UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA
FT. LAUDERDALE DIVISION

CASE NO.: 18-61047-CIV-UNGARO/O'SULLIVAN

UNITED STATES OF AMERICA,

Plaintiff,

v.

US STEM CELL CLINIC, LLC, a Florida limited liability company,
US STEM CELL, INC., a Florida profit corporation, and
KRISTIN C. COMELLA and
THEODORE GRADEL, individuals,

Defendants.

PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT AND SUPPORTING MEMORANDUM OF LAW

Pursuant to Fed. R. Civ. P. 56 and Local Rules 7.1 and 56.1, Plaintiff, United States of America, moves for summary judgment against US Stem Cell Clinic, LLC ("USSCC"), US Stem Cell, Inc., and individuals Kristin C. Comella and Theodore Gradel (collectively, "Defendants"). The Defendants are openly violating the law and endangering patients by manufacturing an unapproved, experimental drug that they claim treats a variety of serious diseases and conditions. But the undisputed evidence and Defendants' admissions demonstrate that Defendants' product is both adulterated and misbranded. The Government is thus entitled to summary judgment and a permanent injunction barring Defendants from continuing to manufacture it. In support of this motion, the Government relies on its memorandum of law, its Statement of Material Undisputed Facts filed herewith, as well as its supporting declarations and exhibits.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Rules

Regulations

INTRODUCTION

Defendants manufacture an illegal, unproven new drug and inject it into patients, purportedly to treat a wide range of diseases and conditions. Without FDA license or approval, Defendants recover adipose tissue (fat) from a patient, process that tissue to obtain cellular components known as stromal vascular fraction (called "SVF" for short), and then inject the SVF along with another drug component into different parts of the patient's body. In doing so, the Defendants are violating the Federal Food, Drug, and Cosmetic Act ("FDCA"), which makes it illegal to manufacture and sell drugs that are produced without adhering to current good manufacturing practice ("CGMP" in FDA parlance) for producing drugs, and further forbids the manufacture and sale of drugs that do not have labeling that bears adequate directions for use. Drugs that fail to meet these requirements are "adulterated" and "misbranded," respectively. Defendants are violating both of these provisions and should be enjoined.

In marketing their drug, Defendants make a host of extravagant, unsubstantiated claims about their product, including that it can treat a variety of serious diseases and conditions, such as amyotrophic lateral sclerosis, Parkinson's disease, spinal cord injuries, stroke, traumatic brain injury, chronic obstructive pulmonary disease, lung disease, and diabetes. As noted in the New England Journal of Medicine, *see infra* Section D of the Statement of Facts, Defendants' conduct amounts to, in effect, experimentation on patients with the potential for "devastating outcomes." And that potential is very real. Defendants' product has been associated with serious adverse events, such as blindness and vision impairment. And even when such calamities are avoided, Defendants' marketing gives unsubstantiated hope to people suffering from serious and sometimes life-threatening conditions. Patients who believe Defendants' claims may forgo proven treatments in favor of expending time and money on Defendants' unapproved product—something Defendants have not shown is either safe or effective.

As noted above, Defendants are violating the FDCA in two basic ways. *First*, Defendants' SVF product is adulterated because Defendants are not abiding by CGMP. FDA inspections of USSCC in 2015 and 2017 revealed serious and obvious CGMP violations by USSCC. CGMP requirements are designed to ensure that drugs (including biological products) have the identity, strength, quality, purity, and other attributes for safe and effective use. Here, the evidence shows that Defendants violated CGMP by failing to aseptically process their SVF product to prevent microbiological contamination or test the product for sterility and for the

presence of endotoxins (which can cause fevers and other health complications), among other violations. Because Defendants' SVF product is not manufactured, processed, packed, or held in compliance with CGMP, it is adulterated. *See* 21 U.S.C. § 351(a)(2)(B).

Second, Defendants' SVF product is misbranded. Under 21 U.S.C. § 352(f)(1), a drug's labeling must bear adequate directions for use. If it does not, the drug is misbranded. The labeling for Defendants' SVF product lacks critical, required information, such as indications for use, dosages, and routes of administration. Further, it is currently impossible to draft adequate directions for use of the SVF product because there is no scientifically valid evidence to show that it is safe or effective for *any* indication.

Defendants do not dispute the evidence of these violations. Defendants admit that they use their SVF product to address patients' symptoms of neurological, autoimmune, orthopedic, and degenerative diseases and conditions, which makes it a "drug" under the FDCA. *See* 21 U.S.C. § 321(g)(1)(B), (C) ("drug" includes all articles "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or "intended to affect the structure or any function of the body of man or other animals."). Defendants admit that FDA's 2015 and 2017 inspections of USSCC found that their manufacture of the SVF product does not comply with CGMP. And Defendants further admit the relevant facts about the labeling of their SVF product and the required information that is missing. Nor is there any question that Defendants' SVF product contains at least one component that has been shipped in interstate commerce. These undisputed facts establish that Defendants' unapproved SVF product is an adulterated and misbranded drug under the FDCA. *See* 21 U.S.C. §§ 351(a)(2)(B) & 352(f)(1).

Based on previous correspondence with FDA, Defendants offer three reasons they believe these basic legal requirements do not apply to them. They claim that (1) their establishment is excepted from FDA regulation under 21 C.F.R. § 1271.15(b) (the "same surgical procedure exception"); (2) their SVF product should not be regulated as a drug or biological product because it meets the criteria at 21 C.F.R. § 1271.10(a) (*i.e.*, minimally manipulated and for homologous use only); and (3) the FDCA does not apply to Defendants at all because Defendants are engaged in the "practice of medicine." These arguments fail for the reasons detailed below.

Because the material facts are not in dispute and Defendants are plainly violating the FDCA, the Government is entitled to summary judgment. Defendants are not simply moving fat

from one place in a patient's body to another or performing a basic skin graft. They are manufacturing a potentially dangerous, unapproved new drug[1] that is both adulterated and misbranded and they are injecting it into their patients. Defendants refuse to comply with the law, and indeed vigorously dispute that they are subject to the FDA's regulatory authority as they continue to experiment on the public in violation of basic FDCA requirements. Permanent injunctive relief is necessary to stop this ongoing violation of law and to protect the public health.

STATUTORY AND REGULATORY FRAMEWORK

The FDCA's overriding purpose is protecting the public health. *See United States v. Dotterweich*, 320 U.S. 277, 280-81 (1943). Consistent with that purpose, the FDCA's adulteration and misbranding provisions are designed to ensure that products regulated by FDA are safe, effective, and properly labeled. *See FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133-34 (2000); *United States v. Bel-Mar Labs., Inc.*, 284 F. Supp. 875, 880-81 (E.D.N.Y. 1968); *United States v. Various Articles of Drugs*, 83 F. Supp. 882, 884-85 (D.D.C. 1949); *see also* 21 U.S.C. § 393(b)(2) (discussing the mission of FDA). Under the statute, a drug is adulterated and misbranded unless it complies with the requirements in 21 U.S.C. §§ 351 and 352. Of particular relevance here, a drug is adulterated under section 351(a)(2)(B) if it is not manufactured in compliance with CGMP, and a drug is misbranded under section 352(f)(1) if its labeling does not bear adequate directions for use.

A. "Drugs" Under the FDCA

An article is a "drug" and subject to the FDCA if it is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or is "intended to affect the structure or any function of the body of man or other animals." 21 U.S.C. § 321(g)(1)(B) & (C). Thus, whether any particular article is a drug depends on its "intended use." *See Whitaker v. Thompson*, 353 F.3d 947, 953 (D.C. Cir. 2004) (under the FDCA, "classification of a substance as a 'drug' turns on the nature of the claims advanced on its behalf"); *United States v. Writers & Research,*

[1] As noted in Section B of the Statement of Facts *infra*, Defendants' SVF product is not licensed or approved by FDA. There are not now, nor have there ever been, any approved new drug applications ("NDAs") pursuant to 21 U.S.C. § 355(b) or (j), nor any approved biologics license applications ("BLAs") pursuant to 42 U.S.C. § 262, filed with FDA for Defendants' SVF product. There are also no Investigational New Drug Applications ("INDs") in effect under 21 U.S.C. § 355(i), for the SVF product.

Inc., 113 F.3d 8, 11 (2d Cir. 1997) ("Regardless of the classification of a drug, if an article is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man it is defined as a drug."); *Nat'l Nutritional Foods Ass'n v. Mathews*, 557 F.2d 325, 333 (2d Cir. 1977) ("[t]he vendors' intent in selling the product to the public is the key element in this statutory definition."). "[I]t is well established that the 'intended use' of a product, within the meaning of the [FDCA], is determined from its label, accompanying labeling, promotional claims, advertising, and any other relevant source." *Action on Smoking & Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980) (internal citations omitted); *see* 21 C.F.R. § 201.128; *Nat'l Nutritional Foods Ass'n*, 557 F.2d at 333-34; *Estee Lauder, Inc. v. FDA*, 727 F. Supp. 1, 2 (D.D.C. 1989) ("Courts have held that the decision as to whether a product is a drug depends on its 'intended use,' which can be determined from objective evidence such as the product's current and past containers, instructions, and advertisements.").

The FDCA prohibits taking any action with respect to a drug "if such act is done while such article is held for sale . . . after shipment in interstate commerce and results in such article being adulterated or misbranded." 21 U.S.C. § 331(k). Under the FDCA, a drug is adulterated if "the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with [CGMP] to assure that such drug meets the requirements of [the FDCA] as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess." 21 U.S.C. § 351(a)(2)(B); *see* 21 C.F.R. Parts 210-211 (drugs); 21 C.F.R. Parts 600-680 (additional standards for biological products). A drug is misbranded under the FDCA "unless its labeling bears adequate directions for use" and the drug does not fall within a regulatory exemption from that requirement. 21 U.S.C. § 352(f)(1); *see* 21 C.F.R. § 201.5. For a more fulsome discussion of the adulteration and misbranding provisions of the FDCA, please see Sections B and C of the Argument section.

B. "Biological Products" Under the PHSA

In addition to being regulated as a drug under the FDCA, Defendants' SVF product is also a "biological product" subject to the requirements of the Public Health Service Act

("PHSA"), 42 U.S.C. § 262.[2] A "biological product" includes any "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or *analogous product* . . . , applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i) (emphasis added). A product may be both a drug and a biological product. *See, e.g.*, *United States v. Regenerative Scis., LLC*, 741 F.3d 1314, 1319 (D.C. Cir. 2014) ("Both of these wide-ranging definitions clearly apply to the [appellants' stem cell product], an article derived mainly from human tissue"); *CareToLive v. von Eschenbach*, 525 F. Supp. 2d 952, 957 (S.D. Ohio 2007) ("Biological products can also be drugs, and are generally subject to the same statutory and regulatory requirements that apply to drugs."); *United States v. Loran Med. Sys., Inc.*, 25 F. Supp. 2d 1082, 1084-86 (C.D. Cal. 1997) (cell product made from neonatal rabbit and human fetal cells was a drug and a biological product).

A product that has been licensed under the PHSA is not required also to have an approved new drug application under the FDCA; in every other respect, however, the FDCA applies. 42 U.S.C. § 262(j). Thus, although the fact that a drug can also be a biological product may affect the applicability of certain statutory and regulatory requirements, it does not exempt the product from other provisions of the FDCA, including the provisions applicable to the adulteration and misbranding of drugs at issue in this case.

C. Regulation of "HCT/P's"

Regulations promulgated under the PHSA apply to human cells, tissues, or cellular or tissue-based products, known as "HCT/P's." 21 C.F.R. § 1271.3(d) (defining HCT/P's as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."). Certain HCT/P's that meet four specific criteria at 21 C.F.R. § 1271.10(a) can be effectively regulated by controlling the communicable disease risks they present. These HCT/P's, sometimes referred to as "361 HCT/P's," are regulated solely under section 361 of the PHSA and the HCT/P regulations (21 C.F.R. Part 1271), even if such HCT/P's would otherwise meet the FDCA's definition of a "drug" or the PHSA's definition of a "biological product." The regulations also identify certain

[2] The government is not bringing charges under the PHSA for reasons that are beyond the scope of this motion, but certain provisions of the PHSA are discussed because they are relevant to arguments we anticipate Defendants will raise.

circumstances under which an establishment is excepted from FDA's HCT/P regulations. *See, e.g.*, 21 C.F.R. § 1271.15(b) (the "same surgical procedure" exception). Unless an HCT/P meets *all four* of the criteria in 21 C.F.R. § 1271.10(a) for regulation solely under section 361 of the PHSA, or unless one of the exceptions in 21 C.F.R. § 1271.15 applies (including the "same surgical procedure" exception raised by Defendants), the HCT/P is regulated as a drug, device, and/or biological product under the PHSA and/or the FDCA and is subject to the FDCA's adulteration and misbranding provisions. *See* Final Registration Rule, 66 Fed. Reg. at 5449 (Jan. 19, 2001); 21 C.F.R. §§ 1271.15 & 1271.20.

As set forth below, Defendants' SVF product does not meet all of the Section 1271.10(a) criteria and is thus not eligible for regulation solely under section 361 of the PHSA and 21 C.F.R. Part 1271. Nor does the same surgical procedure exception or any other Section 1271.15 exception apply. The Defendants are in direct violation of their legal obligations, and summary judgment is appropriate.

STATEMENT OF FACTS

A. The Defendants

Defendant USSCC is a Florida limited liability company with its principal place of business located at 12651 Sunrise Blvd., Suite 104, Sunrise, Florida 33323, within the jurisdiction of this Court. Statement of Undisputed Material Facts ("SMUF") ¶ 1.

Defendant US Stem Cell, Inc., is a Florida profit corporation with its principal place of business at 13794 Northwest 4th Street, Suite 212, Sunrise, Florida 33325, within the jurisdiction of this Court. SMUF ¶ 2.

Defendant Kristin C. Comella is the "Chief Scientific Officer" of both USSCC and US Stem Cell, Inc. SMUF ¶ 3. She is responsible for overseeing the daily operations at USSCC, including but not limited to overseeing patient scheduling and hiring and firing employees. *Id.* She has stated that she wrote the procedures for Defendants' process for isolating SVF from adipose tissue and administering it to patients, and she has trained doctors on manufacturing and using the SVF product. *Id.* She performs her duties at USSCC's Sunrise facility. *Id.* She does not have a medical degree and is not a licensed physician. *Id.*

Defendant Theodore Gradel is a minority investor in USSCC. SMUF ¶ 4. He has been a "managing member" of USSCC. *Id.* As of November 13, 2017, Defendant Theodore Gradel was listed with the Florida Division of Corporations as an "authorized person" and a "manager"

for USSCC. *Id.* He was identified to FDA investigators as an individual to whom correspondence regarding USSCC should be sent. *Id.* He participated on behalf of USSCC in an FDA inspection of USSCC in 2015. *Id.* He does not have a medical degree and is not a licensed physician. *Id.*

B. The Defendants' SVF Product

USSCC manufactures, or causes to be manufactured, the SVF product from a patient's adipose tissue (fat) and additional drug components. *See* SMUF ¶¶ 5, 39, 40; *see also* 21 C.F.R. § 1271.3(e) (defining "manufacture" to include, without limitation, "any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor").[3] First, Defendants recover adipose tissue from a patient in an examination room located at USSCC's Sunrise, Florida facility through a mini-liposuction procedure. SMUF ¶ 9. Defendants then incubate the recovered adipose tissue with a solution containing an enzyme that breaks down the tissue to isolate cellular components through enzymatic digestion. SMUF ¶ 10. This step alters the physical properties of the adipose tissue. SMUF ¶ 12-13.

After the enzyme thoroughly digests the tissue, Defendants obtain from it cellular components and reticular fiber network fragments, which they then subject to multiple centrifugations and filtration. SMUF ¶ 10. As a result, many components of the original tissue are broken down and/or discarded. *Id.* Among other things, Defendants' processing removes the adipocytes and the reticular fiber network of the adipose tissue. SMUF ¶ 12. Defendants use various sorts of manufacturing equipment to accomplish these steps, including syringes, cell wash bags, conical tubes, an incubator, a centrifuge, and a filter. SMUF ¶ 10.

Finally, Defendants use saline that has traveled in interstate commerce to resuspend the isolated cells, known as SVF, and create their final product. SMUF ¶¶ 18, 39, 40. That final SVF product is significantly different from the adipose tissue the Defendants recovered from the patient at the outset. Defendants' multi-step manufacturing process significantly alters the

[3] Defendants disagree with the Government's characterization of their production of SVF as a "manufacturing" process that results in a "product," but admit to the underlying factual assertions, which are in paragraphs 10 and 11 of the Complaint. *See* Ans. ¶¶ 10-11. Defendants' disagreement over the characterizations of the manufacturing process are immaterial to the resolution of this case. The parties agree about the steps of the process. SMUF ¶ 40. And the fact that the process results in a "drug" as defined by the FDCA is established as a matter of law (based on undisputed facts). *See, infra,* Argument Section A.

recovered adipose tissue so that it no longer resembles—in structure, function, or otherwise—the tissue originally recovered from patients. SMUF ¶¶ 10, 13.

Defendants' SVF product is intended for "autologous" use in patients (SMUF ¶ 6), which means the "implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered." 21 C.F.R. § 1271.3(a). Defendants generally administer the SVF product intravenously into the patient's bloodstream or by injection into various specific areas of the patient's body. SMUF ¶ 8. The entire process, including recovering the adipose tissue from a patient, manufacturing the SVF product, and administering the SVF product to the patient, occurs at the USSCC facility. SMUF ¶¶ 9, 14.

Defendants' SVF product is not licensed or approved by FDA. SMUF ¶ 21. There have never been any approved new drug applications ("NDAs") filed with FDA pursuant to 21 U.S.C. § 355(b) or (j) for the SVF product. SMUF ¶ 22. Similarly, there are not now, nor have there ever been, any approved biologics license applications ("BLAs") filed with FDA pursuant to 42 U.S.C. § 262 for the SVF product. *Id.* Finally, there are also no Investigational New Drug Applications ("INDs") under 21 U.S.C. § 355(i) in effect for Defendants' SVF product. *Id.* Furthermore, Defendants concede their SVF operations were not in full compliance with FDA's CGMP regulations at the time of FDA's October 22, 2015 to December 7, 2015 inspection and FDA's April 10, 2017 to May 11, 2017 inspection of USSCC. SMUF ¶ 31. Defendants' SVF product does not bear labeling containing indications for use, dosages, routes of administration, and side effects. SMUF ¶ 20.

Despite these uncontested facts, between December 2015 and April 2017, USSCC manufactured the SVF product and used it purportedly to treat more than [redacted] patients at USSCC's Sunrise, Florida facility. SMUF ¶ 24. Despite the fact that there have been no adequate and well-controlled studies performed with the Defendants' SVF product demonstrating that it is safe or effective for any indication (SMUF ¶ 27), Defendants continue to market their SVF product as capable of treating a variety of serious diseases or conditions, including, but not limited to, amyotrophic lateral sclerosis ("ALS"), Parkinson's disease, spinal cord injuries, stroke, traumatic brain injury, chronic obstructive pulmonary disease ("COPD"), lung disease, and diabetes. SMUF ¶ 7.

C. Inspectional History and Prior Warnings

FDA warned Defendants as early as December 7, 2015, that their conduct violates the FDCA and poses a serious risk to the public health. FDA inspected USSCC from October 22 through December 7, 2015, and again from April 10 through May 11, 2017. SMUF ¶¶ 29-30. At the end of each inspection, FDA investigators issued to Defendant Kristin C. Comella a list of specific inspectional observations ("Form FDA 483") outlining areas of non-compliance observed during the inspection. *Id.* For example, during the 2017 inspection, FDA investigators observed that USSCC did not manufacture its SVF product under aseptic conditions or properly test it to check for the presence of objectionable microorganisms. SMUF ¶ 32-33. FDA sent a Warning Letter, dated August 24, 2017, to Defendant Comella reiterating the ways in which Defendants violated the law. SMUF ¶ 34. Defendants responded by arguing that the FDCA did not apply to their activities. SMUF ¶¶ 29-30, 34; *see* Ans. ¶¶ 50-52; *see also* Waltrip Decl. ¶¶ 25-28, Atts. 77-80.[4]

---

[4] Although they are not binding and do not have the force and effect of law, FDA has issued several documents consistently outlining its thinking on many of the matters at issue in this case. They include the following:

- Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception- Guidance for Industry, November 2017 (hereinafter, "SSPE Final Guidance"), *available at* https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM419926.pdf (Last accessed: March 10, 2019);
- Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use; Guidance for Industry and Food and Drug Administration Staff," (hereinafter "MM Final Guidance") dated November 2017 and corrected December 2017, *available at* https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm585403.pdf (Last accessed: March 10, 2019);
- Proposed Approach to Regulation of Cellular and Tissue-Based Products, FDA Dkt. No. 97N-0068 (Feb. 28, 1997) ("Proposed Approach") at 9, *available at* https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM062601.pdf (Last accessed: March 10, 2019).

See also:

- Guidance for Industry and FDA Staff - Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products: Draft Guidance, Dec. 2014, *available at* https://wayback.archive-

D. Adverse Medical Events

Evidence of patient harm is not required to establish a violation of the FDCA or to obtain an injunction to stop those violations. But here, the Government's concerns are very real. During FDA's inspection of USSCC's facilities, investigators reviewed several records that documented serious adverse events involving the SVF product, including the following:

- On June 16, 2015, a patient with macular degeneration suffered a loss of vision in both eyes after Defendants' SVF product was injected into them. SMUF ¶ 36. The day after the SVF product injections, a physician documented multiple hemorrhages in both eyes. *Id.* On June 29, 2015, a physician determined that the patient suffered detached retinas and was legally blind at 20/400 in both eyes, even after being corrected with glasses. *Id.*

- On the same day, June 16, 2015, another patient with macular degeneration experienced eye pain and blurry vision upon treatment with Defendants' SVF product. SMUF ¶ 35. The patient went to the emergency room, where she was diagnosed with intraocular pressure of over 90 mm Hg in her right eye and 73 mm Hg in her left eye. *Id.* She suffered a separation of the retina from the vitreous (the gel-like substance that fills the back of the eye between the lens and the retina), bilateral vitreous hemorrhages (leakage of blood from ruptured blood vessels in and around the virtreous), ocular hypertension (high pressure inside the eye), and uveitis (an inflammation of the middle layer of the eye). *Id.*

- On May 15, 2016, a patient received intravitreal injections of Defendants' SVF product, ostensibly as a treatment for macular degeneration. SMUF ¶ 37. After the injections, the patient suffered complete vision loss. *Id.*

- In March 2017, the New England Journal of Medicine ("NEJM") issued a report on these three "serious adverse events" involving "[b]linding visual outcomes" experienced by Defendants' patients. SMUF ¶ 38. The NEJM report recognized that experimentation on patients in this manner could lead to "devastating outcomes." *Id.* The NEJM report also noted that the patients' complications were "probably due to the stem-cell preparations" and that some may have been caused "when enzymes such as trypsin [ ] used in the preparation of the stem cells [ ] contaminate the injections." *Id.* at 1052. NEJM acknowledged the "toxic effects . . . caused by the injected material, which may have included the enzymes used in the preparation." *Id.*

STANDARD FOR SUMMARY JUDGMENT

Summary judgment is appropriate where the record shows "no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed. R. Civ.

---

it.org/7993/20170721165837/https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm427692.htm (Last accessed: March 10, 2019).

P. 56(a)). The Supreme Court has explained that "the mere existence of ***some*** alleged factual dispute between the parties will not defeat an otherwise properly supported motion for summary judgment." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 247-48 (1986). Moreover, "there is no issue for trial unless there is sufficient evidence favoring the non-moving party . . . to return a verdict for that party. If the evidence is merely colorable, or is not significantly probative, summary judgment may be granted." *Id.* at 249-50 (internal citations omitted).

ARGUMENT

There are no genuine disputes of material fact here. Defendants admit nearly all the relevant facts, and the remainder are beyond dispute. *First*, the facts show that Defendants' SVF product is a "drug" under the FDCA and a "biological product" under the PHSA. *Second*, the record shows that Defendants violate the FDCA by selling an adulterated and misbranded SVF product after at least one component of the product has traveled in interstate commerce. *Third*, Defendants cannot excuse their violations as falling within the "practice of medicine" or as falling within an exception from regulation under the FDCA for certain HCT/P's.[5] *Finally*, there is no question that Defendants will continue their illegal conduct unless enjoined by this Court.

A. Defendants' SVF Product Is a Drug Subject to the FDCA

Defendants admit all the facts necessary to establish that their SVF product is a drug within the meaning of the FDCA. As discussed *supra* at Section A of the Statutory and Regulatory Framework, whether an article is a drug depends on its intended use, which may be shown, *inter alia*, by how the product is promoted in its labeling and marketing. 21 U.S.C. § 321(g)(1)(B) & (C); 21 C.F.R. § 201.128; *Action on Smoking & Health*, 655 F.2d at 239. The "intended use" of a product refers to the objective intent of the persons legally responsible for its labeling. *United States v. Lane Labs-USA, Inc.*, 324 F. Supp. 2d 547, 567 (D.N.J. 2004), *order modified*, 328 F. Supp. 2d 520 (D.N.J. 2004), *aff'd*, 427 F.3d 219 (3d Cir. 2005).

Defendants' SVF product is a "drug" under the FDCA, which the statute defines as any "article" that is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or is "intended to affect the structure or any function of the body of man or other

[5] The Government addresses in this section some of the arguments Defendants previously raised in this litigation and to FDA. Although some of those arguments overlap with the affirmative defenses in Defendants' Answer, the Government does not attempt to respond to all of those affirmative defenses in this brief. The Government reserves the right, of course, to respond to Defendants' affirmative defenses when and if Defendants substantively raise them.

animals." 21 U.S.C. § 321(g)(1)(B) & (C). The SVF product falls squarely within this definition. That is clear both because Defendants promote it to the public to treat a variety of serious diseases and conditions in a variety of contexts and because Defendants admit they use SVF to address patients' symptoms of neurological, autoimmune, orthopedic, and degenerative medical conditions and/or diseases, including, but not limited to, ALS, Parkinson's disease, spinal cord injuries, stroke, traumatic brain injury, COPD, lung disease, and diabetes.[6] SMUF ¶ 7. Statements made by Defendants that further establish the intended uses of the SVF product—and thus its status as a "drug"—include:

- USSCC's website, usstemcellclinic.com, includes the statement that the company "offer[s] a variety of therapies" for "some of the most common conditions" including "neurological . . . autoimmune . . . degenerative" and other conditions, including ALS, Parkinson's disease, spinal cord injuries, stroke, traumatic brain injury, Rheumatoid Arthritis, congestive heart failure, kidney disease, and liver disease. SMUF ¶ 23.

- Records collected during FDA inspections document Defendants' manufacture of the SVF product to purportedly treat patients with ALS, Parkinson's disease, COPD, heart disease, pulmonary fibrosis, and other medical conditions. SMUF ¶ 24.

- A USSCC brochure marketing the SVF product, collected during FDA's 2017 inspection, states that "[s]tem cell therapy may promote the regeneration of healthy tissue, bone, or cartilage" and "has proven to be a better alternative for people facing debilitating conditions such as COPD, Degenerative Disc Disease, Osteoarthritis, and many others where traditional medicine falls short of delivering satisfactory results." SMUF ¶ 25.

- In a video posted on YouTube, Defendant Kristin Comella, representing US Stem Cell's corporate predecessor Bioheart, Inc., said, "At Bioheart, we focused on utilizing . . . fat-derived stem cells, originally focusing on patients with cardiac indications, patients who have had a heart attack or have developed congestive heart failure, and then have moved into other indications, including things like COPD, or lung disease; things like diabetes or limb ischemia; and also injuries, things like spinal cord injuries and orthopedics." SMUF ¶ 26.

Because there is no genuine dispute that the "intended use" of the SVF product is to treat, cure, and/or mitigate a variety of diseases and medical conditions or to affect the structure or any function of the body, it is a "drug" under the FDCA. *See* SMUF ¶ 7. Thus, as with other drugs,

[6] Although Defendants attempt to deny that the SVF product is a "treatment" (Ans. ¶ 7), they admit that they use SVF to "address symptoms" of medical conditions and diseases. SMUF ¶ 7. Defendants cannot credibly argue that a product used to "address symptoms" of a disease is not used to cure, mitigate, and/or treat that disease. *Cf.* 21 U.S.C. § 321(g)(1)(B).

the SVF product is subject to the FDCA's adulteration and misbranding provisions. *See* 21 C.F.R. § 1271.20; Final Registration Rule, 66 Fed. Reg. 5449 and 5456 (Jan. 19, 2001).

B. Defendants Violate the FDCA By Adulterating Their SVF Product

To show that Defendants violate 21 U.S.C. § 331(k) by adulterating their SVF product, the Government must establish: (1) the SVF product is a drug within the meaning of 21 U.S.C. § 321(g)(1)(B) or (C); (2) the SVF product is held for sale after one or more of its components have been shipped in interstate commerce; and (3) Defendants cause their SVF product to become adulterated—here by failing to comply with CGMP. As set out above, the SVF product is a drug. *See, supra*, Section A of the Argument. Further, it contains components shipped in interstate commerce and is adulterated, as detailed below.

1. Defendants' SVF Product Is Held for Sale After Shipment of One or More of its Components in Interstate Commerce

Section 331(k) prohibits taking any action with respect to a drug "if such act is done while such article is held for sale . . . after shipment in interstate commerce and results in such article being adulterated or misbranded." 21 U.S.C. § 331(k). A product is "held for sale" if it is used for any purpose other than personal consumption. *United States v. Torigian Labs., Inc*., 577 F. Supp. 1514, 1521 (E.D.N.Y. 1984), *aff'd*, 751 F.2d 373 (2d Cir. 1984) (unpublished table decision); *United States v. Articles of Drug . . . Hydralazine HCL*, 568 F. Supp. 29, 31 (D.N.J. 1983); *see United States v. Diapulse Corp. of Am.*, 514 F.2d 1097, 1098 (2d Cir. 1975); *see also United States v. Sullivan*, 332 U.S. 689, 697 (1948) (section 331(k) intended to "extend [FDCA's] coverage to every article that had gone through interstate commerce until it finally reached the ultimate consumer"); *United States v. Evers*, 643 F.2d 1043, 1050 (5th Cir. 1981) ("A practicing physician may also fall within the bounds of this section. . . . Doctors holding drugs for use in their practice are clearly one part of the distribution process, and doctors may therefore hold drugs for sale within the meaning of [21 U.S.C. § 331(k)]."). Defendants' SVF product is "held for sale" by Defendants because they market and offer that product to patients who have serious or life-threatening diseases or conditions—commercial purposes other than Defendants' own personal consumption. SMUF ¶ 5.

Defendants' SVF product also satisfies section 331(k)'s requirement that it be "after shipment in interstate commerce" because at least one component of the SVF product (*e.g.*,

Sodium Chloride Injection) has traveled in interstate commerce.[7] The FDCA defines "drug" to include components of a drug. 21 U.S.C. § 321(g)(1)(D). Courts consistently have interpreted section 331(k) and section 321(g)(1)(D) to mean that the final drug product (here, the SVF product) need not have been shipped in interstate commerce in completed form to satisfy the requirement. *See, e.g.*, *Baker v. United States*, 932 F.2d 813, 814-15 (9th Cir. 1991) ("the 'shipment in interstate commerce' requirement is satisfied even when only an ingredient is transported interstate"); *United States v. Dianovin Pharms., Inc.*, 475 F.2d 100, 103 (1st Cir. 1973) ("appellants' use of components shipped in interstate commerce to make vitamin K for injection brought their activities within section 331(k), and conferred jurisdiction to restrain violations thereof upon the district court"); *Regenerative Scis.*, 741 F.3d at 1320-21. When one of a drug's components has been shipped in interstate commerce, including that component in manufacturing an article of drug that is or becomes adulterated or misbranded violates 21 U.S.C. § 331(k). *Dianovin Pharms.*, 475 F.2d at 103.

Defendants do not appear to dispute—nor could they—that this requirement is satisfied. Defendants admit that they receive 0.9% Sodium Chloride Injection, USP, packed in 10 mL vials from [redacted] SMUF ¶ 19. Defendants further admit that they use the 0.9% Sodium Chloride Injection to resuspend the SVF cells, and that the resulting product is administered to patients. SMUF ¶¶ 5, 39. The Sodium Chloride Injection sold by [redacted] is manufactured by [redacted], in [redacted], Georgia. SMUF ¶ 19. Further, as a general matter, Congress has specified that "the connection with interstate commerce required for jurisdiction" in "any action to enforce the requirements of [the FDCA] respecting a . . . drug . . . shall be presumed to exist." 21 U.S.C. § 379a; *see United States v. Chung's Prods. LP*, 941 F. Supp. 2d 770, 795 (S.D. Tex. 2013); *Torigian Labs., Inc.*, 577 F. Supp. at 1521. As a result, Defendants' SVF product is held for sale after shipment of one or more of its components in interstate commerce.

2. Defendants Adulterate Their SVF Product

Defendants do not abide by important safety regulations in manufacturing their SVF product and thus that product is adulterated. Defendants admitted that they do not comply with CGMP. SMUF ¶ 31. Under the FDCA, a drug is adulterated if "the methods used in, or the

[7] Of note, Defendants' process for manufacturing the SVF product also includes the use of cell wash solution and enzyme that have traveled in interstate commerce. *See* SMUF ¶¶ 10, 16.

facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with [CGMP] to assure that such drug meets the requirements of [the FDCA] as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess." 21 U.S.C. § 351(a)(2)(B). Defendants' admissions and other undisputed facts show that their SVF product is adulterated.

CGMP regulations establish minimum requirements applicable to drugs, as well as biological products, to ensure that they have the identity, strength, quality, purity, and other attributes necessary for safe and effective use. *See* 21 C.F.R. Parts 210-211 (drugs); 21 C.F.R. Parts 600-680 (additional standards for biological products). Violation of a single CGMP regulation is sufficient to make a drug adulterated. *See United States v. W. Serum Co.*, 498 F. Supp. 863, 867-68 (D. Ariz. 1980) ("There is no allegation that the FDA has exceeded its authority in requiring full compliance [with CGMP]."), *aff'd*, 666 F.2d 335 (9th Cir. 1982); *United States v. 789 Cases, More or Less, of Latex Surgeons' Gloves*, 799 F. Supp. 1275, 1287 (D.P.R. 1992).

When drugs are not manufactured or held in conformance with CGMP, they are adulterated as a matter of law, regardless of whether the products are actually deficient in any way. 21 U.S.C. § 351(a)(2)(B); *John D. Copanos & Sons, Inc. v. FDA*, 854 F.2d 510, 514 (D.C. Cir. 1988) ("Drugs produced in violation of these CGMP regulations are deemed to be adulterated without the agency having to show that they are actually contaminated."); *see also United States v. Radix Labs., Inc.*, 963 F.2d 1034, 1038 n.4 (7th Cir. 1992) ("If a drug is not manufactured in conformity with CGMP it is adulterated."); *W. Serum Co.*, 498 F. Supp. at 867 (government need not prove the drug is deficient to be adulterated for failure to comply with CGMP; the FDCA "is concerned with the manner in which a drug is produced as well as its composition and content"); *Regenerative Scis.*, 741 F.3d at 1323 ("it is undisputed that appellants' facilities, methods, and controls for processing the Mixture violated federal manufacturing standards in numerous respects. Therefore, the Mixture is *per se* adulterated, regardless of any other safety protocols appellants happen to use.").

Defendants do not contest the fact that their operations do not comply with CGMP requirements. SMUF ¶ 31. The evidence collected by FDA investigators during inspections of USSCC's facility in 2015 and 2017 showed significant CGMP violations. SMUF ¶¶ 29-30, 32-

33. Defendants failed to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, in violation of 21 C.F.R. § 211.113(b) (SMUF ¶ 32); failed to conduct appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms, in violation of 21 C.F.R. § 211.165(b) (SMUF ¶ 33); and failed to establish a system for monitoring environmental conditions to prevent contamination during aseptic processing, in violation of 21 C.F.R. § 211.42(c)(10)(iv) (SMUF ¶ 44). FDA investigators presented their observations to Defendant Comella at the close of each inspection. SMUF ¶¶ 29-30. The undisputed evidence thus shows that Defendants do not comply with CGMP, and thus their SVF product is adulterated. *See* 21 U.S.C. § 351(a)(2)(B).

C. Defendants Violate the FDCA By Misbranding Their SVF Product

A drug is misbranded under the FDCA "unless its labeling bears adequate directions for use" and the drug does not fall within a regulatory exemption from that requirement. 21 U.S.C. § 352(f)(1). Defendants' SVF product labeling does not bear adequate directions for use for three different reasons, any one of which is sufficient to establish misbranding under 21 U.S.C. § 352(f)(1). Specifically: (1) the SVF product does not bear labeling that contains information required for adequate directions for use, as defined in 21 C.F.R. § 201.5; (2) the SVF product is an unapproved prescription drug that is not excepted from labeling requirements requiring directions under which a lay person can use the drug safely; and (3) it is currently impossible to draft adequate directions for use because there is no scientifically valid evidence to show that the SVF product is safe or effective for any indication.

1. Defendants' SVF Product Does Not Bear Labeling That Contains Information Required for Adequate Directions for Use

Under the relevant regulations, "adequate directions for use" are "directions under which the layman can use a drug safely and for the purposes for which it is intended." 21 C.F.R. § 201.5; *see also United States v. Algon Chem., Inc.*, 879 F.2d 1154, 1156 (3d Cir. 1989) ("Courts have consistently upheld the FDA's interpretation of this provision as requiring adequate directions for use of the drug by a *layman*."); *United States v. Articles of Drug (Rucker Pharmacal)*, 625 F.2d 665, 673 (5th Cir. 1980) (a "drug's labeling must contain adequate directions for a consumer to engage in self-medication."); *United States v. Two Units, More or Less, of an Article or Device, Consisting of a Power Unit and a Chair*, 49 F.3d 479, 482 (9th Cir.

1994) (medical device is "misbranded if it does not bear adequate directions to enable a layperson to use it safely.").

The misbranding regulations at 21 C.F.R. § 201.5 provide that directions for use are inadequate unless the drug's labeling contains, among other things: quantity of dose, including the usual quantities for each of the uses for which it is intended and usual quantities for persons of different physical conditions; frequency and duration of administration; time of administration in relation to time of meals, onset of symptoms, and other factors; and route or method of administration. 21 C.F.R. § 201.5; *see also Regenerative Scis.*, 741 F.3d at 1323-24 ("The FDCA also provides that a drug 'shall be deemed to be misbranded' if its label omits certain information"); *Nature Food Centres, Inc. v. United States*, 310 F.2d 67, 69-71 (1st Cir. 1962) (a drug is misbranded if labeling fails to state all intended uses for which it is marketed); *Alberty Food Prods. v. United States*, 194 F.2d 463, 464 (9th Cir. 1952) (adequate directions for use must include statement of "the purposes and conditions for which the drug was intended and sufficient information to enable a layman to intelligently and safely attempt self medication"); *see also United States v. An Article of Device . . . "Hubbard Electrometer,"* 333 F. Supp. 357, 362 n.5 (D.D.C. 1971) ("Accompanying labeling must specify the conditions for which the device is intended and sufficient information under which the device can be used safely and effectively for the purposes for which it is intended to be used.").

Defendants admit that they do not label the SVF product with indications for use, dosages, or routes of administration. SMUF ¶ 20. Thus, the labeling for Defendants' SVF product does not include all of the information required by 21 C.F.R. § 201.5. This alone is sufficient to render the SVF product misbranded under 21 U.S.C. § 352(f)(1).

2. The SVF Product Is an Unapproved Prescription Drug That Is Not Excepted from Labeling Requirements

Defendants' SVF product is not only an unapproved drug; it is also an unapproved prescription drug. The FDCA specifies that a drug is a prescription drug if, due to "its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, [the drug] is not safe for use except under the supervision of a practitioner licensed by law to administer such drug . . . ." 21 U.S.C. § 353(b)(1)(A); *see United States v. Munoz*, 430 F.3d 1357, 1367 (11th Cir. 2005). Defendants' SVF product satisfies this definition in at least two ways. First, it is intended to be administered intravenously or by injection into specific areas of the body. SMUF ¶ 8. Medical expertise, licensure, and appropriate training is

necessary to administer products by intravenous, subcutaneous, or intramuscular injections. SMUF ¶ 43. Because the intended method of using the SVF product requires medical training, it is a prescription drug. *See* SMUF ¶ 42. Second, scientific literature documents the harmful effects that may occur as a result of administering products from adipose tissue using routes of administration such as those intended for Defendants' SVF product. SMUF ¶ 41. Those harmful effects include administration site reactions such as swelling, tendonitis, and intra-articular pain, as well as systemic reactions manifested by transient fever, facial flushing and myalgia, and pulmonary embolism. *Id.* The potential for harmful effects means the SVF product is not safe for use except under the supervision of a practitioner licensed by law to administer such a drug. Lapteva Decl. ¶¶ 35-36. Accordingly, due to the method of its use and potential for harmful effects related to the product's administration, Defendants' SVF product is a prescription drug. *See* 21 U.S.C. § 353(b)(1)(A); Lapteva Decl. ¶ 38.

The labeling for a *prescription* drug, like the SVF product, cannot, as a matter of law, satisfy the requirement that it bear adequate directions for use by a layperson. A prescription drug, by its nature, may be used safely only under the supervision of a physician. *See* 21 U.S.C. § 353(b)(1); *Articles of Drug (Rucker Pharmacal)*, 625 F.2d at 670. Because prescription drugs can be used safely only at the direction, and under the supervision, of a physician, directions under which the layperson could use a drug safely cannot be written for a prescription drug. *Articles of Drug (Rucker Pharmacal)*, 625 F.2d at 673 (it is not possible to provide a layperson with adequate directions for use for a prescription drug); *United States v. Baxter Healthcare Corp*., 712 F. Supp. 1352, 1359 (N.D. Ill. 1989), *aff'd*, 901 F.2d 1401 (7th Cir. 1990); *United States v. An Article of Drug . . . Mykocert*, 345 F. Supp. 571, 573 (N.D. Ill. 1972).

As a prescription drug that cannot, by definition, bear adequate directions for use by a layperson, the SVF product is *per se* misbranded unless it qualifies for an exemption from section 352(f)(1). *Articles of Drug (Rucker Pharmacal)*, 625 F.2d at 673 ("Since a prescription drug by definition can be used only under a physician's supervision, and is unsuitable for self-medication, such a drug must qualify for a regulatory exemption created by FDA" under section 352(f)); *United States v. Premo Pharm. Labs., Inc.*, 511 F. Supp. 958, 977 n.23 (D.N.J. 1981) ("A drug is misbranded if it is a prescription drug that is an unapproved new drug, because a prescription drug cannot bear the adequate directions for use required by statute, section 352(f)(1), and the lack of an approved [new drug application] means that there is no FDA

exemption from the adequate directions for use requirement") (citations omitted). Defendants cannot meet the burden of showing that they qualify for such an exemption.[8] *See United States v. 9/1 Kg. Containers*, 854 F.2d 173, 176 (7th Cir. 1988) (claimant bore burden of proof that drugs qualified for exemption to requirement that drug labeling bear adequate directions for use). Thus, for this second—independent—reason, the SVF product is misbranded under the FDCA.

3. It Is Currently Impossible to Draft Adequate Directions for Use for the SVF Product

The third, independent (and most fundamental) basis for determining that the SVF product is misbranded is that it is currently impossible to draft adequate directions for use of the SVF product because there is no scientifically valid evidence to show that it is safe or effective for *any* indication. Adequate directions for use, which include information about, among other things, indications, dosages, and routes of administration, must be based on data derived from well-controlled scientific testing. *See United States v. Undetermined Quantities of Articles of Drug*, 145 F. Supp. 2d 692, 702 (D. Md. 2001) ("Essentially, in the absence of investigations or clinical data demonstrating the safety and efficacy of the drugs, there can be no adequate instruction for their *safe* use."); *United States v. Miami Serpentarium Labs., Inc.*, 1981-82 FDC L. Rptr. Dev. Trans. Binder ¶ 38,164 at 38,931 (S.D. Fla. Mar. 30, 1982) ("Adequate directions for use—including indications, contraindications, dosages, routes of administration, warnings, side effects, and necessary collateral measures—are premised on a body of animal and clinical data derived from extensive, scientifically controlled testing."). Because no well-controlled studies have been conducted on Defendants' SVF product, there is no scientifically valid evidence to show the SVF product is safe or effective for any indication, or on which to base the directions for use. *See* SMUF ¶ 27, 28. As a result, Defendants cannot draft "adequate

[8] For example, 21 C.F.R. § 201.115(a) permits a "new drug" to be exempt from section 352(f)(1) "[t]o the extent . . . such exemption is claimed in an approved" new drug application. Defendants' SVF product is a new drug. *See* 21 U.S.C. § 321(p)(1); SMUF ¶¶ 27-28; *Weinberger v. Hynson, Westcott, & Dunning, Inc.*, 412 U.S. 609, 629-30 (1973) (in the absence of "any evidence of adequate and well-controlled investigation supporting the efficacy of [a drug], *a fortiori* [the drug] would be a 'new drug' subject to the provisions of the [FDCA]"). Because the SVF product is a new drug and it is unapproved (SMUF ¶ 22), it cannot qualify for the exemption in 21 C.F.R. § 201.115. *See Articles of Drug (Rucker Pharmacal)*, 625 F.2d at 675. Further, the SVF product also fails to qualify for the exemption for prescription drugs for human use. *See* 21 C.F.R. § 201.100. Among other things, its label does not bear information required under 21 C.F.R. 201.100(b) & (c)(1). *See* SMUF ¶ 20; Lapteva Decl. ¶ 43.

directions for use" for the "safe[]" use of their SVF product within the meaning of 21 C.F.R. § 201.5, and the SVF product is misbranded under 21 U.S.C. § 352(f)(1) because it does not—and cannot—bear adequate directions for use.

For all of these independent reasons, Defendants' SVF product is misbranded under 21 U.S.C. § 352(f)(1), because its labeling does not, and cannot, bear adequate directions for use.

D. The "Same Surgical Procedure" Exception Does Not Apply, Nor Does the SVF Product Qualify as a "361 HCT/P"

In previous correspondence to FDA, Defendants argued that the adulteration and misbranding provisions of the FDCA do not apply to them. That is so, they claim, because they qualify for the "same surgical procedure" exception at 21 C.F.R. § 1271.15(b), and because their SVF product meets all the criteria in 21 C.F.R. § 1271.10(a) for regulation solely under section 361 of the PHSA and the regulations in Part 1271. For the reasons explained below, Defendants cannot meet their burden to show that either exception applies. *See Regenerative Scis.*, 741 F.3d at 1322 ("appellants ultimately bear the burden of establishing that [21 C.F.R. § 1271.10(a)] applies").

1. The Same Surgical Procedure Exception at 21 C.F.R. § 1271.15(b) Does Not Apply.

Defendants first claim their SVF product should be excepted from the FDCA's public health protections because its manufacture takes place in the context of same-day surgery and contains the patient's own cells. Ans. at 10 ("Third Affirmative Defense"). Defendants are invoking what is known as the "same surgical procedure" exception, which provides:

> You are not required to comply with the requirements of [21 C.F.R. Part 1271] if you are an establishment that removes HCT/P's from an individual and implants ***such HCT/P's*** into the same individual during the same surgical procedure.

21 C.F.R. § 1271.15(b) (emphasis added).

The same surgical procedure exception does not apply here because the SVF product—comprised of cells, saline, and perhaps other components left behind from the manufacturing process—implanted into patients is *not* the HCT/P that Defendants remove from patients. The same surgical procedure exception is specific to implantation of "*such* HCT/P's," a phrase that describes the antecedent HCT/P's "remove[d] . . . from an individual." By the text of the regulation, the same surgical procedure exception thus applies only where an HCT/P is removed from a patient and then the HCT/P is implanted back into the patient. If the removed HCT/P is transformed via processing so that it is no longer "such HCT/P," then the exception does not

apply. In other words, "such HCT/P's" must mean HCT/P's in the form removed from the body. This construction is the only plausible one, as any alternate construction would render the word "such" meaningless. *See, e.g., United States v. Bowen*, 100 U.S. (10 Otto) 508, 512 (1879) (reading the statutory phrase "all such pensioners" to refer to the subset of pensioners previously referenced in the statutory text, since construing the phrase otherwise would treat the word "such" as surplusage); *United States v. Canals-Jimenez*, 943 F.2d 1284, 1287 (11th Cir. 1991) ("A basic premise of statutory construction is that a statute is to be interpreted so that no words shall be discarded as being meaningless, redundant, or mere surplusage.").[9]

While very limited processing steps, such as rinsing, cleansing, sizing, or shaping, may allow an HCT/P to remain in its original form, the adipose tissue that Defendants recover from patients undergoes a dramatic transformation into something that is plainly different from "such HCT/P" as was removed from the individual. *See* Yong Decl. ¶¶ 23-27. Adipose tissue—the HCT/P recovered from patients—is a structural tissue composed of cells surrounded by a reticular fiber network and interspersed small blood vessels. SMUF ¶¶ 11, 45. Defendants break down that adipose tissue under [redacted] conditions to aid enzymatic digestion and isolate cellular components. SMUF ¶ 10. The enzyme digests much of the tissue by disrupting and digesting the reinforced basement membrane to dissociate the cellular contents of the adipose tissue. SMUF ¶ 12.

What remains of the adipose tissue following Defendants' enzymatic digestion, filtration, centrifugation, and other processing cannot be considered "tissue" at all. SMUF ¶¶ 10-13. Rather, the organized structure of the adipose tissue has been destroyed and all that remains is a heterogeneous collection of cells suspended in a saline solution. *See* SMUF ¶ 46. The HCT/P that Defendants remove from patients is thus *not* the HCT/P that is later implanted, Yong Decl.

[9] The phrase "such HCT/P's" is not ambiguous, but even if it were, then FDA's interpretation should be accorded substantial deference because its interpretation "necessarily require[s] significant expertise and entail[s] the exercise of judgment grounded in policy concerns." *See Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994), *quoting Pauley v. BethEnergy Mines, Inc.*, 501 U.S. 680, 697 (1991); *see also United States v. Regenerative Scis.*, LLC, 878 F. Supp. 2d 248, 258 (D.D.C. 2012). FDA's interpretation of "such HCT/P's" is documented in the SSPE Final Guidance. That guidance states, "An HCT/P remains 'such HCT/P' when it is in its original form. Generally, the only processing steps that will allow an HCT/P to remain 'such HCT/P' are rinsing, cleansing, sizing, and shaping." SSPE Final Guidance at 5.

¶¶ 25-26, and is accordingly not "such HCT/P's" within the meaning of 21 C.F.R. § 1271.15(b). As a result, the same surgical procedure exception does not apply. *See also* Yong Decl. ¶ 27.

2. Defendants' SVF Product Fails to Meet All of the Criteria in 21 C.F.R. § 1271.10(a) for Regulation Solely under Section 361 of the PHSA

FDCA requirements do not apply to an HCT/P that meets the criteria in 21 C.F.R. § 1271.10(a), which is instead regulated solely under section 361 of the PHSA and the regulations in 21 C.F.R. Part 1271. A "Section 361" HCT/P must meet all four of the criteria.[10] 21 C.F.R. §§ 1271.10(a) & 1271.20. The criteria specify, *inter alia*, that the HCT/P must not be more than "minimally manipulated" and must be "intended for homologous use only." 21 C.F.R. § 1271.10(a)(1)-(2); 21 C.F.R. § 1271.20; 66 Fed. Reg. at 5456.[11] As with the same surgical procedure exception, Defendants cannot meet their burden of demonstrating that their SVF product satisfies these criteria for regulation solely under section 361 of the PHSA and the regulations in 21 C.F.R. Part 1271. *See Regenerative Scis.*, 741 F.3d at 1322.

a. Defendants' SVF Product Is More than Minimally Manipulated

Defendants' SVF product is more than minimally manipulated. *See* 21 C.F.R. § 1271.10(a)(1). In defining "minimal manipulation," the Part 1271 regulations distinguish between "structural tissue" and "cells or nonstructural tissues." 21 C.F.R. § 1271.3(f). As noted above, the adipose tissue Defendants recover from patients is structural tissue. SMUF ¶ 11, 45. Adipose tissue is comprised of cells surrounded by a reticular fiber network and interspersed small blood vessels, divided into lobes and lobules by connective tissue septa. SMUF ¶ 45. For such structural tissue "minimal manipulation" means "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or

[10] This memorandum does not further discuss whether the USSCC SVF product meets the criteria at 21 C.F.R. § 1271.10(a)(3) or (a)(4), because such analysis would be unnecessary in light of the fact that it fails to meet the criteria at 21 C.F.R. § 1271.10(a)(1) and (a)(2).

[11] In promulgating the 21 C.F.R. Part 1271 regulations, FDA was concerned with preventing the transmission of communicable diseases, understanding necessary processing controls (*e.g.*, to prevent contamination that could result in an unsafe or ineffective product), preserving product integrity and function, and ensuring clinical safety and effectiveness. Proposed Approach at 9. FDA explained that clinical safety and effectiveness concerns depend in part on the extent of manipulation of the cells or tissues. *Id.* at 11. For example, the agency noted, *inter alia*, that "[i]mproper handling . . . can allow cells or tissues to become contaminated (*e.g.*, bacterial contamination during collection, processing, storage, or transplantation, or cross contamination from other contaminated tissues)." *Id.* at 15.

replacement." 21 C.F.R. § 1271.3(f)(1).

Defendants' transformation of adipose tissue into the SVF product is clearly outside this definition. Defendants break down adipose tissue with enzymatic digestion to isolate cellular components (*i.e.*, SVF). SMUF ¶ 10, 12. By isolating and removing the adipocytes and all of the structural components from adipose tissue, Defendants alter the original relevant characteristics relating to the tissue's utility to provide cushioning and support, which is essential to the tissue's utility for reconstruction, repair, or replacement. Yong Decl. ¶ 32. Unlike adipose tissue, SVF does not provide cushioning and support. SMUF ¶ 13. Indeed, in processing SVF from adipose tissue, Defendants deliberately eliminate such characteristics by breaking down the adipose tissue's extracellular matrix and removing the adipocytes. *See* SMUF ¶¶ 12, 13. By any measure, this wholesale change to the original tissue constitutes far more than "minimal manipulation" for structural tissue, within the meaning of 21 C.F.R. § 1271.3(f)(1). Yong Decl. ¶¶ 32-33. Defendants' failure to meet this criterion is alone sufficient to render the regulatory scheme in 21 C.F.R. § 1271.10(a) inapplicable.

b. Defendants' SVF Product Is Not Intended for Homologous Use Only

Defendants' SVF product also fails to meet the 21 C.F.R. § 1271.10(a) criteria in that it is not "intended for homologous use only." *See* 21 C.F.R. § 1271.10(a)(2). "Homologous use" means "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that *performs the same basic function or functions* in the recipient as in the donor." 21 C.F.R. § 1271.3(c) (emphasis added).[12] Whether an HCT/P is intended to perform the same basic function or functions in the recipient as in the donor is determined from the manufacturer's "labeling, advertising, or other indications of . . . objective intent." 21 C.F.R. §§ 1271.3(c) & 1271.10(a)(2).

As described above, the SVF product Defendants inject into patients is not in any way meant to perform the same basic function(s) of the adipose tissue recovered from those patients—quite the opposite. *See*, *supra*, Sections D.1 and D.2.a of the Argument; Yong Decl. ¶ 36. The basic function of adipose tissue is to provide cushioning and support, such as for skin

[12] The homologous use requirement reflects the fact that there are "increased safety and effectiveness concerns for HCT/P's that are intended for a non-homologous use, because there is less basis on which to predict the product's behavior, whereas HCT/P's for homologous use can reasonably be expected to function appropriately (assuming all of the other criteria are also met)." *See* Yong Decl. ¶ 34.

and organs. SMUF ¶¶ 11, 45. Examples of homologous uses of adipose tissue would be to provide similar cushioning and support in other parts of the body, such as to fill voids in the face or hands, for cosmetic reasons, or for transplantation into the breast for reconstruction or augmentation. *See* Yong Decl. ¶ 34. Defendants do not promote the SVF product for cushioning, support, or anything similar to it. Rather, they market their product as a treatment for a remarkable array of serious diseases and conditions such as ALS, Parkinson's disease, spinal cord injuries, stroke, traumatic brain injury, COPD, lung disease, and diabetes, among others. SMUF ¶ 7. Such uses bear no resemblance to any basic function of adipose tissue. *See* Yong Decl. ¶ 36.

In addition to failing these criteria, the SVF product is not a proven treatment for any disease or condition, and has not been generally recognized as safe or effective. SMUF ¶ 28. That absence of proof of safety and effectiveness is another "meaningful indicator" that regulation of the product as a section 361 HCT/P "is not sufficient." *See* 66 Fed. Reg. at 5458 (Jan. 19, 2001) ("[P]romotion of an HCT/P for an unproven therapeutic use, such as curing cancer, would clearly make it inappropriate to regulate the HCT/P solely under 361 of the [PHSA] and the regulations that will be in part 1271.").[13]

* * *

Defendants subject the adipose tissue they recover to processing that far exceeds minimal manipulation and then promote their SVF product for uses that bear no resemblance to the function of adipose tissue in the donor (patient) before it was recovered. The SVF product thus meets neither the "minimally manipulated" nor the "homologous use only" criteria under 21 C.F.R. § 1271.10(a). It is not a Section 361 HCT/P, but a drug and biological product subject to the FDCA's adulteration and misbranding provisions. *See* 21 C.F.R. § 1271.20; 66 Fed. Reg. at 5458. This is clear on the evidence and the plain text of the regulations discussed above, but even if it were not, FDA's conclusions in this regard (*see* MM Final Guidance) would be entitled to "substantial deference." *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994); *see*

[13] To the extent that Defendants may argue that their "research" will develop data that will help Defendants understand the safety or effectiveness of their product, the FDCA does not permit such experimentation without an investigational new drug application ("IND") in effect. *See* 21 U.S.C. § 355(i); 21 C.F.R. § 312.2(a). Defendants concede that they do not have an IND in effect for the SVF product. SMUF ¶ 22.

also United States v. Regenerative Scis., LLC, 878 F. Supp. 2d 248, 258 (D.D.C. 2012).

E. It is Irrelevant Whether Defendants Engage in the "Practice of Medicine"

Defendants have argued in the past that their conduct should not be subject to FDCA requirements because they are engaged in the "practice of medicine." *See* Waltrip Decl. ¶¶ 25, 26, 28. As an initial matter, Defendants offer no explanation regarding how USSCC, a limited liability company; US Stem Cell, Inc., a corporation; and Defendants Comella and Gradel, who are not physicians (SMUF ¶¶ 3-4), could possibly engage in the practice of medicine.

But regardless, the FDCA contains no exemption for the conduct at issue here. The Court of Appeals for the D.C. Circuit rejected a similar argument in *Regenerative Sciences*, a case that involved adulteration and misbranding of an autologous stem cell product isolated from patients' bone marrow or synovial fluid. *See Regenerative Scis.*, 741 F.3d at 1318. The defendants in *Regenerative Sciences* argued that their product was not subject to regulation under the FDCA because the activity at issue was a "medical procedure" rather than a drug or biological product. *Id.* at 1319. The court rejected the defendants' argument and recognized that the government did not seek to "restrict the use of an autologous stem cell *procedure*," but to enforce the FDCA as it applied to the regulated *article* at issue—*i.e.*, the defendants' misbranded and adulterated stem cell product. *Id.* As with anyone else who manufactures or distributes a drug, the FDCA "appl[ies] to doctors." *Id.*

Like in *Regenerative Sciences*, the Government seeks to enjoin specific FDCA violations related to the manufacture of adulterated and misbranded drugs. Defendants cannot credibly claim that their manufacture of the SVF product falls within the "practice of medicine." Nor can they explain what legal effect the "practice of medicine" claim would have on otherwise violative conduct. Any defense on this basis should therefore be rejected.

F. A Permanent Injunction is Required to Stop the Defendants' FDCA Violations

1. Legal Standard

The government seeks a statutory injunction to restrain violations of a remedial public health statute. 21 U.S.C. § 332(a). Where, as here, a statute specifically authorizes injunctive relief to enforce Congressional policy, the government need not show irreparable harm. *United States v. City & County of San Francisco*, 310 U.S. 16, 31 (1940). As the Eleventh Circuit has stated, where "an injunction is authorized by statute and the statutory conditions are satisfied . . . the usual prerequisite of irreparable injury need not be established and the agency to whom the

enforcement of the right has been entrusted is not required to show irreparable injury before obtaining an injunction." *Gresham v. Windrush Partners, Ltd.*, 730 F.2d 1417, 1423 (11th Cir. 1984) (*quoting United States v. Hayes Int'l Corp.*, 415 F.2d 1038, 1045 (5th Cir. 1969)); *see also United States v. BioAnue Labs., Inc.*, No. 5:13-CV-188 (MTT), 2014 U.S. Dist. LEXIS 99962, at *13-14 (M.D. Ga. July 23, 2014) ("The Government must demonstrate the Defendants violated the [FDCA] and that there is a likelihood of future violations. . . . the agency need not prove irreparable injury or the inadequacy of other remedies as required in private injunctive suits" (citations omitted)). Instead, the government must show only that the defendants violated the statute and that there is some "cognizable danger of recurrent violation[s]" to obtain a statutory injunction. *United States v. W.T. Grant Co.*, 345 U.S. 629, 633 (1953); *United States v. Sene X Eleemosynary Corp.*, 479 F. Supp. 970, 981 (S.D. Fla. 1979) (irreparable harm is presumed); *United States v. Diapulse Corp. of Am.*, 457 F.2d 25, 27-28 (2d Cir. 1972).

Both corporations and individuals may be found liable for violations of the FDCA. The Supreme Court has held that the FDCA "imposes not only a positive duty to seek out and remedy violations when they occur but also, and primarily, a duty to implement measures that will insure that violations will not occur." *United States v. Park*, 421 U.S. 658, 672 (1975). To establish individual liability under the FDCA, the government need only show that the defendants "had, by reason of [their] position in the corporation, responsibility and authority either to prevent in the first instance, or promptly to correct, the violation complained of, and that [they] failed to do so." *Park*, 421 U.S. at 673-74; *see also United States v. Gel Spice Co.*, 601 F. Supp. 1205, 1211-12 (E.D.N.Y. 1984).

2. Defendants Are Violating the FDCA and Will Continue to Violate the FDCA Unless Enjoined

As shown above, Defendants violated the FDCA by causing the adulteration and misbranding of a drug while it was held for sale after shipment of one or more of its components in interstate commerce. *See*, *supra*, Sections B and C of the Argument. An injunction is necessary to bring Defendants into compliance with the law and to prevent future violations.

Defendants know that their SVF product and conduct violate the FDCA. Yet they continue to flout the law and market the SVF product as beneficial for patients with serious diseases and conditions despite lacking proof of its safety or effectiveness. Rather than work to comply with the law, Defendants claim that it does not apply to them. Defendants use that argument to ignore significant and repeated CGMP violations that could directly impact the

safety of their product. *See* SMUF ¶¶ 29-34; *see generally*, Melhem Decl. For example, investigators in 2015 found Defendants failed to establish and follow written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, a critical means of ensuring safety. SMUF ¶ 32. The 2017 inspection revealed the same deficiency. *Id.* Similarly, FDA investigators observed during both the 2015 and 2017 inspections that Defendants failed to test through appropriate laboratory testing that each batch of the SVF product was free of objectionable microorganisms. SMUF ¶ 33. Defendants' pattern of violative conduct and insistence that they need not follow the law leaves no doubt that they will continue to violate the FDCA absent an injunction.

The two individual defendants should be enjoined along with the corporate entities. Defendant Kristin Comella is the "Chief Scientific Officer" of both USSCC and US Stem Cell, Inc. SMUF ¶ 3. She is responsible for overseeing the daily operations at USSCC, including but not limited to overseeing patient scheduling, hiring and firing employees, and processing of SVF. *Id.* She has stated that she wrote the procedures for the manufacture of the SVF product, and she has trained doctors on manufacturing and using the SVF product. *Id.* With her input into the SVF manufacturing process and her oversight over the daily activities at USSCC, Defendant Comella is personally liable for the FDCA violations described in this action.

Defendant Theodore Gradel is a minority investor in USSCC, and he has been a "managing member" of the company. SMUF ¶ 4. As of November 13, 2017, Defendant Gradel was listed with the Florida Division of Corporations as an "authorized person" and a "manager" for USSCC. *Id.* He personally participated on behalf of USSCC in the FDA inspection of USSCC in 2015. *Id.* He also was identified to FDA investigators as an individual to whom correspondence regarding USSCC should be sent. *Id.* As a partial owner and former managing member of USSCC, as well as someone represented to the Florida state government as an "authorized person" and "manager," Defendant Gradel had the responsibility and authority to prevent and/or correct violations of the FDCA. Further, Defendant Gradel's participation in the 2015 inspection and his identification as someone who should receive correspondence on behalf of the firm demonstrates that, not only did he have sufficient legal authority and responsibility to prevent a violation of the FDCA by virtue of the positions and titles he held, but he was also personally empowered to understand activities at USSCC and to speak to FDA investigators on behalf of the firm.

The risks posed by Defendants' violations, as guided by Defendants Comella and Gradel, underscore the need for injunctive relief. Defendants manufacture an experimental drug and biological product in a manner that does not comply with CGMP, thereby posing significant risks to the consumers who receive it. *See, e.g.*, SMUF ¶¶ 32, 33, 44. The drug itself has not been subjected to any adequate and well-controlled clinical trials. SMUF ¶ 27. Therefore, it has not been shown to be safe and effective, through valid scientific evidence, for the treatment of any disease or condition, much less the serious diseases and conditions for which Defendants promote its use. SMUF ¶ 28. Indeed, as discussed above, significant adverse medical events have been reported following administration of Defendants' SVF product. Those events include one patient who was deemed legally blind in both eyes and another who suffered complete vision loss after receiving Defendants' SVF product. SMUF ¶¶ 35-38.

These adverse events, known risks, and FDA warnings have not stopped Defendants' illegal conduct. An injunction is necessary.

CONCLUSION

Defendants' admissions and the uncontested evidence accompanying this motion show there is no genuine dispute of material fact. Defendants are violating well-established law and endangering the public by manufacturing an adulterated and misbranded experimental drug. The government therefore requests that this Court grant its motion for summary judgment and permanently enjoin Defendants from causing the adulteration and misbranding of their drugs in violation of the FDCA.

DATED: March 11, 2019.

Respectfully Submitted,

JOSEPH H. HUNT
Assistant Attorney General

JAMES M. BURNHAM
Deputy Assistant Attorney General
Civil Division

GUSTAV W. EYLER
Acting Director
Consumer Protection Branch

ROGER J. GURAL
Roger J. Gural
Trial Attorney
Consumer Protection Branch
United States Department of Justice
P.O. Box 386
Washington, DC 20044
Tel.: 202.307.0174
Email: roger.gural@usdoj.gov

Counsel for United States of America

Of Counsel:
ROBERT P. CHARROW
General Counsel

STACY CLINE AMIN
Chief Counsel
Food and Drug Administration
Deputy General Counsel
Department of Health and Human Services

PERHAM GORJI
Deputy Chief Counsel for Litigation

MICHAEL D. HELBING
Associate Chief Counsel for Enforcement
United States Food and Drug Administration
Office of the Chief Counsel
White Oak 31, Room 4426A
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Telephone: 240.402.6165

ARIANA FAJARDO ORSHAN
UNITED STATES ATTORNEY

JAMES A. WEINKLE
Assistant United States Attorney
Florida Bar No. 0710891
99 N.E. 4th Street, Suite 300
Miami, Florida 33132
Tel.: 305.961.9290
Fax: 305.530.7139
Email: James.Weinkle@usdoj.gov

Counsel for United States of America