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UNITED STATES OF AMERICA

UNITED STATES DISTRICT COURT

FOR THE CENTRAL DISTRICT OF CALIFORNIA

EASTERN DIVISION

UNITED STATES OF AMERICA,

Plaintiff,

v.

CALIFORNIA STEM CELL TREATMENT CENTER, INC., *et al.*

Defendants.

No. 5:18-CV-01005-JGB-KKx

PLAINTIFF'S REVISED [PROPOSED] FINDINGS OF FACT AND CONCLUSIONS OF LAW

Trial: May 4 – 13, 2021

Honorable Jesus G. Bernal
United States District Judge

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I. INTRODUCTION

This is a statutory injunction proceeding in which the United States, on behalf of the U.S. Food and Drug Administration ("FDA"), seeks to permanently enjoin California Stem Cell Treatment Center, Inc., Cell Surgical Network Corporation, and individuals Elliot B. Lander, M.D., and Mark Berman, M.D., from violating the Federal Food, Drug, and Cosmetic Act ("FDCA"). *See* 21 U.S.C. § 332(a).

The Government filed its Complaint for Permanent Injunction on May 9, 2018. (ECF No. 1). In the Complaint, the Government alleged that Defendants violate the FDCA by causing the adulteration and misbranding of drugs, and by receiving and delivering misbranded drugs, in violation of 21 U.S.C. §§ 331(k) and (c). Defendants filed their Answer to the Complaint on July 17, 2018. (ECF No. 27).

On July 8, 2019, the Government moved for summary judgment on all issues in the Complaint. (ECF No. 45). On January 27, 2020, the Court denied the Government's summary judgment motion and set the matter for trial ("SMJ Order"). (ECF No. 84).

As the Court found in a subsequent ruling, the case "concerns . . . alleged violations of the FDCA" on which the Court had "made no ultimate findings of fact" in its SMJ Order. (ECF No. 102 at 1). The Court ordered the Government to produce evidence at trial to establish any elements where it carries the burden. (*Id.* at 2). Defendants likewise were ordered to produce evidence at trial where they carry the burden. (*Id.*).

The Court conducted a bench trial in this matter from May 4 through 13, 2021.[1] Closing arguments are set for July 9, 2021. Pursuant to the Court's oral order issued on May 13, 2021 (*see* ECF No. 165), the Government respectfully submits the following

[1] Trial transcript citations herein indicate the surname of the witness who testified at the morning (AM) or afternoon (PM) sessions on the following days: *Day 1* (Tues., May 4), *Day 2* (Wed., May 5), *Day 3* (Thurs., May 6), *Day 4* (Fri., May 7), *Day 5* (Tues., May 11), *Day 6* (Wed., May 12), and *Day 7* (Thurs., May 13).

Citations to stipulated facts, which are hereby incorporated by reference, appear in footnotes. For simplicity, and consistent with the Court's SMJ Order, the parties used the term "Treatment" neutrally and without any concession as to whether the case concerned a surgical procedure or a manufactured drug product. For purposes of these proposed findings of fact, however, the Government replaces the word "Treatment" with "product,"

Revised [Proposed] Findings of Fact and Conclusions of Law in support of its claims under the FDCA.[2]

II. PLAINTIFF'S CLAIMS UNDER THE FDCA

A. *Claim 1:* Defendants violate 21 U.S.C. §331(k) (Adulteration)

Defendants violate 21 U.S.C. § 331(k) by causing the adulteration of drugs (*i.e.*, the "CSCTC products"[3]) within the meaning of 21 U.S.C. § 351(a)(2)(B), while they are held for sale after shipment of one or more of their components in interstate commerce.

To prove a violation of 21 U.S.C. § 331(k) for adulteration, the Government must show that: (1) the CSCTC product is a drug; (2) the CSCTC product was held for sale after the CSCTC product or one or more of its components had moved in interstate commerce; and (3) Defendants performed, or caused to be performed, one or more acts which resulted in the CSCTC product being adulterated (such as failing to comply with CGMP). *See id.*; *id.* § 321(g)(1); *United States v. Rhody Dairy, LLC*, 812 F. Supp. 2d 1239, 1243 (W.D. Wash. 2011) (citation omitted).

B. *Claim 2:* Defendants violate 21 U.S.C. §331(k) (Misbranding)

Defendants violate 21 U.S.C. § 331(k) by causing the misbranding of the drugs within the meaning of 21 U.S.C. §§ 352(f)(1), 352(j), and 353(b)(4), while they are held for sale after shipment of one or more of their components in interstate commerce.

To prove a violation of 21 U.S.C. § 331(k) for misbranding, the Government must show that: (1) the CSCTC product is a drug; (2) the CSCTC product was held for sale after the CSCTC product or one of its components had moved in interstate commerce; and (3) Defendants performed, or caused to be performed, one or more acts which resulted in the CSCTC product being misbranded. *See id.*; *id.* § 321(g)(1); *Baker v. United States*, 932 F.2d 813, 814 (9th Cir. 1991); *United States v. Regenerative Sciences, LLC*, 741 F.3d 1314, 1323-1324 (D.C. Cir. 2014); *United States v. Evers*, 643 F.2d 1043, 1047 (5th Cir.

[2] Any finding of fact deemed to be a conclusion of law is incorporated into the conclusions of law. Any conclusion of law deemed to be a finding of fact is incorporated into the findings of fact.

[3] The term "CSCTC products" is defined in Proposed Finding of Fact ¶ 2, *infra.*

1981); *United States v. US Stem Cell Clinic, LLC*, 403 F.Supp.3d 1279, 1299-1300 (S.D. Fla. 2019).

C. *Claim 3:* Defendants violate 21 U.S.C. §331(c) (Misbranding)

Defendants CSCTC, Berman, and Lander violate 21 U.S.C. § 331(c) by receiving drugs that are misbranded within the meaning of 21 U.S.C. §§ 352(f)(1) and 353(b)(4) in interstate commerce and delivering or proffering for delivery such drugs for pay or otherwise.

To prove a charge of receiving misbranded drugs in interstate commerce and delivering or proffering them for pay or otherwise, the Government must show that: (1) the CSCTC product is a drug; (2) Defendants received the CSCTC product or one of its components in interstate commerce; (3) the CSCTC product or one of its components was misbranded when it was received by Defendants; and (4) the CSCTC product was thereafter delivered or proffered for delivery for pay or otherwise. 21 U.S.C. § 331(c); *id.* § 321(g)(1); *Fagan v. AmerisourceBergen Corp.*, 356 F. Supp. 2d 198, 214 (E.D.N.Y. 2004).

III. FINDINGS OF FACT

A. Defendants and their CSCTC Products

i. Defendants Berman and Lander Own and Control Defendant California Stem Cell Treatment Center, Inc.

1. Defendant California Stem Cell Treatment Center, Inc. ("CSCTC") is a California professional corporation founded in 2010, with its principal place of business located at 72-780 Country Club Drive, Suite 301, Rancho Mirage, California 92270 ("CSCTC Rancho Mirage"), and a second establishment located at 120 South Spalding Drive, Suite 300, Beverly Hills, California 90212 ("CSCTC Beverly Hills"), within the jurisdiction of this Court.[4] *See also Ans. ¶ 4; Ex. 11 at 1; Ex. 12 at 1; Trial Tr. Day 5 (PM – Berman) at 83:20-84:10.*

[4] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 1; *see also* Trial Tr. Day 5 (AM) at 90:6-91:5 (Court to sign pre-trial conference order and accept the stipulations).

2. CSCTC manufactures, or has caused to be manufactured, several adipose (fat) derived cellular products ("CSCTC products"), including the following: (1) a product containing "stromal vascular fraction" ("SVF") which is manufactured from a patient's adipose tissue, and then combined with other components (the "SVF product"); (2) a product that combines SVF and Vaccinia Vaccine, Live (the "SVF/Vaccinia product"); and (3) a product containing SVF that has been expanded in culture for CSCTC by a third-party laboratory (the "Expanded SVF product"). *Ans. ¶ 5; Ex. 11 at 1-2; Ex. 12 at 2; Trial Tr. Day 2 (AM – Forster) at 47:17-49:2; Trial Tr. Day 5 (PM – Berman) at 84:16-85:18.* Thus, all three CSCTC products contain some form of adipose tissue-derived SVF. *Trial Tr. Day 5 (PM – Berman) at 84:16-87:6.*

3. Defendant Elliot B. Lander, M.D., a surgeon and board-certified urologist, is the co-owner and Co-Medical Director of CSCTC. He is the most responsible individual at CSCTC Rancho Mirage and performs his duties there, within the jurisdiction of this Court. He manages all firm employees at CSCTC Rancho Mirage, where his activities include recovering adipose tissue from patients and manufacturing CSCTC products. *Ans. ¶ 26; see also Ex. 11 at 7; Ex. 183 at 1; Trial Tr. Day 5 (PM – Berman) at 83:16-84:10.*

4. Defendant Mark Berman, M.D., a board-certified cosmetic surgeon, is the co-owner and Co-Medical Director of CSCTC. He performs his duties at the CSCTC Beverly Hills facility, within the jurisdiction of this Court. He is the most responsible individual at CSCTC Beverly Hills, where his activities include recovering adipose tissue from patients and manufacturing CSCTC products. *Ans. ¶ 27; see also Ex. 12 at 8; Ex. 183 at 1; Trial Tr. Day 5 (PM – Berman) at 83:16-84:10.*

ii. Defendants Berman and Lander Own and Control Defendant Cell Surgical Network Corporation

5. Defendant Cell Surgical Network Corporation ("CSN") is a California corporation founded by Defendants Berman and Lander in 2012 that is registered to do business at 72-780 Country Club Drive, Suite 301, Rancho Mirage, California 92270, the

same address as CSCTC Rancho Mirage, within the jurisdiction of this Court.[5] *See also Ans. ¶ 21.*

6. Defendants Berman and Lander are the co-owners and Co-Medical Directors of CSN. *Ans. ¶¶ 26-27; Ex. 77 at 1.* They are also the co-owners of Cells On Ice, Inc., which has assisted in the recovery of adipose tissue sent outside of the State of California for production into the Expanded SVF product. *Ans. ¶¶ 26-27; Ex. 11 at 7; Ex. 12 at 7; Ex. 36 at 1.*

7. CSN is an affiliation of CSCTC and more than 100 clinics, located throughout the United States and other countries, which use CSN's intellectual property and equipment to manufacture and administer products containing adipose tissue-derived SVF. *Ex. 183 at 1; Ex. 12 at 6; Trial Tr. Day 6 (AM – Berman) at 18:25-19:8; Ex. 10 at 13, 39-41.*

8. Although CSN describes itself as a research organization, it is also a for-profit entity that is engaged in the business of providing SVF-related treatments to patients. *Ex. 68 at 4.*

9. CSN approves doctors to become affiliates or licensees. CSN affiliates are required "to complete training" regarding the manufacture of the SVF product. To maintain their status, CSN affiliates must share research data with Defendants and other CSN affiliates.[6] *See also Trial Tr. Day 5 (PM – Berman) at 59:14-24 (Defendants Berman and Lander have "sole discretion to determine who becomes an affiliate"); Ex. 67 at 3-4.*

10. Once approved for inclusion in the CSN network, CSN affiliates purchase supplies from CSN to make the SVF products.[7] *See also Ex. 67 at 3-4.*

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[5] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 2.

[6] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 4.

[7] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 4.

11. CSN operates a one-employee warehouse at 73700 Dinah Shore Drive, Suite 301, Palm Desert, California 92211, within the jurisdiction of this Court, from which equipment and supplies are shipped to CSN affiliates.[8] *See also Ans. ¶ 25; Trial Tr. Day 6 (AM – Berman) at 18:13-19.*

12. Defendants Berman and Lander charge CSN affiliates approximately $30,000 for their specialized SVF-processing medical device identified as the CSN "Time Machine," and charge another $900 per procedure for the kit of syringes "necessary for the production of SVF." *Def. Ex. 431 at 4; Trial Tr. Day 6 (AM – Berman) at 16:12-23, 17:10-18:19; see generally Ans. ¶ 10.*

13. CSN is responsible for the establishment of the protocols and procedures that CSN affiliates use to manufacture and administer the SVF products. Defendants Berman and Lander co-author the protocols and procedures that are used by CSN affiliates. *Ex. 12 at 6; see generally Exs. 15, 36, 37, 48, 78, 79, 80, 81, 154, 161, and 176.*

14. Defendants Berman and Lander are listed as the "principal investigators" on CSN protocols. *See generally Ex. 12 at 6; see, e.g., Ex. 15 at 2; Ex. 48 at 1; Ex. 78 at 2; Ex. 79 at 2; Ex. 80 at 2; Ex. 81 at 1; Ex. 154 at 2; Ex. 161 at 2, 33, 63, 112, 157, 202, 249, 311, 364, 409, 454; Ex. 176 at 1.*

15. Defendants Berman and Lander refer to CSN affiliate clinics as "sub-investigators."[9] *See also Ex. 12 at 7; Ex. 75 at 3; Ans. ¶ 23 (third sentence).*

16. CSN affiliates are "required to comply with" CSN's "Guidelines for Affiliates," which states that an affiliate "must" do all the following: *(a)* "adhere strictly to CSN research protocols," *(b)* "reasonably follow price guidelines to avoid competition for patient enrollment within the network," *(c)* register all patients into the CSN Database, and *(d)* use Defendants' standardized forms, including specific consent forms for patient

[8] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 3.

[9] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 6.

care and data collection. *Ex. 26 at 3; Trial Tr. Day 6 (AM – Berman) at 22:19-23:20; see also Def. Ex. 431 at 1.*

17. CSN's "Guidelines for Affiliates" describes that affiliates have limited permission to use various trademarks and logos, including logos for California Stem Cell Treatment Center, CSCTC, and Cell Surgical Network.[10] *See also Ex. 26 at 5-6; Trial Tr. Day 6 (AM – Berman) at 16:2-11; Ex. 8 at RFA ¶ 27.*

iii. Defendants Manufacture and Administer the CSCTC Products, and Use Them to Treat Patients

18. The CSCTC products—all of which purportedly contain some form of adipose tissue-derived SVF—are intended for autologous use, which refers to the "implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered." *See 21 C.F.R. § 1271.3(a); Ans. ¶ 6.*

19. Defendants claim that the CSCTC products can be used as treatments for neurological, autoimmune, orthopedic, and degenerative medical conditions and/or diseases, including, but not limited to, cancer, arthritis, stroke, amyotrophic lateral sclerosis ("ALS"), multiple sclerosis ("MS"), macular degeneration, Parkinson's disease, and chronic obstructive pulmonary disease ("COPD"). *Ans. ¶ 7; Ex. 8 at RFA ¶ 20.*

20. CSCTC products are administered to patients using a variety of methods, including *(a)* intravenously; *(b)* by injection into specific areas of the body, including directly into or in an area around the brain; and *(c)* via a nebulizer. CSCTC products are administered at CSCTC Rancho Mirage and CSCTC Beverly Hills, and at other locations such as a radiologist's office in Indian Wells, California. *Ans. ¶ 8; Trial Tr. Day 5 (PM – Berman) at 89:18-90:1, 90:11-91:1-21, 92:6.*

21. Defendants administer certain of their CSCTC products—such as the SVF product—on the same day that the patient's adipose tissue is removed. For intravenous

[10] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 5.

administration, the SVF is added to a 100ml bag of 0.9% Sodium Chloride (NaCl) solution and given to the patient through an intravenous drip. This combination of SVF and Sodium Chloride solution constitutes the "SVF Product." *Ans. ¶ 11; Ex. 8 at RFA ¶¶ 1-4; Ex. 11 at 2, 4; Ex. 19 at 77.*

22. Defendants administer other CSCTC products—such as the Expanded SVF product—weeks, months, and even years after the patient's adipose tissue is removed. *See, e.g., Ex. 36 at 10 (3-4 weeks' processing time); Ex. 37 at 21; Ex. 40; Trial Tr. Day 5 (PM – Berman) at 86:1-22; Trial Tr. Day 5 (Jim – AM) at 15:15-16:2.*

23. CSN affiliate doctors have administered SVF products to over 6,000 patients.[11] *See also Ans. ¶ 22.*

24. Many patients pay thousands of dollars to receive a single dose of the CSCTC product, and some patients pay much more to receive multiple treatments. Defendants have referred to this practice as "patient-funded research." *Ans. ¶ 17; Trial Tr. Day 6 (AM – Berman) at 19:24-20:13.*

25. Defendants Berman and Lander typically charge patients $8,900 per treatment for the SVF product. *Trial Tr. Day 6 (AM – Berman) at 20:14-17; see also Ex. 13 at 3 (fee covers harvesting fat, isolating cells, and deploying cells).* These experimental treatments are not covered by any medical insurance carriers. *Ex. 13 at 3; Trial Tr. Day 6 (AM - Berman) at 20:8-10; Trial Tr. Day 5 (PM - Berman) at 51:8-15.*

26. With respect to the Expanded SVF product, Defendants' protocol explains that, "[w]hile many conditions can be treated with a single treatment, there are a number of conditions that may require multiple interventions. In such cases, having a quantity of SVF cells stored (cryopreserved) would enable the patient to get cells periodically without having to undergo the mini-liposuction procedure prior to each treatment. Cells on Ice is a specialty tissue bank started [by CSN and Defendants Berman and Lander] for the purpose of banking fat and fat derived cells, SVF and other adipose tissue derived

[11] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 6.

products. . . . Stem cells generally can be replicated with the advanced laboratory technologies of Cells on Ice and CSN expects in the future to be able to expand (grow) . . . stem cells so we can return multiple doses for repeat treatments." *Ex. 36 at 18; Ex. 37 at 44; Def. Ex. 429 at 2; see also Ex. 36 at 1; Ex. 10 at 8; Trial Tr. Day 5 (PM – Berman) at 86:1-22; Proposed Finding of Fact at ¶ 2, supra.*

27. The cost schedule for Defendants' Expanded SVF product includes all the following: *(a)* a base charge of $2,500, which includes the cost of a "tissue collection kit," "processing of 30 mL of tissue to stromal vascular fraction (SVF)," "creation" of a "master sample" of SVF, and creation and complimentary one-year storage of up to five SVF master sample aliquots; *(b)* costs ranging anywhere from $5,500 for a single treatment, to $21,000 for six treatments, to $41,500 for twelve treatments; *(c)* annual storage fees of $250/year minimum, and *(d)* a $500 retrieval fee each time the patient's SVF or expanded cells are retrieved, processed, packed, and shipped to an "approved physician or clinic" for administration in a future procedure. *Ex. 36 at 7, 10; Trial Tr. Day 6 (AM – Berman) at 21:1-15, 21:21-22:7; see generally Exs. 37, 40, and 156.*

28. With respect to the SVF/Vaccinia product, Defendants inform their cancer study patients that the product is being administered as "part of a patient funded research protocol" where the patient is "responsible for the cost of the procedure unless otherwise stated." Defendants further inform the cancer patients that they "will not be entitled to any remuneration from any patents or later company profits" by participating in the SVF/Vaccinia study. *Ex. 33 at 10; Ex. 56 at 10; see also Ex. 10 at 7 ("Our treatments and research are patient funded"); see generally Exs. 48, 81.*

B. <u>Defendants Manufacture their Cellular-Based "CSCTC Products" from Patients' Adipose Tissue</u>

i. Defendants' Manufacturing Process Involves the Removal of Adipose Tissue from Patients

29. Production of CSCTC products involves the removal (*i.e.*, the recovery) of adipose tissue from patients at the offices of CSCTC Rancho Mirage and CSCTC Beverly

Hills. The tissue recovery is accomplished by a mini-liposuction procedure, whereby a cannula is used to recover adipose tissue through an incision commonly made in the patient's posterior flank. *Trial Tr. Day 1 (PM – Lagud) at 10-19; Ex. 11 at 4, 9-10; Ex. 19 at 24, 40; Def. Ex. 453; Trial Tr. Day 5 (PM – Berman) at 87:16-19; Def. Ex. 429 at 3 ("a mini-liposuction" is "also known as a tissue harvest procedure").*

30. After the adipose tissue is removed from the patient, the patient leaves the room—and may even leave the premises altogether—so that Defendants can use their adipose tissue to manufacture SVF. *Trial Tr. Day 1 (PM – Lagud) at 4:22-5:6.* The doctor who performs the liposuction hands the patient's adipose tissue off to a technician who, in turn, uses various chemicals, equipment, medical devices, syringes, and supplies to process the adipose tissue into cellular-based SVF. *Ex. 19 at 42, 49-75; Def. Ex. 303 at 2-44; Ex. 18 at 9-16.* The technician's processing of the adipose tissue requires the completion of more than 25 chemical and mechanical processing steps over the course of 1 to 2 hours. *Def. Ex. 303 at 17-44; Ex. 18 at 9-16; Trial Tr. Day 1 (PM – Lagud) at 5:3-6; Ex. 13 at 2.* The resulting cellular-based product (*i.e.*, SVF) is combined with other components and then injected by the doctor into the patient.

31. Adipose tissue is typically defined as a connective tissue composed of predominantly adipocyte cells that are surrounded by an organized extracellular matrix and interspersed small blood vessels, divided into lobes and lobules by connective tissue septa. *Trial Tr. Day 4 (AM – Yong) at 60:19-61:15, 63:15-17; Trial Tr. Day 4 (PM – Yong) at 9:9-14.*

32. The extracellular matrix that adipose tissue contains is comprised of various types of fibrous collagen and resembles the walls of a three-dimensional foam, with each adipocyte occupying a pore cavity of the foam. The extracellular matrix surrounding the adipocytes is also described as a "reinforced basement membrane." Other than adipocytes, adipose tissue also contains some other cells, including preadipocytes, fibroblasts, vascular endothelial cells, and macrophages. *Trial Tr. Day 4 (AM – Yong) at 60:19-61:15, 64:24-65:4.*

33. The extracellular matrix, in addition to holding adipocytes in place, also contains growth factors and interacts with the cells contained within based on the needs of the tissue. *Trial Tr. Day 4 (AM – Yong) at 65:10-20.*

34. Because adipose tissue mainly provides cushioning and support to the body, such as the skin and internal organs, it is a structural tissue. In addition to providing cushioning and support, adipose tissue performs other functions in the body, including storing energy in the form of lipids, and insulating the body. *Trial Tr. Day 4 (AM – Yong) at 68:5-16; Trial Tr. Day 4 (PM – Yong) at 10:11-23; see also Ex. 8 at RFA ¶ 40.*

35. Adipose tissue is naturally located in the body underneath the skin, supporting the skin, and around internal organs such as the kidneys. It is also found behind the eyeball, as well as in the padding on the bottom of the foot. *Trial Tr. Day 4 (AM – Yong) at 68:17-24.*

ii. Defendants' Manufacturing Process Disrupts and Digests the Adipose Tissue Removed from Patients

36. Defendants subject the adipose tissue removed from patients to numerous steps through which many components of the tissue are broken down and discarded. The process involves the addition of a collagenase-containing solution to isolate cell components through enzymatic digestion. It also includes an incubation period, several washing steps using 5% Dextrose in Lactated Ringer's Injection, centrifugation, and filtration. The manufacture of the CSCTC products employs various types of equipment, including a specialized SVF processing device identified as the "Time Machine," syringes, plungers, stoppers, adapters, and a filter. *Ans. ¶ 10; see also Trial Tr. Day 1 (PM – Lagud) at 10-19; see generally Exs. 11, 19, 21-24, and 181; Def. Ex. 453; Trial Tr. Day 5 (AM – Berman) at 110:24-111:6.*

37. Defendants use a collagenase product made in Indiana to prepare their SVF product.[12] The collagenase product, known as CSN-TMAX, is an enzyme mixture that

[12] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 15.

degrades collagen. *Ex. 11 at 40; Trial Tr. Day 5 (AM – Berman) at 110:19-111:6; Trial Tr. Day 5 (PM – Berman) at 16:12-17:12; Def. Ex. 303 at 10; Ex. 76 at 2 ("cells in adipose tissue locked in place by collagen matrix").*

38. Defendants use the collagenase product to disrupt and digest the reinforced basement membrane to dissociate the cellular components of the adipose tissue. *Ex. 11 at 40; Ex. 19 at 56-59; Ex. 76 at 2.*

39. This collagenase-containing enzyme mixture is essential to Defendants' manufacturing process, and is specially made and privately labeled by the pharmaceutical company Roche for Defendants' exclusive use. *Trial Tr. Day 5 (AM – Berman) at 110:19-111:6; Trial Tr. Day 5 (PM – Berman) at 16:12-17:12; Def. Ex. 303 at 10; Ex. 19 at 56-59.*

40. Certificates of Analysis received by Defendants indicate that the enzyme used during production is to be used "for in vitro use only" as opposed to surgical use. *See, e.g., Ex. 45; Def. Exs. 407, 408.* The term *in vitro*, which directly translates as "in glass," is used in research to mean "outside the body" and "working outside of the body only." By contrast, use "inside the body" is considered *in vivo* use. *Trial Tr. Day 4 (AM – Yong) at 79:16-22.*

41. Safety concerns reasonably arise when an enzyme is used to disrupt and digest adipose tissue to isolate cells that are later administered to patients. *See, e.g.*, *Cytori Therapeutics v. FDA*, 715 F.3d 922, 927-928 (D.C. Cir. 2013) (FDA "reasonably raised concerns" about the enzyme's impact on isolated cells that "might be reintroduced into the human body").

42. Defendants' protocols do not require Defendants to confirm that the collagenase-containing enzyme used during production has been eliminated before the CSCTC products are administered to patients. *See, e.g., Ex. 18 at 14; Ex. 19 at 65-66; Def. Ex. 303 at 43-44.*

iii. Defendants Use Multiple Components That Are Shipped in Interstate Commerce to Manufacture and Administer their Cellular-Based CSCTC Products

43. Defendants' preparation and administration of the CSCTC products use one or more components shipped in interstate commerce from places outside the State of California. Components received from outside California include, for example, 0.9% Sodium Chloride Injection, USP and 5% Dextrose in Lactated Ringer's Injection, both of which originate outside the state of California. Defendants' manufacturing process also involves their use of a collagenase product made in Indiana. *Ex. 8 at RFA ¶¶ 6, 8, 11; Ex. 76 at 1-5; Ex. 77 at 1-4; Ex. 11 at 40; Ex. 12 at 12; Trial Tr. Day 5 (PM – Berman) at 25:19-25; Trial Tr. Day 5 (AM – Berman) at 110:19-111:6; Trial Tr. Day 5 (PM – Berman) at 16:12-17:15; Def. Ex. 303 at 4, 10, 11, 16, 23-24, 34, 36, 45.*

iv. Defendants Implant Cellular-Based CSCTC Products in Patients, Not the Adipose Tissue They Removed

44. Defendants' protocols and informed consent forms acknowledge that SVF is "a mixture of cells derived from processed adipose tissue (fat)." *See, e.g., Ex. 36 at 18; Def. Ex. 429 at 3.*

45. After Defendants process intact adipose tissue into SVF, the SVF no longer retains the original form of adipose tissue whereby adipocytes are embedded in an extracellular matrix with interspersed small blood vessels. *Trial Tr. Day 4 (AM – Yong) at 58:17-19, 60:21-61:1, 66:19-68:4; Trial Tr. Day 4 (PM – Yong) at 7:21-8:10.*

46. SVF is a liquified mixture of various types of cells and cell debris that does not contain an extracellular matrix and does not contain adipocytes. *Ex. 8 at RFA ¶¶ 39, 44, 46; Ex. 68 at 2; Trial Tr. Day 5 (PM – Berman) at 87:2-6; Trial Tr. Day 4 (PM – Yong) at 6:3-7, 7:21-24; Def. Ex. 453 at 2 ("After the fat (adipocytes) are removed, these cells are left over and we call this "soup" Stromal Vascular Fraction" or "SVF").*

47. SVF is not comprised of pure stem cells, *Ex. 68 at 2*; *Trial Tr. Day 5 (PM – Berman) at 87:23-25*, but rather consists of preadipocytes, fibroblasts, and endothelial

cells, among various other cell types. *Trial Tr. Day 4 (PM – Yong) at 7:21-24, 8:8-10; Ex. 36 at 17.*

48. According to Defendants' protocol, SVF "is known to contain four different types of adult adipose derived stem cells: mesenchymal cells, endothelial progenitor cells, pericyte progenitors, and hematopoetic stem cells." In addition to stem cells, "SVF contains an abundance of epithelial cells, macrophages, white blood cells, T-reg cells, and cytokine growth factors." *Ex. 154 at 3; see also Trial Tr. Day 6 (AM – Berman) at 52:18-21.*

49. When asked at trial to describe the various cell types that are found in Defendants' SVF, Defendant Berman testified that it contains "[a] large variety of cell types because some [of what] you're taking out is just blood samples. So you have red cells, white cells, platelets, growth factor[s], T regulatory cells. There's stem cells in there obviously, too. So there's a large variety of immunological cells." *Trial Tr. Day 5 (PM – Berman) at 89:2-15.*

50. The group of select isolated cells that Defendants claim comprise SVF does not occur naturally in the body. The cells that comprise SVF are brought together only through elimination of the organized adipose tissue architecture and dismantling of organized multicellular structures (*e.g.*, blood vessels). *Trial Tr. Day 4 (PM – Yong) at 6:8-7:20; see also Ex. 36 at 17.*

51. SVF is not intended to perform the same basic functions of the adipose tissue recovered from Defendants' patients. *Trial Tr. Day 4 (PM – Yong) at 8:24-9:16.*

52. Defendants do not—at any point in the manufacture or administration of their CSCTC products—implant adipose tissue into patients.[13] *Ex. 8 at RFA ¶ 35; Trial Tr.*

[13] Defendants' manufacturing process for the CSCTC products is, therefore, wholly distinguishable from traditional fat grafting procedures, brain dural surgery, and anastomosis (*i.e.*, abdominal surgery)—all of which Defendants concede involve the removal of adipose tissue *and implantation of adipose tissue*, without any of the intervening processing steps that Defendants use to make their CSCTC products. *Cf. Trial Tr. Day 5 (PM – Berman) at 78:20-79:11, 79:20-80;2, 81:25-83:5, Trial Tr. Day 6 (PM – Lander) at 87:22-13, and Trial Tr. Day 7 (PM – Lander) at 6:11-9:15, with Def. Ex. 303 at 17-47.*

Day 4 (PM – Yong) at 8:4-14; Ex. 11 at 7, Ex. 19.

v. Defendants' Manufacturing Process Alters the Properties and Characteristics of the Adipose Tissue Removed from Patients

53. Inconsistent with Defendants' argument regarding the same surgical procedure exception ("SSP exception") in 21 C.F.R. § 1271.15(b), the adipose tissue that Defendants remove from patients is not just modified, but actually dismantled and destroyed, via enzymatic digestion and various other processing steps. *See infra.*

54. Adipose tissue is characterized by an organized microstructure, comprised of its extracellular matrix and the surrounding reinforced basement membrane that surrounds and attaches fat cells, or adipocytes, to the adipose tissue. *Trial Tr. Day 4 (AM – Yong) at 61:18, 64:16-19, 65:2-4.* In addition to adipocytes, various other cell types reside in adipose tissue, and the majority of these cell types are also adhered to the extracellular matrix. *Trial Tr. Day 4 (AM – Yong) at 69:2-6.*

55. Rather than acting as a passive scaffold or glue to hold cells together, the adipose tissue's extracellular matrix is very active, containing growth factors that cells respond to, allowing the cells to interact with the extracellular matrix constantly in order for it to function and survive. *Trial Tr. Day 4 (AM – Yong) at 65:13-22.*

56. One characteristic of adipose tissue is its ability to hold its shape and form. *Ex. 8 at RFA ¶ 45.* Each pore of adipose tissue's extracellular matrix is filled with an adipocyte (composed of lipid oils) that provides impact resistance and cannot be compressed. *Trial Tr. Day 4 (AM – Yong) at 61:19-23, 67:21-68:1.* The lipid oil content of adipose tissue "constitutes 60 to 80 percent of the mass of adipose tissue." *Trial Tr. Day 4 (AM – Yong) at 61:19-23.*

57. Adipose tissue's structure allows it to function, and the tissue's main function is providing cushioning and support to the body (*e.g.*, under the skin, around internal organs, and behind the eyeball). *Trial Tr. Day 4 (AM – Yong) at 68:5-24.*

58. Defendants' processing of adipose tissue to manufacture the CSCTC products alters the tissue's physical properties. *Ex. 8 at RFA ¶ 36; Trial Tr. Day 4 (AM –*

Yong) at 69:18-21; Trial Tr. Day 4 (PM – Yong) at 9:1-5, 9:9-16; accord Trial Tr. Day 6 (PM – Reid) at 38:14-39:3.

59. Defendants' processing of adipose tissue alters the original relevant characteristics of the adipose tissue relating to the tissue's utility for reconstruction, repair, or replacement. *See Trial Tr. Day 4 (AM – Yong) at 72:20-73:1; Trial Tr. Day 4 (AM – Yong) at 74:20-76:19; Trial Tr. Day 4 (PM – Yong) at 9:9-16; Ex. 68 at 2-3.*

60. Defendants' processing of adipose tissue to manufacture the CSCTC products involves removing adipocytes from the adipose tissue.[14] *See also Ex. 8 at RFA ¶ 38; Ex. 19 at 23-62; Ex. 36 at 18.* Removing the adipocytes eliminates the adipose tissue's "bulk," or 60 to 80 percent of its mass, leaving it unable to support or cushion the body. *Trial Tr. Day 4 (PM – Yong) at 9:9-16, 13:7-11.* When the adipocytes are removed, the remaining SVF also cannot perform other functions of the original adipose tissue, such as storing energy, providing thermal insulation to the body, or performing an endocrine or hormonal function. *Trial Tr. Day 4 (PM – Yong) at 10:11-23.*

61. Defendants' processing of adipose tissue to manufacture the CSCTC products also removes the extracellular matrix and interspersed small blood vessels from adipose tissue. *Trial Tr. Day 4 (PM – Yong) at 5:9-19, 69:18-21.*

vi. Defendants' Manufacturing Process Also Alters the Cells Contained in the Adipose Tissue Removed from Patients[15]

a. <u>Defendants' Manufacturing Process Involves the Isolation of SVF Cells from Processed, Enzymatically Digested Adipose Tissue</u>

62. Inconsistent with Defendants' argument regarding the same surgical

[14] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 14.

[15] The Court previously noted that "whether the SVF Procedure alters the SVF cells" would be relevant at trial. (ECF No. 84 at 13.) The Government contends that the relevant question under the same surgical procedure exception analysis of 21 C.F.R. § 1271.15(b) is whether the adipose tissue removed from the patient is "such HCT/P" returned to the

procedure exception in 21 C.F.R. § 1271.15(b), even the cells contained within the adipose tissue that Defendants remove from patients are modified by Defendants' extensive processing. *See infra.*

63. Defendants acknowledge that they "obtain[] the patient's own cells from his/her adipose tissue." *Ex. 9 at ¶¶ 9, 16; Ex. 166.*

64. As mentioned earlier, SVF isolation by Defendants begins with aspiration and recovery of approximately 50 mL of adipose tissue from the individual. *Ex. 18 at 11-12*. The aspirated adipose tissue is centrifuged to remove blood cells, loose lipids, and local anesthetic solution. *Trial Tr. Day 5 (AM – Berman) at 105:11-24; Trial Tr. Day 5 (PM – Berman) at 7:7-15, 8:20-24*. Defendants then add an enzyme mixture that degrades collagen, among other proteins, to the adipose tissue in order to disrupt and digest the reinforced basement membrane to dissociate the cellular components of the adipose tissue. *Trial Tr. Day 5 (PM – Berman) at 103:18-104:2; see also Trial Tr. Day 6 (PM – Reid) at 38:19-39:3*. The digested tissue undergoes a series of processing steps including washing and centrifugation, to separate non-adipocyte cellular and digested structural components of the tissue from dissociated adipocytes and free lipids. *Ex. 11 at 12; Trial Tr. Day 5 (PM – Berman) at 11:5-21*. Defendants next employ filtration whereby the non-adipocytic cells (*i.e.*, SVF) are isolated from the digested structural components of the adipose tissue by pushing the mixture through a filter where the pore size effectively only allows cells below a certain diameter to pass, *i.e.*, the digested structural components of the adipose tissue are filtered out. *Trial Tr. Day 5 (PM – Berman) at 11:19-12:3; Trial Tr. Day 5 (PM – Berman) at 12:23-13:2*. What remains, according to Defendants, is the isolated SVF suspended in a solution to yield approximately 5-10 mL of SVF that is incorporated into the final SVF product. *Ex. 19 at 75; see also id. at 77 (SVF added to 100mL bag of saline and given to patient via IV); Trial Tr. Day 5 (PM – Berman) at 75:18-76:1.*

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patient. Here, it is not. However, even in analyzing Defendants' processing from the level of individual cells rather than adipose tissue, the evidence shows that the individual cells isolated via Defendants' extensive chemical and mechanical processing of adipose tissue are themselves altered.

65. Importantly, Defendants' enzymatic digestion of adipose tissue involves chemical action, not just a physical change to the adipose tissue. *Trial Tr. Day 4 (AM – Yong) at 72:17-25.* Defendants use an enzyme blend of Collagenase I and II, each targeting specific collagen fibers that exist in the extracellular matrix. *Trial Tr. Day 4 (AM – Yong) at 74:1-18.* The enzyme blend also contains thermolysin, a neutral protease or "general purpose enzyme" well known to "attack lots of different proteins" including cell surface proteins that are critical to cell function. *Trial Tr. Day 4 (AM – Yong) at 74:20-24, 75:3-8, 16-20, 76:9-19 (describing cell surface proteins as "what cells use to attach to the extracellular matrix" and "the means by which the cells can sense everything around their environment," and so thus "involved in cell-to-cell signaling," "cell-to-matrix interactions," and "pathogen recognition").*

66. Enzymatic digestion is not analogous to the cutting of adipose tissue with a scalpel. *Trial Tr. Day 4 (AM – Yong) at 76:25-77:1.* Cutting the tissue with a scalpel would be similar to using a knife to cut an apple, while applying an enzyme to digest adipose tissue is like "shooting at the apple with BBs" until "the apple would pretty much be applesauce." *Trial Tr. Day 4 (AM – Yong) at 77:1-22.* Similarly, cutting adipose tissue could be compared to using a knife to cut a soft wood dowel into two pieces, "[b]ut using enzymes would be like unleashing . . . a brood of termites onto the dowel." *Trial Tr. Day 4 (AM – Yong) at 72:1-4, 77:1-22; see also Trial Tr. Day 4 (AM – Yong) at 79:2-7 (describing the continuous chemical activity of an enzyme).*

67. Defendants' assertions that 99.99 percent of their enzyme is eliminated from the SVF is not supported by their own published data. Defendants measured enzymatic activity in Wunsch units—which are specific to collagenase. However, Defendants' CSN TMAX enzyme blend also contains the enzyme thermolysin, whose activity is measured by completely different units. Defendants' data only measured the activity of collagenase and did not even specify whether the activity of Collagenase I or Collagenase II was being measured. The data do not specify whether thermolysin, which is more concerning than collagenase, is actually decreased or washed out. *Trial Tr. Day 4 (PM – Yong) at 63:3-*

15, 77:4-25; *Trial Tr. Day 4 (AM – Yong) at 79:2-7 (describing the continuous chemical activity of an enzyme).*

b. Defendants' Enzymatic Digestion and Processing of Adipose Tissue Alters the Physical and Biological Characteristics of the SVF Cells in the CSCTC Products

68. The enzymatic digestion and other processing steps Defendants undertake to isolate the SVF cells from the adipose tissue alter the physical and biological characteristics of the SVF cells in the CSCTC products. Physical characteristics of cells include shape and physical form (*i.e.*, morphology) and cell surface receptor expression. *See Trial Tr. Day 4 (PM – Yong) at 78:24-25, 79:1-14 (It is "[w]ell-known that cell shape can direct and effect . . . cellular behavior in general."); Trial Tr. Day 4 (AM – Yong) at 86:5-13, 87:23-25 (cell surface markers "identify a cell," "allow cells to recognize each other," and are critical to cell signaling pathways.); Trial Tr. Day 4 (AM – Yong) at 87:11-25. Biological characteristics of cells include their viability, activation state, differentiation, and proliferation potential (i.e., capacity to multiply). Trial Tr. Day 4 (AM – Yong) at 88:1-3.*

69. When tissue is enzymatically digested, cells that are necessarily adhered to the extracellular matrix and normally assume a flat, spread and protruded morphology in their native state change to a contracted, spherical form. *Trial Tr. Day 4 (PM – Yong) at 9:5-8.* Consequently, the inner cytoskeleton of the cells that is responsible for providing mechanical support and for keeping internal cellular structures organized loses tension and extensively rearranges. *Trial Tr. Day 4 (AM – Yong) at 81:19-24 (describing the cytoskeleton's purpose "to control cell shape and movement").* Enzymatic digestion of tissue also cleaves proteins on the surface of the cell, including cell surface receptors that are critical in mediating cell signaling among other key aspects of cellular function and behavior. *Trial Tr. Day 4 (AM – Yong) at 80:5-12 (when cells "are exposed to . . . the harsh conditions of the enzyme, then they are basically ripped from the extracellular matrix and go from an adherent to a free-floating state."); Trial Tr. Day 4 (AM – Yong)*

at 82:3-10; Trial Tr. Day 4 (AM – Yong) at 84:11-21 ("When a cell is free-floating . . . [it] just can't function properly" like "a human submerged in water or out in space without any support or stability [and] no orientation[.]"); Trial Tr. Day 4 (AM – Yong) at 85:18-24, 87:11-88:3; Ex. 68 at 2-3); see also Ex. 11 at 40; Ex. 77; Trial Tr. Day 5 (PM – Berman) at 16:21-17:15.

70. The manufacture of CSCTC's SVF product, for example, involves the dissociation of the extracellular matrix through enzymatic digestion and, consequently, changes in the activation state of cells in the resulting cell suspension. This means the main attributes of cells (*e.g.*, cell surface receptor expression) and their behavior (*e.g.*, signaling activity) change in response to a stimulus. *Trial Tr. Day 6 (AM – Reid) at 86:13-16; Ex. 19 at 58-59; Ex. 68 at 2-3.*

71. Processing that affects the activation state and signaling activity of cells alters cellular processes, their metabolic activity, and the cells' capacity to mediate the behavior of other cells in the case of paracrine signaling. Thus, the *ex vivo* enzymatic processing that dissociates the extracellular matrix of adipose tissue in CSCTC's manufacture of the SVF Product alters the relevant biological characteristics of the cells derived from the adipose tissue. *Trial Tr. Day 4 (AM – Yong) at 80:5-12, 82:3-10, 84:11-21, 87:11-88:3.*

72. Enzymatic digestion of the structural components of adipose tissue (*e.g.*, extracellular matrix and blood vessels) also disrupts critical cell adhesion to other cells and particularly to the extracellular matrix. Cell adhesion to other cells and to the extracellular matrix governs how cells responds to their environment and, consequently, cell behavior. *Trial Tr. Day 4 (AM – Yong) at 80:5-12, 82:3-10, 84:11-21, 87:11-88:3; Trial Tr. Day 6 (AM – Reid) at 77:3-9, 79:17-80:1.*

73. Anchorage-dependent cells, such as the stromal and vascular cells that comprise SVF, will not grow, proliferate, or differentiate—and some cell types will not survive—unless they are attached to extracellular matrix. Thus, the *ex vivo* enzymatic processing that eliminates cell attachment alters the proliferation and differentiation potential of the cells derived from the adipose tissue, as well as the cells' ability receive

nutrients and oxygen to survive. *Trial Tr. Day 4 (AM – Yong) at 84:22-85:2, 83:1-7, 84:7-10, 85:14-17.*

74. When the extracellular matrix is digested, and the dissociated cells are filtered, key cellular functions of these cells, including but not limited to cell adhesion, cell-cell signaling, and cell-extracellular matrix signaling, are effectively abolished. As a result, the different cell types are removed from their organized microenvironment and cannot mediate their specialized roles. *Trial Tr. Day 4 (AM – Yong) at 80:5-12, 82:3-10, 84:11-21, 87:11-88:3.*

75. For example, adipose tissue contains endothelial cells which are organized in clusters and interconnected with cell surface molecules that allow the cells to communicate with each other and work in a synergistic fashion to control blood flow by dilating or shrinking blood vessels. *Trial Tr. Day 4 (AM – Yong) at 86:18-87:17.* Like the other disconnected, free-floating cells that exist in SVF after processing, endothelial cells are no longer working synergistically to mediate these functions. *See Trial Tr. Day 4 (PM – Yong) at 8:8-10.*

76. Other of Defendants' processing steps, such as filtration, are also traumatic to the cells ultimately used in the CSCTC products. *See Trial Tr. Day 4 (PM – Yong) at 6:11-17.*

c. <u>Defendants Did Not—and Cannot—Meet their Burden to Demonstrate that their Processing Does Not Alter Cells Contained in their CSCTC Products</u>

77. Defendants did not meaningfully refute Dr. Yong's testimony establishing that enzymatic digestion and processing of adipose tissue alters the physical and biological characteristics of the SVF cells, and they did not meet their burden to establish that their processing does not alter the cells in their CSCTC products. *See generally testimony of Mark Berman, M.D., Trial Tr. Day 5 (AM – Berman) at 93:4-117:11, and Trial Tr. Day 5 (PM – Berman) at 4:18-78:4; testimony of Lola Reid, Ph.D., Trial Tr. Day 6 (AM – Reid) at 66:7-102:12; and testimony of Elliot Lander, M.D., Trial Tr. Day 6 (PM – Lander) at*

46:7-104:3.

78. Defendants presented no credible evidence that contradicted Dr. Yong's testimony that the stem cells in SVF are modified by Defendants' processing. Rather they only offered testimony from expert witness Lola M. Reid, Ph.D., that suggested that mesenchymal stem cells in SVF were altered only by shifting them from the quiescent state to the regenerative state. *Trial Tr. Day 6 (AM – Reid) at 79:13-80:24, 89:21-91:1, 99:24-101:13.*

79. Dr. Reid testified that the mesenchymal stem cells in SVF are not affected by Defendants' use of a collagenase-containing enzyme. *Trial Tr. Day 6 (AM – Reid) at 79:13-80:24, 99:24-101:13.* However, Dr. Reid's testimony narrowly focused on the impact of Defendants' processing to mesenchymal stem cells alone. *See id.; but see Ex. 154 at 3 (Defendants' protocol claims their SVF "is known to contain four different types of adult adipose derived stem cells: mesenchymal cells, endothelial progenitor cells, pericyte progenitors, and hematopoetic stem cells); Trial Tr. Day 5 (PM – Berman) at 77:13-17 (Defendant Berman testifies that Defendants' SVF products contain both mesenchymal stem cells and hematopoetic stem cells); Trial Tr. Day 4 (PM – Yong) at 7:21-24, 8:8-10; Trial Tr. Day 7 (PM – Yong) at 54:9-19.*

80. But Dr. Reid acknowledged that the cells separated out during Defendants' SVF processing include not only mesenchymal stem cells but also "a number of other cell products, which include precursors to blood vessels and precursors to stroma and the like." *Trial Tr. Day 6 (AM – Reid) at 93:10-94:2.* In fact, only between 1-10 percent of the cells in SVF are actually stem cells. *Trial Tr. Day 7 (PM – Yong) at 54:2-6.* Thus, Dr. Reid offered no evidence about the impact of Defendants' enzymatic digestion or other processing steps on 90-99 percent of the other cells types found in SVF that are not mesenchymal stem cells. *See generally testimony of Lola Reid, Ph.D., Trial Tr. Day 6 (AM – Reid) at 66:7-102:12; see, Trial Tr. Day 7 (PM – Yong) at 54:7-12.*

81. Defendants' SVF consists of a heterogeneous collection of cells and cell debris, only a small percentage of which are stem cells. *Trial Tr. Day 4 (PM – Yong) at*

54:2-6, 5:9-6:7; see also Ex. 154 at 3. As Dr. Yong testified, it is important to know what impact Defendants' processing has on all the various cells in SVF because different cell types react in different ways and will change in different ways in response to the same stimulus. *Trial Tr. Day 7 (PM – Yong) at 54:7-12.*

82. Any changes to cells caused by Defendants' SVF manufacturing process can be identified through testing, such as cell surface marker expression analysis, gene expression analysis, or proteomic analysis. *Trial Tr. Day 4 (PM – Yong) at 15:9-17.* Equipment to perform this testing would be readily available to individuals doing research with cells and cell culture. *Trial Tr. Day 4 (PM – Yong) at 15:18-24.* Neither Defendants nor their expert Dr. Reid proffered the results of any such testing for the CSCTC products to meet Defendants' burden of showing the SVF cells have not changed. *Trial Tr. Day 4 (PM – Yong) at 15:3-8; see generally Trial Tr. Day 5 (AM – Berman) at 93:4-117:11; Trial Tr. Day 5 (PM – Berman) at 4:18-78:4; Trial Tr. Day 6 (AM – Reid) at 66:7-102:12; Trial Tr. Day 6 (PM – Lander) at 46:7-104:3.*

83. The only testing Defendants conduct before administering their SVF product and SVF/Vaccinia products to patients is for cell counting and viability. *Ex. 11 at 41; see Trial Tr. Day 5 (Jim – AM) at 22:10-15; Trial Tr. Day 2 (AM – Forster) at 77:21-78:4.* For the Expanded SVF product, however, Defendants do not require a cell count or testing of cell viability, or testing for bacterial growth. *Ex. 37 at 22.*

84. When performed, Defendants' cell counting and viability testing checks to see what percentage of cells survived Defendants' processing steps, and what percentage did not. *See Ex. 11 at 41; Trial Tr. Day 5 (AM – Jim) at 22:10-15; Trial Tr. Day 2 (AM – Forster) at 77:21-78:4; Def. Ex. 303 at 45, 49.*

85. According to Defendants, they regularly get cell viability results in the range of 75 percent with some results being lower than that, *Ex. 12 at 37*, effectively conceding that their manufacturing process kills at least 25 percent of the SVF cells that were isolated from the tissue.

86. Defendant Berman told FDA investigators that he would administer CSCTC

products to patients only if at least 30 percent of the cells were still viable. *Ex. 12 at 37.* By contrast, Defendant Lander told FDA investigators that he would administer the CSCTC products even if all the cells were dead (*i.e.*, 0 percent viability) and would then recommend the patient come back for another SVF treatment. *Trial Tr. Day 1 (PM – Lagud) at 31:9-18; Trial Tr. Day 5 (AM – Jim) at 27:20-28:1; Ex. 11 at 33.*

87. Under these facts, there is no question that Defendants did not—and cannot—meet their burden to demonstrate that the processing they undertake does not alter the cells contained in the CSCTC products they administer to their patients.

d. The Testimony of Defendants' Expert, Lola Reid, Ph.D., Is Inherently Unreliable and Should Be Disregarded

88. At trial, Defendants offered the expert testimony and opinions of Dr. Lola Reid, whom they qualified as an expert in stem cells. *Trial Tr. Day 6 (AM – Reid) at 72:19-23.*

89. Dr. Reid admitted in her testimony that substantial portions of her expert report were not her own. Dr. Reid identified the portions of her report that she authored as starting on page 19 and continuing to page 27 of her report. This portion of the report contained information providing "[a]dditional scientific background" about "metazoan organisms." *Trial Tr. Day 6 (PM – Reid) at 19:10-20:10.* Dr. Reid did not identify page 7 of her report—which discussed being "asked to provide an opinion as to whether California Stem Cell Treatment Center, Incorporated, or Cal. Stem Cell's, procurement of the patient's own stromal vascular fraction, or SVF, for relocation into another area of the patient's body . . . (SVF procedure) causes any changes to the stem cells collected, and No. 2, whether the use of SVF in surgical procedures is safe and well-tolerated"—or the 11 pages which immediately followed it as being the part of the report she wrote. *See id.; cf. Trial Tr. Day 6 (AM – Reid) at 105:1-25.*

90. When Dr. Reid was questioned about the content of her expert report and opinions, she not only conceded that she had not authored substantial portions of her report, but also stated that she had no idea how those portions had come to be included in

her report. When confronted with a side-by-side comparison of her expert report in this case and of Defendant Lander's expert report in the *United States v. U.S. Stem Cell Clinic* case—and questioned about their extensive similarities, which had been highlighted in yellow by Government counsel for ease of reference—Dr. Reid testified that those portions had been merged with her report, that she had not written the additional portions, and that much of the text in the two reports was identical. *Trial Tr. Day 6 (PM – Reid) at 15:11-17:15.*

91. When asked whether she had, in fact, reviewed the scientific literature cited throughout the footnotes to her expert report upon which her opinions purportedly were based, Dr. Reid testified, "I had nothing to do with the writing of any of the things that you just highlighted or any of the references that you're pointing to. I had nothing to do with that. I was surprised when I saw that merged together with what I had written. What I wrote was completely separate." *Trial Tr. Day 6 (PM – Reid) at 19:2-9, 19:14-18.*

92. Dr. Reid further testified that her report was an "amalgamation" and that she was unfamiliar with how the portions she had authored had been merged with the other material appearing in the report bearing her signature. *Trial Tr. Day 6 (PM – Reid) at 41:24-42:4.* She furthered testified that, "I signed what I wrote and – and sent that in. And how that got merged with the other, I have no idea." *Trial Tr. Day 6 (PM – Reid) at 42:8-9.*

93. Dr. Reid also admitted that she had not even recognized her expert report when Government counsel presented it to her at her deposition. *Trial Tr. Day 6 (PM - Reid) at 10:14-23.* She had never seen two of the three attachments to her report "at any point prior to the deposition," including "when the opinions" in her report "were rendered." Specifically, she had not been given a copy of the safety study authored by Defendants Berman and Lander, which had been included as Attachment 3 to her report. *Trial Tr. Day 6 (PM – Reid) at 6:1-6; Trial Tr. Day 6 (PM - Reid) at 9:12-10:23*. She had also never seen the protocol in Attachment 2 to her report, which contained both pictures and descriptions of Defendants' processing. *Trial Tr. Day 6 (PM – Reid) at 6:4-21.* In

lieu of Attachment 2 to her report, Dr. Reid had been given "a few paragraphs describing what was done to isolate the cells." *Trial Tr. Day 6 (PM – Reid) at 7:11-14.* Although Dr. Reid's purported report opines that Defendants' "use of the enzyme Liberase in processing the adipose tissue didn't affect the cells in the tissue," at her deposition Dr. Reid admitted that she did not know "which Liberase blend of enzymes that defendants use" so she had tried to look it up on the internet. The night before her deposition, Dr. Reid "looked up what are the commercially available forms of Liberase and which tissues are they used for" but as of the date of her deposition, she still "d[id]n't even know what [Defendants] use of those." *Trial Tr. Day 6 (PM – Reid) at 38:19-22, 39:4-8, 39:22-41:2; but see Trial Tr. Day 6 (PM – Reid) at 38:14-18 (acknowledging that "enzymes' impact on adipose tissue can vary based on the mix of chemicals that are used in the enzyme").*

94. Dr. Reid further admitted that did not know the definition of a drug under federal law when she concluded that Defendants' cellular SVF treatments could not be drugs. *Trial Tr. Day 6 (PM – Reid) at 31:23-32:1.* She also conceded that she concluded Defendants' SVF treatments were safe and well tolerated without first reviewing whether any adverse events had been reported in connection with the Defendants' SVF treatments. *Trial Tr. Day 6 (PM – Reid) at 25:14-19.* She testified that at the time she concluded that Defendants' specific SVF treatments were safe and well tolerated, she was not aware of statements by reputable medical associations and publications, including the American Academy of Ophthalmology, the American Lung Association, and The New England Journal of Medicine, expressing concerns about unapproved stem cell treatments and adipose tissue-derived stem cell treatments—particularly from stem cell clinics that charge high fees for their services, administer their treatments in patients' eyes, and/or lack the independent clinical data to support their practices. *Trial Tr. Day 6 (PM – Reid) at 25:14-27:15.*

95. Given the discrepancies between Dr. Reid's report and her testimony at trial, as well as the limitations of the materials Dr. Reid stated she reviewed, the opinions provided by Dr. Reid cannot be relied upon.

C. The Cellular-Based "CSCTC Products" that Defendants Manufacture from Patients' Adipose Tissue are "Drugs" within the meaning of the FDCA

96. Defendants' records, public statements, and information contained on Defendants' websites and elsewhere establish that Defendants intend the CSCTC products to be used purportedly to treat or mitigate a variety of diseases and conditions, or to affect the structure or function of the body—which makes the products "drugs" within the meaning of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 321.

97. A video by Defendant Berman, available at https://www.youtube.com/watch?v=SVVQrosn0gc, describes the SVF product as "magical cells in your fat" and "liquid magic" used to treat patients who have "COPD, heart disease, neurodegenerative problems, . . . interstitial cystitis . . . Peyronie's and erectile dysfunction." *Trial Tr. Day 5 (PM – Berman) at 92:18-95:3; see also Ans. ¶ 30.*

98. A videotaped interview of Defendant Lander, available at https://www.youtube.com/watch?v=otushsFxkzw, promotes SVF "for cancer therapies," arthritis, heart disease, lung disease and interstitial cystitis, and "brain conditions [by] injecting the cells directly into the brain." *Ans. ¶ 30; see also Trial Tr. Day 5 (PM – Berman) at 91:15-94:22.*

99. A CSCTC brochure entitled "Adipose Stem Cell Therapy and You" that Defendants provided to prospective patients markets "a solution rich with your own stem cells" that "can be deployed to treat a number of degenerative conditions and diseases." The brochure notes that there have been "reports of improvements with MS, Muscular Dystrophy, Parkinson's, ALS, and stroke." *Ex. 13 at 1; Ex. 8 at RFA ¶ 52; Trial Tr. Day 5 (PM – Berman) at 98:3-99:2.*

100. Defendants' patient records confirm that CSCTC has, in fact, administered CSCTC products to patients while claiming to treat Parkinson's, ALS, stroke, arthritis, hypothyroidism, spine disc protrusion, radiation necrosis, optic neuropathy, MS, sciatica, migraines, traumatic brain injury, diabetes, renal failure, Alzheimer's, cerebral palsy, COPD, Lyme disease, and more. *See Ex. 14 at 1-4.*

101. Defendants Berman and Lander have authored and disseminated to CSN affiliates various "protocols" and related documents that explain how to manufacture and administer CSCTC products to treat ophthalmic conditions, neurological conditions, knee conditions, Parkinson's disease, cancer, and even COVID-19, among others. *See generally Exs. 15, 16, 18, 36, 48, 79, 80, 81, 154, and 161; Def. Ex. 303.*

102. Defendants Berman and Lander, in their book titled *The Stem Cell Revolution*, claim that CSN affiliates are currently using CSCTC products to treat 47 different diseases and conditions, including Alzheimer's, arrhythmias, asthma, autism, cerebral palsy, congestive heart failure, COPD, critical limb ischemia, dry eyes, erectile dysfunction, lupus, macular degeneration, Peyronie's, renal failure, stroke, traumatic brain injury and concussion. *Trial Tr. Day 5 (PM – Berman) at 96:16-97:23.*

103. CSN's website, available at https://stemcellrevolution.com/currently-studying, lists more than 30 diseases or conditions that CSN is "currently studying," including MS, ALS, cardiomyopathy, lupus, and macular degeneration. *Ex. 10 at 35.*

104. CSN's website, available at http://stemcellrevolution.com/about-us/faqs/, answers the question "Can stem cells treat cancer?" and explains that CSN is involved in "cutting edge clinical trials using stem cells to carry cancer-killing biologic agents deep into cancer tissue that has not responded to conventional therapy." *Ex. 10 at 10.*

105. Inconsistent with Defendants' claims that that they are merely performing "surgery" and "surgical procedures," the CSN website, available at http://stemcellrevolution.com/about-us/faqs/, promotes the CSCTC products as "*non-surgical* alternatives" for degenerative disorders. *See Ex. 10 at 7 (emphasis added).*

106. In a 2017 interview with a University of California Davis School of Medicine professor who publishes a blog discussing regenerative medicine, Defendants claimed that their Expanded SVF product can be used "to potentially mitigate a number of degenerative conditions." *Ex. 75 at 3; Ans. ¶ 60; see generally Trial Tr. Day 2 (PM – Knoepfler) at 72:2-10, 72:14-75:12, 77:5-10.*

107. At trial, Defendant Berman stated that CSCTC and sub-investigator affiliates

had conducted a study to "evaluate whether [Defendants'] SVF treatments could mitigate the symptoms of interstitial cystitis." *Trial Tr. Day 5 (PM – Berman) at 103:11-17.*

108. In the CSCTC brochure entitled "Adipose Stem Cell Therapy and You," Defendants claim that stem cells "appear to be particularly effective in improving painful joints, repairing cartilage and ligaments, and even painful conditions along the spine. There are many clinical trials with stem cells going on right now. In one example, patients suffering from heart attacks have been given their own fat derived stem cells so they could speed up repair of the heart muscle . . . . " *Ex. 13 at 1.*

i. Defendants' CSCTC Products are also "New Drugs" within the meaning of the FDCA

109. There have been no adequate and well-controlled studies performed with the Defendants' CSCTC products demonstrating that they are safe or effective for any indication (*i.e.*, for any intended use). *Trial Tr. Day 3 (AM – Lapteva) at 34:2-16.*

110. Defendants' CSCTC products are not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in their labeling. *Trial Tr. Day 3 (AM – Lapteva) at 20:18-25:22; Trial Tr. Day 3 (AM – Lapteva) at 34:2-16.*

ii. Defendants' CSCTC Products are also "Prescription Drugs" within the meaning of the FDCA

111. Medical expertise, licensure, and appropriate subspecialty training are required to diagnose the diseases and condition(s) that Defendants purport to treat and to determine the appropriate therapeutic intervention(s) for diseases and conditions for which the CSCTC products are used. *Trial Tr. Day 3 (AM – Lapteva) at 38:8-21, 50:20-14; Ex. 26 at 3.*

112. Medical expertise, licensure, and/or appropriate training are required to administer the CSCTC products through the intended parenteral routes of administration. *Trial Tr. Day 3 (AM – Lapteva) at 49:14-50:19; Ex. 26 at 3.*

iii. Defendants' CSCTC Products are also "Biological Products" within the meaning of the PHSA

113. FDA's Center for Biological Products ("CBER") is responsible for regulating the safety, purity, and potency of human biological products, or "biologics" for short. *Trial Tr. Day 1 (AM – Joneckis) at 34:1-6.*

114. Biological products are comprised of living organisms or things produced by a living organism, such as "vaccines, blood and blood components, cellular therapies, gene therapies, proteins, [and] things of that nature, among other products." *Trial Tr. Day 1 (AM – Joneckis) at 34:14-23.*

115. Defendants have long recognized that the SVF they claim to prepare from adipose (fat) tissue is a product, and specifically a biological product. *See, e.g., Ex. 19 at 49 (technologist receives the "syringe of harvested fat from the doctor"), 56-74 (technologist transfers "25-30 cc's of adipose fat tissue" to syringe and then chemically and mechanically processes the tissue), and 75 ("The final product of SVF is now in the 10 cc syringe); Ex. 69 at 2 (Defendants claim that "SVF must be regulated as an autologous biologic"), 3 ("CSN has performed . . . laboratory cultures . . . on approximately 10% of our final products"), and 10 (Defendants do not know how "potential variations in the [components we purchase and use] would affect the strength quality or purity of our final SVF product"); Trial Tr. Day 5 (PM – Berman) at 48:11-13 (describing Defendants' SVF as a "cell product available to our patients").*

116. During even the pendency of this litigation, Defendants published a scientific article claiming that their "SVF is an *autologous biologic product* derived in surgery from the enzymatic digestion of adipose tissue, which is split into its fat fraction (adipocytes) and stromal and vascular fractions (containing regenerative cells)." Defendants' article further described their SVF as a "*stem cell rich biologic product* . . . injected both systemically and regionally into pelvic floor targets"—where in accordance with Defendants' interstitial cystitis protocol—"half of the final 10 cc *SVF product* [was] to be used intervenously [*sic* – intravenously] for systemic treatment and the other half of the

isolated SVF [was] to be injected regionally" into patients' pelvic floors. *Trial Tr. Day 5 (PM – Berman) at 102:13-105:4.*

117. Autologous biological products may be created for individual patients using the patients' own cells. Because these autologous biological products are subject to FDA regulation, CBER routinely reviews applications concerning such products. *Trial Tr. Day 1 (AM – Joneckis) at 52:5-24; Trial Tr. Day 2 (PM – Lapteva) at 100:4-15.*

118. Autologous biological products, such as Defendants' SVF product, can and should be produced "with consistent strength, quality, and purity." *Trial Tr. Day 3 (AM – Lapteva) at 78:17-22.*

iv. Defendants' CSCTC Products are also HCT/Ps under regulations issued pursuant to the PHSA

119. The CSCTC products—all of which Defendants claim contain some form of SVF—are human cells, tissues, or cellular or tissue-based products ("HCT/Ps"), which refers to "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." 21 C.F.R. § 1271.3(d).

120. As noted above, the CSCTC products are intended for autologous use, which refers to the "implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered." *See Proposed Finding of Fact ¶ 18.*

D. In Manufacturing and Administering Their Cellular-Based Drugs, Defendants Violate the FDCA in Multiple Ways

i. Defendants' CSCTC Products are Adulterated Drugs in Violation of the FDCA and its Implementing Regulations

121. FDA investigators inspected CSCTC Rancho Mirage from July 17-26, 2017, and CSCTC Beverly Hills from July 21-27, 2017. *See generally Exs. 11, 12, 38, and 39.*

122. The purpose of the inspection was to determine whether Defendants were manufacturing drugs subject to FDA's jurisdiction and, if so, to conduct an inspection to

see whether Defendants manufactured their drugs in compliance with current good manufacturing practice (CGMP) requirements. *Trial Tr. Day 1 (AM – Lagud) at 88:12-89:1, 90:7-91:12; Trial Tr. Day 2 (AM – Forster) at 44:1-6; Trial Tr. Day 2 (PM – Forster) at 27:11-19; Trial Tr. Day 2 (PM – Christopher) at 59:22-60:1; Trial Tr. Day 5 (AM – Jim) at 6:20-24.*

123. The inspections were conducted by four FDA investigators (*i.e.*, two at each CSCTC facility) who collectively have more than eight decades of experience in conducting inspections to evaluate facility design, operation, manufacturing, and testing procedures required for drugs and biological products. *Trial Tr. Day 1 (AM – Lagud) at 85:19-86:9; Trial Tr. Day 2 (AM – Forster) at 43:14-16; Trial Tr. Day 2 (PM – Christopher) at 40:22-41:8; Trial Tr. Day 5 (AM – Jim) at 5:14-6:11.* Defendants allowed the FDA investigators to enter CSCTC's establishments and cooperated with their investigation. *See generally Exs. 11, 12.*

124. To conduct the inspection, investigators presented their credentials and issued official notices of inspections, toured Defendants' establishments, interviewed firm personnel, reviewed documents, and observed Defendants' SVF manufacturing process live or by video. *See, e.g.*, *Trial Tr. Day 1 (AM – Lagud) at 88:18-92:12, 95:2-17; Trial Tr. Day 2 (AM – Forster) at 44:19-47:16; Trial Tr. Day 5 (AM – Jim) at 7:2-15; Ex. 11 at 1-2, 7, 61; Ex. 12 at 3-4, 44.*

125. The four FDA investigators who inspected Defendants' establishments testified that the inspections revealed serious and obvious CGMP violations at both CSCTC Rancho Mirage and CSCTC Beverly Hills.[16] At the close of the inspections, FDA investigators issued lists of inspectional observations ("Form FDA 483s") to Defendants Berman and Lander. *See Exs. 38, 39; see also Exs. 11, 12.*

126. Specifically, the July 2017 inspections showed that the manner in which Defendants manufacture the CSCTC products did not comply with CGMP. The 2017

[16] As explained in the Proposed Conclusions of Law, *infra*, failure to comply with even one CGMP regulation renders a drug legally adulterated under the FDCA.

inspections showed that the methods, facilities, and controls Defendants used in manufacturing, processing, packing, and holding the CSCTC products did not conform to, and are not operated or administered in conformity with, CGMP. *See* 21 U.S.C. § 351(a)(2)(B) and 21 C.F.R. Parts 210-211; *see also* 21 C.F.R. Parts 600-680 (setting forth additional standards and manufacturing requirements applicable to biological products). *See generally Exs. 11, 12, 38, 39; see Trial Tr. Day 1 (AM – Lagud) at 99:22-100:10; Trial Tr. Day 2 (AM – Forster) at 53:1-13; see also Trial Tr. Day 5 (PM – Berman) at 21:9-19.*

127. The July 2017 inspections showed that 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), because they did not prepare the CSCTC products under aseptic conditions, nor did they validate their manufacturing process to demonstrate that it was aseptic. *Ex. 11 at 31, 35-36, 38; Ex. 38 at 1-2, 4-7; Trial Tr. Day 1 (AM – Lagud) at 101:7-13; Ex. 12 at 19, 26, 29, 32-35; Ex. 39 at 4-5, 7-8; Trial Tr. Day 5 (AM – Jim) at 21:9-13, 21:22-22:2.*

128. For example, the FDA investigators found that at both the CSCTC Rancho Mirage and Beverly Hills facilities, Defendants cleaned the "surgery" rooms where adipose tissue was recovered from patients only three times per week and performed no environmental monitoring to demonstrate that such cleaning was acceptable for aseptic manufacturing. *Ex. 11 at 35-36, 38-39; Trial Tr. Day 1 (AM – Lagud) at 101:20-102:10; Ex. 38 at 3; Trial Tr. Day 1 (PM – Lagud) at 6:9-7:5; Trial Tr. Day 5 (AM – Jim) at 21:9-13; Ex. 12 at 33-34; Ex. 39 at 2-4; see also Trial Tr. Day 5 (PM – Berman) at 21:9-19.*

129. FDA investigators at the CSCTC Rancho Mirage facility observed that Defendants allowed a patient to wear street clothes in the "surgery" room, and that Defendants left the door to the "surgery" room open with a floor fan blowing air through the doorway from elsewhere in the building while recovering adipose tissue and manufacturing the CSCTC products. *Trial Tr. Day 1 (AM – Lagud) at 104:14-18; Trial Tr. Day 1 (PM – Lagud) at 7:6-8:9; Ex. 11 at 35-36, 48-49.*

130. The July 2017 inspections also showed that Defendants did not subject the CSCTC products to appropriate laboratory testing to ensure that they were free of objectionable microorganisms, as required by 21 C.F.R. § 211.165(b), to ensure the safety of those products. *Trial Tr. Day 2 (AM – Forster) at 72:15-18; Ex. 12 at 33; Ex. 39 at 3.* For example, Defendants performed no sterility or endotoxin testing on batches of autologous SVF product at their CSCTC Rancho Mirage and Beverly Hills facilities at the time of FDA's 2017 inspections. *Trial Tr. Day 2 (AM – Forster) at 73:1-16; Trial Tr. Day 5 (AM – Jim) at 22:10-15, 26:9-20; Ex. 38 at 2-3; Ex. 39 at 3-4.* Additionally, although CSCTC's SVF/Vaccinia Vaccine Safety Protocol stated that "[a]liquots of each cell suspension will be set aside for endotoxin testing and sterility testing . . . [and] SVF will only be released for injection after confirmation of endotoxin assay results of level of EU less than or equal to 5EU/kg/hr and negative gram stain results," Defendants did not follow these guidelines at either CSCTC facility. *Ex. 11 at 25; Ex. 48 at 6.*

131. CSCTC also failed to establish a system for monitoring environmental conditions to prevent contamination during aseptic processing, as required by 21 C.F.R. § 211.42(c)(10)(iv). For example, during FDA's 2017 inspections of the CSCTC facilities, Defendants manufactured the SVF and SVF/Vaccinia products in a "surgery" room with no environmental monitoring program. Defendants did not perform any type of surface, air, or personnel monitoring for viable microorganisms, nor any active air monitoring for non-viable particles. *Trial Tr. Day 1 (PM – Lagud) at 21:9-22:21; Ex. 11 at.38-39, Ex. 12 at 33-34, Ex. 38 at 3), Ex. 39 at 3-4.*

132. CSCTC failed to establish written procedures for production and process control designed to assure the drug products have the identity, strength, quality and purity they purport or are represented to possess, as required by 21 C.F.R. § 211.100(a), because they failed to validate the manufacturing process and perform in-process testing and establish specifications for a safe and effective final product. *Trial Tr. Day 2 (AM – Forster) at 54:7-55:18; Ex. 11 at 33, 41; Ex. 38 at 3-4, 7; Ex 39 at 1.* Specifically, although Defendants Berman and Lander stated that CSCTC performed viability and cell

count testing on the final SVF product, the testing was performed without any specifications or release criteria, and no other testing was performed. *Trial Tr. Day 2 (AM – Forster) at 77:19-79:1; Trial Tr. Day 5 (AM – Jim) at 22:10-15; Ex. 11 at 33, 41; Ex 12 at 37.* Additionally, Dr. Lander stated that regardless of the SVF testing results, he would still administer the patient's cells back to the patient. *Trial Tr. Day 5 (AM – Jim) at 27:14-28:1; Ex. 11 at 33.*

133. CSCTC failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity, as required by 21 C.F.R. § 211.160(b). *Trial Tr. Day 1 (PM – Lagud) at 29:3-20; Trial Tr. Day 3 (AM – Lapteva) at 78:17-20; Ex. 11 at 39-41, Ex. 12 at 36, Ex. 38 at 3-4, 7, Ex. 39 at 3-8.*

134. For example, CSCTC failed to establish specifications/acceptance criteria and did not perform testing on the components used to manufacture their SVF product, including the TMAX enzyme used to process adipose tissue. Although Defendants obtained Certificates of Analysis ("COAs") for the TMAX enzyme, several COAs stated that the product was "For in Vitro Use Only." Defendants, however, were using it in a clinical setting to prepare the CSCTC products. *Ex. 11 at 39-41; Ex. 12 at 35-36; Ex. 45.*

135. Additionally, the Defendants failed to evaluate the impact of freezing/thawing on the TMAX enzyme used in their manufacture of SVF products. *Ex. 11 at 46-47.*

136. No testing was performed on ACAM2000 Vaccinia Virus vaccine prior to mixing it with SVF for administration to patients. *Ex. 11 at 39, 46; Ex. 48 at 5-7.*

137. As to the Expanded SVF product, there was no documentation showing when the expanded cells were received at CSCTC's Rancho Mirage facility, or the condition of expanded cells upon receipt, or the condition under which the expanded cells were stored. In addition, although Defendants' protocol for frozen or expanded cells states that "a

sample should be evaluated on site for gram stain or rapid infection evaluation . . . [or alternatively] sent out for routine culture to validate the maintenance of sterility during transportation as a further validation of the reported laboratory sterility . . . . " Dr. Lander confirmed that such measures were not performed. *Ex. 11 at 29, 46; Ex. 36 at 3.*

138. FDA investigators also found that CSCTC failed to establish written procedures regarding the receipt, evaluation, and investigation, and reporting of adverse events, as required by 21 C.F.R. 211.198(a). *Trial Tr. Day 5 (AM – Jim) at 29:4-8; Ex. 38 at 9-12.* This CGMP provision requires that written procedures for investigating adverse events be in place. *Trial Tr. Day 5 (AM – Jim) at 29:9-15; Ex. 38 at 9-12.*

139. Defendants received reports of adverse events related to the administration of the CSCTC products by CSN affiliates. *Ex. 8 at RFA ¶ 17.*

140. CSCTC did not establish a central location in which to maintain all reports of adverse events or complaints. *Trial Tr. Day 5 (AM – Jim) at 28:8-15.*

141. When FDA investigators requested information regarding adverse events, Defendants provided documentation of the adverse events in many different forms from different locations in Defendants' offices, and in some cases made phone calls to retrieve information regarding adverse events. *Trial Tr. Day 5 (AM – Jim) at 28:12-29:3.*

142. CSCTC maintained a database where affiliates and patients could report adverse events. FDA investigators found multiple deficiencies in the information maintained in this database. FDA investigators determined that not all patients were entered into the database and not all serious adverse events were included in the database. Further, FDA investigators did not find evidence of any evaluation of the adverse events within the database. *Trial Tr. Day 5 (AM – Jim) at 41:6-42:5.*

143. Although CGMP regulations require the manufacturer of a product to investigate reported adverse events, CSCTC stated that it provides information relating to adverse events to CSCTC's Institutional Review Board ("IRB") and that IRB is responsible for conducting the investigation. *Trial Tr. Day 5 (AM – Jim) at 29:24-30:5, 31:5-13.*

144. There is a CGMP requirement for receiving the reports of adverse events and for evaluating the adverse events to determine if they are related to a specific product and to evaluate if corrective actions need to be taken. *Trial Tr. Day 5 (AM – Jim) at 29:9-15.*

145. FDA investigators concluded that CSCTC was inconsistent in receiving information regarding adverse events and inconsistent in conducting the evaluation or investigation and corrective actions. *Trial Tr. Day 5 (AM – Jim) at 29:16-23.*

146. For example, on February 6, 2017, a patient with COPD lost consciousness and was hospitalized after being treated with Defendants' SVF product intravenously and with a nebulizer at CSCTC Beverly Hills. Defendants did not identify the event as an adverse event. Yet Defendants noted in the patient's records that in the future, the patient should only receive intravenous SVF and "NO nebulizer." *Ex. 8 at RFA ¶ 14; Ex. 61 at 3.*

147. On April 16, 2016, a patient who received SVF product injected through a catheter into the area around the brain at CSCTC Beverly Hills was hospitalized when testing revealed evidence of infection. *Ex. 8 at RFA ¶ 15.*

148. On March 21, 2016, a patient who received SVF product in her knee at CSCTC Beverly Hills reported experiencing an infection and being unable to walk for six months. The customer file contained a note from Defendant Berman stating, "Not all treatments are successful. Not really adverse event from SVF." *Ex. 8 at RFA ¶ 16; Ex. 62 at 1.* After reviewing CSCTC's records, FDA investigators concluded that "[t]his event was not investigated and not reported to FDA." *Ex. 38 at 10; Trial Tr. Day 2 (AM – Forster) at 93:10-94:7.*

149. Upon review of the files of cancer patients treated with Defendants' SVF/Vaccinia product, FDA investigators found no evidence that Defendants investigated to determine if the death of the patients was related to the SVF/Vaccinia product. *Trial Tr. Day 2 (AM – Forster) at 94:8-95:9; Ex. 56; Trial Tr. Day 2 (AM – Forster) at 95:15-96:1; Ex. 59; Trial Tr. Day 2 (PM – Forster) at 8:3-15; Trial Tr. Day 5 (AM – Jim) at 42:6-44:8; Ex. 11 at 20-25; Ex. 65.*

150. Defendants have never disputed the FDA investigators' factual findings that Defendants were not in compliance with CGMP, but have instead argued that CGMP requirements should not apply to their CSCTC products at all. *See generally Exs. 69, 70.*

ii. Defendants' CSCTC Products are Misbranded Drugs

a. <u>The CSCTC Products Lack Required Labeling Information</u>

151. Labeling on the CSCTC products lacks indications for use, dosages, routes of administration, and side effects. *Trial Tr. Day 3 (AM – Lapteva) at 38:22-39:2.* The labeling on the CSCTC products does not identify them as "Rx only." *See Ans. ¶ 12; Ex. 9 at Rog. ¶ 19, and Ex. 166; Trial Tr. Day 5 (PM – Berman) at 13:6-9; Ex. 11 at 33; Ex. 12 at 20; Exs. 21, 22, 23, 24; Ex. 19 at 75; see generally Def. Ex. 453.*

152. Additionally, the expanded mesenchymal stem cells lack directions for use, dosage, routes of administration, and potential side effects when received and Defendants do not otherwise label them upon receipt. *Ex. 12 at 12, 20-21; Ex. 30 at 1-2.*

153. Prescription drugs are required to have adequate directions for use and must be administered under the supervision of a licensed practitioner. *Trial Tr. Day 3 (AM – Lapteva) at 55:6-18.*

154. Because Defendants' products are used to treat chronic medical conditions and systemic diseases, the products require adequate instructions for use in order to understand what kind of therapeutic effect to expect, how to administer the products safely, and a number of other pieces of information that are important for appropriate use of the products. *Trial Tr. Day 3 (AM – Lapteva) at 38:8-18.*

155. Also known as prescribing information, adequate directions for use include different elements important for the safe and appropriate use of the product. Among other things, they must include for what conditions the product should be used (*i.e.*, its indications); conditions for which a product should not be used (*i.e.*, its contraindications); any warnings or precautions about potentialities or observed toxic effects or adverse events; appropriate dosing; route of administration; regimen for administration; duration

of administration; and all of the important information in order to enable a licensed practitioner to use the product appropriately with the expectation of certain therapeutic benefit and an understanding of the potential toxicities that may occur in an individual patient based on previously observed effects. *Trial Tr. Day 3 (AM – Lapteva) at 55:21-56:15; see, e.g., Ex. 189.*

156. Adequate directions for use are derived from adequate and well-controlled clinical studies of the product wherein the therapeutic benefit would be demonstrated and the adverse events would be observed and carefully collected, recorded, and reported, and then documented in order to characterize the product's safety profile. *Trial Tr. Day 3 (AM – Lapteva) at 56:20-57:12.*

157. Published clinical study data available in the scientific literature for adipose tissue-derived stem cell therapies are uninterpretable and do not establish the safety or effectiveness of any of the CSCTC products for any of the conditions for which they are marketed and used. *Trial Tr. Day 3 (AM – Lapteva) at 31:14-22.*

158. Published studies in the field of adipose tissue-derived stem cell therapies are very early in their development. Most studies are laboratory or animal studies; very few human studies exist for these products. None of the published studies are adequate and well-controlled and they lack pertinent features of adequate design. *Trial Tr. Day 3 (AM – Lapteva) at 32:2-33:11.* Therefore, no conclusions can be made with respect to the safety or efficacy of adipose-derived stem cell treatments based upon these studies. *Trial Tr. Day 3 (AM – Lapteva) at 34:4-16.*

159. Based on the available information about adipose tissue-derived stem cell therapies in general, and Defendants' CSCTC products in particular, it is not possible to create adequate directions for use for Defendants' products. *Trial Tr. Day 3 (AM – Lapteva) at 57:15-58:1.*

b. <u>The SVF/Vaccinia Product is Dangerous to Health When Used in the Manner Suggested in Its Labeling</u>

160. Defendants have manufactured an SVF/Vaccinia product involving a

combination of SVF and Vaccinia Vaccine, Live. *See Ans. ¶ 14; Exs. 11 at 2; Ex. 12 at 5; Trial Tr. Day 5 (PM – Berman) at 72:20-73:5.*

161. Vaccinia Vaccine, Live, is also known by its proprietary name ACAM2000. ACAM2000 is an FDA-approved biological product for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection. The vaccine's labeling is required to display a "black box warning" designed to call attention to serious or life-threatening product risk, including swelling of the heart tissues, brain, or spinal cord. *Ans. ¶ 14; 21 C.F.R. § 201.57(c)(l); see also Ex. 11 at 2; Ex. 12 at 5, Ex. 189); Trial Tr. Day 5 (PM – Berman) at 72:20-73:5.*

162. The black box warning in the ACAM2000 labeling contains "a warning regarding myocarditis and pericarditis and various other possible side effects associated with even the safe use and approved use of ACAM2000." The labeling also discusses the "increased risks [posed] in vaccinees who have certain conditions that contraindicate them for receiving ACAM2000 among other things." The black box warning further states that "ACAM2000 is a live Vaccinia virus that can be transmitted to people who have close contact with the vaccinee and that the risks in contacts are the same as those for the vaccinee." *Trial Tr. Day 7 (PM – Lander) at 25:8-26:2; Ex.189 at 1, 3.*

163. Although Defendant Lander claimed that ACAM2000 is "one of the safest drugs in history," he admitted on cross-examination that he was not aware that ACAM2000 carried a black box warning from the FDA. *Trial Tr. Day 7 (PM – Lander) at 24:16-18.* He also was not aware that a black box warning is the FDA's most stringent warning for drugs or devices on the market. *Trial Tr. Day 7 (PM – Lander) at 24:21-24.*

164. The FDA-approved labeling for ACAM2000 requires that it be administered by a skilled practitioner because of potential toxicity, the method of use, and the collateral measures to the use of the treatments. *Ex. 189 at 1, 3 (see "Dosage and Administration"); Trial Tr. Day 3 (AM – Lapteva) at 53:24-54:14.*

165. Some of the toxicities associated with ACAM2000 include encephalopathy and encephalitis, meaning inflammation around the brain; pericarditis and myocarditis,

meaning inflammation around the heart; and different types of rashes from mild to pretty severe generalized Vaccinia infection. *Ex. 189 at 1; Trial Tr. Day 3 (AM – Lapteva) at 53:24-54:5.*

166. ACAM2000 is not a water, crystalloid, or storage or preserving agent. *Trial Tr. Day 4 (PM – Yong) at 14:25-15:2.*

167. The approved method of administration of ACAM2000 is through percutaneous scarification in which the vaccine is delivered through the skin after a certain incision is made with a needle. *Trial Tr. Day 3 (AM – Lapteva) at 54:6-11; Ex. 189 at 1, 3.* ACAM 2000 "should not be injected by the intradermal, subcutaneous, intramuscular, or intravenous route." *Ex. 189 at 1, 3.*

168. Defendants used ACAM2000 through a different route of administration. Specifically, Defendants combined the Vaccinia Virus with SVF and administered it to patients intravenously. *Trial Tr. Day 3 (AM – Lapteva) at 54:11-13.*

169. Based upon the FDA-approved labeling for ACAM2000, intravenous use and delivery into the bloodstream is not an approved route of administration. *Trial Tr. Day 3 (AM – Lapteva) at 54:15-25; Ex. 189 at 1, 3.*

170. The FDA-approved labeling for Vaccinia Vaccine/ACAM2000 contains contraindications about not using the vaccine in people who are immunocompromised. People with advanced cancers are an immunocompromised population. Defendants treated patients with advanced cancers with ACAM2000. *Trial Tr. Day 3 (AM – Lapteva) at 54:24-55:4; Ex. 189 at 1, 3, 6.*

171. Defendants have promoted and used their SVF/Vaccinia product as a purported treatment for a variety of advanced-stage cancers. *Ans. ¶14; Trial Tr. Day 2 (AM – Forster) at 56:1-11; Ex. 11 at 20-24; Ex. 12 at 43; Ex. 33 at 33; Ex. 60 at 1; Ex. 65 at 1-2; see generally Ex. 48.*

172. The SVF/Vaccinia product was administered to patients intravenously or directly into patients' tumors. The SVF/Vaccinia product contained amounts of the vaccine that greatly exceeded the vaccine's labeled dose. *See Ans. ¶ 14; Ex. 8 at RFA*

¶ *22; Ex. 33 at 33.*

173. The ACAM2000 that Defendants used to manufacture their SVF/Vaccinia product was shipped in interstate commerce from the Centers for Disease Control ("CDC") in Georgia. *Ex. 77 at 2; Ex. 33 at 33; Ans. ¶ 15.*

174. Although Defendant Lander's request to the CDC represented that "the vaccine was needed for vaccination of employees conducting 'virus research,'" neither Defendant Lander nor or any his employees received a vaccination with the ACAM2000 received. *Ex. 77 at 2.*

iii. Defendants' CSCTC Products are Unapproved Drugs

175. Defendants are well aware that FDA—not the California State Medical Board—is the agency charged with regulating the approval of new drugs and treatments in the United States. *Trial Tr. Day 6 (AM – Berman) at 42:3-17; Ex. 33 at 15.*

176. Prior to the commercialization and marketing of a drug or biological product, a New Drug Application ("NDA") or Biologics License Application ("BLA") must be submitted to and approved by FDA. The application must include the information on the product's safety and efficacy necessary for FDA to make a determination as to whether product can be commercialized and marketed to patients. *Trial Tr. Day 1 (AM – Joneckis) at 41:9-23.*

177. There are not now, nor have there ever been, any approved new drug applications ("NDAs") filed with FDA pursuant to 21 U.S.C. § 355(b) or (j) for the CSCTC products.[17] *See also Ans. ¶ 19; Ex. 75 at 3; Trial Tr. Day 1 (AM – Joneckis) at 48:9-13, 49:8-23.*

178. 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 CSCTC

[17] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 8.

products.[18] *See also Ans. ¶ 19; Trial Tr. Day 1 (AM – Joneckis) at 48:9-18, 49:8-23; Ex. 75 at 3.*

179. None of the CSCTC products have been licensed or approved by FDA for any use.[19] *See also Ans. ¶ 18; Ex. 11 at 1, 5; Ex. 12 at 45; Ex. 26 at 11; Ex. 68 at 2-3.*

iv. Defendants' CSCTC Products Are Being "Studied" in Humans without Applicable FDA Oversight for Drugs

180. Defendants are well aware that FDA—not the California State Medical Board—is the government agency that "reviews all research and information for the approval of drugs and treatments for the public." *Trial Tr. Day 6 (AM – Berman) at 42:3-13, 43:1-18; Ex. 33 at 15.*

181. Prior to testing a drug or biological product in humans, the product sponsor is "required to file a regulatory submission so that [FDA] can review their information and make a determination as to whether [FDA] believe[s] it is safe to go ahead and study [the product] in human clinical studies." *Trial Tr. Day 1 (AM – Joneckis) at 38:14-23.*

182. For a drug or biological product, the sponsor is required to file an Investigational New Drug Application ("IND"). *Trial Tr. Day 1 (AM – Joneckis) at 38:23-25.*

183. Upon receipt of an IND, FDA reviews the sponsors' preclinical studies to assess the safety. FDA also reviews information related to the sponsor's proposed clinical trials—such as the qualification of the study's investigators—to make a determination of the overall risk of the product, and determine if it is safe to proceed in human trials. *Trial Tr. Day 1 (AM – Joneckis) at 39:1-14.*

184. Before initiating any human (*i.e.*, clinical) trials with an investigational drug

[18] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 9.

[19] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 7.

or biological product, a sponsor must have an approved (*i.e.*, effective) IND from FDA, as well as IRB approval.[20] IRB approval is obtained in addition to, not in lieu of, obtaining an effective IND from FDA for the study of the drug or biological product. *Trial Tr. Day 1 (AM – Joneckis) at 39:22-40:22; see also Ex. 33 at 15 (Defendants understand the distinct roles of FDA and IRBs).*

185. If FDA does not approve the IND, FDA places hold on the application on a "clinical hold" which prevents the product sponsor from conducting human trials. *Trial Tr. Day 1 (AM – Joneckis) at 46:1-12.*

186. INDs can be placed on hold for a variety of reasons. For example, FDA may not have sufficient information to assess the safety, or the relative potential benefit of the particular drug or biological product. Or FDA may feel the product is unsafe given the benefit-to-risk ratio. *See Trial Tr. Day 1 (AM – Joneckis) at 40:23-41:8.*

187. Although Defendants have had discussions with FDA concerning their desire to study the SVF/Vaccinia product pursuant to an IND under 21 U.S.C. § 355(i), no IND is currently in effect for that product or for any of Defendants' other CSCTC products.[21] *See also Ans. ¶ 20; Ex. 12 at 5; Ex. 77 at 1-2; Trial Tr. Day 1 (AM – Joneckis) at 48:3-8; 49:8-23.* All of the INDs that Defendants have submitted to FDA to date are on "clinical hold." *Trial Tr. Day 1 (AM – Joneckis) at 46:1-12, 46:24-47:11, 47:22-48:8.*

188. Defendants' CSCTC products have been associated with reports of adverse events in humans. Defendants' records show that a patient who received an "SVF surgical procedure" in her eyes from a CSN affiliate on or about September 8, 2016, reported a retinal detachment. *See generally Ex. 63; Ex. 8 at RFA ¶ 18.* Defendants subsequently told affiliates that SVF was no longer to be injected into patients' eyes. *Ex. 8 at RFA ¶ 19; Ex. 11 at 17; Trial Tr. Day 6 (AM – Berman) at 40:1-7 ("Our SVF product has had*

[20] An IRB is a review board whose assigned role is to protect the rights and welfare of the patients or subjects in the study. IRBs monitor the study and have the ability to deny, change, or modify the study. *Trial Tr. Day 1 (AM – Joneckis) at 40:5-16.*

[21] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 10.

very rare adverse events and the one significant adverse event - retinal detachment - was reported to the IRB and eliminated shortly thereafter."); Ex. 15 at 8, 16-17, 35; Ex. 16 at 1; Trial Tr. Day 6 (AM – Berman) at 26:2-27:9.

189. Dr. Berman has been interviewed in a number of public forums about this particular patient and the retinal detachments that ensued. In a 2017 interview with *The Atlantic*, Defendant Berman conceded that Defendants "should have waited longer to make sure there were no serious side effects after [the patient] was injected in the first eye." He was further quoted as saying, "That's a pretty good lesson learned. Unfortunately it was learned by doing them." *Trial Tr. Day 6 (AM – Berman) at 27:10-28:10.*

190. Defendants have continued to use disapproved equipment—namely, their SVF-processing device known as the CSN Time Machine—to manufacture the CSCTC products they administer to patients. *See generally Ex. 175; Def. Ex. 303; Ans. ¶ 10.*

191. There are not now, nor have there ever been, any approved Premarket Applications ("PMAs") for Defendants' Time Machine device authorizing Defendants to use the device to treat patients. *Trial Tr. Day 1 (AM – Joneckis) at 49:4-7; 49:8-23.*

192. There are not now, nor have there ever been, any 510(k) clearances for Defendants' Time Machine device, confirming that defendants could use that medical device in an investigation involving a human. *Trial Tr. Day 1 (AM – Joneckis) at 48:24-49:3, 49:8-23.*

193. There are not now, nor have there ever been, any approved Investigational Device Exemption applications ("IDEs") for Defendants' Time Machine device, which would authorize them to use that medical device in any research involving humans. *Trial Tr. Day 6 (AM – Joneckis) at 48:19-23, 49:8-23.*

194. Although Defendants submitted an IDE to use their Time Machine in human studies, FDA disapproved Defendants' application. In a disapproval letter dated June 14, 2017, FDA informed Defendants that because Defendants "ha[d] not fully addressed the issues cited in [FDA's] December 1st, 2016, and our March 8, 2017, letters," the agency "regret[s] to inform you that your application remains disapproved, and you may not begin

your investigation." *Ex. 175 at 1; Trial Tr. Day 6 (AM – Berman) at 43:19-45:1.*

195. Defendants are well aware that FDA has never changed its position on the regulatory status of the CSN Time Machine. Even as of the date of the bench trial in this matter, Defendants' CSN Time Machine remains disapproved. *Trial Tr. Day 6 (AM – Berman) at 45:2-7.*

E. Defendants Continued to Manufacture and Administer the CSCTC Products, Despite Knowing FDA's Position that They Violated the FDCA

i. Defendants Knew FDA's Position that the SVF Product Violated the FDCA

196. Prior to the July 2017 inspections, Defendants knew that a CSN affiliate had received a Warning Letter from FDA in December 2015 concerning the affiliate's preparation and administration of SVF.[22] *See also Ans. ¶ 5; Ex. 67 at 3-4 (Defendants know CSN affiliates all use the same training, methods, equipment, and protocols).*

197. Both during and following the July 2017 inspections, Defendants asserted to FDA that they did not manufacture drugs or biological products and that they were not subject to the FDCA.[23] *See also Ans. ¶ 61; Trial Tr. Day 2 (AM – Forster) at 51:1-16; see generally Exs. 69, 70.*

198. In response to Defendants' assertions, an FDA official reiterated the agency's position that the CSCTC products were not lawful and that Defendants' conduct must stop. In an October 2017 email, the FDA official informed Defendants that following a review of FDA's inspections, FDA had found that HCT/Ps manufactured from adipose tissue by CSCTC and CSN are drugs under the FDCA and biological products under the PHSA, and are subject to the statutory and regulatory requirements applicable to both products. The FDA official further informed Defendants that they did not qualify for any exception in 21 C.F.R. 1271.15, nor did their products meet all the criteria in 21 C.F.R. 1271.10(a) for

[22] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 11.

[23] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 12.

regulation solely under section 361 of the PHSA and regulations in 21 C.F.R. Part 1271. The FDA official told Defendants that in order to lawfully market their particular adipose tissue-derived HCT/Ps, a valid BLA would have to be in effect, and while still in the development stage, the products could only be used in humans if Defendants had an IND in effect. Notwithstanding Defendants' "fundamental problem with the regulations and how FDA applies them" and disagreement that SVF is drug, the FDA official informed Defendants that their "HCT/Ps from adipose tissue, nevertheless, are drugs and biological products . . . which you continue to market without premarketing authorization." *Trial Tr. Day 6 (AM – Berman) at 37:9-16, 38:6-39:16.*

ii. Defendants Knew FDA's Position that the SVF/Vaccinia Product Violated the FDCA

199. In August 2017, United States Marshals seized five vials of ACAM2000 that Defendants used to prepare their SVF/Vaccinia product for the purported treatment of cancer patients. *Ans. ¶ 63; Defs. Ex. 383; Trial Tr. Day 6 (AM – Berman) at 47:13-48:20.*

200. The Government filed a civil forfeiture action against the defendant vials of ACAM2000 on August 23, 2017. *Defs. Ex. 383 at 1.* Defendants were given notice of the seizure action. *Trial Tr. Day 5 (AM – Berman) at 48:2-9.*

201. During additional communications with FDA in August and October 2017, Defendants reiterated that they were not subject to the FDCA.[24] *See also Trial Tr. Day 6 (AM – Berman) at 36-40; see generally Exs. 69, 70.*

202. The only reason Defendants stopped offering the SVF/Vaccinia product is because FDA and California state health authorities worked together to embargo and seize the ACAM2000 that Defendants were using to make the treatment. *Trial Tr. Day 5 (PM – Berman) at 72:20-73:9; Trial Tr. Day 1 (AM – Defs.' Opening) at 17:10-18:11.* Put another way, but for the Government's efforts to limit Defendants' access to ACAM2000, including completion of a civil forfeiture action and initiation of this case, Defendants

[24] This fact was stipulated to by the parties ahead of trial. *See* Proposed Final Pre-Trial Conference Order (ECF No. 113-1 at 2-4), Stipulated Fact 13.

would have continued their human experimentation. *Compare Defs.' Proposed Finding of Fact 118 (ECF No. 124-1 at 22) (describing their SVF/Vaccinia product as an "experimental treatment") with Trial Tr. Day 4 (AM – Lapteva) at 17:22-18:11.*

203. The Government's seizure of ACAM2000 does not prevent Defendants from trying to obtain ACAM2000 again, or to combine SVF with any other live virus or vaccine. Rather it "remains [Defendants'] position that [they] can take something that is unapproved, like SVF, combine it with something that is approved, and use that to treat diseases and conditions"—all because they are doctors and/or conducting clinical research. *Trial Tr. Day 6 (AM – Berman) at 48:2-20.*

204. Although Defendants allegedly have no desire to resume the SVF/Vaccinia product without "proper regulatory approval in the future," *see Trial Tr. Day 5 (PM – Berman) at 73:10-13, Trial Tr. Day 6 (PM – Lander) at 103:21-24,* "they don't want to say, well, we'll never do this again" because their research and treatments change as "medicine evolves." *See, e.g., Trial Tr. Day 1 (AM – Defs.' Opening) at 17:18-18:7; Trial Tr. Day 5 (AM – Berman) at 105:25-107:1; Trial Tr. Day 6 (PM – Lander) at 68:4-22.*

iii. Defendants Knew FDA's Position that the Expanded SVF Product Violated the FDCA

205. To manufacture their Expanded SVF product, Defendants sent recovered adipose tissue to a third-party firm located outside of the State of California. The outside firm used enzymes and laboratory equipment, including a centrifuge and a filter, to produce SVF from the adipose tissue. It then cultured the SVF to expand it to a higher cell density. The Expanded SVF products subsequently were returned in interstate commerce to CSCTC Rancho Mirage and CSCTC Beverly Hills and administered to patients. *See Ans. ¶ 16; Ex. 8 at RFA ¶ 23; Trial Tr. Day 5 (PM – Berman) at 57:11-15; Trial Tr. Day 5 (AM – Jim) at 15:19-16:16; Trial Tr. Day 2 (AM – Forster) at 85:7-18; Ex. 30 at 1; Ex. 35; Ex. 37.*

206. But Defendants are well aware that, "[t]he collection, shipment, processing, storage and use of stored cells and tissues are regulated in the United States by the US

Department of Health and Human Services (HHS), the Food and Drug Administration (FDA) and State Health Departments." *Def. Ex. 429 at 1.*

207. Defendants also have long known that cell culturing constitutes drug manufacturing that is subject to FDA regulation. In their book *The Stem Cell Revolution*, Defendants Berman and Lander wrote, "What CSCTC definitely does not do is culture cells to increase their strength in numbers. We cannot by law. Although, cell culturing is currently par for the course in Spain, Russia, Sweden, Asia and offshore, here in the United States if you grow . . . cells, then by definition you become a drug manufacturer. And at that point you're under the auspices of the FDA." *Trial Tr. Day 7 (PM – Lander) at 28:1-21; see also Ans. ¶ 60; Ex. 75 at 3-4.*

208. In January 2018, FDA sent a Warning Letter to the third-party New Jersey firm that supplied Defendants with expanded cells for use in the Expanded SVF product. FDA's 2018 Warning letter to the contract manufacturer explained that FDA approvals were required for the expanded SVF products and identified evidence of significant CGMP violations.[25] *See generally Ex. 90.*

209. Defendants did not stop manufacturing and administering the Expanded SVF product, even after their New Jersey contract manufacturer received the Warning Letter. After the New Jersey firm's attorneys advised it not to release any more expanded cells, Defendants redirected their patients to an alternative source for expanded cells, namely from a Florida company called U.S. Stem Cell. *Trial Tr. Day 6 (AM – Berman) at 49:19-52:6.* When a federal court in the Southern District of Florida later enjoined U.S. Stem Cell from manufacturing its adipose tissue-derived SVF products,[26] the Florida company

[25] Whether Defendants' previous New Jersey contract manufacturer allegedly has since obtained an effective IND is a red herring. It is undisputed that the Defendants in this case do not have any effective INDs, *see Stipulated Fact 10*, and FDA witness Dr. Christopher Joneckis confirmed that IND approval only permits *the sponsor of the IND*—not other third parties—to proceed with clinical studies. *Trial Tr. Day 1 (AM – Joneckis) at 77:25-78:10.* Moreover, the contract manufacturer's voluntary compliance with the FDCA neither prevents nor excuses Defendants' violations of the same.

[26] *United States v. U.S. Stem Cell Clinic, LLC*, 403 F. Supp. 3d 1279 (S.D. Fla. 2019), *aff'd*, 19-13276, --- F.3d ---, 2021 WL 2213288 (11th Cir. June 2, 2021).

promptly sold its stem cell-related inventory to American Cell Technology ("ACT")—a newly formed Florida company managed by Defendant Berman's son, Sean Berman, who serves as CSCTC's Director of Scientific Research and CSN's Head of Operations. *Trial Tr. Day 6 (AM – Berman) at 52:7-17; Ex. 12 at 13; Ex. 11 at 9.*

210. According to Defendants, CSN is currently working with ACT to treat COVID-19 patients pursuant to a CSN protocol. *Trial Tr. Day 6 (AM – Berman) at 52:18-21.* The CSN protocol, titled "Clinical Efficacy of Autologous Stromal Vascular Fraction SVF or Autologous Laboratory Expanded Mesenchymal Stem Cells (MSCs) for Acute COVID-19 Infection," calls for the use of "autologous MSCs previously expanded and prepared at American Cell Technology." *See generally Ex. 154 at 9, 3.*

211. On cross-examination, Defendant Lander confirmed that Defendants intend to keep manufacturing and administering the Expanded SVF product, even in the absence of FDA approval. *Trial Tr. Day 7 (PM – Lander) at 26:3-27:24.*

IV. CONCLUSIONS OF LAW

A. Jurisdiction and Venue Are Established

1. The Court has jurisdiction over the parties and the subject matter of this action pursuant to 21 U.S.C. § 332(a) and 28 U.S.C. §§ 1331, 1337, and 1345.

2. Venue in this district is proper under 28 U.S.C. §§ 1391(b) and (c).

B. Defendants and their CSCTC Products are Subject to FDA Regulation

i. The CSCTC Products are Drugs under the FDCA

3. The Federal Food, Drug, and Cosmetic Act ("FDCA") defines a drug as any "article," or component thereof, 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 animals." *See* 21 U.S.C. § 321(g)(1)(B), (C), and (D). The intended use of a product may be shown, *inter alia*, by how the product is promoted in its labeling and marketing. 21 C.F.R. § 201.128; *Action on Smoking & Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980); *United States v. Lane Labs USA, Inc.*, 324 F. Supp. 2d 547, 566-67 (D.N.J. 2004), *order modified*, 328 F. Supp. 2d 520 (D.N.J. 2004), *aff'd*, 427

F.3d 219 (3d Cir. 2005); *United States v. U.S. Stem Cell Clinic, LLC*, 403 F. Supp. 3d 1279, 298-99 (S.D. Fla. 2019), *aff'd*, 19-13276, --- F.3d ---, 2021 WL 2213288 (11th Cir. June 2, 2021).

4. The CSCTC products are "drugs" within the meaning of the FDCA, 21 U.S.C. § 321(g)(1)(B) and (C), because Defendants promote the CSCTC products to the public for treating a wide range of serious diseases and conditions in a variety of contexts. Defendants' records, public statements, and information contained on Defendants' websites and elsewhere establish that the CSCTC products are intended to be used in the treatment or mitigation of diseases in man and/or to affect the structure or function of the body. *See* Proposed Findings of Fact ¶¶ 96-108.

5. Because Defendants' "intended use" of the CSCTC products is to treat or mitigate a variety of diseases and medical conditions, or to affect the structure or any function of the body, the CSCTC products are "drugs" under the FDCA and are subject to the FDCA's adulteration and misbranding provisions. *See* 21 U.S.C. §§ 351, 352; 21 C.F.R. § 1271.20; Final Rule Concerning Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5447, 5449 and 5456 (Jan. 19, 2001) (to be codified at 21 C.F.R. Part 1270).

6. The CSCTC products are "prescription drugs" within the meaning of 21 U.S.C. § 353(b)(1)(A) because, due to their toxicity or other potentiality for harmful effect, or the method of their use, or the collateral measures necessary to their use, they are not safe for use except under the supervision of a practitioner licensed by law to administer such drug. *See* Proposed Findings of Fact ¶¶ 111-112.

7. The CSCTC products are "new drugs" within the meaning of 21 U.S.C. § 321(p), because they are not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in their labeling. *See* Proposed Findings of Fact ¶¶ 109-110.

ii. The CSCTC Products are Biological Products under the PHSA

8. FDA's Center for Biologics Evaluation and Research ("CBER") is responsible for regulating the safety, purity, and potency of human biological products, often referred to as "biologics" for short.[27] *See* Proposed Finding of Fact ¶ 113.

9. Biological products are comprised of living organisms or things produced by a living organism, such as "vaccines, blood and blood components, cellular therapies, gene therapies, proteins, [and] things of that nature, among other products." *See* Proposed Finding of Fact ¶ 114.

10. The CSCTC products are "biological products" within the meaning of the Public Health Service Act ("PHSA"), 42 U.S.C. § 262(i), because each is a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings."[28]

iii. The CSCTC Products are HCT/Ps under Regulations issued pursuant to the PHSA

11. 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 C.F.R. § 1271.3(d). The CSCTC products are "human cells, tissues, or cellular or tissue-based products" (*i.e.*, HCT/Ps) under FDA regulations promulgated pursuant to the PHSA. The adipose tissue Defendants remove from patients to produce their CSCTC products is an HCT/P. 21 C.F.R. § 1271.3(d); *U.S. Stem Cell Clinic (11th Cir.)*, --- F.3d ---, 2021 WL 2213288 at *5 ("both adipose tissue and stromal-vascular fraction are HCT/Ps").

12. The CSCTC products are intended for autologous use, which refers to the "implantation, transplantation, infusion, or transfer of human cells or tissue back into the

[27] https://www.fda.gov/about-fda/fda-organization/center-biologics-evaluation-and-research-cber.

[28] Section 262 of Title 42 of the United States Code corresponds to "section 351" of the PHSA.

individual from whom the cells or tissue were recovered." *See id.* § 1271.3(a).

C. The CSCTC Products are Regulated under both the FDCA and the PHSA, and Must Comply with FDCA Adulteration and Misbranding Prohibitions

13. 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"); *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).

14. Because the CSCTC products are drugs under the FDCA and are biological products under section 351 of the PHSA, they are subject to the provisions of both statutes, including the FDCA's adulteration, misbranding, and premarket approval requirements. *See* 21 U.S.C. §§ 351, 352; 21 C.F.R. § 1271.20.

D. The CSCTC Products are Adulterated under the FDCA

15. A drug shall be deemed 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 current good manufacturing practice 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).

16. FDA's current good manufacturing practice ("CGMP") requirements for drugs are set forth in regulations codified in 21 C.F.R. Parts 210 and 211, *inter alia*.

17. Failure to comply with even one CGMP regulation renders the drugs legally adulterated. *United States v. 789 Cases, More or Less, of Latex Surgeons' Gloves*, 799 F. Supp. 1275, 1287 (D.P.R. 1992); *see United States v. Undetermined Quantities . . . Proplast II*, 800 F. Supp. 499, 502 (S.D. Tex. 1992) (finding that substantial compliance with CGMP is not sufficient if FDA determines that full compliance is necessary).

18. At trial, four FDA investigators with a collective eight decades of experience

in conducting inspections and evaluating facility design, operation, manufacturing, and testing procedures testified about Defendants' multiple violations of CGMP, including but not limited to their failure to aseptically process their drugs to prevent microbiological contamination or test the products for sterility and for the presence of endotoxins which can cause fevers and other health complications, as well as their failure to adequately investigate adverse events. Defendants did not dispute the accuracy of the FDA investigators' observations, but rather argued that they should not have to comply with CGMP. *See* Proposed Findings of Fact ¶¶ 123-150.

19. Because Defendants do not manufacture the CSCTC products in a manner that conforms to CGMP, the CSCTC products are adulterated within the meaning of the FDCA, 21 U.S.C. § 351(a)(2)(B).

E. The CSCTC Products are Misbranded under the FDCA

20. Defendants' CSCTC products also run afoul of several of the FDCA's misbranding prohibitions.

21. First, the CSCTC products are misbranded within the meaning of the FDCA, 21 U.S.C. § 352(f)(1), because they are drugs and their labeling fails to bear adequate directions for use and because they are not exempt from the requirements of 21 U.S.C. § 352(f)(1). As the Government's expert Dr. Larissa Lapteva explained, the CSCTC drug products do not bear adequate directions for use for three different reasons, any one of which is sufficient to establish misbranding: *(a)* the CSCTC drug products do not bear labeling that contains information required for adequate directions for use, as defined in 21 C.F.R. § 201.5; *(b)* the CSCTC drug products are unapproved prescription drugs that are not excepted from labeling regulations requiring directions under which a lay person can use the drug safely; and *(c)* it is currently impossible to draft adequate directions for use because there is no scientifically valid evidence to show that the CSCTC products are safe or effective for any indication (*i.e.*, intended use). *See* Proposed Findings of Fact ¶¶ 151-159.

22. The CSCTC products are further misbranded within the meaning of the

FDCA, 21 U.S.C. § 353(b)(4), because they are prescription drugs and, at times prior to dispensing, their labels fail to bear, at a minimum, the "Rx only" symbol. *See* Proposed Findings of Fact ¶ 151.

23. The SVF/Vaccinia product—which Defendants have used to purportedly treat cancer patients—is additionally misbranded within the meaning of the FDCA, 21 U.S.C. § 352(j), because it is "dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. § 352(j); *see also United States v. 62 Packages, More or Less, of Marmola Prescription Tablets*, 142 F.2d 107, 110 (7th Cir. 1944) (Section 352(j) does not require that the drug be dangerous to the health of all the patients who take it as prescribed or recommended, but only that it be "dangerous to the public health at large if used as recommended by its vendors"). Here, Defendants' unauthorized experiment treating cancer patients with an unproven product containing live vaccinia virus not only put the patients at risk, but also represented a risk to the public health because people in close contact with those patients could have been infected with live virus. *See* Proposed Findings of Fact ¶¶ 160-174.

F. Defendants Cause the Adulteration and Misbranding of the CSCTC Products (*i.e.*, Drugs) in Violation of Section 331(k) of the FDCA

i. The CSCTC Products are Drugs that are "Held for Sale" within the Meaning of Section 331(k)

24. The heart of the FDCA's enforcement provisions is codified at 21 U.S.C. § 331, which enumerates specific prohibited acts.

25. 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).

26. A drug is "held for sale" if it is used for any purpose other than personal consumption. *Regenerative Scis.*, 741 F.3d at 1320 (rejecting a narrow reading of 21 U.S.C. § 331(k), as at odds with "a statutory scheme designed to regulate the safety of

drugs at every stage of their distribution"); *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)]."); *U.S. Stem Cell Clinic*, 403 F. Supp. 3d at 1298 n.11.

27. The Ninth Circuit has clarified that a drug or device used in treatment of a patient is "held for sale" as long as there is a commercial relationship between the doctor and the patient and the product is one that is meant to be "consumed" in the process. *United States v. Kaplan*, 836 F.3d 1199, 1209-10 (9th Cir. 2016) (holding that a physician's use of a medical device on a patient is covered by the FDCA phrase "held for sale" because the single-use device was "meant to be 'consumed' in the course of treating a patient—just like a drug").

28. A "sale in the strict sense" does not have to occur to bring a physician within the reach of section 331(k). *Kaplan*, 836 F.3d at 1209 (rejecting appellant doctor's argument that he had not sold the devices to his patients, but merely used them on patients "during the conduct of his medical practice"). The Ninth Circuit rejected the argument that "held for sale" must be interpreted narrowly—and cannot be read to mean "held for use" by a practicing physician—because it was "in direct contravention to out-of-circuit caselaw stating that a physician's *use* of a device on a patient is covered by the statutory phrase 'held for sale.'" *Id.* (emphasis added).[29] Accordingly, section 331(k)'s "held for sale" analysis does not focus narrowly on whether a physician charges for the device (or drug) consumed in the course of treating the patient, but focuses "more generally on the

[29] *See Kaplan*, 836 F.3d at 1209 (citing *Evers*, 643 F.2d at 1050); *see also Diapulse Corp.*, 514 F.2d at 1098 ("Such devices, used in the treatment of patients, may properly be considered 'held for sale' within the meaning of the [FDCA], 21 U.S.C. § 331(k)."); *United States v. Rhody Dairy, L.L.C.*, 812 F. Supp. 2d 1239, 1244 (W.D. Wash. 2011) ("[S]everal cases have held that drugs and devices used in the treatment of patients are 'held for sale' by doctors as part of the distribution process."); *United States v. Device Labeled "Cameron Spitler Amblyo-Syntonizer"*, 261 F. Supp. 243, 246 (D. Neb. 1966) (holding that a physician was not exempt from the requirements of the FDCA when he used misbranded devices in the treatment of his patients even though he did not sell the devices in the commercial sense).

commercial nature of the transaction, actors, and products" at issue. *See id.*

29. Here, Defendants' CSCTC products are "held for sale" within the meaning of section 331(k). Defendants are practicing physicians engaged in the business of providing the CSCTC products to patients to treat a variety of diseases and conditions, including but not limited to cancer, arthritis, stroke, multiple sclerosis, macular degeneration, and Parkinson's disease. Many patients pay thousands of dollars to receive a single CSCTC product, and some patients pay much more to receive multiple treatments—a practice that Defendants have referred to as "patient-funded research." *See* Proposed Findings of Fact ¶ 24. Defendants are commercial actors who market and offer their CSCTC products to patients for commercial purposes other than Defendants' own personal consumption, thereby rendering the CSCTC products "held for sale" within the meaning of section 331(k) of the FDCA.

ii. The CSCTC Products are Drugs that are Held for Sale "After Shipment in Interstate Commerce" within the Meaning of Section 331(k)

30. Evidence adduced at trial shows that Defendants' CSCTC products (which are drugs) satisfy section 331(k)'s "after shipment in interstate commerce" requirement because at least one component of the CSCTC products (*e.g.*, 0.9% Sodium Chloride Injection, USP, better known as "saline") has traveled in interstate commerce. *See* Proposed Findings of Fact ¶ 43¶ X, X. Moreover, "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).

31. Defendants' CSCTC products contain multiple components shipped from other states. Components received from outside of California that Defendants use in the preparation and administration of the CSCTC products include saline and 5% Dextrose in Lactated Ringer's Injection, both of which originate outside the State. Defendants' manufacturing process also involves a collagenase-containing enzyme product (also

known as CSN TMAX) made in Indiana. The Vaccinia Vaccine, Live (also known as ACAM2000) used to manufacture the SVF/Vaccinia product was shipped in interstate commerce from Georgia. And components of Defendants' Expanded SVF product came from a firm in New Jersey. *See* Proposed Findings of Fact ¶¶ 43, 173, 205.

32. The movement in interstate commerce of even a single component of a CSCTC product—let alone multiple components—is sufficient to render the product "held for sale after shipment in interstate commerce" within the meaning of the FDCA. Nevertheless, Defendants contend that the interstate commerce nexus is not satisfied because only the SVF component of the CSCTC products is relevant, and the SVF itself is not shipped in interstate commerce after being isolated from patients' adipose tissue. *See, e.g.*, Defs.' Mem. Contentions of Facts and Law, ECF No. 108 at 22; Defs.' Trial Br. at 4:12-13. This contention conflicts with both the plain language of the statute and decades of case law.

33. The FDCA defines "drug" to include components of a drug, 21 U.S.C § 321(g)(1)(D), and courts consistently have interpreted sections 331(k) and 321(g)(1)(D) to mean that not every drug ingredient has to be transported interstate to establish a violation of section 331(k). *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"); *Regenerative Scis.*, 741 F.3d at 1320. Section 321(g)(1)(D)'s reference to "component" is not restricted and includes more than just the drug's active ingredient or ingredients. Moreover, FDA regulations define "component" broadly to mean "*any* ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product." *See* 21 C.F.R. § 210.3(b)(3) (emphasis added).[30]

34. The final drug product (here, the CSCTC products) need not have been

[30] Thus, the Government would satisfy the interstate commerce requirement of section 331(k) even under Defendants' inapt interpretation because the collagenase-containing enzyme product (*i.e.*, CSN TMAX) that is essential to their processing of the CSCTC products was obtained from a source outside of California.

shipped in interstate commerce in completed form to satisfy section 331(k)'s "after shipment in interstate commerce" requirement. Rather "the 'shipment in interstate commerce' requirement is satisfied even when only an ingredient is transported interstate." *Baker*, 932 F.2d at 814-15; *United States v. Dianovin Pharms., Inc.*, 475 F.2d 100, 103 (1st Cir. 1973); *Regenerative Scis.*, 741 F.3d at 1320-21; *U.S. Stem Cell Clinic*, 403 F. Supp. 3d at 1298 n.11; *cf.* 21 U.S.C. § 321(g)(1)(D) (defining "drug" to include components of a drug for purposes of the FDCA). When even one of a drug's components has been shipped in interstate commerce, using that component to manufacture an article of drug that is or becomes adulterated or misbranded violates 21 U.S.C. § 331(k). *See Dianovin Pharms.*, 475 F.2d at 103.

35. Likewise unavailing is Defendants' argument that applying the FDCA violates the Commerce Clause of the U.S. Constitution because Defendants perform their purported procedures within the state of California. Even if the inquiry were limited only to particular procedures, the Supreme Court has confirmed Congress's authority to regulate even "purely local activities that are part of an economic class of activities that have a substantial effect on interstate commerce." *Gonzales v. Raich*, 545 U.S. 1, 17 (2005) (internal quotations and citations omitted); *cf.* 21 U.S.C. § 379a; *see Chung's Prods.*, 941 F. Supp. 2d at 795.

36. When the D.C. Circuit confronted this very issue in *Regenerative Sciences*, it found that even where the purported medical procedure "occur[ed] entirely within the state," the cellular product nonetheless had "sufficient connection to interstate commerce to permit federal regulation under the Commerce Clause." *Regenerative Scis.*, 741 F.3d at 1314, 1320.

37. Both the constitutional and statutory requirements for interstate commerce are satisfied here, as Defendants manufacture their CSCTC products using at least one component shipped in interstate commerce, such as 0.9% Sodium Chloride Injection, USP (*i.e.*, saline), from outside of California.

38. Accordingly, Defendants violate 21 U.S.C. § 331(k) by causing the adulteration of CSCTC products within the meaning of 21 U.S.C. § 351(a)(2)(B), while they are held for sale after shipment of one or more of their components in interstate commerce.

39. Defendants also violate 21 U.S.C. § 331(k) by causing the misbranding of CSCTC products within the meaning of 21 U.S.C. §§ 352(f)(1), 352(j), and 353(b)(4), while they are held for sale after shipment of one or more of their components in interstate commerce.

iii. Defendants' Expanded SVF Product (or Components Thereof) are Misbranded Drugs that are Received in Interstate Commerce and Delivered for Pay or Otherwise in Violation of Section 331(c)

40. Section 331(c) prohibits the receipt in interstate commerce of any drug that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.

41. Here, Defendants' Expanded SVF product is a drug made from a component—namely, expanded cells—that Defendants receive from a third-party firm outside of California. The Expanded SVF product is misbranded because it lacks adequate directions for use and lacks the "Rx only" symbol, *supra*. Defendants deliver the misbranded Expanded SVF product to their patients who pay them for their services. *See* Proposed Findings of Fact ¶¶ 27, 151-159, 205.

42. Defendants CSCTC, Berman, and Lander violate 21 U.S.C. § 331(c) by receiving drugs (or components thereof) that are misbranded within the meaning of 21 U.S.C. §§ 352(f)(1) and 353(b)(4) in interstate commerce and delivering or proffering for delivery such drugs for pay or otherwise.

G. Defendants Have No Legally Valid Defense to their Violations of the FDCA's Adulteration and Misbranding Prohibitions in Sections 331(k) and (c)

i. Defendants Failed to Meet their Burden to Prove that their Establishments Qualify for the SSP Exception in 21 C.F.R. § 1271.15[31]

43. Defendants erroneously contend that they qualify for the SSP exception, which provides that establishments that remove HCT/Ps from an individual and implant *such* HCT/Ps into the same individual during the same surgical procedure are not subject to FDA's Part 1271 regulations. *See* 21 C.F.R. 1271.15(b).

44. Issued pursuant to the PHSA, the Part 1271 regulations create an electronic registration and listing system for certain establishments that manufacture HCT/Ps and establish donor-eligibility, current good tissue practice requirements, and other procedures to prevent the introduction, transmission, and spread of communicable diseases by HCT/Ps. *See* 21 C.F.R. § 1271.1(a).

45. Part 1271 regulations recognize that HCT/Ps are subject to one of two tiers of FDA regulation based on the risk they pose to public health, either:

- *(1)* HCT/Ps (such as Defendants' CSCTC products) that are regulated as drugs and biological products under the FDCA and PHSA that are subject to premarket approval requirements as well as various regulatory requirements (such as the FDCA's CGMP regulations in Parts 210 and 211, and the PHSA's HCT/P regulations in Part 1271, etc.). *See* 21 C.F.R. § 1271.1(c); *see also id.* § 1271.20;

or

- *(2)* HCT/Ps that are regulated solely under "section 361" of the PHSA, (which is codified at 42 U.S.C. § 264) and the Part 1271 regulations, because

[31] The Government does not concede that the SSP exception is a defense to Defendants' violations of the FDCA's adulteration and misbranding provisions under the facts of this case. But even if it were, Defendants' establishments do not qualify for the SSP exception as a factual or legal matter.

they meet all four regulatory criteria described in 21 C.F.R. § 1271.10. *See id.* § 1271.1(b).

46. Part 1271 regulations also identify five types of establishments that are excepted from complying with all Part 1271 requirements, namely:

- (1) establishments that use HCT/Ps *solely* for nonclinical scientific or educational purposes;
- (2) carriers that accept, receive, carry, or deliver HCT/Ps in the usual course of business as a carrier;
- (3) establishments that only recover reproductive cells or tissue and immediately transfer them into a sexually intimate partner of the cell or tissue donor;
- (4) establishments that do not recover, screen, test, process, label, package, or distribute, but *only* receive or store HCT/Ps solely for implantation, transplantation, infusion, or transfer within their facility; and
- (5) establishments that remove HCT/Ps from an individual and implant *such* HCT/Ps into the same individual during the same surgical procedure.

See 21 C.F.R. § 1271.15(a)-(e) (emphases added).

47. None of section 1271.15's narrow exceptions to Part 1271 compliance apply to Defendants' establishments.

48. As noted above, Defendants' CSCTC products are drugs subject to the FDCA. Although Defendants assert that their violations of the FDCA are purportedly acceptable under the SSP exception in section 1271.15(b), their arguments are unavailing.

49. Section 1271.15(b) unambiguously describes the limited circumstances wherein an establishment can avail itself of the SSP 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[32] from an individual

[32] "HCT/P" distinguishes between tissues and cells and is 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 C.F.R. § 1271.3(d). Here, the HCT/P that

> and implants *such* HCT/P's into the same individual during the same surgical procedure.

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

50. Applying traditional tools of construction, including the rule that all words be given effect, *First Charter Financial Corp. v. United States*, 669 F.2d 1342, 1350 (9th Cir. 1982), the phrase "such HCT/P's" makes clear that the HCT/P implanted in the patient must be the HCT/P in the form removed from the patient for the SSP exception to apply. Put another way, section 1271.15(b) does not apply where the HCT/P ultimately implanted in an individual is not "such" HCT/P that had been removed from that individual. *See U.S. Stem Cell Clinic (11th Cir.)*, --- F.3d ---, 2021 WL 2213288 at *6 ("the plain text of the regulation suggests that 'such HCT/Ps' must be in their original form (rather than subjected to extensive processing)").

51. Defendants' establishments do not qualify for the SSP exception because Defendants remove from patients one HCT/P—*i.e.*, adipose tissue—and following processing implant a different HCT/P—*i.e.*, a cellular product containing SVF combined with other drug components such as saline or vaccinia vaccine.[33] As a factual matter, there

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is removed from the individual is adipose tissue. The individual then leaves the room (and sometimes even leaves the premises) while Defendants subject the removed adipose tissue to extensive chemical and mechanical processing to manufacture a cellular product they refer to as "liquid magic," or SVF. *See* Proposed Findings of Fact ¶¶ 29-30, 64, and 97.

[33] Defendants erroneously contend that the Government's interpretation means that cells could never qualify for the SSP exception because they are always removed from a larger system, even though the definition of "HCT/P" includes cells. But Defendants are wrong for two reasons. First, as the Government's expert Dr. Carolyn Yong confirmed, it *is* possible to remove cells from an individual without removing other parts of the individual's body. *See* Trial Tr. Day 4 (PM – Yong) at 18:2-10 (noting that a human ovocyte [*sic* – oocyte] is one such example of such a cell that can be removed). Second, FDA has addressed this issue by excluding many cells from the definition of HCT/P, such as "cell factors," "cells derived from animals" and "blood components." *See US Stem Cell Clinic*, 403 F. Supp. 3d at 1290 n.6, *aff'd*, 19-13276, ---F.3d ---, 2021 WL 2213288 (11th Cir. June 2, 2021) (citing 21 C.F.R. § 1271.3(d)(1)-(8)). Here, the Government's interpretation of the SSP exception is the only one that accords with the facts of this case – and the only one that distinguishes between tissues and cells, thereby giving effect to all the words in the definition of an HCT/P. *See First Charter*, 669 F.2d at 1350.

is no question that Defendants remove adipose tissue from their patients. And Defendants admit that the SVF they implant is not adipose tissue. Defendants' manufacturing process fundamentally alters the adipose tissue that they removed from the patient,[34] and further alters the physical and biological characteristics of the cells originally contained in the tissue.[35] In short, "such HCT/P" is not being implanted. *See* Proposed Findings of Fact ¶¶ 29-42, 44-61, and 62-95.

52. "[S]uch HCT/P's" means HCT/Ps in the form removed from the body. *U.S. Stem Cell Clinic (11th Cir.)*, --- F.3d ---, 2021 WL 2213288 at *6; *U.S. Stem Cell Clinic*, 403 F. Supp. 3d at 1288-89 (emphasis added) (finding "the text of § 1271.15(b) unambiguously supports the FDA's interpretation that 'such HCT/P's' refers to the antecedent HCT/P removed from the patient in its original form."). The SSP exception may apply to establishments where adipose tissue is removed from a patient, and "such" adipose tissue is then returned to the same patient in the same surgical procedure. For example, where a surgeon removes adipose tissue from one part of a patient's body and returns the tissue to another part of the patient's body for reconstructive purposes (*i.e.*, for facial or breast augmentation). But it does not apply where, as here, adipose tissue is removed from a patient, the tissue is enzymatically digested to destroy its structural components, and then centrifuged and filtered to isolate a collection of free-floating cells and cell debris which (unlike adipose tissue) does not contain adipocytes or an

[34] As the Government's expert Dr. Carolyn Yong explained, adipose tissue contains adipocytes and an extracellular matrix that gives the tissue structure. Defendants remove adipose tissue and subject it to extensive chemical and mechanical processing. Defendants then administer to patients a solution made up of various types of free-floating cells and cell debris, drug components such as saline or ringer's injection, and any processing components left behind from the destruction of the adipose tissue. *See* Proposed Findings of Fact ¶¶ 29-42, 44-61. *See also* Proposed Findings of Fact ¶¶62-95. The text of the SSP exception does not contemplate this kind of transformation of the HCT/P removed.

[35] The Court instructed the Government to present evidence regarding "whether the SVF Procedure alters the SVF cells" at trial. *See* fn.15, *supra* (citing ECF No. 84 at 13). Even if the Court were to find that the SVF cells (*i.e.*, not adipose tissue) are the relevant "HCT/P," for purposes of its section 1271.15(b) analysis, Defendants still do not implant "such HCT/P" that was removed from their patients.

extracellular matrix. Proposed Findings of Fact ¶¶ 29-42, 44-61. *See also* Proposed Findings of Fact ¶¶ 62-95.

53. Ignoring the plain text of the regulation, Defendants claim the SSP exception applies because they allegedly return certain adipose tissue-derived cells back into the patient's body. However, Defendants overlook the changes effected by their extensive chemical and mechanical processing of the adipose tissue they removed. In addition to violating the rules of statutory construction by rendering meaningless the word "such," Defendants' selective application of the SSP exception would swallow the rule, with serious public health consequences here and in future cases.[36] Moreover, the broad interpretation of "such HCT/P's" offered by Defendants was recently rejected by the 11th Circuit:

> The regulation exempts only establishments that remove HCT/Ps from a patient and implant "such HCT/Ps" back into the same patient. As the district court in this case correctly explained, the word "such" in legal documents is typically used to refer back to an antecedent. *See* 403 F. Supp. 3d at 1288-89. Here, this means the HCT/Ps implanted must be the same as the antecedent HCT/Ps – that is, the HCT/Ps that were removed. If significant processing steps expose the HCT/Ps to foreign substances and alter their form prior to reimplantation, then the HCT/Ps cease to be the same as they were at the time of removal.

[36] The Government construes the phrase "such HCT/Ps" consistent with the plain language, the structure and regulatory history of Part 1271, and Congressional and regulatory intent, as courts must. *See Kisor v. Wilkie*, 139 S. Ct. 2400, 2415-16 (2019) (requiring courts to exhaust all traditional tools of construction before concluding that a rule is ambiguous); *U.S. Stem Cell Clinic (11th Cir.)*, --- F.3d ---, 2021 WL 2213288 at * (applying *Kisor* and finding 21 C.F.R. § 1271.15 unambiguous). But even if this Court were to find the phrase ambiguous, 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)*; Kisor,* 139 S. Ct. at 2417-19.

> This interpretation seems, at the outset, to be the more natural of the two readings.

U.S. Stem Cell Clinic (11th Cir.), --- F.3d ---, 2021 WL 2213288 at *5.

54. Here, Defendants' "unnatural" interpretation of the SSP exception would allow an establishment to remove any tissue from any part of a patient, perform any number and type of manufacturing steps on that tissue in relation to any purported surgical procedure (regardless of the public health risk associated with any of those steps), inject the end product into any part of the patient, and then invoke the SSP exception as long as the end product contained one or more cells that were present in the original tissue—no matter how wildly different the end product might be. But Defendants are wrong, as the phrase "such HCT/P" in the SSP exception does not mean "any HCT/P."

55. Moreover, the opinions on cell alteration proffered by defense expert, Lola M. Reid, Ph.D., are inherently unreliable. Proposed Findings of Fact ¶¶ 88-95. Expert opinions that merely parrot another expert must be discounted. *See, e.g.*, *Abrams v. Ciba Specialty Chem. Corp.*, No. 08-cv-0068-WS-B, 2010 WL 779283, *4 & n.9 (S.D. Ala. Mar. 2, 2010) (excluding opinion of expert that merely "served as a conduit" for another undisclosed expert). The wide latitude afforded an expert's basis for their opinion under Rule 703 does not allow an expert to simply adopt the opinion of another or vouch for its truth absent that expert's own analysis. *See K&N Eng'g, Inc v. Spectre Performance*, No. EDCV 09-1900VAP (DTBx), 2011 WL 13131157, at *10 (C.D. Cal. May 12, 2011) (citation omitted); *see also Villagomes v. Lab. Corp. of Am.*, No. 2:08-cv-00387-RLH-GWF, 2010 WL 4628085 at *4 (D. Nev. Nov. 8, 2010) (citations omitted) (Rule 703 "is not a license for an expert witness to simply parrot the opinions of non-testifying experts.")

56. Accordingly, Defendants did not—and cannot—meet their burden of establishing that the § 1271.15(b) exception to "the requirements of [21 C.F.R. Part 1271]" applies here. *See* 21 C.F.R. § 1271.15(b); *United States v. Regenerative Scis., LLC*, 741 F.3d 1314, 1322 (D.C. Cir. 2014) (citing *United States v. First City Nat'l Bank of Houston*, 386 U.S. 361, 366 (1967); *FTC v. Morton Salt Co.*, 334 U.S. 37, 44-45 (1948); *Harry C.*

Crooker & Sons v. Occupational Safety and Health Review Comm'n, 537 F.3d 79, 85 (1st Cir. 2008).

ii. Defendants' Claim that They Lacked "Adequate Notice" of the Inapplicability of the SSP Exception is Unreasonable and Unfounded

57. Defendants' sole purported affirmative defense suggests that the Government's case is based on an alleged "new interpretation" of the SSP exception that they consider "arbitrary and capricious."[37] *See* Defs.' Mem. Contentions of Fact and Law, ECF No. 108 at 21-22. This argument lacks merit.

58. Even if inadequate notice were an affirmative defense to selling adulterated and misbranded drugs that pose a risk to public health—which it is not—Defendants have had years of notice (in addition to the text of the regulation itself) that the SSP exception would not apply to them.

59. Defendants' claim that they were unfairly surprised by the Government's assertion that their establishments do not qualify for the SSP exception is both unreasonable and unfounded. The FDA regulations, FDA guidance, and recent court cases involving very similar products all set out a consistent position. *See U.S. Stem Cell Clinic (11th Cir.)*, --- F.3d ---, 2021 WL 2213288 at *5 ("FDA's view is all the more persuasive because it is consistent with its early (as well as its recent) pronouncements"). Moreover, Defendants' past statements and conduct confirm that they were personally aware that the SSP exception would not apply to their CSCTC products.

60. Consistent with the final text of the SSP exception, the regulatory history of

[37] To the extent Defendants are claiming that this case violates the Administrative Procedure Act ("APA"), Defendants did not bring an APA case, or even file a counterclaim under the APA. Furthermore, the APA is not a defense, but is an independent cause of action where, under circumstances not present here, a reviewing court may "hold unlawful and set aside agency action" found to be arbitrary and capricious. *See* 5 U.S.C. §§ 704, 706(2); *Bennett v. Spear*, 520 U.S. 154, 176-77 (1997); *Fla. Power & Light Co. v. Lorion*, 470 U.S. 729, 743-44 (1985); *Camp v. Pitts*, 411 U.S. 138, 142 (1973); *Citizens to Preserve Overton Park v. Volpe*, 401 U.S. 402, 419 (1971).

Part 1271 has made clear since at least 1997 that "[c]ells and tissues that were manipulated extensively, combined with non-tissue components, or were to be used for other than their normal functions would be regulated as biologics or devices requiring premarket approval by FDA." *See* Def. Ex. 378 ("1997 Proposed Approach")[38] at 7; *see also U.S. Stem Cell Clinic*, 403 F. Supp. 3d at 1291.

61. When FDA was considering the creation of the SSP exception in the 1998 Proposed Rule, the agency made clear that the exception would be very narrow: "For example, a surgeon might remove a saphenous vein from a patient for use in a later coronary bypass in the same patient. Registration and listing would not be required unless the saphenous vein was stored with other cellular or tissue-based products." *See* Proposed Rule Concerning "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products" ("1998 Proposed Rule"), 63 Fed. Reg. 26744, 26748 (May 14, 1998); *cf.* 21 C.F.R. § 1271.3(e) (the "storage" of any human cell or tissue constitutes "manufacturing"); *see also U.S. Stem Cell Clinic*, 403 F. Supp. 2d at 1291.

62. In 2001, the Final Rule codifying the SSP exception (in the same form it exists today) reemphasized that it would apply only in very limited circumstances. The preamble to the Final Rule stated that "hospitals that store autologous cells or tissues for subsequent application in the same patient" would qualify for the SSP exception "so long as the hospital does not engage *in any other activity encompassed within the definition of manufacture*" such as "expand[ing] the cells or tissues." *See* Final Rule Concerning Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing ("2001 Final Rule"), 66 Fed. Reg. 5447, 5460 (emphasis added); *U.S. Stem Cell Clinic*, 403 F. Supp. 3d at 1291-93. Thus, the plain text of the SSP exception and its regulatory history make clear that the exception applies and was intended

[38] Contrary to Defendants' claims, FDA's 1997 Proposed Approach was not a guidance document, and FDA has never announced or described it as such. The 1997 Proposed Approach was, in effect, an Advance Notice of Proposed Rulemaking. *See* https://www.reginfo.gov/ public/jsp/eAgenda/Abbrevs.myjsp. The 1997 Proposed Approach described FDA's early thinking about the regulation of human cellular and tissue-based products, and solicited public comments to inform the APA notice-and-comment rulemaking that later ensued.

to apply in limited circumstances where an HCT/P was removed from a patient, and such HCT/P thereafter was returned to the same patient, without intervening manufacturing steps. Manufacturing means "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." 21 C.F.R. § 1271.3(e).

63. While not in themselves binding, FDA's 2014 and 2017 guidance documents reiterated the agency's longstanding view of the exception's very limited application. In its 2014 Draft Guidance,[39] FDA included illustrative examples of HCT/Ps used in surgical procedures that would be entitled to the SSP exception, including "autologous skin grafting and coronary artery bypass surgery involving autologous vein or artery grafting." *See* 2014 Draft Guidance at 4. FDA also reaffirmed that an establishment that processes an HCT/P after removal and prior to implantation generally would not qualify for the SSP exception. *Id.* at 5; *cf.* 21 C.F.R. § 1271.3(e) (the processing of any human cell or tissue constitutes manufacturing).

64. FDA's Final Guidance,[40] issued in 2017, confirmed yet again that an establishment that processes an autologous HCT/P after removal and prior to implantation generally would not qualify for the SSP exception. *Id.* at 7. The Final Guidance reiterated the exception's narrow reach and noted that for the SSP exception to apply, the HCT/Ps removed from the patient must "remain 'such HCT/Ps;' they are in their original form." *See* 2017 Final Guidance at 4; *accord* 2014 Draft Guidance at 3. The Final Guidance noted that "[g]enerally, the only processing steps that will allow an HCT/P to remain 'such HCT/P' are rinsing, cleansing, sizing, and shaping." 2017 Final Guidance at 5.

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[39] *Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception, Draft Guidance for Industry* (Oct. 2014), https://web.archive.org/web/20170404000725/https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM419926.pdf ("2014 Draft Guidance").

[40] *Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception, Guidance for Industry* (Nov. 2017), https://www.fda.gov/media/89920/download ("2017 Final Guidance").

65. Defendants understood the SSP exception and its limitations. *See* Proposed Findings of Fact ¶¶ 196-198. For example, Defendant Lander spoke (on behalf of the Defendants in this case) at FDA's public hearing soliciting comments about the 2014 Draft Guidance and must have known what that document said.[41] In fact, Defendants later submitted regulatory applications for multiple CSCTC products at issue in this litigation in (albeit unsuccessful) attempts to obtain FDA's authorization to study their CSCTC products in human clinical trials. *See* Proposed Findings of Fact ¶¶ 187, 193-194.

66. FDA's formal notice-and-comment rulemaking process under the APA, explanatory guidances, Federal Register notices concerning FDA's rulemaking and guidances, and attendant opportunities for notice, hearing, and comment have provided sufficient opportunity for Defendants to both hear and be heard regarding FDA's longstanding interpretation of the SSP exception. *See, e.g.*, *Pinnacle Armor, Inc. v. United States*, 648 F.3d 708, 717 (9th Cir. 2011).

67. Defendants cannot plausibly claim that they are now unfairly surprised by the regulatory text and the narrow circumstances to which it applies. Nor can they credibly claim that FDA, in its 2017 Final Guidance or elsewhere, somehow reversed its position to Defendants' detriment. Indeed, had FDA ever suggested that the SSP exception did apply to the type of extensive processing at issue here, that truly would have been a "substantive change[]" in FDA's interpretation. *Contra* Defs.' Proposed Finding of Fact 13 (ECF No. 124 at 7).

68. Defendants' attendant complaint that FDA filed this enforcement action before the expiration of a three-year grace period that was announced in a different guidance document is baseless. *Contra* Defs.' Mem. Contentions of Facts and Law, ECF No. 108 at 22.

[41] *See* Tr. of Part 15 Hearing: Draft Guidances Relating to the Regulation of Human Cells, Tissues, or Cellular or Tissue-based Products at 148-153 (Sept. 12, 2016); *see also* 81 Fed. Reg. 23661 (April 22, 2016).

69. In 2017, FDA issued a non-binding guidance document entitled "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use" (the "MM/HU Guidance").[42] The MM/HU Guidance explained FDA's longstanding interpretation of the 21 C.F.R. § 1271.10(a)(1) criterion of minimal manipulation and the §1271.10(a)(2) criterion of homologous use—which are two (of four) regulatory criteria that an HCT/P must meet in order to qualify for limited regulation by FDA. The regulatory criteria for limited regulation of HCT/Ps under section 1271.10 are distinct from the establishment-based exceptions to Part 1271 requirements under section 1271.15(b). *See* Proposed Conclusion of Law ¶¶ 43-46, *supra*.

70. The MM/HU Guidance explained that FDA generally intended to exercise enforcement discretion only with respect to certain premarket approval requirements for a period of 36 months. MM/HU Guidance at 1. However, the guidance clarified that such enforcement discretion would only be applied where "use of the HCT/P does not raise reported safety concerns or potential significant safety concerns." *Id.* at 21.

71. The guidance further clarified that FDA's enforcement focus would be on products with higher risk profiles:

> FDA intends to focus enforcement actions on products with higher risk, including based on the route and site of administration. For example, actions related to products with routes of administration associated with a higher risk (*e.g.*, those administered by intravenous injection or infusion, aerosol inhalation, intraocular injection, or injection or infusion into the central nervous system) will be prioritized over those associated with a lower risk (*e.g.*, those

[42] *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use, Guidance for Industry* (corrected Dec. 2017), https://wayback.archive-it.org/7993/20180125064843/https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585403.pdf

administered by intradermal, subcutaneous, or intra-articular injection).

MM/HU Guidance at 21.

72. The non-binding MM/HU Guidance's announcement of FDA enforcement discretion for certain HCT/Ps "does not establish any rights for any person and is not binding on FDA or the public." MM/HU Guidance at 1. Moreover, the enforcement discretion policy was never intended to excuse the violations of manufacturers or health care providers who were offering unapproved regenerative medicine products that have the potential to put patients at significant risk. MM/HU Guidance at 21. The policy did not apply to products—such as Defendants' CSCTC products—that have been associated with reported safety concerns or have the potential to cause significant safety concerns to patients. *Id.*

73. Under its enforcement power, FDA has absolute discretion as to whether to bring an enforcement action under the FDCA. *See Heckler v. Chaney*, 470 U.S. 821, 831 (1985). *Id.* at 831. FDA has no obligation to refrain from enforcing against Defendants' violations of the FDCA with respect to their adulterated and misbranded CSCTC products, despite defense protestations to the contrary.

iii. Defendants Could Not Meet Their Burden to Prove that the CSCTC Products Meet all Four Criteria in 21 C.F.R. § 1271.10(a) to Qualify for Limited FDA Regulation

74. Defendants have never attempted to argue that the CSCTC products meet all the regulatory criteria to qualify for limited FDA regulation, as described in 21 C.F.R. § 1271.10(a).[43] *See* Defs.' Summ. J. Opp'n at 34-35 (contending that the Government's analysis of the minimal manipulation criterion of section 1271.10(a) was "irrelevant to this dispute"); Defs.' Mem. Contentions of Fact and Law, ECF No. 108 (making no

[43] Whereas the SSP exception provides that certain establishments do not have to comply with FDA's Part 1271 requirements, the regulation contains another provision, 21 C.F.R. section 1271.10, through which certain products may be subject only to limited FDA regulation.

mention of section 1271.10); Defs.' Proposed Findings of Fact and Conclusions of Law, ECF No. 124-1 at 29 n.2 (arguing that "21 C.F.R. § 1271.10 is inapplicable here"); Defs.' Trial Br., ECF No. 150 (making no mention of section 1271.10).

75. But even if Defendants had not waived this argument, the CSCTC products do not meet all of the regulatory criteria in 21 C.F.R. § 1271.10(a) to qualify for limited FDA regulation under section 361 of the PHSA[44] and Part 1271 only.

76. Minimal manipulation is defined for "structural tissue" as "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement." 21 C.F.R. § 1271.3(f)(1). For "cells or nonstructural tissues," minimal manipulation is defined as "processing that does not alter the relevant biological characteristics of cells or tissues." 21 C.F.R. § 1271.3(f)(2). Because the adipose tissue removed from the patient is structural tissue, the definition in 21 C.F.R. § 1271.3(f)(1) applies here.

77. Defendants transform adipose tissue by breaking it down through enzymatic digestion and removing adipocytes and structural components. Defendants have thereby altered the original relevant characteristics essential to the HCT/P's utility for reconstruction, repair, or replacement. *See* Proposed Findings of Fact ¶¶ 53-61. Therefore, the CSCTC products are more than minimally manipulated within the meaning of 21 C.F.R. § 1271.10(a)(1) and § 1271.3(f).

78. The CSCTC products also are not "intended for homologous use only" within the meaning of 21 C.F.R. § 1271.10(a)(2) and § 1271.3(c). Homologous use means "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). 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.

[44] Section 264 of Title 42 of the United States Code corresponds to "Section 361" of the PHSA.

§ 1271.10(a)(2).

79. Because Defendants market the CSCTC products as treatments for a broad array of serious diseases and conditions (such as cancer, arthritis, stroke, ALS, MS, macular degeneration, Parkinson's disease, and COPD) and not for the basic functions of either adipose tissue (*i.e.*, providing cushioning and support) or even the basic functions Defendants claim the cells in SVF have (*i.e.*, regenerative functions), the CSCTC products are not "intended for homologous use only" within the meaning of 21 C.F.R. § 1271.10(a)(2) and § 1271.3(c). *See U.S. Stem Cell Clinic (11th Cir.)*, --- F.3d ---, 2021 WL 2213288 at *7; *see generally* MM/HU Guidance at 21-22 ("HCT/Ps that are intended for non-homologous use, particularly those intended to be used for the prevention or treatment of serious and/or life-threatening diseases and conditions, are also more likely to raise significant safety concerns than HCT/Ps intended for homologous use because there is less basis on which to predict the product's behavior in the recipient, and use of these unapproved products may cause users to delay or discontinue medical treatments that have been found safe and effective through the New Drug Application or BLA approval processes.")

80. The SVF/Vaccinia product involves the combination of an HCT/P with "another article" (namely, a smallpox vaccine) within the meaning of 21 C.F.R. § 1271.10(a)(3). Proposed Finding of Fact ¶ 160. Thus, this particular CSCTC product fails to meet yet another regulatory criterion set forth in section 1271.10(a).

81. Defendants did not attempt to—and certainly could not—meet their burden of establishing that each of the SVF, SVF/Vaccinia and Expanded SVF products meets all four of the regulatory criteria in 21 C.F.R. § 1271.10(a). *See* 21 C.F.R. § 1271.10(a); *First City Nat'l Bank*, 386 U.S. at 366 (holding that the general rule is that the burden is carried by the one who "claims the benefit of an exception to the prohibition of a statute"); *Morton Salt*, 334 U.S. at 44-45; *Crooker & Sons*, 537 F.3d 79 at 85.

82. Accordingly, because Defendants' CSCTC products do not meet the criteria set out in § 1271.10(a), and their establishments do not qualify for any of the exceptions

in § 1271.15, the CSCTC products "will be regulated as a drug . . . and . . . biological product under the [FDCA] and . . . section 351 of the PHS[A], and applicable regulations in title 21 [of the Code of Federal Regulations,]" which "include, but are not limited to" CGMP regulations in 21 C.F.R. §§ 210.1(c), 210.2, [and] 211.1(b), . . . which [in turn] require [Defendants] to follow the procedures in subparts C and D of . . . [P]art [1271]." *See* 21 C.F.R. § 1271.20; *see also* 21 U.S.C. §§ 351, 352.

iv. Defendants' Claim that They Do Not Manufacture "Drugs" Fails as a Matter of Law

83. The FDCA regulates drug manufacturing and distribution in the United States. 21 U.S.C. §§ 301, *et seq.*

84. Defendants contend that their CSCTC products cannot be "drugs" because they supposedly are "unlike traditionally manufactured pharmaceutical drugs." Defs.' Mem. Contentions of Fact and Law, ECF No. 108 at 34. Whether a product subjectively resembles so-called "traditional" drugs is irrelevant. *See U.S. Stem Cell Clinic (11th Cir.)*, --- F.3d ---, 2021 WL 2213288 at *3 ("While the lay person may not think of stem cells as a 'drug,' the FDCA's definition of that word is expansive; any 'article[] intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease' is a drug for purposes of the statute."); *Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 395 (5th Cir. 2008); *see also Loran Med. Sys.*, 25 F. Supp. 2d at 1086-87 (holding that defendants' cellular product for the treatment of diabetes was both a biological product and a new drug subject to FDA's regulatory authority under the PHSA and FDCA). The broad statutory definition, 21 U.S.C. § 321(g)(1)(B) & (C), and decades of case law hold that the intended use of a product makes it a drug. *See, e.g.*, *Whitaker v. Thompson*, 353 F.3d 947, 953 (D.C. Cir. 2004) (classification as a "drug" under the FDCA "turns on the nature of the claims advanced on its behalf"); 21 C.F.R. § 201.128. Defendants intend their products to be used to treat cancer, arthritis, COPD, stroke, and other diseases and conditions. With these intended uses, the CSCTC products are drugs—just like the stem cell products in *Regenerative Sciences* and *U.S. Stem Cell Clinic*.

85. There is also no question that Defendants "manufacture" the CSCTC products. "Manufacture means, but is not limited to, 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." 21 C.F.R. § 1271.3(e). Because SVF does not occur naturally in the body,[45] Defendants employ numerous processing steps to derive SVF from adipose tissue they remove (*i.e.*, recover) from patients. *See* Ans. ¶¶ 5, 9, 10. Their efforts alter the physical properties of the removed adipose tissue and result in a liquified mixture of cells and cell debris that is missing the extracellular matrix and adipocytes found in adipose tissue. Proposed Findings of Fact ¶¶ 36-50, 53-61, 64; s*ee also* 21 C.F.R. § 1271.3(e). Because production of the Defendants' CSCTC products requires, *inter alia*, the recovery, processing, labeling, and in some cases the storage of human cells or tissue, such activity constitutes "manufacturing" for FDA regulatory purposes.

v. Defendants' Practice of Medicine-Related Defenses are Legally Unfounded and Do Not Justify Non-Compliance with the FDCA

86. Defendants claim that the FDCA does not apply to them because they are simply physicians who are practicing medicine and performing surgery. But even doctors must comply with FDCA requirements. The FDCA "enacts a comprehensive, uniform regulatory scheme for the distribution of drugs." *Regenerative Scis.*, 741 F.3d at 1319-20. Congress did not create a broad "practice of medicine" exception that allows physicians to do whatever they please. *Id.* "[W]hile the [FDCA] was not intended to regulate the practice of medicine, it was obviously intended to control the availability of drugs for

[45] Defendants erroneously claim that SVF is "naturally occurring" in the body. *See, e.g.*, ECF No. 124 at 11, Defs.' Proposed Finding of Fact 42. It is not. Although the heterogenous mix of cells comprising SVF are isolated from adipose tissue, the Government's expert Dr. Carolyn Yong explained that SVF is not readily available for removal from an individual and merely refers to a liquified mixture of the various types of cells and cell debris obtained through Defendants' processing of adipose tissue. Proposed Findings of Fact ¶¶ 44-50.

prescribing by physicians." *Evers*, 643 F.2d at 1048*; see also U.S. Stem Cell Clinic*, 403 F. Supp. 3d at 1300 n.12.

87. At trial, Defendants raised yet another practice of medicine-related defense—this one based on an exemption from FDA registration under 21 U.S.C § 360(g) for "practitioners licensed by law to prescribe or administer drugs or devices and who manufacture, prepare, propagate, compound, or process drugs or devices solely for use in the course of their professional practice." 21 U.S.C. § 360(g)(2). This argument seemingly conflicts with the defense's theory of the case, as Defendants would have to concede that they are, in fact, manufacturing or processing drugs as part of their medical practice for this provision even to apply.[46] Importantly, however, section 360(g)(2) does not authorize doctors to use *unapproved* drugs, even in their "practice of medicine." *See Cowan v. United States*, 5. F. Supp. 2d 1235, 1240 (N.D. Okla. 1998) ("[T]he 'medical practice exemption' referenced . . . is a *very limited* exemption from the *registration* requirements of the FDCA. [A party's] assertion that this exception provides a broad-based exemption to all physicians from the requirements of the Food, Drug, and Cosmetic Act is incorrect.") (emphasis in original); *see also U.S. v. Algon Chemical Inc.*, 879 F.2d 1154, 1160 (3d Cir. 1989) (noting that medical practice exemption does not allow one to acquire unapproved drugs).

vi. Defendants' Off-Label Use Arguments Contradict Controlling Ninth Circuit Authority

88. Although Defendants claim they merely engage in "off-label uses" of drugs and other medical products, that argument fails because—as Defendants admit—the CSCTC products have not been approved by FDA for any use. *See* Proposed Findings of Fact ¶¶ 177-179, 187; *Regenerative Scis.*, 741 F.3d at 1324-25 (stem cell "Mixture" that

[46] The Government agrees that Defendants manufacture drugs, but does not concede that Defendants and their CSCTC products meet all the criteria for exemption from registration under 21 U.S.C. § 360(g)(2). The Court need not reach this issue, however, to resolve this case. At most, section 360(g)(2) excuses compliance with FDCA registration requirements only. It does not allow Defendants to manufacture or acquire unapproved drugs, such as the CSCTC products, in violation of other provisions of the FDCA.

was not approved by FDA for any purpose is a misbranded drug even if prescribed by appellant doctors); *see also Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 349-50 (2001) (discussing permissible off-label use of "*legally marketed* device[s]") (emphasis added).

89. Moreover, the Ninth Circuit has noted that "off-label use does not immunize a physician who uses adulterated products." *Kaplan*, 836 F.3d at 1211. Although "off-label use allows physicians to prescribe *lawful* drugs for unapproved uses, off-label use of *adulterated* products is beyond the scope of the privilege." *Id.* (citing *Evers*, 643 F.2d at 1049) (emphases added) (internal quotations omitted). Thus, it is well-settled that "[w]hile a physician may exercise professional judgment in the off-label use of *unadulterated* products, nothing in the FDCA or caselaw suggests that the use of *adulterated* products is ever permissible." *Id.* (emphases added).

vii. Defendants' Constitutional and Statutory Arguments about Patients' Rights to Control Their Own Cells Lack Merit

90. Defendants continue to suggest without basis that the Government may not pursue this enforcement action because Defendants' patients have a constitutional right to control their tissues and cells. But there is no constitutional right to receive unapproved drugs, regardless of their composition. *See United States v. Rutherford*, 442 U.S. 544, 552 (1979) (terminally ill patients do not have a constitutional right to obtain the unapproved drug Laetrile); *Abigail All. for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695, 711 (D.C. Cir. 2007) (terminally ill patients have no constitutional right to unapproved experimental drugs).

91. Moreover, the federal "right to try" provisions that were codified in 21 U.S.C. § 360bbb-0a do not apply to Defendants' unapproved CSCTC products. The CSCTC products do not meet the statutory definition of an "eligible investigational drug" that patients have a "right to try" because, *inter alia*, the CSCTC products have been placed on clinical hold, are not subject to an effective IND or a filed NDA or BLA, and have not been studied in a completed, FDA-approved Phase 1 clinical trial. *See* 21 U.S.C.

§ 360bbb-0a(2); *see also* Proposed Findings of Fact ¶¶ 177-179, 187. Thus, the FDCA's "right to try" provisions decidedly do not permit Defendants' to use their unapproved drugs to treat patients.

viii. Defendants' Belief that They Are Not Subject to FDA Inspection Evidences a Misapprehension of the Law

92. FDA is responsible for protecting the public health by ensuring the safety, efficacy, and security of drugs, biological products, and medical devices.[47] *See* 21 U.S.C. § 393.

93. Pursuant to FDCA section 704, which is codified at 21 U.S.C. § 374, FDA "officers or employees duly designated by the Secretary" of Health and Human Services, "upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any . . . establishment in which . . . drugs [or] devices . . . are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction . . . and (B) to inspect . . . such . . . establishment, finished and unfinished materials, containers, and labeling therein." 21 U.S.C. § 374(a)(1) (first sentence).

94. FDA has expanded authority to inspect records and related materials of establishments manufacturing, processing, packing, or holding prescription drugs, unless an exception applies. *See* 21 U.S.C. §§ 374(a)(1), (a)(2). Specifically, unless subject to an exception in 21 U.S.C. § 374(a)(2), in the case of an establishment in which nonprescription drugs intended for human use or prescription drugs are manufactured, processed, packed, or held, FDA's inspection shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether nonprescription drugs intended for human use or prescription drugs which are adulterated or misbranded within the meaning of the FDCA, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of the FDCA, have been or are being manufactured, processed, packed, transported, or

[47] https://www.fda.gov/about-fda/what-we-do.

held in any such place, or otherwise bearing on violation of the FDCA. 21 U.S.C. § 374(a)(1) (third sentence).

95. Although FDA's expanded access to inspect records described in the immediately preceding paragraph does not apply to "practitioners licensed by law to prescribe or administer drugs, or prescribe or use devices, as the case may be, and who manufacture, prepare, propagate, compound, or process drugs, or manufacture or process devices solely for use in the course of their professional practice," 21 U.S.C. § 374(a)(2)(B), Section 374(a)(1) authorizes FDA to inspect an establishment in order to determine whether the facility is engaged in activities within the agency's jurisdiction. *See, e.g.*, *Wedgewood Vill. Pharm., Inc. v. United States*, 421 F.3d 263, 273 (3d Cir. 2005) (explaining that FDA sometimes cannot establish whether jurisdiction applies or not without first conducting an establishment inspection and obtaining information).

96. It is "within the discretion of the FDA to identify those entities that require inspection 'for the purpose of enforcement of [the FDCA].'" *United States v. Drug-Deslorelin Injectable (Vial)*, No. CV 04-381-KSF, 2005 WL 8165651, at *14 (E.D. Ky. Mar. 23, 2005) (citing *In re Establishment Inspection of: Wedgewood Vill. Pharmacy, Inc.*, 270 F. Supp. 2d 525, 543 (D.N.J. 2003), *subsequently aff'd sub nom. Wedgewood Vill. Pharmacy, Inc. v. United States*, 421 F.3d at 263).

97. Moreover, the class of entities to be inspected under Section 374—namely, "any factory, warehouse, or establishment in which . . . drugs [or] devices . . . are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or . . . any vehicle being used to transport or hold such . . . drugs [or] devices. . . in interstate commerce"—is broader than the class of entities subject to registration with FDA under 21 U.S.C. 360(g). *Wedgewood*, 270 F. Supp. 2d at 543; *see also id.* at 539 (explaining that "the class of entities Congress intended to be registered is contained in Section 360(g)"). Thus, even "practitioners licensed by law to prescribe or administer drugs or devices and who manufacture, prepare, propagate, compound, or process drugs or devices solely for use in the course of their professional practice" who

are exempt from registration[48] under 21 U.S.C. § 360(g)(2) are nonetheless subject to FDA inspection under 21 U.S.C. § 374 – most notably FDA's authority under the first sentence of 21 U.S.C. § 374(a)(1). *See id.* Here, FDA's inspection of Defendants' establishments evidenced obvious and serious violations of CGMP which, in view of the processing video "*Cell Surgical Network Video: How to Isolate SVF*" that Defendants played at trial *(see Def. Ex. 453)*, it appears Defendants have yet to correct.[49]

H. The Government Is Entitled to a Statutory Injunction against Defendants' Violations of Sections 331(k) and (c) of the FDCA

i. A Statutory Injunction is Necessary to Protect the Public Health

98. Under 21 U.S.C. § 332(a), district courts have jurisdiction to enjoin violations of Section 331 of the FDCA. *United States v. Organic Pastures Dairy Co.*, 708 F. Supp. 2d 1005, 1011 (E.D. Cal. 2010); *United States v. Innovative Biodefense, Inc.*, 2019 WL 2428672, at *3 (C.D. Cal. June 5, 2019). The FDCA's injunctive power should be exercised in light of its purpose to protect the public health, *see United States v. An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 798 (1969), and is appropriate when the United States establishes that the defendant has violated the applicable statute and that there exists "some cognizable danger of recurrent violation." *United States v. W.T. Grant Co.*, 345 U.S. 629, 633 (1953); *Rhody Dairy*, 812 F. Supp.2d at 1245-46.

99. Both corporations and individuals may be found liable for violations of the

[48] As noted above, the Government does not concede that Defendants and their CSCTC products are exempt from registration under 21 U.S.C. § 360(g)(2). The Government similarly does not concede that Defendants would be excepted from the third sentence of 21 U.S.C. § 374(a)(1) under 21 U.S.C. § 374(a)(2)(B). But even if they are, FDA inspection of Defendants' establishments to determine whether the CSCTC products are adulterated, misbranded, or otherwise in violation of the FDCA would still be lawful and appropriate under 21 U.S.C. § 374. Specifically, FDA would retain its authority to inspect Defendants' establishment pursuant to its authority in the first sentence of 21 U.S.C. § 374(a)(1). Any effort by Defendants to delay, deny, or limit FDA's inspection, or refusal to permit entry or inspection would automatically render Defendants' drugs adulterated under the FDCA. *See* 21 U.S.C. § 351(j).

[49] *Cf.* Trial Tr. Day 1 (AM – Defs.' Opening) at 21:18-27:6; *with* Trial Tr. Day 1 (PM – Lagud) at 9:16-19:2; Trial Tr. Day 2 (AM – Lagud) at 22:22-24:25.

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).

100. Once the United States establishes the existence of the statutory violation,[50] the burden shifts to the defendants to show that "there is no reasonable expectation that the wrong will be repeated." *W.T. Grant Co.*, 345 U.S. at 633 (citation and quotation marks omitted). A district court may issue an injunction if it concludes that the injunction is necessary to prevent future violations. *United States v. Articles of Drug*, 825 F.2d 1238, 1248 (8th Cir. 1987) (internal citations omitted).

101. Here, Defendants violate sections 331(k) and (c) of the FDCA by causing the adulteration and misbranding of drugs while held for sale after shipment of one or more of their components in interstate commerce, and by receiving in interstate commerce misbranded drugs that they deliver to patients for pay or otherwise. Defendants know or should know that their CSCTC products and conduct violate the FDCA. Rather than comply with the law, Defendants continue to claim that the law does not apply to them. 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. An injunction is necessary to bring Defendants into compliance with the law and to prevent future violations.

[50] Where, as here, the United States seeks an injunction authorized by statute, it need not prove irreparable harm because harm is presumed when the statute is violated. *United States v. Odessa Union Warehouse Co-op*, 833 F.2d 172, 176 (9th Cir. 1987).

102. Moreover, although evidence of patient harm is not required to establish a violation of the FDCA or to obtain an injunction, the Government's safety concerns are real. The risks posed by Defendants' violations, as guided by Defendants Berman and Lander, further underscore the need for injunctive relief. Defendants manufacture unapproved experimental drugs in a manner that does not comply with CGMP, thereby posing significant risks to the consumers who receive them. The drugs themselves have not been subjected to any adequate and well-controlled clinical trials. Therefore, they have not been shown to be safe and effective, through valid scientific evidence, for the treatment of any disease or condition, much less the litany of serious diseases and conditions for which Defendants promote their use. Significant adverse medical events have been reported following administration of Defendants' CSCTC products. These adverse events, known risks, and FDA warnings have not stopped Defendants' illegal conduct. An injunction is necessary to protect the public health.

ii. The Statutory Injunction Must Include All Three CSCTC Products

103. Throughout this litigation, Defendants have claimed that injunctive relief is inappropriate with respect to their Expanded SVF and SVF/Vaccinia products, because they allegedly were not making those products and purportedly had "no intention" of manufacturing them again. *See, e.g.*, Defs.' Summ. J. Opp'n, ECF No. 59 at 37 (claiming Defendants "ceased performing the [Expanded SVF] procedure as of December 2017" and have "no interest in performing [it] in the future absent appropriate regulatory approval"); Defs.' Contentions, ECF No. 108 at 20 (repeating those same two claims). Defendants' trial testimony confirms that this simply is not true. *See* Proposed Findings of Fact ¶¶ 203-204, 209-21.

104. But even assuming, *arguendo*, Defendants have stopped making their SVF/Vaccinia and Expanded SVF products, "the court's power to grant injunctive relief survives discontinuance of the illegal conduct." *W.T. Grant Co.*, 345 U.S. at 633; *see also Odessa*, 833 F.2d at 176. "[M]ere cessation of violative activities is not, of itself, grounds

for denial of a statutory injunction sought to protect the public health. This is particularly true where such cessation arises only as a result of . . . threatened litigation." *United States v. Sene X Eleemosynary Corp. Inc.*, 479 F. Supp. 970, 981 (S.D. Fla. 1979) (internal citation omitted).

105. In analyzing whether an injunction is appropriate after a defendant claims to have voluntarily ceased the illegal behavior, a court should consider "the bona fides of the expressed intent to comply, the effectiveness of the discontinuance and, in some cases, the character of the past violations." *W.T. Grant Co.*, 345 U.S. at 633; *United States v. Bob Lawrence Realty, Inc.*, 474 F.2d 115, 126 (5th Cir 1973) (citing these *W.T. Grant* factors). Applying the *W.T. Grant* factors here, the cognizable danger of future violations is clear.

106. Defendants have a history of manufacturing and administering unapproved drugs that could inflict serious harm on the public. That history suggests that if not enjoined, Defendants would continue to pursue such activities. For example, Defendants' SVF/Vaccinia product combined SVF with ACAM2000—a smallpox vaccine containing live virus—and injected that unapproved experimental product in late-stage cancer patients. If the Government had not acted to limit Defendants' access to the smallpox vaccine by executing a civil seizure action[51] and initiating this case, Defendants would have continued their human experimentation. *See* Proposed Findings of Fact ¶¶ 199-204.

107. Additionally—and despite multiple misrepresentations to the contrary—Defendants did not stop manufacturing and administering their Expanded SVF product even after FDA sent a Warning Letter[52] to Defendants' third-party contract manufacturer in January 2018 and initiated this case. The evidence clearly shows that after that third-party New Jersey laboratory received the Warning Letter and was advised by its own

[51] *See* Def. Ex. 383, *United States v. Five Articles of Drug, ACAM2000, Vaccinia Vaccine, Live*, No. SACV17-01449-JVS (KESx), 2018 WL 6318834 (C.D. Cal Jan. 30, 2018).

[52] *See* Ex. 90, "Warning Letter [to] American CryoStem Corporation" (Jan. 03, 2018), also available at https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/american-cryostem-corporation-535041-01032018 (last accessed: June 2, 2021).

attorneys not to release any more expanded cells, Defendants did not stop providing the Expanded SVF product to their patients. Rather Defendants merely redirected their patients to an alternative source for expanded cells, namely from a Florida company called U.S. Stem Cell. When a federal court in the Southern District of Florida later enjoined U.S. Stem Cell from manufacturing its adipose tissue-derived SVF products, the Florida company promptly sold its stem cell-related inventory to American Cell Technology ("ACT")—a newly formed Florida company managed by Defendant Berman's son, Sean Berman, who serves as CSCTC's Director of Scientific Research and CSN's Head of Operations. On cross examination, Defendant Berman confirmed that CSN is currently working with ACT to treat COVID-19 patients pursuant to a CSN protocol. Defendant Lander admitted that Defendants intend to keep manufacturing and administering the Expanded SVF product, even in the absence of FDA approval. *See* Proposed Findings of Fact ¶¶ 208-211.

108. Given this background, there can be no assurance that Defendants will stop experimenting with SVF and other unapproved, potentially dangerous drugs in the future. The only way to ensure Defendants comply with the FDCA is to issue an injunction regarding the full range of Defendants' SVF-related products. Excluding two of the three CSCTC products from the scope of the injunction—as Defendants advocate—would create an enormous loophole to exploit at their patients' expense and incentivize resumption of the same illegal practices that led to the initiation of this case. Indeed, Defendants' continuing denial that their SVF products are drugs and refusal to stop distributing adulterated and misbranded drugs in the absence of government intervention only reinforces the need for permanent injunctive relief. *See W.T. Grant*, 345 U.S. at 633.

109. Accordingly, Plaintiff, the United States of America, is entitled to a statutory injunction to protect the public health because the evidence shows that Defendants have repeatedly violated *(a)* 21 U.S.C. § 331(k) by causing the adulteration and misbranding of drugs while holding them for sale after shipment of one or more of their components in interstate commerce, and *(b)* 21 U.S.C. § 331(c), by receiving misbranded drugs in

interstate commerce and delivering or proffering for delivery such drugs for pay or otherwise. Based on these repeated violations, there is a reasonable expectation that Defendants will continue to violate the FDCA in the future if not enjoined.

SO ORDERED. An order of permanent injunction will issue separately.

DATED: _____

_____
HONORABLE JESUS G. BERNAL
United States District Judge

Presented by:

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CERTIFICATE OF SERVICE

I hereby certify that on this 8th day of June 2021, I electronically filed a true and correct copy of the foregoing PLAINTIFF'S REVISED [PROPOSED] FINDINGS OF FACT AND CONCLUSIONS OF LAW through the Court's CM/ECF system, which will send a notice of electronic filing to the following counsel of record listed below:

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