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ALERT

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Ninth Circuit Appeal May Significantly Affect FDA's Authority to Regulate Stem Cell Clinics

Attorneys
Joshua Oyster
Beth P. Weinman
Austin D. Laroche

On October 27, 2022, the United States government appealed a rare defeat in an injunction case brought under the Federal Food, Drug, and Cosmetic Act ("FDCA") to the U.S. Court of Appeals for the 9th Circuit. The appeal followed the denial of an injunction by the U.S. District Court for the Central District of California that would have prevented a stem cell clinic in California from continuing to market and administer adipose-derived stem cell products to patients for a variety of serious diseases and conditions. The district court ruled that the stem cell products produced at the clinic were not subject to regulation as "drugs" under the FDCA and that one of the medical procedures through which the products were administered met the criteria for the same surgical procedure exception ("SSP Exception"), which exempts procedures from Food and Drug Administration ("FDA") regulation. The court's ruling conflicts with recent precedents, including a Florida district court decision that was affirmed by the 11th Circuit, which held that the SSP Exception did not apply to a very similar set of facts and that the stem cell products at issue were in fact drugs.

A 9th Circuit decision to uphold the district court decision would create a circuit split regarding the applicability of the SSP Exception and could impact the legal interpretation of what constitutes a "drug" in the context of human cells, tissues, and cellular and tissue-based products ("HCT/Ps"). Such a split could fundamentally alter FDA's ability to regulate stem cell therapies. The government's appeal in the 9th Circuit will no doubt be closely watched in 2023 by stem cell clinics and other healthcare providers who perform procedures with a patient's own cells and tissues.

This Alert summarizes the applicable regulatory framework for HCT/Ps and recent policy developments, analyzes the different outcomes between the two recent FDCA injunction cases involving stem cell clinics, and discusses the implications for future oversight of such clinics by FDA and other government regulators, depending on the outcome of the 9th Circuit appeal.

I. The HCT/P Regulatory Framework

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."[1] Significantly different regulatory frameworks can apply to HCT/Ps, depending on the processing method used to create the HCT/P and its intended use, as discussed further below.

HCT/Ps Regulated Solely Under Section 361 of the Public Health Service Act and Part 1271.

Certain HCT/Ps are regulated solely under section 361 of the Public Health Services Act ("PHSA") and corresponding FDA regulations that establish a set of safety standards tailored primarily to prevent the introduction, transmission, or spread of communicable diseases.[2] Generally, manufacturers of these products must be registered with FDA, list the HCT/Ps they market, comply with current good tissue practices, and comply with requirements related to reporting adverse events and labeling. However, such products are not regulated as "drugs" or "devices" and do not require FDA premarket review, approval, or clearance before they can be marketed. In order for an HCT/P to be regulated solely under section 361 of the PHSA, it cannot be more than "minimally manipulated," and it must be "intended for homologous use only," among other criteria.[3] "Homologous use" is the "repair, construction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor."[4] In other words, the party offering the procedure must intend that the HCT/P will perform the same basic function before and after it is implanted.

HCT/Ps Regulated Under Section 351 of the PHSA.

HCT/Ps that do not qualify for regulation solely under section 361 are regulated solely under section 351 of the PHSA.[5] These products must obtain FDA approval, clearance, or a biologics license before they can be marketed, and the facilities in which they are manufactured are subject to applicable registration and listing requirements for drugs (including biologics) and devices. Such facilities are also required to comply with current good manufacturing practices ("cGMP") and all the other FDA requirements applicable to drugs, biologics, or devices.

HCT/Ps Exempt from FDA Regulation.

HCT/Ps may be wholly exempt from the requirements in FDA's HCT/P regulations in 21 C.F.R. Part 1271 if they meet an exception listed in 21 C.F.R. 1271.15. One of those exceptions, the SSP Exception, applies when an establishment "removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure." HCT/Ps that meet the SSP Exception are not subject to FDA oversight. In establishing this exemption, the agency has made a judgment that the removal of cells or tissues from an individual and reimplantation in the same person during the same surgery, without any further processing of the tissue, does not raise any greater communicable disease risks than the risks typically associated with surgery.[6]

II. FDA Policies and Administrative Enforcement

FDA has become increasingly concerned in recent years about clinics that market injections of stem cell treatments as cures for a host of diseases and conditions without scientific evidence to support the safety and efficacy of the treatments for the marketed uses. In FDA's view, such procedures are "clearly illegal, . . . offer little hope, and, even worse, may pose significant risks to the health and safety of vulnerable patients."[7]

To address this concern, in 2017, FDA announced a policy framework for the development and oversight of regenerative medicine products and cellular therapies.[8] As part of this initiative, FDA issued several draft and final guidances, including one on the SSP Exception that explains what it means to implant "such HCT/P's." The guidance states, "An HCT/P remains 'such HCT/P' when it is in its original form. Generally, the only processing steps that will allow an HCT/P to remain 'such HCT/P' are rinsing, cleaning, sizing and shaping."[9]

Alongside the new framework, FDA announced its intention to increase enforcement oversight of cellular therapies, with a particular focus on products raising significant safety concerns and "unscrupulous actors" that make deceptive assurances to patients based on unproven products and "unsafe science."[10] Since 2017, FDA has issued more than 20 warning letters to stem cell clinics that market their HCT/Ps as treatments for various diseases or conditions.

III. Analysis of Stem Cell Clinic Cases

On behalf of FDA, the Department of Justice ("DOJ") filed lawsuits in 2018 seeking to enjoin two separate stem cell clinics from treating patients with adipose-tissue-derived stem cell products marketed for a variety of serious health conditions and diseases, including Parkinson's disease, brain and spinal cord injuries, arthritis, stroke, congestive heart failure, lung disease, and diabetes. The conflicting outcomes in these cases raise questions about the future of FDA's authority to regulate such clinics and whether the SSP Exception gives them a judicially recognized "get out of jail free" card enabling them to avoid FDA scrutiny altogether.

A. *United States v. U.S. Stem Cell Clinic, LLC ("U.S. Stem Cell")*

On May 9, 2018, the DOJ filed suit in the Southern District of Florida to enjoin U.S. Stem Cell Clinic from continuing to misbrand and adulterate a stem cell product it was allegedly marketing and administering to patients to cure a host of serious diseases.[11] The complaint alleged that the clinic was manufacturing a drug product referred to as "stromal

vascular fraction" or "SVF" in a facility that did not comply with cGMP, thus adulterating that SVF drug product while it was held for sale after a component of the SVF was shipped in interstate commerce.[12] Specifically, U.S. Stem Cell Clinic lacked procedures to prevent contamination during aseptic processing of the SVF, and the clinic did not test the SVF for objectionable microorganisms. The complaint also alleged that the clinic was misbranding the SVF because its labeling lacked adequate directions for the product's intended uses. Additionally, the complaint documented numerous adverse events that occurred after SVF treatments, including loss of sight and hospitalization. U.S. Stem Cell Clinic argued that its administration of SVF to patients was exempt from FDA's jurisdiction entirely under the SSP Exception.[13]

The district court boiled the dispute down to the question of whether the SVF implanted into the patient constitutes "such HCT/P's" that were removed from the patient, which would then qualify it for the exception under 21 C.F.R. § 1271.15(b).[14] The court agreed with FDA that the removed HCT/P was adipose tissue, and because that tissue was subject to significant processing to isolate the stem cells and create the SVF, the implanted SVF was no longer in its original form and did not constitute "such" HCT/P that was originally removed from the patient. Defendants argued that "such HCT/P's" did not need to be identical to what was explanted, but merely related to or "of the same class, type, or sort." Because the regulation did not provide any criteria to limit what might constitute the same "class, type, or sort," however, the court found that the defendants' interpretation would create ambiguity, whereas FDA's interpretation was simple, straightforward, and consistent with dictionary definitions of the regulation's terms and the context in which they appear.

After finding that the SSP Exception did not apply, the court found that the SVF was a drug regulated under section 351 of the PHSA because it failed at least one of the criteria for regulation solely under section 361. Specifically, the court found that the intended use of the adipose tissue was not a homologous use since adipose tissue, or fat, is a structural tissue and the SVF that was implanted into patients was implanted for the purposes of curing a host of diseases wholly unrelated to its structural role in the body. The court ordered the injunction the government had sought.

U.S. Stem Cell Clinic unsuccessfully appealed the district court's decision to the 11th Circuit.[15] When examining the SSP Exception, the circuit court agreed with FDA's reasoning that the cell-containing solution reinjected into the patient was not "such HCT/P" as was removed, because of the substantial processing necessary to isolate the SVF from the adipose tissue. Specifically, the court found the isolation process involved in the procedure "goes much farther than simple rinsing or sizing" allowed in FDA's SSP Exception guidance.[16] When analyzing whether the relevant treatment was eligible for regulation solely under section 361, the court focused on section 361's homologous use requirement. Referencing the clinic's marketing materials, the court concluded that the clinic did not intend the reinjected SVF to perform the same basic function as the SVF had performed prior to the procedure. Thus, the court concluded that the SVF was subject to regulation as a drug under section 351 of the PHSA and was both adulterated and misbranded.

B. *United States v. California Stem Cell Treatment Center, Inc. ("California Stem Cell")*

On May 9, 2018, the government also filed a lawsuit seeking to enjoin California Stem Cell Treatment Center from administering various stem cell treatments to patients based on the same theories and similar allegations asserted in *U.S. Stem Cell*.[17] Furthermore, the complaint alleged that the clinic's products had been associated with adverse events, including serious infections that required hospitalization. However, in contrast to the Southern District of Florida in *U.S. Stem Cell*, in January 2020, Judge Bernal of the Central District of California denied FDA's motion for summary judgement, holding that whether the SSP Exception exempts the clinic's treatments from FDA oversight was a triable issue of fact.[18]

A subsequent bench trial addressed whether three specific medical procedures qualified for the SSP Exception, or rather involved the administration of HCT/Ps regulated under the PHSA. The court issued its findings of fact and conclusions of law in August 2022.[19]

1. SVF Surgical Procedure

The "SVF Surgical Procedure" involved the collection of a patient's SVF cells through liposuction. The SVF cells were then mechanically separated from adipose tissue, filtered, and suspended in a saline solution, before being reinserted into the same patient's body as part of the same procedure. When describing the SVF Surgical Procedure in the findings of fact, Judge Bernal noted that all the materials used to isolate SVF cells are FDA-approved drugs or FDA-cleared devices, and the procedure does not create any new material or introduce any foreign article into the body.

Ultimately, the court concluded that the SVF Surgical Procedure qualified for the SSP Exception. Judge Bernal focused on the definition of HCT/P, which explicitly includes the terms "tissues" and "cells." He reasoned that because cells can only be removed from a patient along with larger systems, such as the tissues or organs they comprise, limiting application of the SSP Exception to the entire tissue removed from a patient and ignoring the target cells would inappropriately eliminate the word "cells" from the definition of HCT/P.[20] Accordingly, the court found, both the removed adipose tissue and the SVF cells contained therein are HCT/Ps, and the very same SVF cells removed were reinserted during the procedure, satisfying the "such HCT/P" provision. This conclusion conflicts with that of the 11th Circuit in *U.S. Stem Cell*, which found the adipose tissue itself to be the HCT/P that must be reimplanted into the patient for the SSP Exception to apply.

The court also determined that the manipulation performed during the SVF Surgical Procedure did not significantly alter the SVF cells within the adipose tissue—allowing the cells to remain "such HCT/P's" that were removed from the patient. Judge Bernal explained that (1) the SSP Exception lacks any requirement that the HCT/Ps be unaltered before reinsertion into the patient during the same procedure; (2) the SVF Surgical Procedure did not alter the SVF cells' biological characteristics, ability to differentiate, or viability; and (3) the SSP Exception does not require the surgeon to implant everything that was removed in order to apply, and the technique used to process the SVF cells was similar to the "rinsing [and] cleansing" or "sizing and shaping" expressly permitted by SSP Exception Guidance.[21] These conclusions also contradict the 11th Circuit in *U.S. Stem Cell*, which concluded that the mechanical separation and processing involved in the HCT/P procedure fundamentally changed the HCT/P and the cells reinserted were not the same HCT/P that was removed from the patient.

2. Expanded MSC Surgical Procedure

The "Expanded MSC Surgical Procedure" involved removing a patient's adipose tissue and sending it to a GMP-compliant tissue bank to isolate the mesenchymal stem cells ("MSCs"). The third-party tissue bank then replicated and stored the MSCs until the same patient requested them for implantation into his or her body.

Because the MSCs are held in storage, rather than being extracted and reimplanted during the same procedure, the court found that the SSP Exception did not apply to the Expanded MSC Surgical Procedure. Judge Bernal next concluded that the MSCs are not "drugs" under the FDCA, and, therefore, are not subject to FDCA's premarket approval, adulteration and misbranding, and other drug-related provisions, holding:

> As a threshold matter, the cells involved in the Expanded MSC Surgical Procedure are not drugs. They are human cells removed from patients and then reintroduced into those same patients. They are not fungible goods that can be sold, mass produced, or patented . . . Defendants are engaged in the practice of medicine, not the manufacture of pharmaceuticals.[22]

The implication of this holding is that the HCT/Ps created during the "Expanded MSC Surgical Procedure" are subject to FDA regulation but solely under section 361 of the PHSA. Also, unlike the court in *U.S. Stem Cell*, Judge Bernal did not base his conclusion on an analysis of the criteria in 21 C.F.R. Part 1271.10 to make this determination.

3. SVF/ACAM2000 Treatment

The "SVF/ACAM2000 Treatment" was an experimental treatment that involved isolating SVF cells and then adding ACAM2000, an FDA-approved smallpox vaccine, before injecting the resulting mixture into the same patient's body. Defendants had stopped performing SVF/ACAM2000 Treatment prior to FDA's confiscation of all the vials of ACAM2000 from the clinic supplier's lab in August 2017.

The court determined that because the SVF/ACAM2000 Treatment involved adding SVF cells to a vaccine that had been shipped in interstate commerce, the treatment constituted the manufacture of a drug regulated under the FDCA.[23] Nevertheless, he concluded that the government lacked standing for injunctive relief because the defendants had ceased performing the treatment after FDA seized their supply of ACAM2000, prior to the initiation of the lawsuit.[24]

What to Watch From the Appeal of *California Stem Cell*

Judge Bernal's ruling marked a rare defeat for the government in an FDCA injunction case.[25] The stem cell industry will no doubt be watching the government's appeal closely, especially considering public criticism of the district court decision. The International Society for Cell & Gene Therapy ("ISCT"), for example, has rejected the court's characterization of SVF as a "naturally occurring, circulating, and unaltered biological entity that are simply relocated from adipose tissue to other diseased parts of the body."[26] The ISCT also noted the court had failed to consider whether the devices used by the defendants had actually been authorized by FDA for the purpose of producing stem cell therapies.

If the 9th Circuit were to affirm the district court's holding, the resulting circuit split could undermine FDA's authority to regulate clinics like U.S. Stem Cell Clinic and California Stem Cell Treatment Center. The case could make its way to the Supreme Court, where deference to an agency's interpretation of its own ambiguous regulations is far from assured.[27]

Even if the Supreme Court were to agree with the 9th Circuit's interpretation of the SSP Exception, clinics seeking to market comparable stem cell treatments are likely to face risks in the absence of robust scientific evidence to support their advertising and marketing claims. The Federal Trade Commission ("FTC") has taken enforcement action against stem cell clinics based on its jurisdiction over advertising, bringing its first such action against a stem cell clinic in 2018.[28] In that case, FTC sought permanent injunctive and other equitable relief against a clinic that advertised that its stem cell therapy could effectively treat serious medical issues, including autism, Parkinson's disease, and cerebral palsy, without having scientific evidence to support these claims. Under the terms of the negotiated consent decree, the defendants were required to pay $3.31 million and notify current and former patients of the settlement. Defendants were also prohibited from making future health claims without having adequate substantiation. Similarly, FTC in conjunction with the Georgia State Attorney General brought an action against a Georgia-based stem cell clinic and its owners for making unsubstantiated claims about the efficacy of their stem cell treatment in treating various orthopedic conditions.[29] State Attorneys General have also pursued enforcement action against stem cell clinics using their own state consumer protection and false advertising laws.[30]

Should other courts agree that the SSP Exception shields stem cell clinics from FDA scrutiny, FDA may attempt to revise its regulations to narrow the scope of the exception, but such a process could be lengthy, burdensome for the agency, and not assured of success against a future legal challenge. Regardless of how this issue ultimately shakes out, however, stem cell clinics that market therapies without sufficient scientific support are likely to continue to face scrutiny, and any instances of patient injury, like those alleged in *U.S. Stem Cell* and *California Stem Cell*, will no doubt serve to ratchet up the pressure from regulators.

Ropes & Gray will continue to monitor developments in this area. If you have any questions, please contact any member of Ropes & Gray's FDA regulatory practice or your usual Ropes & Gray advisor.

1. 21 C.F.R. Part 1271.3(d).
2. 42 U.S.C. § 264.
3. 21 C.F.R. § 1271.10(a).
4. 21 C.F.R. § 1271.3(c).
5. 42 U.S.C. § 262.
6. U.S. Food and Drug Administration, *Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception* (Nov. 2017), *available at*: https://www.fda.gov/media/89920/download.
7. U.S. Food and Drug Administration, *Statement from FDA Commissioner Scott Gottlieb, M.D. on the FDA's new policy steps and enforcement efforts to ensure proper oversight of stem cell therapies and regenerative medicine* (Aug. 28, 2017), *available at:* https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fdas-new-policy-steps-and-enforcement-efforts-ensure.
8. U.S. Food and Drug Administration, *FDA announces comprehensive regenerative medicine policy framework* (Nov. 15, 2017), *available at:* https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regenerative-medicine-policy-framework; Gottlieb, *supra* note 7.
9. U.S. Food and Drug Administration, *Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception*, 7 (Nov. 2017), *available at:* https://www.fda.gov/media/89920/download.
10. Gottlieb, *supra* note 7.
11. *United States v. U.S. Stem Cell Clinic, LLC*, 403 F. Supp. 3d 1279 (S.D. Fla. 2019).
12. Complaint, *United States v. U.S. Stem Cell Clinic, LLC*, 403 F. Supp. 3d 1279 (S.D. Fla. 2019).
13. 21 C.F.R. § 1271.15(b).
14. *United States v. U.S. Stem Cell Clinic, LLC*, 403 F. Supp. 3d 1279 (S.D. Fla. 2019).
15. *United States v. U.S. Stem Cell Clinic, LLC*, 998 F.3d 1302 (11th Cir. 2021).
16. *Id.*
17. Plaintiff's Notice of Motion and Motion for Summary Judgment, *United States v. California Stem Cell Treatment Center, Inc.*, No. EDCV 18-1005 JGV (KKx) (C.D. Cal. Jul. 08, 2019).
18. Order Denying the Government's Motion for Summary Judgment, *United States v. California Stem Cell Treatment Center, Inc.*, No. EDCV 18-1005 JGV (KKx) (C.D. Cal. Jan. 27, 2020).
19. Findings of Fact and Conclusions of Law, *United States v. California Stem Cell Treatment Center, Inc.*, No. EDCV 18-1005 JGV (KKx) (C.D. Cal. Aug. 30, 2022).
20. *Id.* at 14.
21. *Id.* at 14–15.
22. *Id.* at 16.
23. *Id.* at 17.
24. *Id.*
25. *See* Beth Weinman, Josh Oyster, & Jessica Band, *Deconstructing the Consent Decree: A Primer and Recent Trends for FDCA Injunctions*, FDLI Update (Winter 2020), *available at: https://www.fdli.org/2020/11/deconstructing-the-consent-decree-a-primer-and-recent-trends-for-fdca-injunctions/*.
26. International Society for Cell & Gene Therapy, *ISCT Issues Response to US Federal Judge Ruling on FDA Regulation of Cell and Gene Therapies* (Sept. 12, 2022), *available at:* https://www.isctglobal.org/telegrafthub/blogs/lauren-reville/2022/09/12/isct-issues-response-to-us-federal-judge-ruling-on.
27. Beth Weinman, Douglas Hallward-Driemeier, Greg Levine, Emerson Siegle, & Rebecca Williams, *Kisor May be a New Dawn For Challenges to FDA Actions*, LAW360 (Dec. 2, 2019), *available at*: https://www.law360.com/articles/1222885/kisor-may-be-a-new-dawn-for-challenges-to-fda-actions.
28. Order on Stipulation for Permanent Injunction and Monetary Judgement, *Federal Trade Commission v. Regenerative Medical Group, Inc. et al.*, No. 8: 18-cv-01838 (C.D. Cal. Oct. 25, 2018), *available at:* https://www.ftc.gov/system/files/documents/cases/regenerative_medical_group_signed_order_10-25-18.pdf
29. Federal Trade Commission, *FTC, Georgia Attorney General Sue Stem Cell Institute of America Co-Founders for Deceptive Joint Pain Cure-All Marketing Scheme* (Aug. 17, 2021), *available at*: https://www.ftc.gov/news-events/news/press-releases/2021/08/ftc-georgia-attorney-general-sue-stem-cell-institute-america-co-founders-deceptive-joint-pain-cure.
30. *See, e.g.,* New York State Office of the Attorney General, *Attorney General James Secures $5.1 Million Judgement Against New York City Stem Cell Clinic for Scamming Patients Out of Thousands Through False Advertising* (Nov. 24, 2021), *available at:* https://ag.ny.gov/press-release/2021/attorney-general-james-secures-51-million-judgment-against-new-york-city-stem; Office of the Attorney General, *Carr Sues Elite Integrated Medical for Deceptive Claims Made to Elderly and Disabled Consumers Regarding Stem Cell Therapy* (Sep. 14, 2020), *available at*: https://law.georgia.gov/press-releases/2020-09-14/carr-sues-elite-

integrated-medical-deceptive-claims-made-elderly-and; Washington State Office of the Attorney General, *AG Ferguson files lawsuit against US Stemology for peddling unproven, untested cell treatments* (Mar. 15, 2022), *available at*: https://www.atg.wa.gov/news/news-releases/ag-ferguson-files-lawsuit-against-us-stemology-peddling-unproven-untested-stem.