility who are listed in the table immediately below were engaged in the two subject GLP studies, but the FDA investigator was unable to obtain a complete and current record of their training, experience, and job description. You were only able to provide the employees’ certificates of completion of web-based animal care training courses by the American Association for Laboratory Animal Science (AALAS) and the CVs and resumes of almost all the employees involved in the studies.

(b)(4), (b)(6)	Missing Documents
(b)(4), (b)(6)	Summary of experience; Job description
(b)(4), (b)(6)	Summary of experience; Job description
(b)(4), (b)(6)	Summary of experience; Job description
(b)(4), (b)(6)	Job description

(b)(4), (b)(6)	Job description
(b)(4), (b)(6)	Job description
(b)(4), (b)(6)	Job description
(b)(4), (b)(6)	Job description

In your response dated July 16, 2019, you indicated that you would maintain a current summary of training and experience and job description for all individuals engaged in or supervising the nonclinical studies.

Your response is not adequate because it lacks updated documentation of training and experience and job description for each individual who is either engaged in or supervising your current and planned nonclinical studies.

It is necessary to document the training and experience for each person who is either engaged in the conduct of the study or supervising the conduct of the study for assurance that each person has the appropriate training and experience to adequately perform the tasks that are related to his or her roles and responsibilities pertaining to the nonclinical study. Also, documentation of the training and experience and job description for each individual is important for maintaining accountability and for ensuring that each individual clearly understands his or her roles and responsibilities in the study.

Please provide updated documentation of training and experience and job description for each individual who is either engaged in or supervising your current and planned nonclinical studies.

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

Within 15 working days of receiving this letter, please provide documentation of the additional corrective and preventive 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 testing facility. 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 58.202.

Your response should reference “CTS # EC190337/E001” and be sent to:

Attention: Sheena A. Green, M.S.
Assistant Director, Clinical Evidence Quality Team 2
Food and Drug Administration
Center for Devices and Radiological Health
Office of Clinical Evidence & Analysis
DCEA1: Division of Clinical Science & Quality
10903 New Hampshire Avenue
Building 66, Room G202
Silver Spring, Maryland 20993-0002

A copy of this letter has been sent to FDA’s OBIMO – West via e-mail at ORABIMOW.Correspondence@fda.hhs.gov. Please send a copy of your response to that office.

If you have any questions about the content of this letter, please contact Bill Riemenschneider at 301-796-9682 or Bill.Riemenschneider@fda.hhs.gov.

Sincerely yours,
/S/

Soma Kalb, PhD
Director
DCEA1: Division of Clinical Science and Quality
Office of Clinical Evidence & Analysis
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

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