WARNING LETTER

# US Stem Cell Clinic, LLC

**MARCS-CMS 524470 — 24/08/2017**



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**Delivery Method:** UPS

**Content current as of:**
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**Recipient:**
Ms. Kristin Comella
US Stem Cell Clinic, LLC
12651 W. Sunrise Blvd., Suite 104
Sunrise, FL 33323
United States

**Issuing Office:**
Florida District Office
United States

U.S. FOOD & DRUG ADMINISTRATION

U.S. Food and Drug Administration
Office of Biological Products Operations
Division I

**VIA UPS NEXT DAY AIR**
**w/ DELIVERY CONFIRMATION**

**WARNING LETTER**

**OBPO 1 17-02**

August 24, 2017

Ms. Kristin Comella
Chief Scientific Officer
US Stem Cell Clinic, LLC
12651 W. Sunrise Blvd., Suite 104
Sunrise, FL 33323

Dear Ms. Comella:

During an inspection of your firm, US Stem Cell Clinic, LLC (USSC)**1** located at 12651 W. Sunrise Blvd., Suite 104, Sunrise, FL 33323, conducted between April 10 and May

11, 2017, the Food and Drug Administration (FDA) found that your firm recovers and processes adipose tissue, a structural tissue, from donors for autologous use. Your firm uses **(b)(4)** to **(b)(4)** components from adipose tissue, which are further processed into stromal vascular fraction (SVF). Your SVF product is generally administered intravenously or intrathecally for a variety of diseases or conditions.

Records gathered during the inspection reflect that your SVF product is intended to treat a variety of diseases and conditions, including, but not limited to, Parkinson's disease, amyotrophic lateral sclerosis (ALS), chronic obstructive pulmonary disease (COPD), heart disease, and pulmonary fibrosis. In addition, on your website you claim to "offer stem cell treatments" for "neurological . . . autoimmune . . . degenerative" and other conditions, including but not limited to "Parkinson's, ALS . . . Rheumatoid Arthritis, Crohn's, Colitis, Lupus . . . COPD, Diabetes, [and] Congestive Heart Failure." See http://usstemcellclinic.com.

Therefore, your SVF product is a drug under section 201(g) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) [21 U.S.C. 321(g)] and a biological product as defined in section 351(i) of the Public Health Service Act (PHS Act) [42 U.S.C. 262(i)].**2** It is also a human cell, tissue, or cellular or tissue-based product (HCT/P) as defined in 21 CFR 1271.3(d). **3**

Your SVF product does not meet all of the criteria in 21 CFR 1271.10(a), and therefore does not qualify for regulation solely under section 361 of the PHS Act [42 U.S.C. 264] and the regulations in 21 CFR Part 1271. Specifically, your SVF product does not meet the minimal manipulation criterion set forth in 21 CFR 1271.10(a)(1) and defined for structural tissue, such as adipose tissue, in 21 CFR 1271.3(f)(1). Your product does not meet this criterion because your processing alters the original relevant characteristics of the adipose tissue relating to the tissue's utility for reconstruction, repair, or replacement.

In addition, your SVF product fails to meet the 21 CFR 1271.10(a) (2) criterion that the HCT/P be "intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent." As noted above, the SVF product is intended for use in the treatment of a variety of diseases or conditions. Because the SVF product is not intended to perform the same basic function or functions of adipose tissue, such as cushioning the body, using the SVF product for treatment of these diseases or conditions is not homologous use as defined in 21 CFR 1271.3(c). As a result, your SVF product does not qualify for regulation solely under section 361 of the PHS Act and 21 CFR Part 1271.

Please be advised that in order to lawfully market a drug that is a biological product, a valid biologics license must be in effect [21 U.S.C. 355(a); 42 U.S.C. 262(a)]. Such licenses are issued only after a showing of safety and efficacy for the product's intended use. While in the development stage, such products may be used in humans only if the sponsor has an investigational new drug application (IND) in effect as specified by FDA regulations [21 U.S.C. 355(i); 21 CFR Part 312]. Your SVF product is not the subject of an approved biologics license application (BLA) **(b)(4)**.

Additionally, during the inspection, FDA investigators documented evidence of significant deviations from current good manufacturing practice (CGMP) and current good tissue practice (CGTP) between December 8, 2015, and April 17, 2017, in the manufacture of at least **(b)(4)** lots of your SVF product. These deviations from CGMP and CGTP include deviations from section 501(a) (2) (B) of the FD&C Act, and 21 CFR Parts 210, 211, and 1271. Many of these deviations were the same or similar to the observations listed on the Form FDA 483 issued to you at the conclusion of FDA's previous inspection of your firm between October 22 and December 7, 2015.

At the close of the April-May 2017 inspection, FDA investigators issued a list of inspectional observations (Form FDA 483), which described a number of significant objectionable conditions relating to your facility's compliance with CGMP and CGTP. These include, but are not limited to the following:

1. Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, namely, your SVF product, including procedures for validation of all aseptic and sterilization processes [21 CFR 211.113(b)]. For example:

a. Your firm recovers adipose tissue and manufactures autologous SVF from this adipose tissue. During the period December 8, 2015 –April 17, 2017, your firm manufactured at least **(b)(4)** batches of SVF product. Your firm failed to validate and document your aseptic manufacturing process or to establish written procedures to prevent microbiological contamination of the SVF product. Your firm administers the SVF product by various methods, including intravenously and intrathecally. By the nature of its method of administration, the SVF product purports to be sterile and is expected to be sterile.

b. **(b)(4)** testing of the **(b)(4)** used in the manufacture of the SVF product is not performed.

c. On May 3, 2017, our investigators observed an accumulation of dust on two air vents in the room where the SVF product is manufactured.

d. Your firm failed to use disinfectant agents that are appropriate for use for cleaning the **(b)(4)**, the **(b)(4)**, and the **(b)(4)**, which are located inside the aseptic processing area. For example, you use non-sterile **(b)(4)** and non-sterile wipes and do not use a sporicidal agent.

2. Failure to establish written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100(a)]. Specifically, you **(b)(4)** the **(b)(4)** components from adipose tissue through **(b)(4)** and **(b)(4)**, which are further processed into your SVF product by **(b)(4)** and **(b)(4)**. You have not validated the manufacturing process for your SVF product.

3. Failure to perform appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms [21 CFR 211.165(b)]. Specifically, you failed to perform appropriate laboratory testing, including sterility and endotoxin testing, on at least **(b)(4)** batches of the SVF product manufactured between December 8, 2015, and April 17, 2017. Such laboratory testing is necessary for the SVF product, which by the nature of its method of administration is required to be free of objectionable microorganisms.

4. Failure to have an adequate system for monitoring environmental conditions in an aseptic processing area [21 CFR 211.42(c) (10) (iv)]. Specifically, your firm has not established an adequate system for environmental monitoring in the aseptic processing area where the SVF product is manufactured.

5. Failure to establish and follow written procedures for cleaning and maintenance of equipment [21 CFR 211.67(b)]. For example:

a. Your firm has not established any written procedures for cleaning or maintenance for the **(b)(4)**, the **(b)(4)**, or the **(b)(4)**.

b. Your firm is using a **(b)(4)**, manufactured by **(b)(4)** during the manufacture of the SVF product. This **(b)(4)** has not been certified or

qualified for its intended use.

6. Failure to have a written record of major equipment cleaning, maintenance and use [21 CFR 211.182]. Specifically, your firm lacks records reflecting that cleaning, sanitizing, and inspections of equipment have been performed prior to, during, or after the manufacture of each batch of SVF product.

7. Failure to ensure that manufacturing personnel wear clean clothing appropriate for the duties they perform, including protective apparel, such as head, face, hand, and arm coverings, as necessary to protect drug products from contamination [21 CFR 211.28(a)]. Specifically, your firm failed to ensure that employees engaged in the processing of the SVF product wear clothing necessary to protect the drug from contamination. For example, non-sterile surgical masks and bouffant caps are worn during the processing of the SVF product.

8. Failure to maintain laboratory controls that include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure the components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality and purity [21 CFR 211.160(b)]. For example, you have not established procedures for testing the final SVF product, including tests for identity, strength, quality, and purity.

9. Failure to establish and follow written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures [21 CFR 211.80(a)]. Specifically, you failed to establish and follow written acceptance criteria for components. You also failed to establish and follow written procedures for sampling, testing, or examining each lot of components received and released for use in the manufacture of at least **(b)(4)** batches of SVF product during the period December 8, 2015 and April 17, 2017. Components received and used by your firm to manufacture the SVF product include, but are not limited to, **(b)(4)**, and **(b)(4)**.

10. Failure to ensure that each lot of components, drug product containers, and closures are withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit [21 CFR 211.84(a)]. For example, the **(b)(4)** used in the manufacture of the SVF product is for research use only, as stated on the manufacturer's product insert which was provided by your firm. Your firm lacks evidence, such as testing, to demonstrate this component meets all specifications of identity, strength, quality, and purity.

11. Failure to establish a quality control unit that has the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated [21 CFR 211.22(a)].

12. Failure to prepare batch production and control records for each batch of drug product produced with complete information relating to the production and control of each batch. These records shall include documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished [21 CFR 211.188(b)]. For example, you did not document each significant step in the manufacture, processing, packing, or holding of each batch of your SVF product, including the identify of each batch of component or in-process material used and all persons performing each significant step.

13. Failure to establish and follow written procedures describing the handling of all written and oral complaints regarding a drug product [21 CFR 211.198(a)]. Specifically, your firm has not established written procedures for handling complaints, including procedures to determine whether an investigation is needed.

14. Failure to prominently label the SVF product as "for autologous use only" and "not evaluated for infectious substances." [21 CFR 1271.90(c) (1) and (2)].

The FDA investigators also documented that you impaired their ability to conduct the April-May 2017 inspection. For example, you delayed the inspection by refusing to allow entry except by appointment only and denied the investigators access to your employees. Please be aware that it is a prohibited act to refuse to permit entry or inspection as authorized by section 704 of the FD&C Act [21 U.S.C. 374]. See 21 U.S.C. 331(f). In addition, under section 501(j) of the FD&C Act, 21 U.S.C. 351(j), when an owner, operator, or agent delays, denies, limits, or refuses an inspection, the drugs may be deemed adulterated. See FDA Guidance, Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection, available at www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf.

**Review of Inspectional Response**

We acknowledge receipt of your written response, dated May 16, 2017, and note that it did not address any of the observations identified on the Form FDA 483. Instead, you claim, among other things, that you are not required to comply with the requirements of 21 CFR Part 1271, because your firm qualifies for the same surgical procedure exception at 21 CFR 1271.15(b). The same surgical procedure exception applies to an establishment that removes HCT/Ps from an individual and implants "such HCT/Ps" into the same individual during the same surgical procedure. Among other things, the HCT/Ps your firm removes from individuals (adipose tissue) plainly are not the HCT/Ps that are used (SVF) following processing by various means (e.g., **(b)(4)** or **(b)(4)**). Therefore, your firm does not qualify for the same surgical procedure exception.

You also claim that your product is exempt from regulation "because the procedures practiced at USSC do not involve more than 'minimal manipulation.'" As detailed above, your product does not meet this criterion set forth in 21 CFR 1271.10(a) (1), because your processing alters the original relevant characteristics of the adipose tissue relating to the tissue's utility for reconstruction, repair, or replacement.

You further state that your firm's manufacture of the SVF product falls within the practice of medicine and beyond FDA's jurisdictional reach. As explained, your SVF product is a drug as defined in section 201(g) of the FD&C Act and a biological product as defined in section 351(i) of the PHS Act. FDA is charged with enforcing the FD&C Act as it applies to FDA-regulated articles such as your SVF product.

Neither this letter nor the observations noted on the Form FDA 483, which were discussed with you at the conclusion of the inspection, are intended to be an all-inclusive list of deficiencies that may exist at your facility. It is your responsibility as management to ensure that your firm is in compliance with the FD&C Act, PHS Act, and all applicable regulations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include seizure and/or injunction.

Further information about IND requirements for biological products may be obtained through the Division of Regulatory Project Management, Office of Tissues and Advanced Therapies, at (240) 402-8190 or OTATRPMS@fda.hhs.gov. Please include a copy of this letter with your initial submission to CBER.

Please notify this office in writing, within 15 working days of receipt of this letter, of

any steps you have taken or will take to correct the noted deviations and to prevent their recurrence. Include any documentation necessary to show that correction has been achieved. If you do not believe your product is in violation of the FD&C Act, PHS Act, or applicable regulations, include your reasoning and any supporting information for our consideration. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which all corrections will be completed.

Your response should be sent to the U.S. Food and Drug Administration, Florida District Office, 555 Winderley Place, Suite 200, Maitland, FL 32751, or emailed to Randall.Morris@fda.hhs.gov . If you have any questions regarding this letter, please contact Mr. Randall L. Morris, Compliance Officer at (407) 475-4741.

Sincerely,
/s/
Elizabeth A. Waltrip
Program Division Director, Acting

cc: U.S. Stem Cell, Inc.
13794 NW 4th Street
Suite 212
Sunrise, Florida 33325

**1** US Stem Cell Clinic, LLC is a subsidiary of US Stem Cell, Inc., which was formerly known as Bioheart, Inc.

**2** The definition of "drug" includes "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man." 21 U.S.C. 321(g). The term "biological product" means "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. 262(i) (1).

**3** HCT/Ps are defined as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." 21 CFR 1271.3(d).