No. 22-56014

IN THE

United States Court of Appeals for the Ninth Circuit

UNITED STATES OF AMERICA,

Plaintiff-Appellant,

v.

CALIFORNIA STEM CELL TREATMENT CENTER, INC., A CALIFORNIA CORPORATION; ET AL.,

Defendants-Appellees,

On Appeal from the United States District Court
for the Central District of California – Eastern Division
No. 5:18-cv-01005-JGB-KK
The Honorable Jesus G. Bernal

BRIEF FOR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH AND INTERNATIONAL SOCIETY FOR CELL & GENE THERAPY AS *AMICUS CURIAE* IN SUPPORT OF APPELLANT

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CORPORATE DISCLOSURE STATEMENT

Pursuant to Rules 26.1 and 29(a)(4)(A) of the Federal Rules of Appellate Procedure, counsel for *amici curiae* states that the International Society for Stem Cell Research (ISSCR) and the International Society for Cell and Gene Therapy (ISCT) are non-profit, tax-exempt organizations that have issued no stock, that ISSCR and ISCT do not have parent corporations, and that no publicly held company has 10% or greater ownership in ISSCR or ISCT.

TABLE OF CONTENTS

Page

TABLE OF CONTENTS—Continued

Page

TABLE OF AUTHORITIES

Page(s)

CASES:

STATUTES:

TABLE OF AUTHORITIES—Continued

Page(s)

TABLE OF AUTHORITIES—Continued

Page(s)

OTHER AUTHORITIES:

TABLE OF AUTHORITIES—Continued

Page(s)

TABLE OF AUTHORITIES—Continued

Page(s)

TABLE OF AUTHORITIES—Continued

Page(s)

INTEREST OF *AMICUS CURIAE*[1]

The International Society for Stem Cell Research (ISSCR) is an independent, global, nonprofit organization that promotes excellence in stem cell science and its applications to human health. Since its founding in 2002, ISSCR has been committed to advancing stem cell research with the ultimate goal of achieving a world where stem cell science is encouraged, ethics are prioritized, and discovery improves understanding and advances human health. ISSCR is comprised of 4,500 scientists, physicians, educators, ethicists, and business leaders across 80 countries.

ISSCR publishes guidelines to help prevent the marketing of unproven stem cell therapies. These guidelines are designed to encourage its members and the stem cell research community to responsibly and ethically study and prescribe treatments, while also assuring the public of the integrity of stem cell science and its translation to medicine.

The International Society for Cell & Gene Therapy (ISCT) is a society of over 3,000 cell and gene therapy experts across five geographic regions and with representation from over 60 countries with a shared vision to translate cell and gene

[1] Pursuant to Fed. R. App. P. 29(a)(2), *amici curiae* certify that all parties have consented to the filing of this brief. Pursuant to Fed. R. App. P. 29(a)(4)(E), *amici curiae* certify that no counsel for any party authored this brief in whole or in part. No entity or person, aside from *amici curiae*, their members, or their counsel, made any monetary contribution intended to fund the preparation or submission of this brief.

interventions into safe and effective therapies that improve patients' lives worldwide. Among other activities, ISCT raises awareness about unproven cellular interventions by establishing task forces and committees, and publishing manuscripts that examine the prevalence and effect of unproven cell interventions, with the ultimate goal of minimizing risks and ensuring benefits to patients by promoting the clinical testing of these interventions.

In 2013, ISCT established the ISCT Committee on the Ethics of Cell and Gene Therapy (the "ECGT Committee"), formerly known as the ISCT Presidential Task Force on the Use of Unproven and/or Unethical Cell and Gene Therapies. The ECGT Committee seeks to identify key ethical issues associated with the development, regulatory authorization, and distribution of cell and gene interventions, in order to promote and share effective strategies between scientific/medical societies, health-care stakeholders, patient associations, and individuals, promoting the role of rigorous research and appropriate investigation and application of cell based therapies.

ISSCR and ISCT submit this brief in support of the appellant, the United States, because the marketing and use of unproven stem cell therapies, such as the stromal vascular fraction ("SVF") products and expanded SVF products at issue here, violate the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and FDA's risk-based approach to regulating such therapies. Importantly, these

violations jeopardize the safety of patients, which is why FDA regulation is required, and the marketing of such unproven products is opposed by ethical stem cell researchers globally.

INTRODUCTION

I. REGULATORY BACKGROUND

A. FDA Regulation of Drugs and Biological Products

The U.S. Food and Drug Administration (FDA or Agency) is responsible for protecting the public health and regulating products critical to the daily life of Americans, including drugs and biological products. It does so under authority granted by the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 *et seq.*, and the Public Health Service Act (PHSA), 42 U.S.C. § 201 *et seq.* and accompanying regulations. These laws require that new drugs be studied, reviewed, and approved under a "new drug application" (NDA). 21 U.S.C. § 355(a).

The Agency employs a structured framework for its review of NDAs, through which it evaluates whether a drug is safe and effective for its intended use. *See generally, id.* A sponsor must demonstrate a drug's benefit by providing "substantial evidence" of effectiveness, which typically includes one or more adequate and well-controlled clinical trials in which the safety and effectiveness of a new drug is evaluated. *See* 21 U.S.C. § 355(d); *see also* Food and Drug Administration, *Draft Guidance for Industry – Demonstrating Substantial Evidence of Effectiveness for*

Human Drug and Biological Products, at 1 (Dec. 2019). FDA then balances the effectiveness of the drug against risks under the conditions of use defined in the labeling, to determine whether the benefits outweigh the risks of the drug. *See id*.; *see also* Food and Drug Administration, *Draft Guidance for Industry – Benefit-Risk Assessment for New Drug and Biological Products*, at 4 (Sept. 2021). These decisions, including any uncertainties concerning the benefit risk assessment, are "within [FDA's] area of expertise." *See A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995).

Similarly, biological products must be marketed under a biologics license application (BLA), which FDA issues upon being provided with evidence that the biological product is safe, pure, and potent. 42 U.S.C. § 262. FDA has interpreted this mandate to require similar showings of "substantial evidence" of effectiveness to support licensure of a biological product, including the requirement that substantial evidence be shown by adequate and well-controlled investigations. *See* 21 U.S.C. § 355(d); *see also* 21 C.F.R. § 601.25(d)(2) (2015), *revoked as no longer necessary* 81 Fed. Reg. 7445 (Feb. 2016); Food and Drug Administration, *Draft Guidance for Industry – Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*.

In addition, drugs and biological products must be appropriately labeled, *see* 21 U.S.C. § 352(a), must be manufactured in accordance with current good

manufacturing practices, *see* 21 U.S.C. § 351(a)(2)(B), and are subject to mandatory post-marketing safety reporting, among other requirements. 21 C.F.R. §§ 314.80(c)(1)(iii); 600.80.

As part of these reporting requirements, NDA and BLA application holders must submit to FDA post-marketing safety reports of adverse events, including both nonserious and serious adverse events, whether expected or unexpected. 21 C.F.R. §§ 310.305; 314.80; 314.98; 600.80; 600.81. These reporting requirements assure that FDA remains aware of any potential threats to the public health and allows the Agency to take necessary action, such as updating product labeling or recommending a recall. *See* 21 U.S.C. § 355(o)(4); 21 C.F.R. § 7.40.

FDA also has a voluntary reporting system, called MedWatch, through which health professionals, patients, and consumers can, but are not required to, report adverse events. *See generally*, Food and Drug Administration, *MedWatch: The FDA Safety Information and Adverse Event Reporting Program*. Although these reports are voluntary, they serve important roles in protecting the public health. After the FDA evaluates the submitted reports, FDA may issue safety alerts or send letters to health care professionals. *See id*. These adverse event reports may also result in changes to the drug or biological product's labeling, withdrawal of the product, or further post-marketing research. Food and Drug Administration, *MedWatch: Managing Risks at the FDA*.

In contrast to FDA regulation of drugs and biological products, FDA generally does not regulate the practice of medicine or the provision of medical services. *See United States v. Evers*, 643 F.2d 1043, 1048 (5th Cir. 1981). This means that activities falling outside the scope of FDA jurisdiction, such as those not involving an FDA-regulated product, are not subject to agency oversight and the requirements described above.

B. Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

The PHSA authorizes the Surgeon General, with approval of the Secretary of the U.S. Department of Health and Human Services (DHHS), to make and enforce regulations that "are necessary to prevent the introduction, transmission, or spread of communicable diseases . . . " within the States. 42 U.S.C. § 264(a) (Section 361 of the PHSA). Under this statutory authority, FDA, an agency of DHHS, has promulgated regulations to prevent the introduction, transmission, or spread of communicable diseases through HCT/Ps, which can be used in circumstances as varied as skin grafts, bone healing matrixes, and reproductive tissues. *See generally* 21 C.F.R. Part 1271.

FDA defines HCT/Ps 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). FDA's regulatory framework for HCT/Ps requires registration of facilities, mandates donor screening to determine eligibility,

establishes Current Good Tissue Practice requirements to decrease the risk of contamination, and provides for inspections of manufacturing facilities. *See generally* 21 C.F.R. Part 1271. These regulations address the need for supplemental measures that help protect against the higher risk of transmitting communicable diseases carried by cells and tissues, compared with other drugs and biologics regulated under NDAs and BLAs. *See* Food and Drug Administration, *Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement*, 69 Fed. Reg. 68612, 68613 (Nov. 24, 2004). Consequently, the HCT/P regulations generally supplement rather than supersede the cGMP regulations governing drugs and the Quality System Regulation governing medical devices. 21 C.F.R. § 1271.15; *see also* 69 Fed. Reg. at 68613-14, 68616, 68624.

FDA adopted a risk-based approach when promulgating the HCT/P regulations, *id.* at 68613, and recognized that in some limited circumstances the transplantation of HCT/Ps poses no risks beyond those covered by state laws in regulating the practice of medicine. In these circumstances, the HCT/Ps are not subject to the more substantial requirements applicable to drugs, biologics and medical devices. *See* Food and Drug Administration, *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use: Guidance for Industry and Food and Drug*

Administration Staff (July 2020). Consequently, when an HCT/P falls within one of the narrow exceptions enumerated in FDA regulations, *see* 21 C.F.R. § 1271.15, or meets criteria allowing an HCT/P to be regulated solely under section 361 of the PHSA and 21 C.F.R. Part 1271, *see* 21 C.F.R. § 1271.10, it is not regulated by FDA as a drug, device, and/or biological product under the FDCA and/or section 351 of the PHSA. In other words, FDA permits certain HCT/Ps to be used under a standard specifically designed to address the risks of communicable diseases. It exempts a small number of HCT/Ps from those standards because it has deemed the risks of those products to be low. All other HCT/Ps are subject to the full panoply of federal regulations that apply to drugs and biologics, including the requirements for rigorous study, careful evaluation, and the balancing of potential risks and benefits *before* they can be used in clinical practice. *See id.*

C. Same Surgical Procedure Exception to the Regulation of HCT/Ps

The HCT/P exception at issue here is the "same surgical procedure exception" (SSP Exception), which provides that an establishment is not required to comply with the requirements of the HCT/P regulations if it removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure. 21 C.F.R. § 1271.15(b).

Through draft guidance published October 2014 and finalized November 2017, FDA interpreted the phrase "such HCT/Ps" as a requirement that the HCT/P be in its original form:

> Generally, the only processing steps that will allow an HCT/P to remain "such HCT/P" are rinsing, cleansing, sizing, and shaping . . . Accordingly, even processing that may be considered minimal manipulation within 21 CFR 1271.10(a), will typically cause the HCT/P to no longer be "such HCT/P" under 21 CFR 1271.15(b), if the processing is not limited to rinsing, cleansing, sizing, or shaping.

See Food and Drug Administration, *Guidance for Industry – Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception* at 5 (Nov. 2017) (the "SSP Guidance").

In late 2014, FDA solicited comments on this and other HCT/P-related guidances, including the now withdrawn "Human Cells Tissues, and Cellular and Tissue Based Products HCTPs From Adipose Tissue: Regulatory Consideration; Draft Guidance for Industry" (Adipose Draft Guidance). *See* 79 Fed. Reg. 63348 (Oct. 2014); 79 Fed. Reg. 77012 (Dec. 2014); 79 Fed. Reg. 77414 (Dec. 2014). The HCT/P proposed guidances garnered significant public attention, leading FDA to reopen the comment period in October 2015 and to hold a public hearing on the proposals in 2016. *See* 80 Fed. Reg. 66847, 66844-49 (Oct. 2015).

Many comments and testimony addressed SVF and FDA's determination that the processing and manipulation required to generate SVF from adipose tissue would

not qualify for the SSP exception. *See* Food and Drug Administration, *Part 15 Hearing: Draft Guidances Relating to the Regulation of Human Cells, Tissues, or Cellular or Tissue-Based Products* (Sept. 2016). Johnson & Johnson, a company that described itself as engaged in the discovery, development, study, and manufacture of HCT/Ps, proposed that tissues or cells processed in the operating room by centrifugation should fall within the SSP exception. *See* Comment from Johnson & Johnson, Docket No. FDA-2014-D-1584-0201 (Oct. 2016). Comments also included general objections to FDA regulation of therapies involving SVF. *See, e.g.*, Comment from Todd McAllister, Docket No. FDA-2014-D-1584-0148 (Oct. 2015) (stating "[t]he safety of same day therapies (PRP, SVF, minimally manipulated stem cells etc.) has been demonstrated in thousands of patients. While the benefit of some of these therapies is yet to be determined, it is via physician driven innovation that these therapies will become the next pillar of healthcare."). FDA did not finalize the Adipose Guidance, and instead incorporated certain provisions into other guidances, including the SSP Guidance. *See* 82 Fed. Reg 221 (Nov. 2017).

In finalizing the SSP Guidance in 2017, FDA stated "[t]he material in this guidance related to adipose tissue, together with the material in the final guidance entitled 'Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use; Guidance for

Industry and Food and Drug Administration Staff' dated November 2017 (Minimal Manipulation and Homologous Use Guidance) related to adipose tissue, supersedes the Adipose Draft Guidance." *See id*.

Despite receiving some comments to the contrary on the Adipose Guidance, FDA determined that centrifugation solely to remove debris, but not centrifugation for cell isolation, cell expansion, cell activation, or enzymatic digestion, would remain within the SSP exception. *See* SSP Guidance. Consequently, FDA found that SVF derived from adipose tissue would not qualify for the exception. *See id.* In the final SSP Guidance, FDA specifically describes the isolation of SVF from adipose tissue as an example of processing that does not allow an HCT/P to remain "such HCT/P":

> Example 7-2: Adipose tissue is recovered by tumescent liposuction and processed (e.g., enzymatic digestion, mechanical disruption) to isolate cellular components, commonly referred to as stromal vascular fraction, which is considered a potential source of adipose-derived stromal/stem cells. *Cell isolation would typically cause the adipose tissue to no longer be "such HCT/P" and the establishment would generally not be considered to qualify for the exception* under 21 CFR 1271.15(b).

Id. (emphasis added). Accordingly, FDA both solicited public input for its policies related to HCT/Ps, through comments and testimony, and responded to public concerns by withdrawing the Adipose Guidance while retaining guidelines related to the isolation of SVP from adipose tissue in other HCT/P guidances.

D. Adverse Event Reporting Requirements

Under FDA regulations, manufacturers and distributors of drugs must report adverse events received or otherwise obtained. 21 C.F.R. §§ 314.80; 310.305. This includes individual case safety reports (ICSRs), which are defined as "a description of an adverse drug experience related to an individual patient or subject." 21 C.F.R. § 314.80. ICSRs must include information sufficient to provide the agency with a comprehensive picture of the drug use, the patient experiencing the issue, and the medical setting. *See id.* HCT/P facilities must report certain adverse reactions related to communicable diseases. *See* 21 C.F.R. §§ 1271.330; 1271.350.

In contrast, none of the reporting requirements under the FDCA extend to HCT/Ps that fall under the SSP Exception. For products falling under this exception, the only reports of adverse events or reactions submitted to FDA are voluntary. *See, e.g.*, 21 C.F.R. §§ 20.111; 20.112.

Voluntary reports of adverse events from either health care professionals or the patients experiencing the events are unlikely to contain all of the necessary information to connect an event with a product, as there is no explicit obligation for reporters to provide all the necessary information. *See generally*, Food and Drug Administration, *Guidance for Industry: E2E Pharmacovigilance Planning* (Apr. 2005) at 11. Incomplete reports significantly limit the ability of the Agency to identify the location of the intervention, the seriousness of the intervention, and the

appropriate response. *See* Peter Marks and Stephen Hahn, "*Identifying the Risks of Unproven Regenerative Medicine Therapies,*" 324 J. AM. MEDICAL ASSOC. 241 (June 17, 2020); The PEW Charitable Trusts, *Harms Linked to Unapproved Stem Cell Interventions Highlight Need for Greater FDA Enforcement* (June 2021).

FDA and the National Institutes of Health (NIH) have acknowledged underreporting publicly, and have explained the difficulties in regulating unapproved products that are not subject to typical oversight. For example, NIH's website includes an acknowledgment that "rogue clinics, driven by profits, are taking advantage of patients desperate for cures and are claiming dramatic results, often exaggerated in sensational media testimonials. . . . However, these clinics almost always work without FDA regulatory approval and outside of legitimate clinical trial approaches." Wai et al., *Putting Stem Cell-Based Therapies in Context*¸ SCIENCE, HEALTH AND PUBLIC TRUST (Nov. 16, 2022). FDA has also acknowledged underreporting in a publication in the Journal of the American Medical Association, stating "[b]ecause these unproven regenerative medicine therapies are being administered without regard to the FDA's regulatory oversight, it is impossible to know with certainty the number of individuals who have experienced serious adverse events following their administration." *See* P. Marks and S. Hahn, "*Identifying the Risks of Unproven Regenerative Medicine Therapies.*"

The difficulty of regulating unapproved stem cell therapies is evidenced by FDA enforcement actions taken in response to adverse events. FDA issued a Warning Letter in 2020 to EUCYT Laboratories LLC, outlining violations related to the company's "stem cell" and "exosome" product called XOsomes, and a product claimed to include "memory T cells" that EUCYT alleged could protect against COVID-19. The products caused multiple serious adverse events that were reported to CDC and the agency by treating physicians, not by EUCYT, and prompted FDA to issue a public safety notice. *See* Warning Letter to Travis H. Bird, EUCYT Laboratories LLC (June 4, 2020) (discussing over 150 sterility failures); *see also* Food and Drug Administration, *Public Safety Notification on Exosome Products* (Dec. 6, 2019). The Agency has issued several other similar letters to companies marketing unapproved stem cell interventions that pose a risk of transmitting communicable diseases. *See e.g.*, Untitled Letter to David Greene, R3 Stem Cell, LLC (May 28, 2019) (stating that R3 Stem Cell's "regenerative stem cell therapies" that were marketed for treating diseases such as dementia and Parkinson's did not fall under any exception and were therefore unapproved biologics that posed high contamination risks); Warning Letter to Edwin Pinos, Genetech, Inc. (Nov. 29, 2018) (umbilical blood-derived cellular products distributed to Liveyon LLC did not meet the HCT/P requirements and were unapproved biologics that posed high contamination risks).

Unproven stem cell therapies marketed directly to consumers by clinics have resulted in patients being blinded, paralyzed, and infected with dangerous pathogens. *See* Kuriyan AE, et al., *Vision Loss after Intravitreal Injection of Autologous "Stem Cells" for AMD*, N. Engl. J. Med., 2017 Mar. 16; 376 11:1047-1053; *see also* Berkowitz AL, et al., *Glioproliferative Lesion of the Spinal Cord as a Complication of "Stem Cell Tourism,"* N. Engl. J. Med., 2016 Jul. 14; 375:196-198; *see also* Perkins, K., et al., *Notes from the Field: Infections After Receipt of Bacterially Contaminated Umbilical Cord Blood—Derived Stem Cell Products for Other Than Hematopoietic or Immunologic Reconstitution—United States, 2018,* CDC Morbidity and Mortality Weekly Report 67(50); 1397 (Dec. 21, 2018). These reports include the use of adipose-derived SVF. In three patients with macular degeneration, injection of adipose-derived SVF into their eyes resulted in blindness. *See* Kuriyan AE, et al, *Vision Loss after Intravitreal Injection of Autologous "Stem Cells" for AMD.*

Additionally, in a study conducted by the PEW Charitable Trust (PEW), the organization identified 360 reported adverse events related to unapproved stem cell and regenerative medicine interventions between 2004 and 2020 from peer-reviewed journals, FDA's adverse event reporting system (FAERS), and consumer reviews on websites such as Google, Yelp, and Facebook. The PEW Charitable Trusts, *Harms Linked to Unapproved Stem Cell Interventions Highlight Need for Greater FDA*

Enforcement. Between 2019 and 2021 alone, PEW identified seven adverse events associated with adipose-derived stromal cells ranging in severity from headaches and dizziness to death. *Id*. at Appendix B.

These studies and reports show the risks of unapproved stem cell therapies are tangible and real, including for adipose-derived stromal cells. The agency has been forced to take several enforcement actions following outbreaks from unapproved therapies that have harmed patients, underscoring the need for FDA's risk-based approach to regulating HCT/Ps. A lack of FDA oversight, caused by reduced federal regulation or by companies that evade FDA regulation, undermines adverse event reporting requirements and makes it harder to identify unapproved stem cell therapies that cause serious illness in patients.

II. SCIENTIFIC BACKGROUND

A. Stem Cell Therapies

Stem cells have the ability to self-renew and to regenerate specialized cells in tissues. Given stem cells' unique regenerative abilities, they have been used as therapies to generate tissues. However, only a limited number of medical conditions can be safely and effectively treated with stem cell therapies. One standard-of-care stem cell therapy is the transplantation of hematopoietic stem cells (HSCs), which are blood-forming stem cells such as those derived from bone marrow or umbilical cord blood, for the reconstitution of the blood-forming and immune systems after

chemotherapy or systemic radiation therapy. *See* Food and Drug Administration, *Approved Cellular and Gene Therapy Products*, https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products (showing FDA has licensed only eight HPC, Cord Blood products); *see also* Barriga F, et al., *Hematopoietic stem cell transplantation: clinical use and perspectives*, BIOL RES 2012; 45(3):307-16. Other proven stem cell therapies include skin grafting in patients with large burns, where the grafted skin is grown from skin stem cells, and limbal/corneal stem cell transplantation in patients whose corneas have been destroyed by chemical burns. *See* Shpichka A, et al., *Skin tissue regeneration for burn injury*, STEM CELL RES THER. 2019 Mar. 15; 10(1):94; *see also* Cavallini GM, et al., *Chemical injury treated with autologous limbal epithelial stem cell transplantation and subconjunctival bevacizumab*, CLIN OPHTHALMOL. 2014 Aug. 30; 8:1671-3.

Unfortunately, bad actors have exploited the promise of stem cell research to market unproven stem cell products in violation of FDA regulations, whose safety and effectiveness have not been proven in controlled clinical trials. *See* Peter Marks and Stephen Hahn, "*Identifying the Risks of Unproven Regenerative Medicine Therapies*." Often, these unproven products are marketed for indications for which no effective stem cell therapy exists. Moreover, these products are commonly marketed to patients using claims that are scientifically implausible and unsupported

by data. As noted, many patients have been harmed medically by these products and many more have been harmed financially and psychologically by paying thousands of dollars for ineffective treatments.

An important characteristic of the proven stem cell therapies – and most successful cell therapies – is that they are intended for homologous use. This means the cells used in the therapy perform the same basic functions in the recipient as in the donor. Stem cells from the same tissue being treated must typically be used, because these are the cells with the potential to successfully replace the cells lost to injury or disease. For example, the transplantation of HSCs to regenerate the blood forming system is a homologous use, but using HSCs with the intent to regenerate nervous system cells or non-hematopoietic cells in visceral organs would be non-homologous uses. *See* Food and Drug Administration, *Proposed Approach to Regulation of Cellular and Tissue-Based Products*, 62 Fed. Reg. 9721 (Mar. 4, 1997).

B. The California Stem Cell Treatment Center (CSCTC) Products

In the SVF Surgical Procedure, the CSCTC extracts a patient's adipose tissue and then isolates certain cellular components from this extract, referred to as SVF.

The resulting product, or "SVF product," is then implanted by the CSCTC back into the patient. *See* Findings of Fact and Conclusions of Law ("FOF/COL"), 1-ER-7.[2]

To generate Expanded Mesenchymal Stem Cells, the CSCTC removes a patient's adipose tissue and sends the adipose tissue to a tissue bank, where mesenchymal cells are isolated, replicated in culture, and stored. The resulting product, the "expanded SVF product," is returned for implantation by the CSCTC into a patient's body upon request. *See id.*, at 1-ER-8-9.

ARGUMENT

III. THE PUBLIC HEALTH SERVICE ACT AND THE FEDERAL FOOD, DRUG, AND COSMETIC ACT ARE CONSUMER PROTECTION STATUTES

FDA is responsible for protecting the public health by implementing, among others statutes, the FDCA and the PHSA. *See* 21 U.S.C § 393; *see generally United States v. Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784 (1969). In implementing these statutes, FDA relies on a staff of internal scientists and physicians who provide the technical expertise necessary for the regulation of drugs and biologics. For example, when deciding whether a product should be approved for use in patients, FDA examines voluminous data provided by applicant organizations related to safety, efficacy, product composition, manufacturing, and quality control.

[2] References to the Excerpts of Record filed by Appellant are referred to as "[Vol. No]-ER-[Page(s)]." References to court filings from the lower record are referred to as "Dkt. No. ___."

Moreover, FDA has standing committees of outside experts that provide scientific and medical advice on these matters. *See* Food and Drug Administration, *Cellular, Tissue, and Gene Therapies Advisory Committee*, https://www.fda.gov/advisory-committees/blood-vaccines-and-other-biologics/cellular-tissue-and-gene-therapies-advisory-committee. Internal and external experts commonly examine hundreds of pages of data from applicants in light of what is known in the scientific and medical literature before making a decision about whether a product should be approved for use in patients.

Courts have long recognized the agency's expertise in implementing these statutes and in evaluating the scientific characteristics and merit of medical therapies. *A.L. Pharma, Inc.*, 62 F.3d at 1490 ("[C]ourts give a high level of deference to an agency's evaluations of scientific data within its area of expertise."); *see also Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995) (FDA's "judgments as to what is required to ascertain the safety and efficacy of drugs falls squarely within the ambit of the FDA's expertise and merit deference from us"), including those derived from human tissues and cells and falling under the 21 C.F.R. Part 1271 framework. *See generally United States v. Regenerative Scis., LLC*, 741 F.3d 1314, 1322-23 (D.C. Cir. 2014) (dismissing arguments that the Part 1271 regulations "exceed the FDA's authority to issue regulations to prevent the introduction,

transmission, or spread of communicable diseases between states.") (internal citation omitted).

Furthermore, courts have long deferred to FDA's scientific findings as published through regulation and guidance intended to protect the public health. *See Schering Corp*, 51 F.3d at 399; *see also Bacto-Unidisk*, 394 U.S. at 791-92 (explaining "[i]t is enough for us that the expert agency charged with the enforcement of remedial legislation has determined that such regulation is desirable for the public health, for we are hardly qualified to second-guess the Secretary's medical judgment."). This includes FDA's implementation of 21 C.F.R. Part 1271 to prevent the transmission and spread of communicable diseases, pursuant to 42 U.S.C. § 264. *Regenerative Scis., LLC*, 741 F.3d at 1322 (stating "[o]ur decision, however, is based on, and gives effect to, the Part 1271 Regulations[.]").

FDA, as the agency tasked with implementing these statutes, has both the mandate and the scientific and medical expertise both to manage the risk of products intended for consumers, and to take appropriate enforcement actions to protect the public from dangerous products.

IV. ISSCR AND ISCT SUPPORT FDA'S APPLICATION OF THE "NEW DRUG" REGULATORY FRAMEWORK TO THE SVF PRODUCTS

In bringing an enforcement matter against CSCTC, the Agency was carrying out its fundamental consumer protection mandate and evaluating the development of innovative therapies against its long-standing emphasis to protect patients' health

and safety. The Agency determined the CSCTC products did not fall into the SSP Exception to FDA's risk-based framework based on its published guidance and facility inspections and were therefore illegally marketed products. In doing so, it acted entirely within its public health mandate and its published (and thoughtful) policies.

A. The SVF Surgical Procedure Does Not Meet the Criteria for Either the Same Surgical Procedure Exception or for Minimal Manipulation

FDA has stated that adipose-derived SVF does not meet the criteria for either the SSP Exception or for minimal manipulation under 21 C.F.R. § 1271.10(a). *See* Food and Drug Administration, *Guidance for Industry – Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception* at 5 (Nov. 2017); Food and Drug Administration, *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use: Guidance for Industry and Food and Drug Administration Staff* (July 2020). Therefore, FDA has made explicit that adipose-derived SVF is regulated as a drug and biological product such that to lawfully market adipose-derived SVF, a valid biologics license must be in effect.

ISSCR and ISCT agree with FDA's interpretation that SVF cells do not meet the criteria for either the SSP Exception or for minimal manipulation under 21 C.F.R. § 1271.10(a). A driving principle of the SSP Exception and the minimal

manipulation standard is that the cells or tissues extracted from a patient must not be processed beyond basic "rinsing, cleansing, sizing, or shaping" steps, because doing so may raise "additional risks of contamination and communicable disease transmission beyond that typically associated with surgery." SSP Guidance at 3. The processing steps of the SVF Surgical Procedure, however, go well beyond the basic "rinsing, cleansing, sizing, or shaping" steps required for the SSP Exception to apply, and include subjecting the adipose tissue to enzymatic digestion, centrifugation for cell isolation rather than purely to remove debris, and filtration to isolate the SVF cells. *From* Trial Tr. Day 4, Yong testimony, 7-ER-800-43, 863-940.

The processing steps of the SVF surgical procedure not only increase the risks of contamination and communicable disease transmission, but also fundamentally change the properties and structure of the SVF cells due to removing them from their natural environment. During the processing of adipose tissue to isolate SVF, the vast majority of the material extracted from the patient is discarded, including the adipose cells. The properties of SVF cells in their natural state are intrinsically linked to their structural functions in the vasculature of adipose tissue. The vasculature is designed to transport blood, but SVF is unable to perform this function once dissociated. In addition, adipose tissue has energy storing and cushioning functions in the human body, but SVF cannot perform these functions once the

adipose cells are discarded. *See* Decl. of C. Yong, Dkt. No. 199, at ¶ 16; *see also* Adipose Draft Guidance at 3. Thus, SVF is unable to perform any of the primary functions of the tissue from which it was extracted. Enzymatic dissociation also cleaves extracellular matrix and other proteins from the surface of cells, altering key cellular functions such as cell adhesion, cell-cell signaling, cell survival, differentiation, proliferation, and pathogen recognition. Isolated SVF cells are therefore widely viewed as being biologically different from normal cells within adipose tissue. *Id.*; *see also* Aronowitz JA, et al., *Mechanical versus enzymatic isolation of stromal vascular fraction cells from adipose tissue*, Springerplus 2015; 4: 713 (Nov. 23, 2015); Lockhart RA, et al., *Use of Freshly Isolated Human Adipose Stromal Cells for Clinical Applications*, 37 AESTHET SURG J S4-S8 (2017). As such, the SVF cells produced by the SVF surgical procedure cannot qualify as "such HCT/P" within the meaning of the SSP Exception, nor can the SVF cells meet the minimal manipulation standard under 21 C.F.R. § 1271.10(a).

The considerations above also apply to the Expanded SVF Products, in which the SVF is grown in culture for weeks to increase the number of mesenchymal stem cells available for injection into patients. Uncultured SVF contains a heterogeneous mixture of mesenchymal, vascular, hematopoietic, and other cells. Lockhart RA, et al., *Use of Freshly Isolated Human Adipose Stromal Cells for Clinical Applications*; *see also* Trial Tr. Day 4, at 60:19-61:15, 7-ER-813-14, and Trial Tr. Day 4, at 7:7-

17, 7-ER-866. But when these cells are added to culture, the vast majority of the cells die, and a rare subset of mesenchymal cells proliferates, dramatically changing the cellular composition of culture-expanded SVF as compared to uncultured SVF. The properties of the "mesenchymal stem cells" that grow out in these cultures are quite different even from the mesenchymal cells that were originally extracted from the SVF. *See* Decl. of C. Yong, Dkt. No. 199, at ¶¶ 29, 39; James, A.W. et al., *An Abundant Perivascular Source of Stem Cells for Bone Tissue Engineering*. Stem Cells Translational Med., 2012 Sept; 1(9):673-84; Kachgal S. and A.J. Putnam, *Mesenchymal stem cells from adipose and bone marrow promote angiogenesis via distinct cytokine and protease expression mechanisms*. Angiogenesis. 2011 Mar.; 14(1):47-59. For example, the mesenchymal cells that are present within adipose tissue in vivo are mainly quiescent, or non-dividing, while cells in culture proliferate extensively, in a way mesenchymal cells have never been shown to do within adipose tissue in vivo. Indeed, mesenchymal cells within adipose tissue have no clear physiological function in tissue repair, in contrast to the claims made by CSCTC for their products. Thus, the Expanded SVF Products also do not qualify as "such HCT/P" within the meaning of the SSP Exception, nor can the Expanded SVF products meet the minimal manipulation standard under 21 C.F.R. § 1271.10(a).

B. The SVF Products and Expanded SVF Products Are Not Intended for Homologous Uses

When grown in culture, adipose-derived SVF has the potential to make bone, fat, and cartilage cells. Thus, one would not expect to be able to use the SVF products and expanded SVF products to treat diseases or conditions caused by defects in cells other than bone, fat, and cartilage, such as the diseases of the nervous system, lung, kidney, pancreas, or other visceral organs. *See* Food and Drug Administration, *Proposed Approach to Regulation of Cellular and Tissue-Based Products*, 62 Fed. Reg. 9721 (Mar. 4, 1997).

Despite this, the CSCTC promotes the SVF products and expanded SVF products for the treatment of a number of diseases and conditions that do not involve cartilage, fat, or bone. For example, the CSCTC has marketed and used SVF products and expanded SVF products to treat cancer, arthritis, stroke, amyotrophic lateral sclerosis, multiple sclerosis, macular degeneration, Parkinson's disease, chronic obstructive pulmonary disease, and diabetes in patients. *See* Plaintiff's Complaint, 2-ER-69, at ¶ 7; Defendants' Answer, 2-ER-55, at ¶ 7; Defendants' Responses to Plaintiff's First Set of Requests for Admission, Dkt. 197, at ¶ 20. But, there is no substantial evidence, as is required for products approved for these serious conditions under NDAs and BLAs, that SVF products or expanded SVF products can be used effectively to treat any of these conditions. As discussed, studies to establish such evidence would typically require at least one adequate and well-

controlled clinical trial in which the CSCTC products were compared to placebo control or standard of care, with enough patients to test safety and efficacy for the indication that is the subject of the claim. Further, not only is there no evidence from controlled clinical trials of CSCTC products, but clinical trials of other SVF products have often failed to demonstrate efficacy when tested for similar indications. *See, e.g.*, Berry, J.D., M.C. Cudkowicz, A. Windebank, *NurOwn, phase 2, randomized, clinical trial in patients with ALS: Safety, clinical and biomarker results*. Neurology. 2019 Dec. 10;93(24):e2294-e2305; Francis, D.P., M. Mielewczik, D. Zargaran, G.D. Cole, *Autologous bone marrow-derived stem cell therapy in heart disease: discrepancies and contradictions*. Int'l Journal of Cardiology. 2013 Oct. 9;168(4):3381-403. The FDA has not approved the use of any SVF or expanded SVF product for the treatment of any indication.

C. The SVF Products and Expanded SVF Products are Drugs

The CSCTC opinion held that the Government's allegations of adulteration and misbranding of an unapproved new drug failed with respect to the SVF products and expanded SVF products because they did not create drugs, and were instead surgical procedures under the practice of medicine and because the potential for commercialization – e.g., whether an article can be "sold, mass produced, or patented" – was not present. *See* 1-ER-16. In doing so, the District Court ignored the statutory definition of "drug," which does not depend on any of these factors.

Moreover, although the District Court stated that the cells in the expanded SVF products were "human cells removed from patients and then reintroduced into those same patients" and were not commercialized as drugs (1-ER-18, at ¶ 29), patients were in fact paying thousands of dollars out of pocket to receive the treatments. Trial Tr. Day 69-ER-1103-04, at 19:24-20:13. The determination of whether the SVF products and expanded SVF products are drugs must be done by evaluating the statutory definition, as opposed to a non-statutory factor such as commercial potential.

Because the SVF products and the expanded SVF products do not fall within any of the HCT/P regulatory exceptions and do not meet the criteria allowing regulation solely under the communicable disease provisions of the PHSA and 21 C.F.R. Part 1271, the products are drugs and biological products subject to the requirements of the FDCA and PHSA.[3]

V. FDA OVERSIGHT IS NECESSARY TO ASSURE THAT ONLY SAFE STEM CELL PRODUCTS REACH PATIENTS

A. Unproven Stem Cell Treatments Have Caused Serious Adverse Events

As discussed, FDA has determined, pursuant to statute and promulgated regulations, that certain HCT/Ps do not fall under the SSP Exception or meet the

[3] Importantly, even the District Court here found the Expanded SVF procedure did not fall under the SSP exception. *See* 1-ER-15.

standards for minimal manipulation and homologous use. Products that have demonstrable and tangible risks should be closely regulated by FDA, the agency tasked with protecting public health. FDA has acknowledged these risks through statements and continued enforcement, including in the area of cell therapies, and must retain the ability to analyze and mitigate the risks posed by unapproved cell therapies.

Without the authority to enforce its determination of risk, FDA cannot adequately protect the public from the risks of unapproved cell therapies. FDA's risk-based approach to HCT/Ps permits a relaxed regulatory framework for procedures used to create and implant cells and tissues that pose no additional risk as compared to surgery, but such a risk-based approach is only effective if the Agency is permitted to determine when, in the interest of safety, a procedure creates an HCT/P that should be regulated. Limiting FDA's ability to narrowly interpret exceptions to regulatory oversight will only increase the number of dangerous and ineffective products that reach patients. If FDA is unable to apply its expert judgment to determine which products pose no risks beyond those covered by state medical laws, patients, who generally do not possess expert medical knowledge or access to data related to the safety and efficacy of individual products, would be exposed to the unchecked promotion of unsafe products. Moreover, clinical trials establishing safety and effectiveness, safety reporting, and post-marketing studies

are not required for products unregulated by FDA. Thus, among other outcomes, an overly broad interpretation of the exceptions will reduce the incentive for further study of these products. The American public will forfeit the opportunity to benefit from evidence-based findings on safety and effectiveness for such products, potentially leading to the proliferation of unsafe and ineffective products.

B. Adverse Events with Unproven Stem Cell Treatments Often Go Unreported

In addition to increasing the risk to patients, hindering FDA oversight and broadening the SSP exception will also lead to more dangerous products going undetected by regulators. *See* discussion of commercialized cell therapies *supra* Part II.C. Because unapproved treatments are not subject to reporting requirements, voluntarily reported cases likely do not comprehensively illustrate the number of adverse events these treatments cause, making it difficult to identify and regulate dangerous products. *See* P. Marks and S. Hahn, "*Identifying the Risks of Unproven Regenerative Medicine Therapies*"; The PEW Charitable Trusts, *Harms Linked to Unapproved Stem Cell Interventions Highlight Need for Greater FDA Enforcement*.

FDA must have the authority to determine which HCT/Ps pose a danger to the public, either because such HCT/Ps are unsafe, ineffective, or both. Moreover, the FDA also considers the composition of products, reproducibility of manufacturing, and quality control. We know from this regulatory experience, and patients who have been harmed by pathogens in contaminated unapproved cell products that

companies who ignore FDA regulation often also ignore good manufacturing processes and effective quality control. *See* Kuriyan AE, et al., *Vision Loss after Intravitreal Injection of Autologous "Stem Cells" for AMD.* Because adverse events are often not reported, the Agency must have a workable framework to help identify and regulate violative products that do not fall within exceptions to FDA regulation. Broadening the exceptions to FDA's established regulatory frameworks – despite FDA's expert, exhaustive, and evidence-based processes – ignores the Agency's expertise and affords companies latitude to market unproven, ineffective, and dangerous therapies.

CONCLUSION

The ISSCR and ISCT agree with the United States that the SVF products and expanded SVF products do not qualify either for the SSP Exception or for regulation solely under the authority of Section 361 of the PHSA and should therefore be subject to FDA's regulatory framework for drugs and biologics, including the requirement that the safety and efficacy of new cell therapies be proven in rigorous clinical trials before they can be marketed to patients. Allowing unproven cell therapies such as those marketed by CSCTC to remain unregulated jeopardizes the safety of patients, the quality of medical care, and frustrates the mandate of the FDA to protect the public from dangerous products.

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Respectfully submitted.

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CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limit of Federal Rule of Appellate Procedure 29(a)(5) because it contains 6931 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f).

2. This brief also complies with the typeface and type-style requirements of Federal Rule of Appellate Procedure 32(a)(5)-(6) because it was prepared in a proportionally spaced typeface using Microsoft Word in New Times Roman 14-point font.

/s/ Christopher J. Cox
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CERTIFICATE OF SERVICE

I certify that I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Ninth Circuit by using the appellate CM/ECF system on June 1, 2023. I certify that all participants in the case are registered CM/ECF users and that service will be accomplished by the appellate CM/ECF system.

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