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Attorneys for Defendants
CALIFORNIA STEM CELL TREATMENT CENTER, INC., CELL SURGICAL NETWORK CORPORATION, ELLIOT B. LANDER, M.D. and MARK BERMAN, M.D.

UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

EASTERN DIVISION

UNITED STATES OF AMERICA,

Plaintiff,

v.

CALIFORNIA STEM CELL TREATMENT CENTER, INC., a California corporation, CELL SURGICAL NETWORK CORPORATION, a California corporation, and ELLIOT B. LANDER, M.D., MARK BERMAN, M.D., individuals,

Defendants.

CASE NO. 5:18-CV-01005-JGB-KK

Hon. Jesus G. Bernal
Riverside, Courtroom 1

[PROPOSED] FINDINGS OF FACT AND CONCLUSIONS OF LAW PURSUANT TO LOCAL RULE 52-3

Action Filed: May 9, 2018
Trial Date: July 28, 2020

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I. GOVERNMENT'S CLAIMS

Claim 1: SVF, or stromal vascular fraction, is adulterated under 21 U.S.C. § 351.

Claim 2: SVF is misbranded under 21 U.S.C. §§ 352 and 353.

Claim 3: Mesenchymal stem cells ("MSC") that have been expanded by a third party ("Expanded MSC Surgical Procedure") is adulterated under 21 U.S.C. § 351.

Claim 4: Expanded MSC Surgical Procedure is misbranded under 21 U.S.C. §§ 352 and 353.

Claim 5: Defendants violate 21 U.S.C. § 331(c) by receiving misbranded Expanded MSC cells.

Claim: 6: SVF combined with ACAM2000 Vaccine, Live ("SVF/ACAM2000 Surgical Procedure") is adulterated under 21 U.S.C. § 351.

Claim 7: SVF/ACAM2000 Surgical Procedure is misbranded under 21 U.S.C. §§ 352 and 353.

II. FINDINGS OF FACT RELATING TO THE GOVERNMENT'S CLAIMS

A. Litigation Background

1. The Government brought this action against Defendants California Stem Cell Treatment Center Inc.; Cell Surgical Network Corporation; Elliot B. Lander, M.D.; and Mark Berman, M.D. for violations of the Federal Food, Drug, and Cosmetic Act, codified as amended at 21 U.S.C. §§ 301, *et seq.* and Public Health Services Act, codified as amended at 42 U.S.C. §§ 201, *et seq.*

2. The Government filed this action on May 9, 2018. Defendants answered on July 17, 2018.

3. The Government moved for summary judgment on July 8, 2019. The Court denied the Government's motion on January 27, 2020.

4. The Government moved to define the scope of trial on March 19, 2020. The Court denied the Government's motion on April 14, 2020, and ordered

that the Government must produce evidence to establish any element where it carries the burden.

5. This action was tried before the Court beginning on July 28, 2020.

B. Regulatory History of the SSP Exception

6. Until 1997, the FDA exerted little to no control over human cellular and tissue-based products.

7. In 1997, the FDA introduced Guidance providing that:

> the agency would ***not assert any regulatory control*** over cells or tissues that are removed from a patient and transplanted back into that patient during a single surgical procedure. The communicable disease risks, as well as the safety and effectiveness risks, would generally be no different than those typically associated with surgery.

(Ex. 88 (emphasis added).)

8. In 2001, the FDA then promulgated the Same Surgical Procedure Exception ("SSP Exception") based on the 1997 Guidance.

9. The SSP Exception exempts from any FDA regulation:

> [A]n establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure.

21 C.F.R. § 1271.15(b).

10. The FDA has not amended the SSP Exception since its promulgation.

11. HCT/Ps are defined as "articles containing or consisting of human cells or tissue that are intended for implantation, transplantation, infusion, or transfer into a human recipient." 21 C.F.R. § 1271.15(b).

12. In 2014, the FDA released a draft guidance that sought to create ambiguity in the SSP Exception. (Ex. 89.)

13. The draft guidance proposed substantive changes that interpret the SSP Exception to exclude surgical procedures that would otherwise qualify for exemption by requiring that the patient's transplanted HCT/P be implanted in its

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"original form," which is very narrowly defined and otherwise limits the types of surgical procedures that would fall within the SSP Exception. (*Id.*)

14. The "original form" language is not included anywhere in the regulation, see 21 C.F.R. § 1271.15(b). Instead, the SSP Exception unambiguously states that a tissue ***or human cell*** is not a drug if it is removed from an individual and then re-implanted in the same individual.

15. The FDA adopted the draft guidance, which was improperly signed by Ana Abrams, in December 2017. (Ex. 87.)

C. <u>The Parties</u>

16. Dr. Berman graduated from Chicago Medical School in 1983. Thereafter, he began his residency in otolaryngology (surgery of the head and neck) at Loma Linda Medical Center. After completing his residency, Dr. Berman joined a multispecialty practice group while opening his own private practice. He has maintained a private practice since at least 1984.

17. Dr. Berman became a board-certified surgeon in otolaryngology in 1983. He became a board-certified surgeon in cosmetic surgery in 1989 and renewed his certification in 2009.

18. Dr. Berman has served as a clinical instructor of facial plastic surgery at University of Southern California School of Medicine since 2001.

19. Dr. Berman has been a practicing surgeon for thirty-seven years.

20. Dr. Lander graduated from University of California, Irvine School of Medicine in 1986. Thereafter he began his residency as a general surgeon and urologist at University of California, Irvine Medical Center. After completing his residency, he began practicing with Kaiser Permanente Medical Group before opening his own practice in 1997.

21. Dr. Lander is a board-certified urologist and fellow of the American College of Surgeons.

22. Dr. Lander has been practicing medicine for thirty-four years.

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23. California Stem Cell Treatment Center is a California professional corporation founded in 2010, with its principal place of business located at 72-780 County Club Drive, Suite 301, Rancho Mirage, California 92770.

24. California Stem Cell Treatment Center is also located at 120 South Spalding Drive, Suite 300, Beverly Hills, California 90212.

25. Cell Surgical Network Corporation ("CSN") is a California corporation founded and owned by Dr. Berman and Dr. Lander and is registered to do business at 72-780 County Club Drive, Suite 301, Rancho Mirage, California 92770.

26. CSN operates a one-employee warehouse at 73700 Dinah Shore Drive, Suite 301, Palm Desert, California 92211.

27. Dr. Berman's facility in Beverly Hills is accredited by the Accreditation Association for Ambulatory Health Care ("AAAHC").

28. Dr. Berman's facility was initially accredited by AAAHC in 1996 and has retained his accreditation since then. Dr. Berman's facility was most recently inspected in February 2018 and its accreditation renewed until May 2021.[1] (Ex. 302.)

29. AAAHC has repeatedly determined that Defendants met all requirements governing patient rights and responsibilities; governance; administration; quality of care; quality management and improvement; maintenance of clinical records and health information; infection prevention, control, and safety; general safety; facilities and environment, anesthesia services; surgical and related services; and pharmaceutical services. (Ex. 302.)

30. In 2010, Defendants began developing the SVF Surgical Procedure as part of their surgical practices and as a cutting-edge surgical procedure designed to address their patients' medical concerns.

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[1] Dr. Lander's Rancho Mirage facility is not an outpatient surgical center; therefore, the California Medical Board's accreditation requirements do not apply.

31. Defendants initiated their research and development of the SVF Surgical Procedure based in large part on the unambiguous position of the FDA that a same day surgical procedure such as the SVF Surgical Procedure would not be subject to FDA regulations.

32. Defendants relied upon the FDA's twenty-year interpretation of the applicable statutes and regulations while developing and expanding their business. Defendants expended significant sums to develop the SVF Surgical Procedure.

33. Defendants have been successfully performing point of care investigative deployment of autologous adipose SVF since 2010.

34. Defendants have collected an abundance of data, developed Institutional Review Board ("IRB")-approved protocols, and maintain medical malpractice insurance for every member of the CSN network.

35. The FDA, in a non-binding guidance document issued on or about November 2017, informed the public, including Defendants, that they would have a three-year grace period (until December 2020) to determine how best to regulate procedures involving HCT/Ps. (Ex. 87 at 21.)

36. The FDA did not wait for that three-year grace period to end before filing this lawsuit, even though Defendants are one of the few organizations that had actually been working with the FDA on an Investigational Device Exemption ("IDE") application through the Center for Biological Evaluation and Research for the CSN-Time Machine System used in the SVF Surgical Procedure.

37. The FDA conducted an inspection of Dr. Lander's Rancho Mirage facility on or about July 17-26, 2017, and conducted an inspection of Dr. Berman's Beverly Hills facility on or about July 21-26, 2017. The FDA provided no further notice to Defendants before filing the litigation in May 2018, well before the three-year grace period expired.

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38. After the Government filed the Complaint and issued press releases relating to the same, Defendants lost a significant number of patients, both current and prospective. (*See* Ex. 382.)

39. Defendants' medical practices have been negatively impacted by the Government's arbitrary, capricious, and unlawful actions.

40. Many CSN members withdrew because of the ongoing litigation. Additionally, many potential new members no longer sought membership or requested refunds for the medical equipment and training with CSN. CSN growth and reputation was damaged worldwide.

D. Claims One and Two: The SVF Surgical Procedure is not a drug, nor is it an adulterated or misbranded drug

1. The SVF Surgical Procedure falls under the SSP Exception

a. The SVF Surgical Procedure involves HCT/Ps

41. Cells are the smallest and most basic functional structural units in the human body. Every organ and tissue in the human body is comprised of cells.

42. SVF is the naturally occurring cellular part of the adipose tissue that does not contain the adipocytes (fat cells).

43. SVF cells are a population comprised of multiple cell types contained in adipose tissue; these include mesenchymal stem cells ("MSC"), hematopoietic cells ("HSC"), early (progenitors) and mature lineage stages of endothelia, pericyte progenitor cells (also called perivascular cells), red blood cells, white blood cells, lymphocytes, and fibroblasts (also called stroma) among other cells.

44. SVF is an HCT/P.

45. Surgeons routinely work on both tissues and cells that make up tissues. Surgery universally involves dissection (cutting and separation) of tissues through mechanical or chemical means, and has evolved to where surgeons can isolate individual cells. Dissected tissues and cells that have been isolated by

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chemical cutting can be surgically relocated and re-purposed to other parts of a patient's body.

46. The SVF Surgical Procedure involves the removal and implantation of human cells, SVF, that exist within the patient's own body.

b. The SVF Surgical Procedure is autologous

47. The SVF Surgical Procedure involves collecting a patient's cell population naturally contained in the patient's own adipose tissue and relocating that cell population back into the same patient. Everything in SVF is already in circulation within the body. Adipose SVF only acts to increase the number of available stem cells to circulation or an injured area.

c. The SVF Surgical Procedure is a single procedure

48. The extraction, isolation, and reimplantation of SVF all occurs during a single, outpatient procedure at a surgical clinic located in California. Defendants sometimes send patients to outpatient radiology for deployment but this remains part of the same day surgical procedure and is transported under well-established chain of custody rules.

d. The SVF Surgical Procedure implants the same cells that were removed

i. The SVF Surgical Procedure isolates SVF cells currently existing in the patient

49. The SVF cells that are implanted are the same cells that were removed from the patient during the SVF Surgical Procedure.

50. The SVF Surgical Procedure is simple for cell isolations (paralleling procedures for isolation of blood cells) and does not change the biological properties of cells that were intended for the purposes of repair and regeneration.

51. During the SVF Surgical Procedure, a licensed physician collects a patient's SVF cells, using a technique called "mini-liposuction via subdermal local anesthesia," which permits the liposuction of the SVF, along with the fat tissue and

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connective tissue that contains it, through use of local anesthesia. Many cells are mechanically separated ("mechanical cutting") from the adipose tissue during the liposuction procedure, as is common in all surgeries.

52. The physician then uses surgical tools—namely, collagenase enzymes and a centrifuge device—to isolate the SVF cell population by removing the adipocyte (fat cells).

53. The SVF is then suspended in a sterile saline solution, after which it is relocated back into the patient's body.

54. The SVF cells taken out of the patient in the performance of the procedure are the same cells that are put back into the patient.

ii. The HCT/Ps that are removed from the patient are the same such HCT/Ps that are implanted

55. SVF's mesenchymal stem cells are regenerative cells that promote healing and regeneration of new tissue. The cells also provide modulation of immune reactions and contain anti-inflammatory properties.

56. SVF's progenitor cells operate as stem cells depending on the environment in which they are placed. Progenitor cells similarly provide regenerative effects, including regulation or amelioration of some conditions.

57. Adipose tissue has the highest number of these regenerative cells of any tissue in the body. There are 100 to 1,000 times more repair cells (mesenchymal stem/progenitor cells) found in adipose tissue than in an equivalent volume of bone marrow. Regeneration and repair are among the most important functions of adipose tissue.

58. The separation of the SVF cells from adipocytes does not break down, damage, or in any way alter the phenotypic traits and biological properties of the SVF cells.

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59. The re-implanted SVF cells' functions include regenerative tissue repair and healing, modulation of immune reactions, and contain anti-inflammatory properties.

60. Collagenase is used to separate the SVF cells, it does not change the physical form or effect of the SVF cells. The GMP-grade collagenase, as used in the SVF Surgical Procedure, has no impact on the viability of the SVF cells, yield of cells, and, most significantly, has no effect on the phenotype (identifying cell markers), the ability of the cells to differentiate, to proliferate, or to function in their intended capacity.

61. Centrifugation helps clean, and with simple filter techniques, size the SVF so that the SVF cells are available for relocation back into the patient. Centrifugation does not change the physical form or regenerative properties of the SVF cells. The centrifugation process does not result in anything being added back to the patient that was not already existing in the patient's body.

62. The cells have not been altered in any substantive way to change them from their naturally occurring state (*i.e.*, they have the same DNA, same cell type, same flow cytometry markers).

2. <u>The SVF Surgical Procedure does not involve manufacturing or any processing that is akin to a pharmaceutical drug or medical device</u>

63. Unlike manufactured drugs, the SVF Surgical Procedure does not produce any cellular or tissue-based product that did not previously exist within the patient.

64. Because the cell population used in the SVF Surgical Procedure is unique to each patient, including the specific stem cell count, the effective amount is entirely dependent on the patient's SVF cells and how those specific cells function to effect repair of damaged tissues in the body. The surgeons use their medical training and the patient's history to design a bespoke treatment.

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3. The FDCA does not apply because the SVF cells are not held for sale after traveling in interstate commerce

a. The SVF cells are not held for sale

65. Defendants do not charge for the SVF cells.

66. Defendants do not sell a person's SVF cells to any other individual.

67. Defendants only charge for the SVF Surgical Procedure.

68. Defendants have provided the SVF Surgical Procedure free of charge to hundreds of patients who wished to undergo the SVF Surgical Procedure but were unable to pay.

b. The SVF cells do not travel interstate nor affect interstate commerce

69. The entirety of the procedure performed by Defendants is performed in California. While the Government argues there is interstate commerce because certain fluids used in the surgical procedures cross state lines, this would make every surgical procedure interstate commerce—contrary to the recognition that surgeries are the practice of medicine and exclusively regulated by State governments.

70. The SVF cells are extracted and isolated from a patient in California. The SVF cells are then returned to that patient in California.

71. The SVF cells are not shipped in interstate commerce after they are isolated.

4. Claim One: The SVF Surgical Procedure Is Not An Adulterated Drug

a. SVF Surgical Procedure complies with all California regulations regarding surgical procedures

72. Dr. Elliot Lander and Dr. Mark Berman are California-licensed medical doctors and board-certified surgeons.

73. The operating rooms in which Defendants perform the SVF Surgical Procedure comply with all health and safety standards established by the California State Medical Board for outpatient procedures.

74. Surgical environments can never be absolutely closed or acceptably closed to the extent required of actual drug production. By its very nature, there must be some air exposure during surgery. Further, surgeons operate on patients and humans who cannot be validated for complete sterility as required for drug manufacturing. Indeed, a patient may have a disease (*e.g.*, human immunodeficiency virus or hepatitis) from which no drug could ever be made, yet a patient would not be harmed by re-introduction of their own SVF cells and legally could not be excluded from receiving their own cells.

75. Defendants' method of SVF processing is virtually a closed procedure with the exception of slight exposure to the operating room air through the aperture of a syringe. All processing is done with sterile surgical equipment on a sterile surgical field with minimal exposure to the operating room air through only a small aperture of the syringe.

76. Sterilization is continually validated. (Ex. 309.) First, each use is logged to certify the time and temperature of each surgical pack that is sterilized. (*Id.*) A spore test using the Autoclave Spore Check procedure is done on a weekly basis. (*Id.*) Further, a licensed clinical equipment inspector conducts an inspection on the autoclave twice a year. (*Id.*)

77. The operating room and all equipment are cleaned between each patient according to California accreditation requirements.

78. At no time is there any laboratory involvement—no laboratory personnel, no laminar flow hood, no pipette exposure, no extraneous handling, etc.—thus no risk of cross-contamination.

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b. The SVF cannot be made uniform

79. Defendants do not manufacture any products but perform a surgical procedure.

80. Unlike manufactured drugs, the SVF Surgical Procedure does not produce any cellular- or tissue-based product to uniform specifications for strength, quality, and purity.

81. Uniform specifications would be impossible given the cellular differences in each patient. The cell population used in the SVF Surgical Procedure is unique to each patient, including the specific stem cell count. The outcomes of the SVF Surgical Procedure are uniquely based on the patient's injury and their own cells and cannot be replicated across patients or even with the same patient at different times.

c. The SVF is naturally occurring

82. SVF is the naturally occurring cellular part of the adipose tissue that does not contain the adipocytes (fat cells).

83. The SVF cells have not been altered in any substantive way to change them from their naturally occurring state (*i.e.*, they have the same DNA, same cell type, same flow cytometry markers).

5. Claim Two: The SVF Surgical Procedure is not a misbranded drug

a. SVF Surgical Procedure is not placed in a container and does not require labeling

84. The SVF cells are not placed in any container for preservation, storage, or later use. They are used as part of the same surgical procedure.

85. Defendants have drafted multiple surgical and user manuals regarding how to safely perform the procedure, including contraindications, sterilization techniques, and detailed step-by-step instructions on how to extract, isolate, and re-implant the SVF cells. (*See, e.g.*, Exs. 303-322.)

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86. Defendants drafted the surgical manual and user manual based on their combined 70 years of surgical experience and updated them to include techniques developed during the thousands of SVF Surgical Procedures that Defendants and their affiliated physicians have performed.

87. These surgical manuals were provided to physicians with the CSN-Time Machine® centrifuge and CSN-Time Machine® incubator.

88. Physicians can request additional information regarding how to perform the SVF Surgical Procedure, including attending a demonstration of the entire process.

89. The syringes containing the SVF cells are labeled with the patient's name, date, and the description "SVF" pursuant to well-defined patient identifier protocols.

b. SVF Surgical Procedure does not require a prescription or "Rx" on its label

90. The SVF cells are not placed in any container for preservation, storage, or later use. The SVF cells are transferred between sterile syringes during three washing phases. After the third washing phase, the SVF cells are re-implanted in the patient through direct injection or intravenously.

91. The syringes containing the SVF cells are labeled with the patient's name, date, and the description "SVF" pursuant to well-defined patient identifier protocols.

E. <u>Claims Three, Four, and Five: The Expanded MSC Surgical Procedure is not an adulterated drug and is not misbranded</u>

1. <u>The Expanded MSC Surgical Procedure</u>

92. A patient is eligible for the Expanded MSC Surgical Procedure where the individual has a medical condition that will require multiple treatments, but the individual is unable or unwilling to undergo multiple liposuctions.

93. During Defendants' Expanded MSC Surgical Procedure, a qualified candidate undergoes liposuction at one of Defendants' facilities. Defendants do not perform the remainder of the SVF Surgical Procedure on the harvested adipose tissue in that appointment.

94. In 2017, Defendants would send the harvested unadulterated adipose tissue to a third-party tissue storage company – American CryoStem Corporation ("ACS") – for isolation of the mesenchymal stem cells ("MSC") and storage of the same. Defendants require that any such third-party storage company be a GMP-grade facility.

95. The third party would isolate the MSC cells from the adipose tissue using a technique that is similar to the SVF Surgical Procedure stated above and is performed under GMP laboratory conditions.

96. The third party would then place the MSC cells in a culture, in which the MSC cells begin to replicate (*i.e.*, expand in number), thereby creating a sufficient number of cells for numerous treatments.

97. When requested by a patient, the third party would then ship the patient's expanded MSC cells in a sterile vial to the patient's requested location.

98. The sterile vial containing the MSC cells were labeled with the patient's name, date, and description pursuant to well-defined patient identifier protocols.

99. After receiving the requested amount of Expanded MSC cells from the third party in a labeled sterile vial, Defendants deploy the Expanded MSC cells into the original patient.

100. Defendants ceased utilizing ACS in connection with the Expanded MSC procedure in or around December 2017, following notice from the FDA that ACS was not complying with GMP regulations.

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2. The Expanded MSC cells are not held for sale and do not fall within the FDCA

101. Defendants do not charge for the Expanded MSC cells.

102. Defendants do not sell a patient's Expanded MSC cells to any other individual.

103. Defendants only charge for liposuction of the patient's adipose tissue.

104. Patients paid a separate facility fee for the banking or storage of the Expanded MSC cells.

3. Claim Three: There is no adulteration of the Expanded MSC Surgical Procedure because the facility complies with all Good Manufacturing Practices that are required by the FDA

105. Defendants do not perform any task other than perform a liposuction surgery on a patient. Defendants then send the adipose tissue to a third-party GMP-grade facility.

106. Defendants do not adulterate, manufacture, process or store the adipose tissue in any respect.

107. After Defendants provide the adipose tissue, the MSC cells are isolated at the GMP-grade facility.

108. ACS represented to Defendants that they were a GMP-grade facility.

109. Defendants inspected the ACS facility to verify GMP compliance and confirmed the sterility of ACS's expanded cell products before contracting with ACS to isolate MSC cells from adipose tissue, expand the cells, and then store the expanded cells.

110. However, Defendants ceased working with ACS in or around December 2017 following notice from the FDA that ACS was not complying with GMP regulations.

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4. Claim Four: There is no misbranding of the Expanded MSC Surgical Procedure

111. Defendants have drafted multiple surgical and user manuals regarding how to safely perform the liposuction procedure, including contraindications, sterilization techniques, and detailed step-by-step instructions on how to harvest the adipose tissue.

112. Defendants label the harvested adipose tissue with the patient's name, date of harvest, and description of material pursuant to patient identifier protocols.

5. Claim Five: Defendants do not receive a misbranded drug through the Expanded MSC Surgical Procedure

113. Defendants provide detailed instructions through the various surgical manuals (deployment manuals) on how to safely redeploy the expanded MSC cells.

114. Except that the liposuction and deployment will occur on different days, the deployment procedure of the SVF cells and Expanded MSC cells is the same.

115. The Expanded MSC cells are returned to a physician who has been trained in the entirety of the SVF Surgical Procedure as well as Expanded MSC protocols, including the IRB-approved deployment protocols for the expanded MSC cells.

116. At all times, the vials containing the Expanded MSC cells are labeled with the patient's name, date, and description pursuant to patient identifier protocols.

117. Defendants ceased working with ACS in or around December 2017 following notice from the FDA that ACS was not complying with GMP regulations. Defendants have not received any MSC cells from ACS since then.

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F. Claims Six and Seven: The SVF/ACAM2000 Surgical Procedure is not an adulterated or misbranded drug

1. The SVF/ACAM2000 Surgical Procedure

118. The SVF/ACAM2000 Surgical Procedure is a limited experimental treatment only available to individuals with terminal cancer for whom traditional treatment has failed.

119. ACAM2000 is an FDA-approved vaccine with minimal side effects.

120. ACAM2000 is generally used as a vaccine for smallpox; however, the vaccine is not derived from the smallpox virus and cannot cause smallpox.

121. In addition, ACAM2000 is an oncolytic virus, meaning that it has the ability to kill cancer cells.

122. Defendants used ACAM2000 for an off-label purpose, which is explicitly permitted under the FDCA. Physicians may utilize any FDA-approved drug for an off-label purpose that they determine is the best course of treatment for their patients.

123. The entire stockpile of ACAM2000 has been purchased by the federal government for inclusion within the country's Strategic National Stockpile and may only be distributed by specific government agencies. It is not publicly available, but researchers may request vials for studies.

124. Defendants obtained ACAM2000 from StemImmune for a planned safety study with the United States Department of Defense.

125. Defendants developed a safety study to test the risks and potential benefits of the SVF/ACAM2000 Surgical Procedure in conjunction with Aladar Szalay Ph.D., a world leader in oncolytic virus studies, who had previously treated 120 individuals through studies.

126. Defendants developed the safety study based on the FDA's prior request for human safety data in connection with their IDE application.

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127. To qualify for the safety study, the study participant is evaluated by an independent board of three leading oncologists and must have (1) Stage 4 metastatic cancer, (2) no traditional treatment options, (3) life expectancy of three to six months, and (4) be ambulatory and able to undergo liposuction.

128. The study participants sign lengthy, IRB-approved informed consent forms regarding the investigational nature of the treatment.

129. When ACAM2000 is injected into a patient, the patient's immune system immediately attacks the injected virus; thereby creating antibodies to the vaccine but also killing the virus before it is able to affect the cancer cells.

130. Stem cells are used as a "Trojan horse," transporting and protecting the virus so that the body's immune system does not destroy the virus before it can reach the cancer cells.

131. The ACAM2000, transported and protected via the SVF, then attacks and kills the cancer cells.

132. During the SVF/ACAM2000 Surgical Procedure, the physician isolated SVF cells using the SVF Surgical Procedure technique; then, the physician added a small amount of ACAM2000 to the isolated SVF cells.

133. Next, the physician placed the SVF/ACAM2000 into the CSN Time Machine incubator for fifteen minutes.

134. Finally, the SVF/ACAM2000 was administered to the study participant from which the SVF was removed.

135. The study participants were followed closely for adverse events.

136. To date, there have been no serious adverse events linked to the SVF/ACAM2000 Surgical Procedure.

137. Instead, in numerous cases, the tumors shrank and three and a half years later, ten of the twenty-six terminal cancer study participants are still alive.

138. Defendants cannot perform the SVF/ACAM2000 Surgical Procedure without access to ACAM2000.

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139. Defendants have not performed the SVF/ACAM2000 Surgical Procedure since August 25, 2017, when the FDA confiscated vials of ACAM2000 from StemImmune's (research sponsor) laboratories at the University of California, San Diego.

2. The SVF/ACAM2000 Surgical Procedure is not sold nor do the SVF cells affect interstate commerce

a. Defendants Do Not Charge for the SVF/ACAM2000 Surgical Procedure

140. Defendants do not charge study participants for the SVF/ACAM2000 Surgical Procedure.

141. Indeed, Defendants paid for independent laboratory and radiology fees for all study participants.

b. The SVF cells do not travel interstate nor affect interstate commerce

142. The entirety of the SVF/ACAM2000 Surgical Procedure is completed in California.

143. The SVF cells are extracted and isolated from a study participant in California. The ACAM2000 is immediately added the SVF cells and then the SVF cells are returned to that study participant in California.

144. The SVF/ACAM2000 cells are not shipped in interstate commerce.

3. Claim Six: There is no adulteration of the SVF/ACAM2000 Surgical Procedure

a. SVF/ACAM2000 Surgical Procedure complies with all California regulations regarding surgical procedures

145. Dr. Elliot Lander and Dr. Mark Berman are California-licensed medical doctors and board-certified surgeons.

146. The FDA approved ACAM2000 as a prescription pharmaceutical in 2007.

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147. Defendants would receive ACAM2000 from StemImmune on the day of the procedure in its original sealed vial.

148. The operating rooms in which Defendants performed the SVF/ACAM2000 Surgical Procedure comply with all health and safety standards established by the California State Medical Board for outpatient procedures.

149. Surgical environments can never be absolutely closed or acceptably closed to the extent required of actual drug production. By its very nature, there must be some air exposure during surgery.

150. Defendants' method of SVF/ACAM2000 processing was virtually a closed procedure with the exception of slight exposure to the operating room air through the aperture of a syringe. All processing was done with sterile surgical equipment on a sterile surgical field with minimal exposure to the operating room air through only a small aperture of the syringe.

151. Sterilization is continually validated. (Ex. 309.) First, each use is logged to certify the time and temperature of each surgical pack that is sterilized. (*Id.*) A spore test using the Autoclave Spore Check procedure is done on a weekly basis. (*Id.*) Further, a licensed clinical equipment inspector conducts an inspection on the autoclave twice a year. (*Id.*)

152. The operating room and all equipment are cleaned between each patient according to California accreditation requirements.

153. At no time was there any laboratory involvement—no laboratory personnel, no laminar flow hood, no pipette exposure, no extraneous handling, no bulk or batch processing, etc.—thus no risk of cross-contamination.

154. The ACAM2000 added to the SVF cells was manufactured pursuant to FDA good manufacturing practices regulations.

b. The SVF/ACAM2000 cannot be made uniform

155. Defendants do not manufacture any products but perform a surgical procedure.

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156. Unlike manufactured drugs, the SVF/ACAM2000 Surgical Procedure does not produce any cellular- or tissue-based product to uniform specifications for strength, quality, and purity.

157. Uniform specifications would be impossible given the cellular differences in each patient. The cell population used in the SVF/ACAM2000 Surgical Procedure is unique to each patient, including the specific stem cell count. The outcomes of the SVF/ACAM2000 Surgical Procedure are uniquely based on the patient's own cells and cannot be replicated across patients or even with the same patient at different times.

4. Claim Seven: There is no misbranding of the SVF/ACAM2000 Surgical Procedure

a. SVF/ACAM2000 Surgical Procedure is not placed in a container and does not require prescription drug labeling

158. The SVF/ACAM2000 cells were not placed in any container for preservation, storage, or later use. They were used as part of the same surgical procedure.

159. The syringes containing the SVF/ACAM2000 cells were labeled with the study participant's name and date pursuant to well-defined patient identifier protocols.

160. The SVF/ACAM2000 Surgical Procedure was only completed through Defendants' medical practices. It was not part of the Cell Surgical Network.

161. Defendants thoroughly explained the potential risks and benefits of the procedure to study participants, who acknowledged their understanding by signing an informed consent form.

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b. SVF/ACAM2000 Surgical Procedure does not require a prescription or "Rx" on its label

162. The SVF/ACAM2000 cells were not placed in any container for preservation, storage, or later use. The SVF cells were transferred between sterile syringes during three washing phases. After the third washing phase, ACAM2000 was added to the SVF cells, and the SVF/ACAM2000 Cells were incubated for fifteen minutes in the operating room and re-implanted in the patient through direct injection or intravenously.

163. The syringes containing the SVF/ACAM2000 cells were labeled with the patient's name and date pursuant to well-defined patient identifier protocols.

III. FINDINGS OF FACT RELATING TO DEFENDANTS' AFFIRMATIVE DEFENSE: LACK OF ADEQUATE NOTICE

164. The FDA released a draft guidance in 2014 that proposed substantive changes that interpret the SSP Exception to exclude surgical procedures that would otherwise qualify for exemption by requiring that the patient's transplanted HCT/P be implanted in its "original form," which is very narrowly defined and otherwise limits the types of surgical procedures that would fall within the SSP Exception. (Ex. 89.)

165. The "original form" language is not included anywhere in the regulation, see 21 C.F.R. § 1271.15(b).

166. The FDA adopted the draft guidance in December 2017. (Ex. 87.) The adoption of the guidance is not a valid modification of the existing regulation because it was not subject to a proper notice and comment period and was not signed by a United States Senate confirmed officer.

167. In 2010, Defendants began developing the SVF Surgical Procedure as part of their surgical practices and as a cutting-edge surgical procedure designed to address their patients' medical concerns.

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168. Defendants initiated their research and development of the SVF Surgical Procedure based in large part on the unambiguous position of the FDA that a same day surgical procedure such as the SVF Surgical Procedure would not be subject to FDA regulations.

169. Defendants have been successfully performing point of care investigative deployment of autologous adipose SVF since 2010 and through CSN since 2012.

170. Defendants have relied upon the FDA's twenty-year interpretation while developing and expanding their business. Defendants have expended significant sums to develop the SVF Surgical Procedure.

171. Defendants have collected an abundance of data, developed IRB-approved protocols and maintain medical malpractice insurance for every member of the CSN network.

172. Further, the 2017 Guidance states that, for some health care providers, the FDA will not allege any violation for three years. However, the FDA fails to identify to whom the three-year grace period applies. Instead, the FDA has arbitrarily enforced the new requirement, singling out Defendants yet declining to address medical procedures that involve significantly more manipulation of the HCT/Ps.

173. The FDA conducted an inspection of the two CSCTC facilities in July 2017, before the Guidance was finalized. The FDA provided written notices of inspection, to which Defendants responded. The FDA provided no further notice to Defendants.

174. Instead, the FDA filed the complaint in May 2018, well before the three-year grace period expired.

175. The Government does not purport to regulate substantially similar practices. For example, the FDA allows the use of certain stem cells extracted from bone marrow even though the cells are essentially identical to the cells found

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in adipose tissue. Like the SVF Surgical Procedure, when bone marrow is subjected to centrifugation, the stem cells are isolated, and the leftover adipose tissue is discarded.

176. Neurosurgeons similarly isolate autologous fat from around the patient's umbilical area, crush that fat with a "Spence Cranioplastic roller" to transform it into a thin foil on a separate table in the operating room, and return that "foil" to the patient during the same procedure to repair, not cushion the brain's lining. This is far more processing of the tissue than Defendants' SVF Surgical Procedure yet exempted from FDA regulation because it is appropriately recognized as the practice of medicine.

177. Further, vein or artery grafts are often used for coronary artery bypass surgery. The vein is harvested and processed, including sizing, to prepare it for other surgical uses than what it was intended for, but it is not subject to FDA regulation.

IV. CONCLUSIONS OF LAW

A. The SSP Exception applies to the SVF Surgical Procedure

1. The appropriate unit of comparison is the SVF Cell itself. The SSP Exception unambiguously demands that the characterization of the removal focus on the target of the removal—either the cell or the tissue—rather than the largest system removed. The SSP Exception explicitly includes both "cells" and "cellular-based products," through its use of the term "HCT/Ps." *See* 21 C.F.R. § 1271.3(d); 21 C.F.R. § 1271.15(b).[2] Cells can only be removed from a patient along with larger systems, such as the tissues or organs that they make up.

[2] 21 C.F.R. § 1271.10 is inapplicable here because the stem cells are not biologics regulated under the PHS Act. Therefore, there is no requirement that the cells be "minimally manipulated."

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2. The SVF Surgical Procedure is autologous because it involves collecting a patient's cell population naturally occurring in the patient's adipose tissue and relocating that cell population back into the same patient.

3. The SVF Surgical Procedure is a single outpatient procedure.

4. Defendants "removes HCT/Ps from an individual and implants such HCT/Ps." *See* 21 C.F.R. § 1271.15(b). The SSP Exception does not have any requirement that the HCT/Ps be unaltered before reinsertion into the patient. While the Government attempts to assert 21 C.F.R. § 1271.10 applies, the regulation is entirely inapplicable because the stem cells are not biologics regulated under the PHS Act. Therefore, there is no requirement that the cells be "minimally manipulated."

5. Regardless, the SVF cells are not altered and remain "such HCT/P" that was removed from the patient. The SVF cells retain their essential phenotypic and genotypic traits. SVF's mesenchymal stem cells are regenerative cells that promote healing and regeneration of new tissue. SVF's mesenchymal stem cells also provide modulation of immune reactions and anti-inflammatory properties. SVF's progenitor cells operate as stem cells depending on the environment in which they are placed. Progenitor stem cells similarly provide regenerative effects, including regulation or amelioration of some conditions. The SVF cells that are re-implanted remain regenerative cells that modulate immune reactions, provide anti-inflammatory properties, and provide regenerative effects.

6. In conclusion, the SSP Exception applies to the SVF Surgical Procedure.

1. <u>The FDA's interpretation of the SSP Exception is not entitled to deference</u>

a. The SSP Exception is unambiguous on its face

7. The SSP Exception is unambiguous. *See Kisor v. Wilkie*, 139 S. Ct. 2400, 2414 (2019) ("[T]he possibility of deference can arise only if a regulation is

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genuinely ambiguous."); *see also Christensen v. Harris County*, 529 US 576, 588 (2000) ("The regulation in this case, however, is not ambiguous . . . . To defer to the agency's position would be to permit the agency, under the guise of interpreting a regulation, to create *de facto* a new regulation.").

8. Here, the FDA, under the guise of interpretation, is attempting to substantively change, and thereby create, a new regulation that the HCT/Ps must remain in their "original form." The Supreme Court has repeatedly rebuked such efforts. *See Azar v. Allina Health Serv.*, 139 S. Ct. 1804, 1810-11 (2019) (requiring substantive regulatory changes to comply with APA notice and comment requirements and requirements to meet with stakeholders). The adoption of the 2017 Guidance is not a valid modification of the existing regulation because it was not subject to a proper notice and comment period and was not signed by a United States Senate-confirmed officer.

9. 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. § 1271.15(b). The regulation is not ambiguous. Under the explicit terms of the regulations, the SVF Surgical Procedure falls within the exception as the SVF cells are removed and implanted in the same surgical procedure. The FDA's interpretation that seeks to create ambiguity is not entitled to deference.

b. The FDA's interpretation of the SSP Exception is unreasonable

10. The Government's interpretation of the SSP Exception is unreasonable and creates enforcement inconsistency: it makes no logical sense to assert that the SSP Exception applies to a procedure where physical cutting is necessary to isolate needed tissue but not where chemical "cutting" is necessary to isolate needed cells—especially given the use of both "cells" and "tissue" in the SSP Exception. *See Kisor*, 139 S. Ct. at 2415–16 ("[T]he agency's reading must

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fall within the bounds of reasonable interpretation . . . a requirement an agency can fail.").

11. A characterization that focuses on the target of the removal is more reasonable than one that includes everything that was removed. Undoubtedly, most if not all surgical removals take out more biological matter than what was targeted. Take, for example, the removal of an artery for implantation back in the body. *See* U.S. Dep't Health & Human Services, Food & Drug Admin., *Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception* (Nov. 2017) ("SSP Exception Guidance Document") ("Examples [of procedures considered same surgical procedures] include autologous skin grafting, and coronary artery bypass surgery involving autologous vein or artery grafting."). Along with the needed artery, a surgeon may remove some blood. She may also remove more artery tissue than what will ultimately be needed. The SSP Exception does not require that the surgeon implant everything that was removed—including the removed blood and excess artery—for it to apply. Similarly, if a piece of muscle and its overlying fascia were removed in order to provide a fascial graft, the muscle (tissue) would no longer have its ability to repair, reconstruct or replace, but the "tissue product" (*i.e.* the fascia) would still retain its biological characteristics and could be utilized. But again, the surgeon is not required to implant everything that was removed. The SSP Exception Guidance expressly recognizes that processing steps such as "rinsing [and] cleansing" or "sizing and shaping," including "dilation," "cutting," "meshing," of HCT/P's do not take a procedure out of the SSP Exception. (*See* Ex. 87 at 9–10.)

12. The logic that not all that is removed must be implanted applies to the SVF Procedure as well. The SSP Exception would unobjectionably apply to a procedure that removed only SVF cells and then implanted only those same SVF cells back into the patient. But that technology does not yet exist. Accordingly,

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Defendants must remove SVF cells as part of a larger biological system. And like the surgeon who washes the blood from the artery and cuts it down to the right size, Defendants use an enzyme and a centrifuge to isolate the targeted HCT/P's from the unneeded biological material that was also removed.

13. Finally, this reading of the SSP Exception is entirely consistent with the Government's assertion that the implanted HCT/P's be "in the form removed from the patient." It is also consistent with the Guidance Document's statement that "[a]n HCT/P remains 'such HCT/P' when it is in its original form." (Ex. 87 at 7.) If SVF cells are removed from a patient and those same cells are implanted back into the same patient without alteration of the cells themselves, they are "in the form removed" and "in [their] original form"—even when they were removed along with other biological material that was not ultimately implanted back. As explained above, the phenotypic and genotypic traits of the SVF cells do not change, further demonstrating that the same SVF cells that were removed are re-implanted.

14. The FDA's unreasonable interpretation is not entitled to deference.

c. The FDA's interpretation should not be considered because it constitutes unfair surprise

15. The FDA's interpretation of "such HCT/Ps" under the 2017 Guidance pronounces an entirely new position regarding the applicability of the SSP Exception—and directly contradicts twenty years of FDA pronouncements on the issue, resulting in "unfair surprise" to Defendants and others providing autologous SVF surgical therapies.

16. Further, the FDA informed the public, including Defendants, that they would have a three-year grace period (until December 2020) to determine how best to regulate procedures involving HCT/Ps. (*See* Ex. 87 at 21.) The FDA did not wait for that three-year period to end for Defendants, even though Defendants are

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one of the few organizations that had actually been working with the FDA on an IDE application through the Center for Biological Evaluation and Research.

17. The FDA's interpretation constitutes unfair surprise and is not entitled to deference.

B. <u>The Government exceeds its Constitutional authority because neither the SVF Surgical Procedure, Expanded MSC Surgical Procedure, nor SVF/ACAM2000 Surgical Procedure are sold in interstate commerce</u>

18. The FDA unlawfully extends its authority because it attempts to extend federal regulations to an article that does not affect interstate commerce, as required by the Commerce Clause, U.S. Const. art. I, § 8, cl. 3, and that is not shipped in interstate commerce, as defined by the FDCA, 21 U.S.C. § 321(b).

19. Because the SVF cells, Expanded MSC cells, and SVF/ACAM2000 cells are not shipped or sold in interstate commerce, the FDA's interpretation not only exceeds the scope of the Commerce Clause, but it also exceeds the FDA's statutory authority. *See 62 Cases, More or Less, Each Containing Six Jars of Jam v. United States*, 340 U.S. 593, 600 (1951) ("In our anxiety to effectuate the congressional purpose of protecting the public, we must take care not to extend the scope of the statute beyond the point where Congress indicated it would stop."); *see Panama Ref. Co. v. Ryan*, 293 U.S. 388, 430 (1935) ("[T]here are limits of delegation which there is no constitutional authority to transcend."). Section 331(k) prohibits "any . . . act with respect to a food, drug, device, tobacco product, or cosmetic, if such act is done while such article is held for sale (whether or not the first sale) ***after shipment in interstate commerce*** and results in such article being adulterated or misbranded." 21 U.S.C. § 331(k) (emphasis added). The FDCA defines "interstate commerce," as "(1) commerce between any State or Territory and any place outside thereof, and (2) commerce within the District of Columbia or within any other Territory not organized with a legislative body." 21

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U.S.C. § 321(b). Because the article must be ***shipped*** in interstate commerce, rather than merely affect interstate commerce, the scope of the FDCA does not reach to the full extent of the Commerce Clause.

20. Indisputably, the SVF cells are not shipped in interstate commerce.

21. As to the Expanded MSC Surgical Procedure, the patients are not paying for any product (nor could they pay for their own cells) but are instead paying for a surgical procedure and separately for isolation and storage.

22. Finally, the SVF/ACAM2000 cells are not shipped in interstate commerce. Nor do the study participants pay for the SVF/ACAM2000 Surgical Procedure.

23. Finally, the uniqueness of the SVF cells used in each surgical procedure present further constitutional implications. The FDA is seeking to regulate not only an individual's private relationship with her physician, but also the individual's use of her body and medical decisions. These are not a "'class of activities' that have a substantial effect on interstate commerce." *Gonzales v. Raich*, 545 U.S. 1, 17 (2005). Rather, these are activities that implicate fundamental rights of privacy and bodily autonomy. *See Griswold v. Connecticut*, 381 U.S. 479, 485 (1965). To hold that the FDA can regulate the SVF Surgical Procedure and its related procedures as if the SVF cells were any other commodity ignores the fundamental and constitutional difference between drugs shipped in interstate commerce and an individual's right to control his/her own body and the cells therein.

C. <u>The FDA does not have authority to regulate physicians performing surgery, instead this is a health and safety concern that is exclusively a state's jurisdiction</u>

24. Pursuant to the FDCA, the FDA has the authority to regulate drugs (21 U.S.C. § 321), and pursuant to the Public Health Service Act (42 U.S.C. § 201), the authority to regulate biological products. However, Congress explicitly

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rejected "any intent to directly regulate the practice of medicine." *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 ¶ n.5 (2001) (citing Beck & Azari, FDA, Off–Label Use, and Informed Consent: Debunking Myths and Misconceptions, 53 Food & Drug L.J. 71, 72 (1998) (stating that "[o]ff-label use is widespread in the medical community and often is essential to giving patients optimal medical care, both of which medical ethics, FDA, and most courts recognize")); *U.S. ex rel. Modglin v. DJO Glob. Inc.*, 114 F. Supp. 3d 993, 999 (C.D. Cal. 2015), *aff'd sub nom. United States v. DJO Glob., Inc.*, 678 F. App'x 594 (9th Cir. 2017).

25. Defendants are physicians who are practicing medicine and performing surgery using FDA-cleared medical devices and FDA-approved prescription pharmaceuticals.[3] Title 21 of the United States Code section 360 exempts "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" from registering with the FDA. The FDA cannot modify this law via regulation, particularly not in a manner that violates notice and comment procedure and the Appointments Clause of the United States Constitution. And, as courts have recognized, the FDA generally does not regulate doctors—particularly those using office-based drugs or biologicals for the sole use of their patients. *Buckman*, 531 U.S. at 350; *see also Houston v. Medtronic, Inc.*, No. 2:13–cv–01679–SVW (SHx), 2014 WL 1364455, *1 n.1 (C.D. Cal. April 2, 2014) ("Physicians are permitted to use Class III devices in off-label manners"); *U.S., ex rel. Modglin*, 114 F. Supp. 3d at 999; *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196, 200 (S.D.N.Y. 2015). Thus, at a

[3] The Government's argument that the SVF Surgical Procedure falls within the FDCA because it is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man" is illogical. Based on that standard, every surgery and medical procedure would fall under the province of the FDA.

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minimum, the Defendants' actions are protected as lawful "off-label" uses of FDA-approved drugs and medical devices.

26. Indeed, allowing the FDA to expand its regulatory authority to encompass Defendants' medical procedures would allow the FDA to regulate not only an individual's private relationship with his/her physician, but also the individual's use of his/her body and medical decisions. *See Roe v. Wade*, 410 U.S. 113 (1973). These are activities that implicate fundamental rights of privacy and bodily autonomy. *See Griswold*, 381 U.S. at 485. Thus, to hold that the FDA can regulate the SVF Surgical Procedure and its related procedures as if the SVF cells were a saleable commodity ignores the fundamental and constitutional differences between drugs and an individual's right to control her body.

27. Defendants are permitted to use FDA-cleared medical devices and FDA-approved pharmaceuticals in the manner best suited to care for and treat their patients. While SVF cells are not a drug for the reasons stated above, and even if it was, each step of the process for the SVF Surgical Procedure, Expanded MSC Surgical Procedure, and SVF/ACAM2000 Surgical Procedure uses FDA-cleared and/or approved medical devices and pharmaceuticals. Defendants are practicing medicine, not engaging in the creation of pharmaceuticals.

D. <u>There is no adulteration as each procedure meets all California regulations governing surgery centers and/or complies with FDA GMP requirements</u>

1. <u>California law governs the safety of surgery centers</u>

28. Defendants have continually complied with California law governing surgery centers. California law provides that "[n]o association, corporation, firm, partnership, or person shall operate, manage, conduct, or maintain an outpatient setting in this state, unless the setting is []: . . . [a]n outpatient setting accredited by an accreditation agency approved by the division pursuant to this chapter." Cal. Health & Safety Code § 1248.1(g). Further, the Medical Board of California has

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set minimum standards for accreditation, which each accreditation agency must adopt to ensure the health and safety of outpatient procedures. *Id.* at § 1248.15(a). These minimum requirements relate to (1) proper licensing of health staff, (2) facility safety and emergency training requirements, (3) maintenance of clinical records, (4) a system for patient care and monitoring procedures, and (5) quality assessment and improvement. *Id.* The accreditation agency must inspect the facility as often as necessary and no less often than once every three years. *Id.* at § 1248.35.

29. Drs. Berman and Lander have complied with California law governing health and safety requirements of outpatient surgery facilities. Defendants met all requirements governing patient rights and responsibilities; governance; administration; quality of care; quality management and improvement; maintenance of clinical records and health information; infection prevention, control, and safety; general safety; facilities and environment, anesthesia services; surgical and related services; and pharmaceutical services.

2. The SVF Surgical Procedure does not manufacture drugs

30. Defendants' SVF Surgical Procedures are patently distinct from traditional pharmaceutical drug production. The stereotypical pharmaceutical drug has a chemical composition that does not vary over time, and this uniformity makes it easy for the FDA to treat the drug uniformly with respect to production, inspection, labeling and, thus, sales. In comparison, the stem cells that Defendants remove from a patient for later reinsertion lack this uniformity, and thus cannot be mass-produced or effectively labeled and sold. And, significantly, unlike traditionally manufactured pharmaceutical drugs, SVF—like the BRCA1 and BRCA2 genes at issue in *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013)—cannot be patented because they are naturally-occurring human body parts that are a "product of nature and not patent eligible merely because it has been isolated." *Id.* at 579. Thus, applying a regulatory regime

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crafted to oversee the pharmaceutical drug industry to naturally-occurring stem cells simply makes no practical sense; especially where the SVF is the sole property of the patient, could never be made the same way twice, and could never be sold.

3. The Expanded MSC cells were isolated in a GMP facility

31. Further, Defendants' Expanded MSC Surgical Procedure at a facility that complies with all GMP regulations. Defendants transmit adipose tissue to a GMP compliant facility, and only once it arrives at the GMP facility are the MSC cells isolated. Accordingly, there is no adulteration as the entirety of the isolation complies with FDA regulations regarding good manufacturing practices.

4. SVF/ACAM2000 merely includes the addition of an FDA-approved pharmaceutical

32. The SVF/ACAM2000 Surgical Procedure begins with isolating SVF cells in the Beverly Hills or Rancho Mirage surgical center, as detailed above. Next, Defendants incorporate an FDA-approved and GMP-manufactured pharmaceutical to the SVF cells. There is no adulteration of the SVF/ACAM2000 cells.

E. There is no misbranding because each procedure is completed by a trained physician and Defendants provide adequate directions for use

33. Labels on prescription drugs and devices provide the physician, a learned intermediary, with all of the information that the physician needs to make an informed decision regarding course of conduct. *See, e.g.*, *T.H. v. Novartis Pharm. Corp.*, 4 Cal. 5th 145, 164 (2017) ("In the context of prescription drugs, a manufacturer's duty is to warn physicians about the risks known or reasonably known to the manufacturer . . . . If the manufacturer provides an adequate warning to the prescribing physician, the manufacturer need not communicate a warning directly to the patient who uses the drug."); *Motus v. Pfizer Inc.*, 196 F. Supp. 2d

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984, 990-91 (C.D. Cal. 2001) *aff'd sub nom.* 358 F.3d 659 (9th Cir. 2004) ("California follows the learned intermediary doctrine").

34. Defendants provide surgical manuals, user manuals, and the detailed IRB-approved deployment protocols with the CSN-Time Machine® centrifuge and CSN-Time Machine® incubator. *See* 21 U.S.C. § 321(m) (defining "labeling" as any material accompanying a drug or device). Additionally, physicians can request additional information regarding how to perform the SVF Surgical Procedure or Expanded MSC Procedure including attending a demonstration of the entire procedure.

35. The information contained within the surgical manuals, user manuals, and deployment protocols are based upon clinical proof as shown by the numerous articles demonstrating both effectiveness and safety of the SVF Surgical Procedure. Defendants' clinical studies have continuously operated under an IRB protocol and review. *Contra United States v. Cole*, 84 F. Supp. 3d 1159, 1169 (D. Or. 2015) (granting summary judgment where the defendants "conducted no controlled studies and collected no clinical data").

36. The SVF cells are autologous, rarely leave the surgical center, except for occasional injections by an interventional radiologist that signs a proper chain of custody document, and are implanted immediately into the patient. The syringes are labeled with the patient's name, date, and the description "SVF" pursuant to well-defined patient identifier protocols.

37. As part of the Expanded MSC Surgical Procedure, Defendants label the adipose tissue with the patient's name, date, and description of biologic material pursuant to patient identifier protocols before shipping to the third party GMP facility. The third party then isolates, expands, and labels the vials containing MSC cells pursuant to the same patient identifier protocols.

38. The SVF/ACAM2000 Surgical Procedure is only conducted by Defendants given the Government's strict limits on access to ACAM2000. The

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participants in the clinical trials have signed lengthy informed consent forms that notify them of the potential risks of the procedure. Again, it is illogical to require any label on the SVF/ACAM2000 cells because the cells are autologous, never leave the surgical center, and are implanted immediately into the study participants.

39. Defendants have performed the SVF Surgical Procedure over 12,000[4] times for a variety of medical conditions. (*See* Ex. 363 at 2; Ex. 351.) Defendants' patients are followed for short-term and long-term outcomes as well as any adverse medical events. (Ex. 351.) These studies demonstrated that the procedure effectively treated a variety of conditions, with the most positive outcomes involving orthopedic conditions, and minimal adverse events that primarily related to pain from the liposuction. (*Id.*) Thus, the instructions for use are based on adequate clinical studies and data.

40. Additionally, the Government's allegation that at a minimum there should be an "Rx" symbol is irrational. The procedures do not require any prescription because they are surgical procedures. The SVF cells and SVF/ACAM2000 Cells are not placed in any container for preservation, storage, or later use. The SVF cells are transferred between sterile syringes during three washing phases. After the third washing phase, the SVF cells are re-implanted in the patient through direct injection or intravenously (or mixed with ACAM2000 then re-implanted). Again, the SVF cells in each of the surgical procedures are labeled pursuant to the standard of care in surgical procedures.

[4] This number includes the 5,000 to 6,000 procedures that Drs. Berman and Lander have completed and those completed by their research partners.

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F. The Government lacks standing to seek injunctive relief for the SVF/ACAM2000 Surgical Procedure and Expanded MSC Surgical Procedure

41. Article III standing requires a present case or controversy, and it is well-settled that "[p]ast exposure to illegal conduct does not in itself show a present case or controversy regarding injunctive relief . . . ." *Lujan v. Defenders of Wildlife*, 504 US 555, 564 (1992).[5] The Ninth Circuit has explained that to satisfy the standing requirements under *Lujan*, a plaintiff seeking prospective injunctive relief "must demonstrate that he has suffered or is threatened with a concrete and particularized legal harm, coupled with a sufficient likelihood that he will again be wronged in a similar way." *Bates v. United Parcel Serv., Inc.*, 511 F.3d 974, 985 (9th Cir. 2007) (citations and quotations omitted); *see also Chapman v. Pier 1 Imports (U.S.) Inc.*, 631 F.3d 939, 946 (9th Cir. 2007) (en banc) (citations and quotations omitted) (holding a plaintiff "must demonstrate a real and immediate threat of repeated injury in the future" for Article III injunctive relief standing). The party asserting the claim has the burden of establishing these elements. *Chandler v. State Farm Mut. Auto. Ins. Co.*, 598 F.3d 1115, 1122 (9th Cir. 2010). A plaintiff must demonstrate standing separately for each form of relief sought. *Los Angeles v. Lyons*, 461 U.S. 95, 109 (1983) (notwithstanding the fact that plaintiff had standing to pursue damages, he lacked standing to pursue injunctive relief).

42. The Government has not met its burden of establishing standing to pursue injunctive relief regarding the SVF/ACAM2000 Surgical Procedure

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[5] Defendants acknowledge that the Government has Article III standing under *Lujan* and does not need to establish the general requirements for standing to bring an action. *See Consumer Fin. Protection Bureau v. Gordon*, 819 F.3d 1179, 1187. However, the Government is still required to make a showing that it has standing to pursue injunctive relief, i.e. that there is a showing that the defendants' conduct is likely to recur. *Id.* at 1197-98.

because Defendants stopped performing the procedure well before the initiation of this lawsuit and have no intention of performing the procedures absent formal regulatory approval or confirmation that the SVF/ACAM2000 Surgical Procedure is not governed by the FDCA, but rather is the practice of medicine.

43. The Government has not met its burden of establishing standing to pursue injunctive relief regarding the Expanded MSC Surgical Procedure using ACS because Defendants stopped performing the procedure using ACS facilities well before the initiation of this lawsuit and have no intention of performing the procedures using ACS facilities absent the FDA's finding that ACS meets all GMP regulations.

G. <u>The Government arbitrarily enforces the SSP Exception</u>

44. The Government's actions depriving Defendants of their property are arbitrary and capricious and fail to provide adequate due process. Due process "bar[s] certain [arbitrary wrongful] government actions regardless of the procedures used to implement them." *Daniels v. Williams*, 474 US 327, 331 (1986). An agency's decision to modify regulations must be rational, based on relevant factors and within the scope of the agency's authority. *Motor Veh. Mfrs. Ass'n v. State Farm Ins.*, 463 U.S. 29, 42-43 (1983). The exacting standards placed on agency decision is required because "the strength of the modern government[] can become a monster which rules with no practical limits on its discretion." *New York v. United States*, 342 U.S. 882, 884 (1951) (dissenting opinion). Finally, where a defendant has modified its behavior based on the prior statements, the agency's action is subject to closer review. *See Nat. Gas Pipeline Co. of Am. v. Fed. Energy Reg. Comm.*, 590 F2d 664 (7th Cir. 1979) (finding agency acted unreasonably when it substantively modified requirements after the company relied on them and acted to its detriment).

45. As explained above, the 2017 Guidance substantively amends 21 C.F.R. § 1271.15 by adding new language (and requirements) to the SSP

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Exception. The FDA fails to provide any meaningful analysis as to why its longstanding understanding of the SSP Exception required change. The FDA's decision to modify the regulations is irrational.

46. Further, the 2017 Guidance states that, for some health care providers, it will not allege any violation for three years. However, the FDA fails to identify to who the three-year grace period applies. Instead, the FDA has arbitrarily enforced the new requirement, singling out Defendants yet declining to address medical procedures that involve significantly more manipulation of the HCT/Ps.

47. The Government fails to provide sufficient reasoning for its arbitrary and capricious actions. The FDA's actions cannot stand, especially here where Defendants relied upon the longstanding regulations to develop a successful new surgical technique and expand their business. An agency decision can be overturned if it is (a) arbitrary and capricious, (b) illegal (fails to follow the APA) or (c) unconstitutional (violating Appointments Clause and property and privacy rights). The FDA's decisions and actions in this case meet all three standards and Defendants are entitled to attorneys' fees due to wrongful prosecution of invalid regulations.

V. DEFENDANTS ARE ENTITLED TO ATTORNEYS' FEES

48. Congress enacted the Equal Access to Justice Act under 28 U.S.C. § 2412 ("Section 2412") to limit the United States government's immunity to an award for costs and fees. Section 2412 was designed as a gap-filler and applies in the absence of another statute that addresses the issue of attorneys' fees in the case at issue. 28 U.S.C. § 2412(b), (d) ("except as otherwise specifically provided by statute . . ."). Section 2412 is generally applicable whenever the federal government is a party in a civil action. 28 U.S.C. § 2412(d).

49. Given the vast resources and power of the Government, Congress determined that parties should be entitled to attorneys' fee where the Government lacks substantial justification for bringing a civil action. Accordingly, Section

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2412(d) permits a court to award attorneys' fees and other expenses to a prevailing party unless the Court finds that the Government was "substantially justified." The Supreme Court has determined that the standard for substantial justification is no different than a "reasonable basis" test. *Pierce v. Underwood,* 487 U.S. 552, 565 (1988). The Court makes one determination regarding the action as a whole, not to each cause of action. *See Ibrahim v. U.S. Dept. of Homeland Sec.*, 835 F.3d 1048, 1054–57 (2016) (holding that court's decision regarding substantial justification requires a "single inquiry focused on the government's conduct in the case as a whole"). Here, the Government has acted unreasonably in contravention of well-established regulatory law. First, the SSP Exception clearly applies the SVF Surgical Procedure on its face. Second, the Government's attempts to rely upon the 2017 Guidance violates well-established principles of administrate law and is not substantially justified. Third, the Government has continued to pursue the injunctive relief as to the Expanded MSC and SVF/ACAM2000 Surgical Procedures though Defendants have (1) ceased using the non-GMP facility for the Expanded MSC Surgical Procedure, and (2) cannot perform the SVF/ACAM2000 Surgical Procedure due to lack of access to ACAM2000. Accordingly, Defendants seek attorneys' fees because the Government lacks substantial justification for continuing the litigation.

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Dated: _____

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HONORABLE JESUS G. BERNAL

United States District Judge

Presented by:

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