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## Inspections, Compliance, Enforcement, and Criminal Investigations

**Brava, LLC 8/28/14**



Department of Health and Human Services

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

August 28, 2014

### WARNING LETTER

#### VIA UNITED PARCEL SERVICE

Carlos Freyre  
Chief Executive Officer/President  
Brava, LLC  
14221 SW 142<sup>nd</sup> Street  
Miami, FL 33186

Dear Mr. Freyre:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at Brava, LLC, from February 4, 2014, to March 14, 2014, by an investigator from the FDA Florida District Office. This inspection was conducted to determine whether your firm's activities and procedures as sponsor of the clinical studies entitled, "Breast Reconstruction and Augmentation with Brava Enhanced Autologous Fat Micro Grafting" (Protocol No. 2004-02 and Protocol No. 2004-03), complied with applicable federal regulations.

The Brava System is a device 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 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 discusses your firm's written response dated April 4, 2014, to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), 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 serious violations of 21 Code of Federal Regulations (CFR) Part 812 – Investigational Device Exemptions, which concern 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 ensure proper monitoring of the investigation and to promptly inform the IRB and FDA of significant new information about an investigation. [21 CFR 812.40 and 21 CFR 812.46(a)]**

A sponsor is responsible for ensuring proper monitoring of the investigation, and that all clinical investigators participating in the investigation adhere to the signed agreement, the investigational plan, applicable FDA regulations, and any other conditions of approval imposed by the reviewing Institutional Review Board (IRB) or FDA. Our review of the inspection report revealed that your firm failed to take appropriate steps to ensure proper monitoring of the above-listed study. Your firm's lack of monitoring resulted in failure to detect the following:

- a. Several clinical investigators, including Dr. **(b)(6)** and Dr. **(b)(6)**, did not obtain informed consent from study participants prior to enrollment in the clinical study or failed to obtain informed consent altogether.
- b. Active study participants were not re-consented with the latest IRB-approved informed consent form, dated June 13, 2013. This revised version included information to inform study participants that FDA regulates the Brava system when it is used in conjunction with fat grafting.

A sponsor who discovers that an investigator is not complying with federal regulations shall promptly either secure compliance or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation.

- c. Dr. **(b)(6)**, a clinical investigator participating in Protocol No. 2004-03, failed to obtain informed consent from all study participants. Subsequently, the local University of Washington IRB, Human Subject Division, terminated their approval for Dr. **(b)(6)**. As the sponsor, you failed to take any immediate actions to secure compliance of this situation or terminate the investigation.

The risks associated with your clinical investigation of the Brava System include bleeding and infection, as well as the risks associated with sedation and anesthesia. Informed consent must be obtained from study subjects before performing any study-related procedures. This helps ensure that subjects are aware of all the potential risks and benefits of participating in the study, so they are able to make informed decisions. It also confirms that subjects are aware that health records identifying them will be used for research purposes and that those records will no longer be completely confidential and may be inspected by FDA.

Sponsors are also responsible for ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation. FDA notified your firm on June 27, 2012, that the investigations involving the use of Brava external expansion on a post-mastectomy breast prior to autologous fat grafting were significant risk (SR) medical device studies requiring an IDE application. There were no records to indicate that the IRB was notified of this information prior to March 2013.

Proper monitoring and prompt reporting to the IRB helps ensure that the subjects' safety, rights, and well-being are protected and that the data are complete and accurate. Periodic monitoring helps detect and address instances where a clinical investigator may not be complying with the investigational plan or agreement. 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.

We reviewed your response to these observations and conclude that it is not adequate. You stated that you instructed all clinical investigators to re-consent all active study subjects. There is no evidence that you followed up on this matter and that active subjects were re-consented.

In your response to this letter, please provide:

- evidence that subjects were re-consented,
- a copy of all newly created standard operating procedures (SOPs) that address the concerns listed above, along with proposed implementation dates, and
- training dates on these new procedures along with a list of staff members, including your research staff and clinical investigators, who were trained.

**2. Failure to prepare and submit complete, accurate, and timely reports regarding withdrawal of an IRB's approval of an investigation, informed consent, and other requested information about the investigation. [21 CFR 812.150(b)(2), 21 CFR 812.150(b)(8), and 21 CFR 812.150(b)(10)].**

A sponsor is responsible for notifying FDA, all reviewing IRBs, and participating investigators of an IRB's withdrawal of approval of an investigation within 5 working days after receipt of the withdrawal. A sponsor is also responsible for submitting to FDA a copy of any report of use of the investigational device without obtaining informed consent, within 5 working days of receipt of such notice. A sponsor is responsible, upon request, for providing FDA with information about any aspect of an investigation. Examples of your failure to fulfill these responsibilities include the following:

- a. There is no evidence that your firm notified the FDA and participating investigators that the University of Washington IRB withdrew approval of Dr. **(b)(6)** investigation within 5 working days of receipt of notice. Dr. **(b)(6)** informed you of this situation on April 25, 2013.
- b. There is no evidence to show that, within 5 working days of receipt of notice, your firm informed FDA that investigators used the Brava investigational device without obtaining informed consent.
- c. As a component of the April 26, 2013, conditional approval letter, FDA requested information regarding the Brava clinical studies. Your firm failed to supply accurate, complete and current information, particularly regarding the total enrollment numbers at Dr. **(b)(6)** clinical site.

We reviewed your response to these observations and conclude that it is not adequate. Your response does not contain documentation to substantiate the corrective and preventive actions you propose or actions you have already taken.

We believe that a teleconference may be helpful to further clarify your responsibilities as a study sponsor and discuss corrective actions that you plan on implementing. We ask that you contact CDR Tamika Allen at (301) 796-1164 or [Tamika.Allen@fda.hhs.gov](mailto:Tamika.Allen@fda.hhs.gov) within two weeks of receiving this letter to propose several dates and times.

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 Act and applicable regulations.

In addition to the violations described above, the FDA inspection also revealed the following concerns:

- a. It appears that your firm did not take appropriate measures to mitigate study bias when a clinical investigator has a financial interest in the outcome of the study, or a proprietary interest in the product. Specifically, it was not clear whether measures were implemented to reduce bias with regard to Dr. **(b)(6)**, Science and Medical Director for Brava, inventor of the Brava system, protocol developer, and Principal Investigator. Please note that FDA may consider clinical studies and the data inadequate if, among other things, appropriate steps have not been taken in the design, conduct, reporting and analysis of the studies to minimize bias. See 21 CFR 54.1(b).
- b. Inconsistencies were identified between the information contained on your website,

www.brava.com, and the information brochure. The website mentions the Brava AFT Systems as a clinical investigation, while the information brochure lacks that information. Please note, promotion and advertisement materials should be approved by the IRB prior to use and should contain consistent information when utilized to recruit subjects into clinical research studies.

Within 15 working days of receiving this letter, please provide documentation of the additional 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 # G130077/E004 and be sent to:

Attention: Veronica J. Calvin, M.A.  
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 Florida's District Office, 555 Winderley Place, Suite 200, Miami, FL 33186. 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><sup>1</sup>.

If you have any questions, please contact Veronica Calvin at (301) 796-5647 or [Veronica.Calvin@fda.hhs.gov](mailto:Veronica.Calvin@fda.hhs.gov).

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

cc:  
Concordia Clinical Research, Inc.  
7 East Frederick Place  
Cedar Knolls, New Jersey, 07927

Page Last Updated: 09/16/2014

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