



U.S. Food and Drug Administration
Protecting and Promoting Your Health

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Inspections, Compliance, Enforcement, and Criminal Investigations

Impladent Ltd. 3/28/14



Department of Health and Human Services

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

MAR 28, 2014

WARNING LETTER

VIA UNITED PARCEL SERVICE

Maurice L. Valen
President and Director of Research and Development
Impladent, Ltd.
198-45 Foothill Avenue
Hollis, NY 11423

Dear Mr. Valen:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at Impladent Ltd, from September 12, 2013 to October 3 2013 by an investigator from the FDA's New York District Office. This inspection was conducted, during the review of your Premarket Notification (510(k)) submission **(b)(4)**, to determine whether your activities as sponsor of the clinical study titled, "**(b)(4)**," complied with applicable federal regulations.

(b)(4), the product investigated in your study, is a combination product under section 503(g) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 353(g), and 21 CFR Part 3, comprised of a device **(b)(4)** material) and a drug **(b)(4)**. The **(b)(4)**, which provides the primary mode of action, is a device under section 201(h) of the Act, 21 U.S.C. § 321(h), 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 any function of the body, and does not achieve its primary intended purpose through chemical action within or on the body and is not dependent upon being metabolized for the achievement of its primary intended purpose. The **(b)(4)** is a drug under section 201(g) of the Act, 21 U.S.C. § 321(g), because it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.

This letter also requests prompt corrective action to address the violations cited and discusses your written response dated October 14, 2013 to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in submissions to the agency 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 (CFR) Part 812 - Investigational Device Exemptions, and Part 50 - Protection of Human Subjects, which concern requirements prescribed under section 520(g) (21 U.S.C. § 360j(g)) of the Act. 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, and our subsequent review of the inspection report, are discussed below:

1. Failure to submit an application to the FDA and obtain FDA and Institutional Review Board (IRB) approval prior to allowing subjects to participate in an investigation [21 CFR 812.20, 21 CFR 812.40 and 21 CFR 812.42].

A sponsor must submit an IDE application for a significant risk device to the FDA (21 CFR 812.40), and shall not begin an investigation until an IRB and FDA have both approved the IDE application (21 CFR 812.42). Your firm failed to comply with the regulations. An example of your firm's failure includes, but is not limited to, the following:

Your firm failed to submit an IDE application to FDA and failed to obtain IRB and FDA approval before enrolling subjects in your clinical study. According to your study protocol, the study investigated the safety and effectiveness of the experimental (b)(4) material (b)(4) and maintenance of (b)(4) sites. Specifically, your firm's study administered the investigational (b)(4) to at least (b)(4) subjects without first obtaining IRB and FDA approval. Because the product is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of subjects, the (b)(4) is a significant risk device, as defined in 21 CFR 812.3(m). As a result, your firm must submit an IDE application to FDA to use (b)(4) in an investigation, as required by 21 CFR 812.20.

Your firm's response is inadequate. In your response, you state that you "do not dispute" FDA's inspectional observation that an investigation was initiated before obtaining FDA approval and IRB approval. Your response further states that this clinical study was terminated in August 2013 and that procedures were initiated to retrieve the investigational devices. During FDA's inspection in September 2013, written documentation to support these statements was absent from your firm's files. Moreover, your files contained letters to clinical investigators at a later date (September 9, 2013) that state your firm has "(b)(4)" and to "(b)(4)." Accordingly, in your response to this letter, please provide FDA with documentation demonstrating that you have discontinued this study by ceasing enrollment, stopping implantation of this device in subjects and halting recruitment of clinical investigators. Also, please provide documentation demonstrating that you have notified all clinical investigator sites in writing of the study's termination, and documentation of the disposition of the investigational products.

2. Failure to ensure that the requirements for obtaining informed consent were met [21 CFR 50.20, 21 CFR 50.25(a)(4), 21 CFR 50.27(a)].

The informed consent documents used in your study were not IRB approved, failed to adequately disclose alternative treatments that might be advantageous to study subjects, and contained impermissible exculpatory language. Examples of your firm's failure include, but are not limited to, the following:

In seeking informed consent, certain information must be provided to each subject, including but not limited to a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. 21 CFR 50.25(a)(4). Here, the consent documents failed to meet this regulatory requirement. Specifically, in the "Alternatives" section the consent form states, "(b)(4)." The "Alternatives" section fails to disclose to subjects the existence of available alternative devices that do (b)(4) and provide (b)(4). For example, (b)(4), (b)(4), (b)(4), and (b)(4),

would be considered appropriate alternative procedures that might be advantageous to the subjects of this study because they **(b)(4)** over time and are replaced by **(b)(4)** during the **(b)(4)** process.

Informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. 21 CFR 50.27(a). The consent forms used in this study were not submitted to and approved by an IRB. As such, informed consent was not documented in accordance with 21 CFR 50.27(a).

No informed consent, whether oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the sponsor from liability or negligence. 21 CFR 50.20. Here, the clinical sites provided informed consent forms to subjects containing impermissible exculpatory language. Specifically, the "Compensation for Injury" section of the informed consent form states, "The Sponsor will not be responsible for any expenses, legal or otherwise, for any treatment I require in the event of any injury incurred as a result of my participation in this study and I will hold them harmless from any judgment."

The informed consent documents used in your clinical investigation did not meet the regulatory requirements.

3. Failure to obtain signed agreements from participating investigators and failure to maintain accurate, complete and current records of product disposition [21 CFR 812.43(c), 21 CFR 812.140(b)(2)].

As a sponsor it is your responsibility to: 1) obtain a signed agreement from each participating clinical investigator (21 CFR 812.43(c)); and 2) maintain accurate, complete and current records of product disposition (21 CFR 812.140(b)(2)). Your firm failed to comply with these requirements. Examples of your firm's failure include, but are not limited to, the following:

a. A sponsor shall obtain a signed agreement from each clinical investigator participating in a study. 21 CFR 812.43(c). Your firm shipped **(b)(4)** to **(b)(4)** but obtained signed clinical investigator agreements from only **(b)(4)** of those **(b)(4)**. For example, your firm shipped **(b)(4)** vials of **(b)(4)** to **(b)(4)** in June 2011. Although your study protocol lists **(b)(4)** as a co-investigator, you did not obtain a signed clinical investigator agreement from **(b)(4)**.

Signed investigator agreements ensure that participating clinical investigators are knowledgeable of the study requirements and the sponsor's expectations when conducting a clinical trial. These agreements also help to confirm that participating investigators understand that the products are for investigational use only and that they must adhere to their responsibilities as a clinical investigator.

b. A sponsor shall maintain accurate, complete and current product disposition records. Records of disposition shall describe the batch number or code marks of any products returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal. 21 CFR 812.140(b)(2). Your firm did not maintain accurate, complete, and current **(b)(4)** disposition records. For example, your firm shipped **(b)(4)** vials of **(b)(4)** to **(b)(4)** in June 2011. During FDA's inspection of Impladent, you stated that your firm contacted **(b)(4)** and requested that he return these vials, and that **(b)(4)** responded that the vials had been misplaced. However, your records did not describe the disposition of these vials.

Your firm's October 14, 2013 written response states that:

- The firm will ensure full traceability of test articles by modifying study protocols and providing a "unique device identifier." However, this does not give adequate assurance for implementation of sufficient preventive measures. For example, modifying study protocols and providing a "unique device identifier" does not ensure that your firm will maintain accurate, complete, and

current device shipment and disposition records.

- The firm will comply with the regulatory requirements for future clinical studies. However, your response does not describe updated or revised standard operating procedures or safeguards to prevent these violations from happening in the future.
- The firm will continue to investigate the root cause to establish a preventative action plan. However, a preventative action plan was not included with your response and no time line for accomplishing your plan was provided.
- The firm will consider hiring new employees or consultants. However, your response does not mention how this action will prevent or address the issues found during inspection, and does not specify how you will train new employees to ensure future compliance.
- The firm will take advantage of existing FDA related resources for training and continuing education materials for employees. However, your response does not include a plan or time line for implementation.

Your response does not contain documentation to substantiate the corrective actions you propose or actions you have already taken. Your proposed corrective actions lack definitive plans and delay corrective actions until unspecified and ambiguous times in the future.

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 Ac and applicable regulations. Sponsor responsibilities for a combination product include compliance with the requirements applicable to each constituent part. A clinical investigation of a combination product is subject to the applicable regulations in 21 CFR Parts 50, 56, 312, and 812.

Within 15 working days of receiving this letter, please provide documentation of the 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 study sponsor. 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.

Your response should reference "CTS # EC130341/E001" and be sent to:

Attention: Linda Godfrey
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room 3446
Silver Spring, Maryland 20993-0002.

A copy of this letter has been sent to FDA's New York District Office. 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>¹.

If you have any questions, please contact Linda Godfrey, (301) 796-5654, Linda.Godfrey@fda.hhs.gov.

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

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1. <http://www.fda.gov/Training/CDRHLearn/ucm162015.htm>