United States v. U.S. Stem Cell Clinic, LLC

NAOMI IGRA & EMILY MARDEN*

WHY IT MADE THE LIST

U.S. Stem Cell Clinic[1] made the list because it validates the Food and Drug Administration's (FDA's) view of its authority in the expanding field of regenerative medicine therapies. The defendant clinic offered a procedure involving the extraction and isolation of stromal and vascular cells ("stromal-vascular fraction" or "SVF") from a patient's body fat for reinjection back into the patient. It marketed the procedure as a treatment for medical conditions ranging from diabetes to osteoarthritis. In FDA's view, this rendered the clinic's SVF product a "drug" under the Federal Food, Drug, and Cosmetic Act (FDCA), as well as a "biological product" under the Public Health Service Act (PHSA). The clinic responded that FDA had no authority to regulate its SVF product because it fell within an exception to the regulation of human cells, tissues, and cellular and tissue-based products (HCT/Ps). In affirming summary judgment for the government, the Eleventh Circuit determined that the claimed exception did not apply and that the SVF product was subject to FDA's regulatory authority.

The court's decision will likely support FDA's campaign against what it views as similar unapproved, adulterated, or misbranded products, including many stem cell and exosome therapies.[2] The timing of the decision is also significant because it followed immediately after the expiration of a grace period FDA offered for the developers of HCT/Ps to consider whether they need to file Investigational New Drug (IND) or marketing applications for their products.[3] Taken together with recent FDA warning letters and consumer alerts, the Eleventh Circuit's decision signals that

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* Naomi Igra is a senior managing associate at Sidley Austin, LLP. Naomi's practice includes representing life science companies in litigation, commercial disputes, and investigations that implicate FDA regulations. Emily Marden is Counsel in the Food, Drug, and Medical Device Regulatory group at Sidley Austin, LLP. Emily's practice focuses on regulatory and strategic questions at the cutting edge, including clinical study, approval, and competitive issues associated with regenerative medicine.

1 United States v U.S. Stem Cell Clinic, LLC, 998 F.3d 1302 (11th Cir. 2021).

2 FDA has sometimes grouped these regenerative medicine therapies together with SVF therapy in its consumer alerts. *E.g.*, U.S. FOOD & DRUG ADMIN., IMPORTANT PATIENT AND CONSUMER INFORMATION ABOUT REGENERATIVE MEDICINE THERAPIES (June 3, 2021), https://www.fda.gov/vaccines-blood-biologics/consumers-biologics/important-patient-and-consumer-information-about-regenerative-medicine-therapies.

3 FDA ended its policy of enforcement discretion on May 31, 2021. It now "expects all establishments that manufacture HCT/Ps regulated as drugs or biological products to have an approved biologics license application (BLA) or an investigational new drug application (IND) in effect." U.S. FOOD & DRUG ADMIN., QUESTIONS AND ANSWERS REGARDING THE END OF THE COMPLIANCE AND ENFORCEMENT POLICY FOR CERTAIN HUMAN CELLS, TISSUES, OR CELLULAR OR TISSUE-BASED PRODUCTS (HCT/PS) (July 9, 2021), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/questions-and-answers-regarding-end-compliance-and-enforcement-policy-certain-human-cells-tissues-or.

purveyors of unapproved regenerative therapies should prepare for increased scrutiny and enforcement activity.

DISCUSSION

Regulatory Background

FDA generally regulates stem cell therapies as HCT/Ps, which are "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."[4] An HCT/P may be a "drug" under the FDCA if it is intended to "diagnose, cure, treat, mitigate or prevent diseases, or [is] intended to affect human bodily function or structure."[5] It may also be a "biological product" under the PHSA.[6] An HCT/P that is a drug and/or a biological product is subject to statutory approval requirements; in addition, the FDCA prohibits the marketing of adulterated or misbranded drugs. However, if an HCT/P meets certain criteria outlined in FDA regulations, it may qualify for more limited regulatory oversight under Section 361 of the PHSA.

Among other requirements, a "Section 361 HCT/P" must be "intended for homologous use only."[7] "Homologous use" is the "repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the *same basic function* or functions in the recipient as in the donor."[8] For example, a heart valve transplant may involve homologous use. If an HCT/P meets the homologous use requirement and other regulatory criteria, it is subject only to the requirements under Section 361 of the PHSA.

HCT/Ps may also be exempt from FDA regulations under the "same surgical procedure exception."[9] Under that exception, an establishment does not have to comply with FDA regulations pertaining to HCT/Ps if it "removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure."[10] A common example is a skin graft whereby healthy skin is removed from one part of a patient's body to treat a severe burn to another region of the same patient's body.

In November 2017, FDA issued guidance on "homologous use" and the "same surgical procedure exception" as part of a comprehensive regenerative medicine policy framework. In announcing the framework, then-FDA Commissioner Scott Gottlieb characterized cell-based regenerative therapies as a "a paradigm shift in the practice of medicine."[11] At the same time, he warned of "unscrupulous actors" making

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4 21 C.F.R. § 1271.3(d).

5 21 U.S.C. § 321(g)(1).

6 42 U.S.C. § 262(i)(1).

7 21 C.F.R. § 1271.10(a)(2).

8 *Id.* § 1271.3(c) (emphasis added).

9 *Id.* § 1271.15(b).

10 *Id.*

11 U.S. FOOD & DRUG ADMIN., STATEMENT FROM FDA COMMISSIONER SCOTT GOTTLIEB, M.D. ON FDA'S COMPREHENSIVE NEW POLICY APPROACH TO FACILITATING THE DEVELOPMENT OF INNOVATIVE REGENERATIVE MEDICINE PRODUCTS TO IMPROVE HUMAN HEALTH (Nov. 15, 2017), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fdas-comprehensive-new-policy-approach-facilitating.

"deceptive claims to patients about unproven, and in some cases, dangerous products."[12] To balance the interests of innovation and public health, FDA adopted a "risk-based approach" to enforcement actions for novel cellular therapies.[13] It generally gave manufacturers of cell and tissue-based products thirty-six months to comply with FDA pre-market review regulations but emphasized that it would not exercise enforcement discretion for products that pose a safety concern.

Factual and Procedural Background

U.S. Stem Cell Clinic, LLC ("the Clinic") is a Florida business that advertises itself as offering the "latest and most exclusive regenerative therapies."[14] The therapy FDA challenged involves the removal of adipose tissue, which is composed primarily of fat cells and collagen fibers but also contains stromal and vascular cells (SVF), some of which are stem cells. The Clinic used a five-step process to isolate the SVF from the adipose tissue, then injected it back into the patient suspended in saline solution or in platelet-rich plasma.[15] The Clinic marketed its SVF procedure as a treatment for a wide range of autoimmune, neurological, and degenerative conditions.[16]

FDA inspected the Clinic in 2015 and 2017. During the inspections, FDA reviewed records of adverse events and observed multiple violations of FDA's current good manufacturing practices (cGMP). The Clinic responded to FDA's observations and a subsequent warning letter by arguing that it was exempt from FDA oversight.[17]

FDA filed suit against the Clinic in the Southern District of Florida in 2018. The complaint characterized the Clinic as "experimenting on patients with adulterated and misbranded drugs."[18] FDA alleged that the Clinic's SVF product was a "drug" under the FDCA and a "biological product" under the PHSA. FDA then explained why the SVF product did not fall within any exception to FDA's regulatory authority. It followed that the SVF product was "adulterated" because it was not manufactured in compliance with cGMP, and "misbranded" because it lacked adequate directions for use.[19]

FDA moved for summary judgment arguing that the court could decide as a matter of law that no exceptions apply and the SVF is an adulterated and/or misbranded drug under the FDCA. The Clinic cross-moved for summary judgement arguing that the court could decide as a matter of law that the same surgical procedure in fact applied and FDA had no authority to regulate the SVF product under the FDCA.[20] The district

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[12] *Id.*

[13] U.S. FOOD & DRUG ADMIN., FDA ANNOUNCES COMPREHENSIVE REGENERATIVE MEDICINE POLICY FRAMEWORK (Nov. 15, 2017), https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regenerative-medicine-policy-framework.

[14] U.S. STEM CELL CLINIC, https://usstemcellclinic.com/ (last visited June 9, 2022).

[15] United States v U.S. Stem Cell Clinic, LLC, 998 F.3d 1302, 1306 (11th Cir. 2021).

[16] *Id.* at 1305.

[17] United States v. U.S. Stem Cell Clinic, LLC, Case No.: 18-CV-61047 (S.D. Fla. May 9, 2018), Dkt. #1 ("Complaint" or "Compl.") at ¶¶ 42–52; *see also Warning Letter, US Stem Cell Clinic, LLC*, U.S. FOOD & DRUG ADMIN. (Aug. 24, 2017), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/us-stem-cell-clinic-llc-524470-08242017.

[18] *Id.* at ¶ 1.

[19] *Id.* at ¶¶ 33–46.

[20] United States v. U.S. Stem Cell Clinic, LLC, 403 F. Supp. 3d 1279, 1287 (S.D. Fla. 2019).

court ultimately agreed with FDA's view and entered an injunction in favor of the government.

The Eleventh Circuit's Decision

The Eleventh Circuit affirmed the district court's judgment, focusing on the core issues of whether the SVF product was outside the scope of the FDCA's adulteration and misbranding provisions under the same surgical procedure exception or as a "Section 361 HCT/P."

First, the court examined the text of the same surgical procedure exception. The central question was whether the Clinic qualified as an establishment that removes HCT/Ps from a patient and then implants "such HCT/Ps" into the same patient.[21] The Clinic argued that it satisfied this requirement because its procedure removed SVF from a patent for reinjection into the same patient. FDA responded that the phrase "such HCT/P" means the that HCT/P removed must be the same as the HCT/P implanted; "[i]f significant processing steps expose the HCT/Ps to foreign substances and alter their form prior to reimplementation, then the HCT/Ps cease to be the same as they were at the time of removal."[22] The Eleventh Circuit agreed with FDA's reasoning, concluding that "[b]y the time the [SVF] is reinjected, it is no longer 'such HCT/P' as the adipose tissue removed from the patient."[23]

The court then turned to the question of whether the Clinic's SVF product satisfied the criteria for a "Section 361 HCT/P." The dispositive issue was whether the Clinic intended the SVF solely for "homologous use" in the sense that it intended the reinjected SVF to "perform the same basic function" as the SVF removed from the adipose tissue. The Eleventh Circuit emphasized that its analysis turned on the Clinic's "objective intent," which could be discerned from the Clinic's own marketing materials. It concluded that the Clinic marketed SVF to treat a "plethora of conditions," which is not the same "basic function" the Clinic alleged SVF performed in the adipose tissue.[24]

Because the SVF product did not satisfy the criteria for the same surgical procedure exception or a "Section 361 HCT/P," the Eleventh Circuit affirmed the judgment of the district court.

IMPACT OF THE CASE

The Eleventh Circuit's decision was a critical victory for FDA. In the words of Peter Marks, Director of the Center for Biologics Evaluation and Research, the decision is "an endorsement of the FDA's work to stop stem cell clinics that place patients at risk."[25]

At the same time, the decision spotlights a similar case pending in the Central District of California against another clinic offering SVF therapy. In that case, Judge Bernal denied the government's motion for summary judgment, concluding that same

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[21] *Id.* at 1296, 1298–1301.

[22] United States v U.S. Stem Cell Clinic, LLC, 998 F.3d 1302, 1308–09 (11th Cir. 2021).

[23] *Id.* at 1310.

[24] *Id.* at 1311.

[25] U.S. FOOD & DRUG ADMIN., INNOVATIVE REGENERATIVE MEDICINE THERAPIES—PATIENT SAFETY COMES FIRST (June 3, 2021), https://www.fda.gov/news-events/fda-voices/innovative-regenerative-medicine-therapies-patient-safety-comes-first.

surgical procedure exception could apply if the SVF cells remain "unaltered" during the course of the SVF procedure. That issue presented a question of fact that precluded summary judgment.[26] The parties proceeded to trial and are still awaiting a decision. Despite the force of the Eleventh Circuit's ruling, providers of stem cell therapies may doubt the scope of FDA's authority as long as the issue remains open before Judge Bernal.

Indeed, stem cell clinics have proliferated notwithstanding FDA's efforts. FDA does not have the resources to bring injunctive actions against the hundreds of stem cell clinics offering procedures like SVF. Moreover, stem cell clinics may just shift to other unapproved therapies that have not been tested in the courts.[27]

Ultimately, the Eleventh Circuit's decision may be most powerful in lending momentum to the efforts of other stakeholders like the Federal Trade Commission and state attorneys general who have stepped up their enforcement activities against stem cell clinics in recent years. In all events, stem cell clinics are sure to be under increased scrutiny in 2022 and beyond. Purveyors of other regenerative medicine therapies would be wise to ensure their products fall within a recognized exception or comply with all FDA regulations that may apply.

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[26] United States v. Cal. Stem Cell Treatment Ctr., Inc., 2020 WL 1289543, at *9 (C.D. Cal. Jan 27, 2020).

[27] *See, e.g.*, William Wan, *Stem Cell Clinics Likely to Flourish Despite Judge's Rebuke*, WASH. POST (June 7, 2019).