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Ninth Circuit Confirms: Certain Stem Cell Products Require FDA Premarket Approval

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On September 27, 2024, in *USA v. California Stem Cell Treatment Center, Inc.*, the US Court of Appeals for the Ninth Circuit issued a decision agreeing with the US Food and Drug Administration (FDA) that the defendants' stem cell product requires premarket drug approval under the Federal Food, Drug, and Cosmetic Act (FDCA), because the stem cells constitute a "drug" that did not qualify for any of the exemptions from the premarket application requirement under FDA's human cell, tissue, and cellular- and tissue-based product (HCT/P) regulation.[1]

This closely watched case is significant because by reversing the lower court's ruling, the Ninth Circuit now joins the US Court of Appeals for the DC Circuit and the US Court of Appeals for the 11th Circuit in concluding that stem cell products require FDA premarket approval similar to other FDA-regulated medical products. It remains to be seen whether the defendants will seek certiorari from the US Supreme Court on the Ninth Circuit's ruling.

FDA's regulation of HCT/Ps

HCT/Ps are articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient.[2] Examples of HCT/Ps include bone, ligament, skin, heart valve, cornea, stem cells derived from blood and reproductive tissue. As relevant here, these products are regulated as drugs under the FDCA based on their intended uses. If a product is intended to affect the structure or any function of the body, or to diagnose, cure, mitigate, prevent or treat a disease, it is a drug under the FDCA.[3] Drugs require an approved or cleared premarket application before they can be lawfully marketed – e.g., a New Drug Application (NDA) or a Biologics License Application (BLA), depending on the type of molecule at issue.

HCT/Ps that are medical products are required to have an FDA-approved application in place to be lawfully marketed unless they meet certain requirements spelled out in FDA's regulations that allow for an HCT/P to be regulated solely under section 361 of the Public Health Service Act. To be a "361" product, an HCT/P must be:

1. Not more than minimally manipulated.
2. Intended for homologous use.
3. Not combined with cells or tissues of any other product except for water, isotonic salt or glucose solution, or a sterilizing agent.
4. For autologous use, allogenic use by a first or second degree blood relative or reproductive use, or does not have a systemic effect and is not dependent upon metabolic activity to achieve its primary function.[4]

Alternatively, FDA regulations may exempt an HCT/P from all FDA regulation if the business that manufactures the HCT/P qualifies for an exception, such as the same surgical procedure (SSP) exception.[5]

The SSP exception applies where the HCT/Ps are removed from an individual and the same HCT/Ps are implanted back into the same individual during the same surgical procedure. If the SSP exception does not apply, the HCT/P will be regulated as a drug and/or biological product, and premarket review will be required.

Procedural history

In 2017, FDA inspected two entities co-founded by two California-licensed physicians: the California Stem Cell Treatment Center and the Cell Surgical Network Corporation. Following these inspections, FDA concluded that the defendants' stem cell products were unapproved drugs, and that the defendants were manufacturing these products in violation of the FDCA. In 2018, FDA sued the defendants seeking a permanent injunction to prevent

them from marketing these unapproved drugs.[6]

In its decision, the US District Court for the Central District of California wrestled with distinguishing between what constitutes a "drug" under the FDCA and what is considered a "medical procedure," when both drugs and surgical procedures are intended for the diagnosis, cure, mitigation, treatment or prevention of disease. The district court noted that there are no FDA-approved surgical procedures. It also noted that the line between "drug" and "procedure" is "especially muddy when licensed medical doctors enter a patient's body, extract that patient's cells, and reintroduce those cells to that patient after some amount of cellular processing."[7]

In its 2022 decision, the district court ultimately held that the defendants' stem cell product was not a "drug" under the FDCA, concluding that the "defendants are engaged in the practice of medicine, not the manufacture of pharmaceuticals."[8] The court also held that the defendants' use of stromal vascular fraction (SVF) during their "SVF surgical procedure" fell within the SSP exception. The court determined that the SSP exception applied to the defendants' stem cell procedure because it concluded that the product was autologous, meaning "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," and that "there is no evidence that the cells are anything other than autologous cells removed from, belonging to and returned back to the patient."[9]

Holding

In reversing the district court's ruling, the Ninth Circuit rejected the district court's conclusions that the defendants' stem cell product was not a drug, and that the SSP exception applied to the defendants' SVF surgical procedure.

Specifically, the Ninth Circuit relied on the plain meaning of the FDCA that broadly defined "drugs" based on the intended use, holding that "the undisputed intent as reflected in [Defendants'] marketing [is] to treat a long list of diseases and to affect structures of the body, such as to regenerate cartilage."[10] In so doing, the Ninth Circuit favorably cited the DC Circuit in *Regenerative Sciences*, which also utilized a plain reading of the FDCA to arrive at a similar conclusion. [11]

The Ninth Circuit dismissed the defendants' argument that classifying their stem cell mixture as a drug would interfere with the practice of medicine. The court pointed out that this argument had already been rejected by the Ninth Circuit in a previous case, *United States v. Kaplan*, which relied on the DC Circuit's decision in *Regenerative Sciences*.[12] In so doing, the Ninth Circuit refused to "classif[y] the distribution of drugs by doctors" as exempt from the FDCA because to do so would create significant gaps in FDA's oversight over pharmaceutical products.[13] Ultimately, the Ninth Circuit concluded that *Kaplan* forecloses the defendants' practice of medicine argument that would take the defendants' stem cell product outside of FDA's drug regulations.[14]

The defendants also attempted to invoke the major questions doctrine, which the court rejected, finding that FDA's regulation of drugs created or used by doctors "is unlike the situations in which the major questions doctrine has been applied."[15] The Ninth Circuit provided a few reasons. First, this case does not raise issues of extreme economic and political significance. Second, FDA's regulation of human cell and tissue products is not a sudden assertion or transformative expansion of authority. Third, the court found no mismatch between the defendants' stem cell product and the statutory scheme, distinguishing this case from the sole Supreme Court case addressing the major questions doctrine in the FDCA context (i.e., *FDA v. Brown and Williamson Tobacco Corp.*). In *Brown*, the Supreme Court ruled that FDA lacked authority to regulate tobacco products, concluding that "there is no room for tobacco products within the FDCA's regulatory scheme."[16] Unlike the Supreme Court, the Ninth Circuit concluded that the defendants' stem cell product "fits comfortably within the FDCA […]."[17]

Finally, the Ninth Circuit held that the SSP exception did not apply here because the "same" HCT/Ps were not removed and implanted back into the patient. In reaching this conclusion, the Ninth Circuit demonstrated a strong grasp of the underlying science involved in the stem cell procedure. The court analyzed the procedure itself, noting that the stem cell procedure here involved subjecting fat tissue to "enzymatic digestion" and multiple rounds of centrifugation to remove the fat cells from the fat tissue in a process that creates the stem cell mixture. The remaining cell mixture is then filtered, and it is this filtered mixture of cells – including stem cells – that is implanted back into the patient.

In determining which HCT/P was removed during the SVF procedure, the district court found that the cells within the removed fat tissue constituted the removed HCT/P, as these cells, not the fat tissue, were the target of the procedure and created the implanted mixture.[18] However, the Ninth Circuit disagreed, holding that this focus is misaligned with the purpose of the HCT/P regulation and the SSP exemption. The court noted that procedures eligible for the SSP exemption should carry relatively low risk, and that processing HCT/Ps introduces risk. Significant processing of fat tissue, which the defendants acknowledge is necessary to produce their stem cell mixture, introduces an amount of risk that the SSP exception was not intended to accommodate.[19] Consequently, the court held that procedures eligible for the SSP exception should not involve significant processing, which disqualified the defendants' stem cell procedure due to its use of significant processing.

What's next?

With three circuit courts now in alignment that certain stem cell procedures are properly regulated as drugs under the FDCA and subject to premarket approval, this decision could have significant implications for any company developing or offering stem cell treatments, particularly those involving SVF.[20] Entities engaged in this industry will need to consider these rulings when developing treatments involving stem cells to ensure they comply with the FDCA and its implementing regulations for premarket drug approval, which includes demonstrating each drug's safety and efficacy for its specific intended uses. Entities that fail to comply with these requirements could face enforcement by FDA and ultimately the Department of Justice, including actions similar to the one the government brought against the defendants in this case.

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Notes

1. 21 CFR 1271.15(b).
2. 21 CFR 1271.3(d).
3. 21 U.S.C. 321(g); 21 U.S.C. 321(h).
4. 21 CFR 1271.10(a).
5. 21 CFR 1271.15.
6. *United States v. Cal. Stem Cell Treatment Ctr.*, No. 22-56014, 8 (9th Cir. September 27, 2024).
7. *United States v. Cal. Stem Cell Treatment Ctr.*, Inc., 624 F. Supp. 3d 1177, 1185 (C.D. Cal. 2022).
8. Ibid, 1189.
9. Ibid, 1187.
10. *United States v. Cal. Stem Cell Treatment Ctr.*, No. 22-56014, 11 (9th Cir. September 27, 2024).
11. Ibid, 12.
12. *United States v. Cal. Stem Cell Treatment Ctr.*, No. 22-56014, 14 (9th Cir. September 27, 2024).
13. Ibid,14.
14. Ibid, 14.
15. Ibid, 15.
16. *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 122 (2000).
17. *United States v. Cal. Stem Cell Treatment Ctr.*, No. 22-56014, 16 (9th Cir. September 27, 2024).
18. *United States v. Cal. Stem Cell Treatment Ctr.*, Inc., 624 F. Supp. 3d 1177, 1187 (C.D. Cal. 2022).
19. *United States v. Cal. Stem Cell Treatment Ctr.*, No. 22-56014, 11 (9th Cir. September 27, 2024).
20. *United States v. Cal. Stem Cell Treatment Ctr.*, No. 22-56014 (9th Cir. September 27, 2024); *United States v. US Stem Cell Clinic, LLC*, 998 F.3d 1302 (11th Cir. 2021); and *United States v. Regenerative Sciences, LLC*, 741 F.3d 1314 (D.C. Cir. 2014).

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