DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Institutional Review Board – Restrictions Imposed

By Certified Mail – Return Receipt Requested

May 13, 2015

William C. Domb, DMD
Chair
Inland Institute of Aesthetic Dentistry Institutional Review Board
190 N. Mountain
Upland, CA 91786

Dear Dr. Domb:

This letter imposing restrictions (IRB Restrictions Letter) informs you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection of the Inland Institute of Aesthetic Dentistry (Inland) Institutional Review Board (IRB) from September 23, 2014 to October 16, 2014, by investigators from the FDA Los Angeles District Office. This inspection was conducted, in part, to determine whether the IRB is in compliance with applicable federal regulations. IRBs that review investigations of devices must comply with applicable provisions of Title 21, Code of Federal Regulations (CFR) Part 56 - Institutional Review Boards, Part 50 - Protection of Human Subjects, and Part 812 - Investigational Device Exemptions.

At the close of the inspection, the FDA investigator presented an inspectional observations Form FDA 483 and discussed the observations listed on the form with you, the IRB Chairperson. We acknowledge receipt of the IRB's written response dated October 28, 2014. We have reviewed the inspection report, the Form FDA 483, and the response. The IRB's written response is inadequate, as explained below.

This IRB Restrictions Letter provides you with written notice describing Inland IRB's noncompliance with (violations of) applicable federal regulations governing the operation and responsibilities of IRBs under 21 CFR Part 56. Inland IRB is required to respond in writing to FDA's Center for Devices and Radiological Health (CDRH) with a description of the corrective actions that will be (or have been) taken by the IRB to achieve compliance with FDA regulations (21 CFR 56.120(a)). The name and address of the person that you should submit your corrective action plan to is provided at the end of the letter. A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. Failure to prepare and maintain adequate documentation, and follow written procedures governing the functions and operations of the IRB. [21 CFR 56.108(a), 56.108(b), and 56.115(a)(6)]

In order to fulfill the requirements of part 56 each IRB must prepare and maintain adequate documentation, and follow written procedures describing IRB functions and operations as specified in the regulations.

The IRB failed to adhere to these requirements. Specifically, the IRB did not prepare and maintain adequate documentation and follow written procedures for the following activities:

- Conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution.
- Determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review.
- Ensuring prompt reporting to the IRB of changes in research activity.
- Ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.
- Ensuring prompt reporting to the IRB, appropriate institutional officials, and FDA of:
    - Any unanticipated problems involving risks to human subjects or others.
    - Any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB.
    - Any suspension or termination of IRB approval.

It is critical that the IRB prepare, maintain, and follow adequate written procedures for its operations. Written procedures are important because they describe how an IRB operates and conducts its major functions, and help to ensure that research is reviewed in a timely manner and that the findings are adequately reported to the institution and the clinical investigator. Compliance with these requirements is intended to protect the rights and welfare of research subjects involved in such investigations. The IRB's lack of written procedures for the review of research may have an adverse impact on the rights, safety, and welfare of research subjects and decrease the integrity and validity of research data.

In the IRB’s response, you state that the IRB will perform all of the functions listed above. This response is inadequate because it fails to address the

requirement to prepare and maintain adequate documentation and follow written procedures describing IRB functions and operations.

Please provide an explanation of the actions that the IRB has taken or plans to take to ensure that the IRB prepares and maintains adequate documentation, and follows adequate written procedures. The response should provide documents relating to proposed and completed actions, such as revised standard operating procedures, and documentation of any actions taken, such as records of staff training, as well as dates trained.

2. **Failure to review proposed research at convened meetings. [21 CFR 56.108(c)]**

Except when an expedited review procedure is used, the IRB is required to review proposed research at convened meetings at which a majority of the IRB members are present, including at least one member whose primary concerns are in nonscientific areas.

The IRB failed to adhere to these requirements. Specifically, for initial review of the study titled **[(b)(4)]** you called each member separately. The board did not have a meeting to discuss the study. Later, members voted and approved it. This is not an acceptable substitute for a convened meeting.

The failure of the IRB to review proposed research at a convened meeting is a serious violation. IRB review of proposed research is conducted at convened meetings so all members of the committee have an opportunity to discuss all the risks and benefits of the research in order to ensure that human subjects are adequately protected. Failure to do so can place subjects at increased risk of harm.

In the IRB's response, you state that the IRB will approve only research reviewed by a majority of eligible members. This response is inadequate because it lacks sufficient detail to ensure that the IRB will review research at convened meetings.

Please provide a more detailed explanation of the actions the IRB has taken or plans to take to ensure that the IRB will review research at convened meetings. The response should provide documents relating to proposed and completed actions, such as revised standard operating procedures, and documentation of any actions taken such as a list of staff trained, as well as dates trained.

3. **Failure to ensure that no IRB member participated in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. [21 CFR 56.107(e)]**

No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflict of interest, except to provide information requested by the IRB.

The IRB failed to adhere to these requirements. Specifically, four clinical investigators and you, the sponsor-investigator, served as members of the IRB and participated in the study titled, **[(b)(4)]**. All five IRB members took part in the IRB's review of this study and voted on the study's approval. This appears to be a significant conflict of interest that should have been recognized and addressed by the IRB. No member of the IRB verified that there was not a conflict of interest.

The IRB's failure to ensure that voting IRB members did not have conflict of interests has lessened the likelihood of a fair and equitable IRB review of the study. As a result, the safety and welfare of human subjects may have been jeopardized and adequate human subject protection measures may not have been implemented.

In the IRB's response, you state that IRB members will recuse themselves from voting when there is a conflict of interest. This response is inadequate because it lacks sufficient detail to ensure that the IRB will not allow members with conflicts of interest to vote.

Please provide a more detailed explanation of the actions the IRB has taken or plans to take to ensure that the IRB will not allow members with conflicts of interest to vote. The response should provide documents relating to proposed and completed actions, such as revised standard operating procedures, and documentation of any actions taken, such as a list of staff trained, as well as dates trained.

4. Failure to require that information given to subjects as part of informed consent is in accordance with 21 CFR 50.25. [21 CFR 50.25(a) and 56.109(b)]

In seeking informed consent, basic elements, and additional elements when appropriate, must be provided to each subject as described in 21 CFR 50.25 (see also 21 CFR 56.109(b)).

The IRB failed to adhere to these requirements. Specifically, the informed consent documents (ICDs) for the study titled, **[(b)(4)]** did not adequately address all eight of the basic elements of informed consent as described in 21 CFR 50.25(a). For example, the ICDs did not include:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that FDA may inspect the records.
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Moreover, it is unclear whether informed consent was documented by the use of a written informed consent form approved by the IRB in accordance with 21 CFR 50.27 where IRB members allegedly approved ICDs over the phone or by email for the study.

A valid informed consent process ensures that research subjects have a clear understanding of risks of participation in a research protocol, have sufficient opportunity to consider whether to participate in the study, and make an informed decision if they decided to participate.

The elements omitted from the ICDs include important information such as the risks and benefits of participating in the study, the extent of the subject’s confidentiality, the subject’s financial burden while participating in the study, important contact information, and statements that the subject is participating in experimentation voluntarily. Study subjects are required to have this information prior to study enrollment. By failing to require the use of appropriate ICDs before enrolling subjects in a clinical investigation, the IRB did not adequately protect the rights and safety of those human subjects.

In the IRB’s response, you state that you will ensure that the IRB will approve only those ICDs containing the required elements. This response is inadequate because it lacks sufficient detail to ensure that the IRB will do so.

Please provide a more detailed explanation of the actions the IRB has taken or plans to take to ensure that the IRB will ensure that the ICDs include the information required by 21 CFR 50.25. The response should provide documents relating to proposed and completed actions, such as revised standard operating procedures, and documentation of any actions taken, such as a list of staff trained, as well as dates trained.

5. **Failure to determine that risks to subjects were minimized and that there were adequate provisions for monitoring the data collected. [21 CFR 56.111(a)(1) and 56.111(a)(6)]**

In order to approve FDA-regulated clinical studies, an IRB must determine that all of the requirements as defined in 21 CFR 56.111 are satisfied. Specifically, an IRB is required to determine that risks to subjects are minimized and that, where appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects.

The IRB failed to adhere to these requirements. Our inspection revealed that the IRB did not have sufficient information for the study titled, **[(b)(4)],** including the following:

- Study endpoints, statistical hypotheses, or a statistical analysis plan.
- A risk analysis or a plan to minimize risk to subjects.
- A specification of the particular model of ozone generator.
- A specification of the maximum amount of ozone that can be administered.
- Data safety monitoring provisions.
- A clinical site monitoring plan.

Without this information, the IRB did not have sufficient information to identify potential risks to subjects and determine that they were minimized.

The failure to ensure that risks to subjects were minimized may have placed study subjects at increased risk of harm associated with the investigational device and any study related procedures. These risks include, but are not limited to, damage to pulmonary tissue leading to respiratory compromise, damage to intraoral soft tissue and mucosa and significant eye irritation or more serious ocular injury if there is significant ozone gas leakage.

Furthermore, our inspection revealed that the IRB did not have adequate provisions for monitoring the data collected to ensure the safety of subjects. Proper monitoring helps ensure that the safety, rights, and well-being of the

subjects are protected and that the data is complete and accurate. Monitoring should be an on-going program performed with the frequency necessary to ensure that the investigation is conducted according to the investigational plan, FDA regulations, and any conditions of approval required by FDA or the reviewing IRB. Monitoring is needed in order to review records, source documents and study procedures for the presence and appropriate documentation of adverse events and protocol deviations.

In the IRB's response, you state that the IRB will require more detailed protocols for future investigations. This response is inadequate because it lacks sufficient detail to ensure that the IRB will determine that risks to subjects are minimized.

The IRB's response also states that the IRB will select monitors for future studies. This response is inadequate because it fails to recognize that selecting monitors is a sponsor responsibility, while the IRB's responsibility is to determine that the research under review contains adequate provisions for monitoring the data collected.

Please provide a more detailed explanation of the actions the IRB has taken or plans to take to ensure that the IRB will determine that risks to subjects are minimized and that there are adequate provisions for monitoring the data collected. The response should provide documents relating to proposed and completed actions, such as revised standard operating procedures, and documentation of any actions taken, such as a list of staff trained, as well as dates trained.

6. Failure to prepare and maintain adequate documentation of IRB activities. [21 CFR 56.115(a)(2) and 56.115(a)(5)]

An IRB is required to prepare and maintain adequate documentation of IRB activities including, but not limited to, IRB meeting minutes and a list of IRB members.

The IRB failed to adhere to these requirements. The IRB has not prepared any documentation of IRB activities, IRB meeting minutes, or a list of IRB members.

It is critical that the IRB prepare and maintain adequate documentation of IRB activities in order to ensure that the rights and welfare of study subjects are protected. An updated member list showing the relationship between each member and the institution is also important to ensure that the IRB's review of research is fair and equitable. It would also prevent the participation of any member who may have a conflict of interest.

In the IRB's response, you state that the IRB will keep records of IRB activities. This response is inadequate because it lacks sufficient detail to ensure that the IRB will prepare and maintain adequate documentation of IRB activities.

Please provide a more detailed explanation of the actions the IRB has taken or plans to take to ensure that the IRB prepares and maintains adequate documentation of IRB activities. The response should provide documents relating to proposed and completed actions, such as revised standard operating procedures, and documentation of any actions taken, such as a list of staff trained, as well as dates trained.

7. **Failure to notify investigators and the institution in writing of its decision to approve or disapprove proposed research activities. [21 CFR 56.109(e)]**

An IRB is required to notify investigators and the institution in writing of its decision to approve or disapprove proposed research, or of modifications required to secure IRB approval of the research.

The IRB failed to adhere to these requirements. The IRB did not notify investigators and the institution in writing of its decision to approve research. Specifically, the IRB approved a study titled, **[(b)(4)],"** at sixteen sites and failed to notify all sixteen investigators and their institutions in writing of its decision to approve this study.

Written notification to clinical investigators documents IRB approval at that site and informs clinical investigators about any conditions of approval. Furthermore, notification to the institution keeps institutional officials apprised of research occurring at their facility. As a result of the IRB's actions, research subjects may have been placed at increased risk of harm and their rights may not have been adequately protected.

The IRB did not address this issue in its response.

Please provide a detailed explanation of the actions the IRB has taken or plans to take to ensure that the IRB will notify investigators and the institution in writing of its decision to approve or disapprove proposed research, or of modifications required to secure IRB approval of the research. The response should provide documents relating to proposed and completed actions, such as revised standard operating procedures, and documentation of any actions taken, such as a list of staff trained, as well as dates trained.

The violations described above are not intended to be an all-inclusive list of problems that may exist at Inland IRB. Inland IRB is responsible for ensuring compliance with the Federal Food, Drug, and Cosmetic Act and applicable regulations.

Based on the serious deficiencies found during this inspection of the IRB, Inland IRB does not meet the requirements of 21 CFR Part 56. We have no assurance

that the IRB's procedures are adequately protecting the rights and welfare of the human subjects involved in research. For this reason, and the reasons described elsewhere in this letter, effective immediately, FDA is placing the following two restrictions on the IRB:

1. **Withholding approval of new studies subject to the requirements of Part 56 that are reviewed by the IRB. [21 CFR 56.120(b)(1)]**

2. **Terminating ongoing studies subject to Part 56, when doing so would not endanger the subjects. [21 CFR 56.120(b)(3)]**

Because FDA is withholding approval of new studies subject to Part 56 that are reviewed by the IRB, a sponsor may not begin any new clinical investigation of a device, either significant or non-significant risk, subject to 21 CFR Part 812, and which is not exempt under 21 CFR 812.2(c). Please notify all affected sponsors and clinical investigators of the restriction.

In the IRB's response, you state that the sponsor has terminated the only study under the IRB's oversight. If the IRB has approved any studies since the conclusion of this inspection, FDA is terminating all such ongoing studies subject to Part 56 when doing so would not endanger the subjects. If the IRB or any sponsor believes that termination would endanger subjects, you should notify FDA. Please notify the affected sponsors and clinical investigators of any termination.

These restrictions will remain in effect until such time as FDA receives from you evidence of adequate corrective action and notifies you in writing that the corrective actions are adequate. These restrictions do not relieve the IRB of its responsibilities to receive and respond to reports of unanticipated problems and unanticipated adverse device effects, and routine progress reports from ongoing studies.

Within 30 working days of receiving this letter, you should respond in writing with a description of the corrective actions that will be taken or that have been implemented to bring the IRB into full compliance with FDA regulations.

Your response should address each item of noncompliance listed above. If you do not believe that the IRB is in violation of FDA requirements, include your reasoning and any supporting information for our consideration. If you assert that full and adequate correction has been achieved, you should include any documentation that affirms your corrective actions. For each action to be accomplished, include the completion, or projected completion, date(s).

Include with your response a copy of the IRB's written communication to each of the affected sponsors and clinical investigators, notifying them of the current FDA-imposed restrictions. In addition, please provide a list of all studies being

reviewed by the IRB that are subject to 21 CFR Part 56, and a list of all studies that are affected by the above restrictions.

Your failure to adequately respond to this letter may result in further Agency action, including further action under 21 CFR 56.120 or disqualification under 21 CFR 56.121.

Your response should reference “CTS # EC140536/E001” and be sent to:

Attention: Adam Donat, MS
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room 3450
Silver Spring, Maryland 20993-0002.

CDRH will carefully consider your written response. Additionally, your corrective actions may be verified during a future inspection.

If you have any questions, please contact Adam Donat, MS, at (301) 796-5316 or Adam.Donat@fda.hhs.gov.

Sincerely yours,

Jan B. Welch, MHS, MT (ASCP) SBB
Acting Director
Office of Compliance
Center for Devices and
Radiological Health

cc:
Kristina C. Borror, Ph.D.
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