Dear Dr. Hurwitz:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection of your clinical site from March 13, 2013, to April 2, 2013, by an investigator from the FDA Philadelphia District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study, “(b)(4),” involving the Invasix Body Tite device, complied with applicable federal laws and regulations. Invasix Body Tite is a device as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act, because it is 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.

According to the documented history of this device at FDA, the Invasix Body Tite device is a significant risk device, under 21 CFR 812.3(m), because it presents a potential for serious risk to the health, safety, or welfare of a subject. Please note that the clinical investigation of Invasix Body Tite device did not have an FDA-approved investigational device exemption (IDE).

The inspection was conducted under a program designed to ensure that data and information contained in requests for IDEs, 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 district office revealed several violations of Title
21, Code of Federal Regulations (CFR), Part 812 - Investigational Device Exemptions and Part 50 – Protection of Human Subjects, which are 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 violations note on the Form FDA 483, your May 23, 2013, written response, and our subsequent review of the inspection report are discussed below.

1. **Failure to ensure that informed consent is obtained in accordance with 21 CFR 50.27, and failure to maintain accurate, complete and current records evidencing informed consent under 21 CFR 812.140(a)(3)(i).**

As a clinical investigator, you are responsible for ensuring that informed consent is obtained in accordance with 21 CFR Part 50. 21 CFR 812.100. Under 21 CFR 50.27(a), informed consent must be documented by the use of a written consent form approved by the IRB and signed and dated by the subject at the time of consent. A copy must be given to the subject. You are responsible for maintaining accurate, complete, and current records of each subject’s case history and exposure to the device, including signed and dated consent forms documenting that informed consent was obtained prior to participation in the study. 21 CFR 812.140(a)(3)(i).

You failed to maintain the consent documents for four subjects. Examples of these failures include:

a. There was no signed consent form found for Subject (b)(6) before investigational use of the Invasix Body Tite on November 25, 2009.

b. The consent form available for Subject (b)(6) was signed on August 14, 2009, more than one month after investigational use of the Invasix Body Tite device.

c. There were no signed consent forms found for Subject (b)(6) and Subject (b)(6) before they received investigational procedures on November 18, 2009, and November 20, 2009, respectively.

An adequate consent process informs study subjects, among other things, of potential risks, benefits, alternatives, and the procedures involved in participating in the investigation. This process allows subjects to make informed decisions on whether to participate in the study and occurs prior to any study procedure. Proper documentation of informed consent is important to ensure that you do not violate the rights of study subjects and to demonstrate that you obtained informed consent in accordance with applicable FDA requirements.

Your written response attributes the lack of signed documentation of informed consent to a loss of the forms. As an investigator, you are required to maintain records relating to your participation in the investigation, under 21 CFR 812.140(a). Your response is inadequate because it does not address how this deficiency will be avoided in the future. Please provide a preventive action plan detailing how you will ensure compliance with requirements for documenting the informed consent process in future studies.

2. **The informed consent document lacked a description of reasonably foreseeable risks or discomforts to the subject. 21 CFR 50.25(a)(2).**

As a clinical investigator, you are responsible for ensuring that informed consent is obtained in accordance with 21 CFR Part 50. 21 CFR 812.100. In seeking informed consent, a description of reasonably foreseeable risks and discomforts must be provided to the subjects. 21 CFR 50.25(a)(2).

You failed to comply with this regulation. Specifically, the consent forms used for Subjects (b)(6) to
(b)(6) did not list reasonably foreseeable risks resulting from the addition of a Limited Abdominoplasty procedure at the same time as the Invasix BodyTite device, including fat necrosis, persistent swelling, and lymphedema. In addition, for Subjects (b)(6), (b)(6), (b)(6), and (b)(6) the consent forms failed to disclose reasonably foreseeable risks associated with general anesthesia, including nerve injury, pneumonia, and heart attack.

It is critical that study subjects remain informed about all potential risks and benefits of participating in the investigation. This process allows subjects to make informed decisions on whether to participate in the study.

Your written response states that the subjects were verbally informed of increased risks of the abdominoplasty procedure with the use of the BodyTite device and additional anesthesia, and that lack of signed confirmation is attributed to clerical error. Your response is inadequate because it does not address how this deficiency will be avoided in the future. Please provide a preventive action plan detailing how your site will ensure that subjects are appropriately informed of all foreseeable risks and discomforts using an IRB-approved consent form.

3. Failure to ensure that the investigation was conducted according to the signed agreement, investigational plan, and applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA. 21 CFR 812.100.

As a clinical investigator, you are responsible for ensuring that an investigation is conducted in accordance with the investigational plan, the signed agreement, and applicable FDA regulations. This includes ensuring that no additional study procedures are conducted, as well as ensuring that all case report forms are completed as stated in the protocol.

You failed to follow the Clinical Investigation Plan, Protocol RAL 1. In addition, the study changes were not reported to the IRB, nor was prior approval obtained from the IRB. Examples of your failure include, but are not limited to, the following:

a. Subjects (b)(6) underwent additional plastic surgery procedures such as Limited Abdominoplasty, which were not described in the protocol, during the same time that the Invasix BodyTite device was used

b. The Protocol RAL 1, under Treatment, states, "Subject will receive sedative and local anesthesia preparation. Tumescent anesthesia may also be used during treatment." Subjects (b)(6), (b)(6), (b)(6), and (b)(6) received general anesthesia, which was not provided for in the protocol.

c. The Protocol RAL 1, under Records and Reports, states that “Data from the pre/post-treatment evaluations, the treatment sessions, complications, if any, and all follow-up evaluations will be recorded on the [case report forms] (CRFs) prepared for this clinical study.” The CRFs were not accurate, complete, and current according to the investigational plan.

Examples of your failure to comply with applicable regulations and the protocol include:

i. There were no CRFs available for subjects (b)(6), (b)(6), (b)(6), (b)(6), (b)(6), and (b)(6).

ii. (b)(6) files had at least one incomplete CRF section. Examples include subjects (b)(6), (b)(6), (b)(6), (b)(6), (b)(6), and (b)(6). For each of these subjects, the following CRF sections had either no data entered or incomplete data: Subject History, Treatment Areas and Parameters, Photography, Weight Measurements, Circumferential Measurements, Tightening Measurements, and Adverse Effects.

d. The Protocol RAL 1, under Adverse Events, states that “[t]he Physician must document on the
Adverse Events form, in standard medical terminology, all adverse signs and symptoms regardless of severity or frequency that are either volunteered by subjects or observed during the course of the study. Included in the description will be the nature of the sign or symptom, the date of onset, whether the event was serious, the severity, the relationship to study treatment or device, the action taken, the date of resolution, and the outcome.” The following subjects’ CRFs did not include adverse events documented in the medical records:

<table>
<thead>
<tr>
<th>Subject</th>
<th>Adverse Events in medical records but not on the CRFs</th>
</tr>
</thead>
<tbody>
<tr>
<td>(b)(6)</td>
<td>nausea and lightheaded</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>skin necrosis, ringing in ears, nausea, fainting, pain</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>melanoma/blue cell nevus</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>Miscarriage</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>superficial burns from device malfunction</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>staph infection of seroma</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>seromas requiring aspiration twice</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>swelling, bruising, scabbed burns</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>bruising, swelling, blisters</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>recurrent seromas requiring aspiration and surgery to repair a cavity</td>
</tr>
<tr>
<td>(b)(6)</td>
<td>superficial burns</td>
</tr>
</tbody>
</table>

Failure to follow the investigational plan may represent serious violations of an investigator’s responsibility to ensure the safety and welfare of study subjects. A decision to perform additional procedures not indicated in the protocol could place subjects at increased risk of surgical complications and complications related to anesthesia. Any additional study procedures should receive prior written approval from the sponsor, FDA, and the IRB to ensure that the procedures are appropriate and the risks to subjects are minimized.

In addition, failure to adequately maintain CRFs in accordance with the investigational plan could compromise the integrity of the study data. Without complete subject CRFs, an accurate assessment of the safety and efficacy of the device may be difficult.

Your written response acknowledges the limited abdominoplasty cases, which you state were added after receiving verbal assurance from the sponsor that those operations fell within the published protocol. Your written response also acknowledges incomplete CRFs, which included incomplete documentation of adverse events. These responses are inadequate because they do not propose corrective or preventive actions to address how these deficiencies will be avoided in the future. Please provide a preventive action plan detailing how you will ensure that clinical studies are conducted according to the signed agreement, investigational plan, applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.

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 clinical investigator to ensure compliance with the Act and applicable regulations.

Within fifteen working days of receiving this letter, please provide written documentation of the actions that 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 clinical investigator. 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 812.119.

You will find information to assist you in understanding your responsibilities and planning your corrective actions in the **FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators**, which can be found at [http://www.fda.gov/oc/ohrt/irbs/](http://www.fda.gov/oc/ohrt/irbs/). Any
submitted corrective action plan must include projected completion dates for each action to be accomplished and a plan for monitoring the effectiveness of your corrective actions.

Your response should reference “CTS # EC130228/E001” and be sent to:

Attention: Veronica J. Calvin
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room 3508
Silver Spring, Maryland 20993-0002.

A copy of this letter has been sent to FDA’s Philadelphia District Office, US Customs House, Room 900, 200 Chestnut Street, Philadelphia, PA 19106. Please send a copy of your response to that office.

The Division of Bioresearch Monitoring has developed introductory training modules in FDA-regulated device clinical research practices, which are available on the FDA website. The modules are for persons involved in FDA-regulated device clinical research activities. These modules are located at the following website address: http://www.fda.gov/Training/CDRHLearn/ucm162015.htm.

If you have any questions, please contact Veronica Calvin at 301-796-5647 or veronica.calvin@fda.hhs.gov.

Sincerely yours,

/S/
Steven D. Silverman
Director
Office of Compliance
Center for Devices and Radiological Health

cc:
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