U.S. FOOD & DRUG ADMINISTRATION

HAND DELIVERED

JUN 2 1 2017

Michael A. Arata, M.D.
President
Synergy Health Concepts, Inc.
4501 Birch St. Ste B
Newport Beach, CA 92660

Dear Dr. Arata:

The Center for Devices and Radiological Health (CDRH or Center), U.S. Food and Drug Administration (FDA), has information indicating that you repeatedly and/or deliberately violated federal regulations in your capacity as a sponsor-investigator in clinical trials with an investigational device, specifically, the Bard ATLAS® Percutaneous Transluminal Angioplasty Balloon Dilation Catheter (Bard device). These violations provide the basis for withdrawal of your eligibility as a clinical investigator to receive investigational products.

Previously, FDA conducted an inspection from April 10 through May 15, 2012, which resulted in FDA issuing to you a Warning Letter dated September 5, 2012 (2012 WL). In the 2012 WL, we explained to you, as a sponsor-investigator, your legal responsibilities. Yet the Center subsequently found that, despite receiving the 2012 WL, you continued to violate FDA regulations by conducting and publishing outcomes of research with the Bard device without, among other things, submitting an Investigational Device Exemption (IDE) application to FDA and obtaining appropriate Institutional Review Board (IRB) and FDA approval prior to allowing subjects to participate in an investigation.

The Center's findings for this action are based upon information obtained during an inspection that FDA conducted from November 16, 2015 through January 28, 2016, as a follow-up to the 2012 WL. FDA conducted this inspection as part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those clinical investigations have been protected. At the conclusion of the inspection, an FDA representative presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. Through your attorney, Benjamin L. England & Associates, LLC., you provided a written response to the Form FDA 483 on March 4, 2016. However, CDRH reviewed your response and determined that the response failed to address the matters under complaint. Accordingly, pursuant to section 812.119 of Title 21, Code of Federal Regulations (CFR), on September 13, 2016, CDRH informed you, by letter titled "Notice of Initiation of Disqualification Proceedings and Opportunity to Explain" (NIDPOE), of the specific matters of concern and offered you an opportunity to respond in writing or at an informal conference. The NIDPOE also gave you the option of entering into a consent agreement with FDA, thereby terminating any administrative proceeding against you. You requested an informal conference and, on October 25, 2016, responded to the NIDPOE in the informal conference. At the conclusion of the conference, you requested and were granted additional time to respond. On January 3, 2017, your attorney stated in an email that 'no additional response would be forthcoming.'

After review of all available information, including the statements you provided at the informal conference, the Center has concluded that your statements are unacceptable because they fail to adequately address the violations set forth in the NIDPOE and below.

Accordingly, you are being offered an opportunity for a regulatory hearing pursuant to 21 CFR Part 16 and 812.119, on the question of whether you are entitled to receive investigational products. You have the right to be advised and represented by counsel at all times. Any regulatory hearing on this matter will be governed by the regulations in 21 CFR Part 16 and the agency's guidelines on electronic media coverage of administrative proceedings, 21 CFR Part 10, Subpart C. Enclosed you will find a copy of these regulations. A listing of the specific violations follows. These are the matters that will be considered at the regulatory hearing. Applicable provisions of the CFR are cited for each violation below.

1. **You repeatedly failed to submit an application to the FDA and obtain institutional review board (IRB) and FDA approval prior to allowing subjects to participate in an investigation [21 CFR 812.20, 812.40, and 812.42].**

In our 2012 WL we explained to you that, as a sponsor-investigator, you must submit to FDA an Investigational Device Exemption (IDE) application for a significant risk device (21 CFR 812.40) and shall not begin an investigation, or part of an investigation, until an IRB and FDA have both approved the application or supplemental application relating to the investigation or part of an investigation (21 CFR 812.42). In the 2012 WL, we notified you of your failure to obtain such approval prior to allowing subjects to participate in your significant risk device investigation of treatment for Chronic Cerebrospinal Venous Insufficiency (CCSVI) with devices not approved for that use. However, despite having received the 2012 WL, you have continued to conduct similar research and allow subjects to participate in an investigation without IRB and FDA approval.

As you did before with CCSVI, you studied the use of the Bard device (i.e., Bard ATLAS® Percutaneous Transluminal Angioplasty Balloon Dilation Catheter) as part of the Transvascular Autonomic Modulation (TVAM) investigation, without obtaining IRB and FDA approval prior to doing so. The TVAM investigation is a modified balloon angioplasty technique, using percutaneous transluminal angioplasty balloon dilation catheters in the internal jugular veins, and azygos veins (vascular lesions). The Bard device is not approved for dilation of jugular, azygos, renal, or iliac veins.

During the NIDPOE informal conference, you stated that the use of the angioplasty balloon device is similar to one used to study CCSVI. There are different terms for the description of the disease as well as indications for treatment, but the intended population is the same, namely, patients diagnosed with 'autonomic dysfunction' and other neurological disease conditions including multiple sclerosis. To reiterate, medical devices used for balloon angioplasty as described in your research are not approved as a treatment modality for autonomic dysfunction or multiple sclerosis. Autonomic dysfunction is ill-defined and could encompass a wide range of situations.

You wrote about the TVAM treatment in the following publications and claimed safety and effectiveness for the treatment. The medical device identified in the literature is similar to one used in a CCSVI research clinical study that you conducted. Examples of the publications in which you made claims of safety and effectiveness for the unapproved TVAM treatment include, but are not limited to, the following:

Phlebology (2013;0(0)1-8) Blood Pressure Normalization Post-jugular Venous Balloon Angioplasty. In this publication, you stated the following:

- "This study is the first in a series…"
- "In addition, venous dilation angioplasty to correct venous obstruction, although controversial, has been shown to have an acceptable safety profile and clinical efficacy…"
- "The study involved MS patients who visited the Endovascular Clinic (Synergy Health concepts, Newport Beach, CA) between 2011 and 2012."
- "It should be noted that authors are engaged in additional studies, aiming to show the close association between CCSVI and ANS dysfunction."

Journal of Endovascular Therapy (2014; 21:417-428) Transvascular Autonomic Modulation: A Modified Balloon Angioplasty Technique for the Treatment of Autonomic Dysfunction in Multiple Sclerosis Patients. In this publication, you stated the following:

- "The safety and efficacy of TVAM in MS patients observed in this pilot study…"
- "…we propose extending the angioplasty procedure beyond dilation of obstructing lesions."
- "In this pilot study, we detail the technique of TVAM and compare the safety of this approach with traditional balloon angioplasty in MS patients."

Hormone Metabolism Research (2015) Neuroendocrine Responses to Transvascular Autonomic Modulation: A Modified Balloon Angioplasty in Multiple Sclerosis Patients. In this publication, you stated the following:

- "Balloon angioplasty (BA) is a treatment modality to correct vascular lesions in multiple sclerosis (MS) patients, who present with chronic cerebrospinal venous insufficiency (CCSVI)."
- "The study involved MS patients who visited the Endovascular Clinic (Synergy Health concepts, Newport Beach, CA, USA)."

Because these publications claim safety and effectiveness of the TVAM treatment, the underlying research involving the use of the TVAM treatment on human subjects constitutes "investigation" under FDA regulations. 21 CFR 812.3(h) ("investigation" means "research involving one or more subjects to determine the safety or effectiveness of a device").

In your investigations you continued to collect data from (b)(4) subjects between April 18, 2013 and September 11, 2013 with TVAM, a modified balloon angioplasty technique, using percutaneous transluminal angioplasty balloon dilation catheters in the internal jugular veins, and azygos veins (vascular lesions). In addition, during your informal conference you stated that you treated (b)(4) of subjects after September 14, 2014.

2. **You deliberately allowed subjects to participate in a study before obtaining approval from the reviewing IRB and FDA prior to initiation of the study [21 CFR 812.100 and 812.110(a)].**

FDA regulations require that clinical investigators determine whether potential subjects would be interested in participating in an investigation, but shall not request the written informed consent of any subjects to participate and shall not allow any subjects to participate before obtaining IRB and FDA approval. As a clinical investigator, in both the CCSVI and TVAM studies, you failed to obtain the required IRB review and approval and allowed subjects to participate without obtaining the IRB's approval. Therefore, there is no assurance that subject risks are minimized and reasonable in relation to anticipated benefits.

From April 18, 2013 through September 11, 2013, you treated [redacted] subjects with the Bard ATLAS® catheter as part of the TVAM investigation without having IRB and FDA approval. As a result, you continued to place subjects at increased risk of serious harm, despite having received the 2012 WL.

3. **You deliberately failed to ensure that IRB-approved informed consent was obtained in accordance with 21 CFR Part 50, and adhere to informed consent requirements [21 CFR 50.20, 50.25(a)(1), 50.27(a), and 812.100].**

An investigator is required to obtain and have written documentation of informed consent 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 (21 CFR 50.27(a)). Moreover, "[n]o informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence" (21 CFR 50.20). Basic elements set forth in 21 CFR 50.25 must be included.

In the 2012 WL, FDA noted that an informed consent shall be documented by the use of a written consent form approved by the IRB. Subsequent to the 2012 WL, you failed to obtain the legally effective informed consent, approved by an IRB (21 CFR 50.27(a)), and that contains the required elements in 21 CFR 50.25. You applied for and received IRB approval for a retrospective chart review; however, there was no approval for an informed consent document. As a result, [redacted] subjects who were treated with TVAM Venous Balloon Dilation Therapy were not provided with an IRB-approved informed consent. The evidence collected indicates that different treatment consent documents were identified in subject records. For example, the physician medical record note stated that:

> "Risks and benefits of the procedure were discussed with the patient including 'off-label' use of a device. The risks include, but are not limited to vessel rupture, re-stenosis, thrombosis, recurrence of symptoms, and post-operative bleeding, including death. The expectations of the results of the procedure were also discussed. The patient understands that results cannot be guaranteed and that improvement of Dysautonomia symptoms are more commonly seen. Knowing these risks, potential benefits, and possible lack of improvement in symptoms, the patient wishes to proceed with the procedure."

This statement in the physician medical record does not substitute for a written consent form that describes research, nor does it contain the required elements, such as "[a] disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject" and "[a]n 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" (21 CFR 50.25). The written consent form is signed by the subject to indicate his or her understanding of participation in research. Moreover, as we explained in the 2012 WL, 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 subject's legally authorized representative at the time of consent. There is no evidence that the subjects understood and agreed to participate in research.

In addition, some subject records contained a "Physician-Patient Arbitration Agreement" that states "Both parties to this contract, by entering into it, are giving up their constitutional rights to have any such dispute decided in a court of law before a jury, and instead are accepting the use of arbitration." This language expressly waives the subject's legal rights and thereby releases, or appears to release, the investigator, the institution or its agents from liability for negligence.

4. **You deliberately represented a device as safe and effective for the purpose of treating various diseases other than those for which FDA has approved them [21 CFR 812.7(d)].**

Under 21 CFR 812.7(d), a sponsor-investigator is prohibited from representing that an investigational device is safe or effective for the purposes for which it is being investigated. However, as a sponsor-investigator, you have deliberately represented in the following publications that the use of balloon angioplasty devices to treat TVAM and CCSVI in what you explicitly designated as studies are safe and effective for the purpose of investigating various diseases other than those for which FDA has approved them:

- *Phlebology (2013;0(0)1-8) Blood Pressure Normalization Post-jugular Venous Balloon Angioplasty*
- *Journal of Endovascular Therapy (2014; 21:417-428) Transvascular Autonomic Modulation: A Modified Balloon Angioplasty Technique for the Treatment of Autonomic Dysfunction in Multiple Sclerosis Patients*
- *Hormone Metabolism Research (2015) Neuroendocrine Responses to Transvascular Autonomic Modulation: A Modified Balloon Angioplasty in Multiple Sclerosis Patients*

These representations violate 21 CFR 812.7(d).

5. **You repeatedly failed to maintain accurate and complete records of receipt, use, and disposition of devices [21 CFR 812.140(a)(2)].**

Previously, we informed you that you are responsible for maintaining accurate, complete, and current records relating to the shipment and disposition of devices. Yet, you did not maintain records of receipt (e.g., shipment record), use, and disposition of the device (e.g., there are no specifics about the type and quantity of the device, dates of receipt and batch number or code mark for the catheters used for the TVAM Venous Balloon Dilation Therapy investigation).

Your repeated failure to maintain device accountability records is a serious violation of your responsibility as a clinical investigator. Maintaining accountability records is particularly important when a device is used to study subjects outside the intended use of that device.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of TVAM. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

Your request for a hearing must be made, in writing, within ten (10) business days of receipt of this letter and should be directed to Scott J. MacIntire, Director, Division of Enforcement, Office of Enforcement and Import Operations, Office of Regulatory Affairs, 10903 New Hampshire Avenue, WO 32, Room 4360, Silver Spring, MD 20993, Telephone (301) 796-8203, Fax (301) 847-8635. If no response to this letter is received by that time, you will be deemed to have waived any right to a regulatory hearing; no hearing will be held and a decision in this matter will be made based on the facts available to the Agency.

A request for a hearing may not rest upon mere allegations or denials but must present specific facts showing that there is a genuine and substantial issue of fact that warrants a hearing. Pursuant to 21 CFR 16.26, a request for a hearing may be denied, in whole or in part, if the Commissioner or his delegate determines that no genuine and substantial issue of fact had been raised by the material submitted. A hearing will not be granted on issues of policy or law. Written notice of a determination of summary judgment will be provided, explaining the reasons for denial of the hearing.

If you wish to respond but do not desire a hearing, you should contact Mr. MacIntire within the time period specified above and send a written response containing your reply. The letter should state that you waive your right to a hearing and that you want a decision on the matter to be based on your written response and other information available to the Agency.

The Agency's offer to enter into a consent agreement remains available. Entering into a consent agreement would terminate the administrative procedures, but would not preclude the possibility of a corollary judicial proceeding.

FDA has not made a final decision at this time on your eligibility to continue to use investigational products. Moreover, there will be no prejudgment of this matter if you decline to enter into a consent agreement and decide instead either to request a regulatory hearing or to request that the decision be based on information currently available to the Agency.

Please inform Mr. MacIntire within ten (10) business days whether you wish to request a hearing or to have this matter resolved by consent agreement or information available to the Agency.

Sincerely,

Melinda K. Plaisier
Associate Commissioner for
Regulatory Affairs

Enclosures
21 CFR Part 10, Subpart C
21 CFR Part 16
21 CFR Part 812