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Legal Sidebar

Ninth Circuit Rules on FDA Regulation of HCT/Ps

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Human cells, tissues, or cellular or tissue-based products (HCT/Ps) consist of human cells or tissues that are intended for use in a human recipient. These products include stem cells and may be used in a number of medical procedures for various purposes. The Food and Drug Administration (FDA) regulates some HCT/Ps as drugs or biologics, generally requiring premarket approval upon a showing that they are safe and effective for their proposed use. FDA allows certain other HCT/Ps, which meet specific criteria, to be used without such approval as long as their use complies with certain regulations intended to minimize the spread of communicable diseases. Still other HCT/Ps are exempt from FDA regulation. Some commentators and industry groups have criticized FDA's regulation of some of these products as drugs out of concern that it will increase the costs or delay the availability of these products. Others have suggested that FDA is not sufficiently stemming the spread of clinics conducting procedures using HCT/Ps that have not been approved as safe and effective.

One procedure involving HCT/Ps that is the subject of a legal dispute involves the removal of fat tissue from a patient, processing the tissue to isolate the stem cells, and then reinserting a mixture containing stem cells into the same patient's knee to facilitate cartilage regrowth. In *California Stem Cell Treatment Center v. FDA*, FDA sued doctors and clinics performing the procedure, alleging that the stem cell mixture used in this procedure is an unapproved drug, and that it does not qualify for the so called same surgical procedure (SSP) exception.

In September 2024, the U.S. Court of Appeals for the Ninth Circuit (Ninth Circuit) held that this stem cell mixture was an adulterated and unapproved drug violative of the Federal Food, Drug, and Cosmetic Act (FDCA) that did not qualify for the SSP exception. The clinic has filed a petition for certiorari in the U.S. Supreme Court; the petition remains pending. This Legal Sidebar provides some background on FDA's regulation of HCT/Ps, examines the decision in *California Stem Cell Treatment Center v. FDA*, and concludes with select considerations for Congress.

Background

Although the FDCA does not expressly address HCT/Ps, FDA regulates HCT/Ps through a risk-based, tiered framework set out in FDA regulations and in statutory requirements pertaining to drugs and biologics. Under this risk-based framework, the default is that HCT/Ps are treated as drugs or biologics;

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that is, unless an HCT/P qualifies for regulation in a lower tier or for an exception, the HCT/P must obtain approval from FDA as a drug or biologic based on a demonstration (that includes data from clinical trials) that the HCT/P is safe and effective for its proposed use. These HCT/Ps raise effectiveness concerns as well as safety concerns for reasons other than an increased communicable disease risk.

Some relatively lower-risk HCT/Ps that meet various criteria, including that they are "minimally manipulated" and are "intended for homologous use"—which means that they are intended to perform the same basic function that they performed prior to their extraction—are not regulated as drugs or biologics. These HCT/Ps are instead subject to regulations intended to prevent the spread of communicable disease; these regulations were promulgated under FDA's authority in Section 361 of the Public Health Service Act. The communicable disease regulations set out requirements related to registration and listing, donor eligibility, and good tissue practice, including those related to facilities, equipment, and storage. Certain HCT/Ps are completely exempt from FDA regulation. One exception, called the same surgical procedure (SSP) exception, applies to HCT/Ps that are removed from an individual and implanted into the same individual during the same surgical procedure.

Recent Litigation: *California Stem Cell Treatment Center v. FDA*

In 2018, FDA sued clinics and doctors who performed a stem cell procedure to facilitate cartilage regrowth. In response to FDA's assertion that the HCT/Ps were unapproved drugs, the defendants argued to FDA's assertion that the HCT/Ps were unapproved drugs that the stem cell mixture was not a drug, and that, even if it were, the procedure was exempt from FDA regulation under the SSP exception. A federal district court ruled for the defendants, but when FDA appealed that decision, the Ninth Circuit reversed, holding that the SSP exception did not apply because the removed HCT/P and the inserted HCT/P were not the same due to the intermediate processing involved in the procedure.

The Ninth Circuit first determined that the stem cell mixture was a drug. The FDCA defines drugs as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or "intended to affect the structure or any function of the body." The court reasoned that the stem cell mixture was intended to treat certain diseases, such as osteoporosis, and it was intended to affect structures of the body by regenerating cartilage. The court therefore concluded that the statutory definition included the stem cell mixture.

The Ninth Circuit then considered the applicability of the SSP exception. It determined, and the parties agreed, that the SSP exception only applies to procedures in which the removed HCT/P and the implanted HCT/P are the same. The parties disagreed, however, about the correct comparators for determining whether the removed and inserted HCT/Ps are the same. In FDA's view, the SSP exception requires courts to view the removed HCT/P as a whole, before it underwent any significant processing. Under this interpretation, the HCT/P removed in the defendants' procedure was the fat tissue, which was not the same as the later-inserted stem cell mixture. The defendants, on the other hand, argued that the SSP exception requires courts to compare the implanted HCT/P with the HCT/P that was "the target of the removal, rather than the largest system removed." The defendants argued that, under this interpretation, the SSP exception applied to their procedure because it targeted for removal and implanted the same stem cells. To resolve this interpretive dispute, the court used traditional tools of statutory construction that focus on "the text, structure, history, and purpose" of the regulation.

Text of the Regulations

The court began its analysis by considering the text of the SSP regulation, which states:

> You are not required to comply with the requirements of this part if you are an establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure.

FDA argued that the use of the word "such" in the phrase "implants such HCT/P's" compelled its interpretation in which the court should compare the removed HCT/P as a whole to the inserted HCT/P to determine whether the HCT/Ps are the same. The defendants conceded that the removed and implanted HCT/P must be the same, but argued instead that the stem cell mixture "should be compared to the cells within the removed tissue, not the tissue as a whole." The court opined that the word "such" does not itself resolve which comparator to use.

The Ninth Circuit also considered the text of the regulatory definition of HCT/P, which defendants argued applied to the stem cells intended for implantation and not to the removed adipose tissue as a whole. The regulatory definition states:

> Human cells, tissues, or cellular or tissue-based products (HCT/Ps) means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.

The defendants argued that this definition suggested that the SSP exception should focus on the article that the doctor "intend[s] for implantation." Here, that would mean the stem cells. The court was not persuaded by this argument because of the clause "articles containing . . . human cells or tissues that are intended for implantation." The court reasoned that the HCT/P definition would include fat tissue because the removed fat tissue contained the cells that are intended for implantation.

The defendants also argued that FDA's interpretation focusing on the largest system would render part of the HCT/P definition superfluous. The definition refers to "cells or tissues," and defendants argued that, because generally cells can only be removed from the body within tissue or other larger systems, procedures would almost never qualify for the SSP exception due to the removal and reinsertion of "cells," rendering that part of the definition superfluous. FDA responded that at least one type of cell can be removed in isolation and that the regulation addressed an area of evolving science where new procedures that can remove isolated cells may emerge. The court agreed with FDA, determining that the word "cells" was not superfluous because it applied in at least one situation. Although the court characterized FDA's reading as "more straightforward and consistent with the . . . text," it ultimately determined that the text did not fully "resolve the interpretive dispute" between the parties because each party's interpretation of the text was "plausible."

Structure and Context of the Regulatory Scheme

The Ninth Circuit next examined the structure and context of the regulation. According to the court, the broader regulatory framework for HCT/Ps establishes three tiers of regulation: "1) full regulation [as a drug or biologic]; 2) limited exemption from regulation and 3) complete exemption from regulation." To qualify for the limited exemption in the second tier, the HCT/P must meet the criteria set out in 21 C.F.R. § 1271.10(a), including that the HCT/P cannot be more than "minimally manipulated." An HCT/P would qualify for complete exemption in the third tier if it qualifies for the SSP exception set out in 21 C.F.R. § 1271.15(b).

FDA argued that under the second tier, because an HCT/P is subject to full regulation if it is more than "minimally manipulated," the SSP exception should not be interpreted as completely exempting procedures that involve substantial manipulation of HCT/Ps. Defendants pointed out that, unlike the limited exemption in the second tier, the SSP exception does not expressly incorporate the "minimal manipulation" requirement, and the omission implies that a procedure can qualify for SSP exemption regardless of how much the HCT/P is manipulated. Defendants further argued that "it is not strange" that some procedures would be exempt from regulation under the SSP exception that do not qualify for the limited minimal manipulation exemption because the limited exemption is available to establishments that transfer HCT/Ps from one donor to a different recipient, whereas the SSP exemption is only available to establishments that remove HCT/Ps and insert them into the same patient.

The court opined that "FDA's understanding of the regulatory framework makes more sense" because the tiered structure implies that a procedure cannot qualify for the SSP exception if it involves more than minimal manipulation of the HCT/P. The court nevertheless determined that the structure of the regulations did not resolve the dispute because, if the defendants were correct that the targeted cells are the correct comparator, the defendants' procedure would not involve more than minimal manipulation of those cells.

History and Purpose of the SSP Regulation

The Ninth Circuit concluded its analysis by examining the history and purpose of FDA's HCT/P regulations. FDA initially proposed the HCT/P regulatory framework in 1997 and finalized it in 2001. When FDA first proposed the framework, it explained that, in the past, FDA's HCT/P regulation "'ha[d] focused on preventing the transmission of communicable disease,'" but that in recent years "scientists ha[d] developed innovative methods of manipulating and using human cells and tissues for therapeutic uses" that raise various public health and regulatory concerns. FDA therefore proposed the tiered approach regulating HCT/Ps "'based on risk and the necessity for FDA review.'" In this context, the FDA stated that the rationale for exempting procedures under the SSP exception is that "[t]he communicable disease risks, as well as safety and effectiveness risks, would generally be no different from those typically associated with surgery." The court identified "ensuring clinical safety and effectiveness" for "tissues that are highly processed" as a "chief purpose" of the regulations. Consistent with this proposal, the final rule established "'a tiered, risk-based regulatory scheme that . . . tailor[s] the degree of scrutiny afforded to different HCT/P's to the risks associated with each of them.'"

The court reasoned that, because the SSP exception is the bottom tier and completely exempt from FDA regulation, procedures qualifying for the exception should involve relatively low risk, or risk "no greater than that typically associated with conventional surgery." "Because processing HCT/Ps introduce[d] risk," procedures that qualified for the SSP exemption "should not involve significant processing." According to the court, the defendants' interpretation conflicted with the HCT/P regulation's history and purpose because, under their interpretation, the SSP exception would have exempted significantly processed HCT/Ps, even though that processing introduced far greater risk than that associated with general surgery. Meanwhile, FDA's interpretation was consistent with the SSP exception's history and purpose.

The court determined that FDA's interpretation was more consistent with the regulation's text, and it was "the only interpretation that makes sense" in light of the tiered, risk-based framework and the regulations' history and purpose. It held that the removed HCT/P must be viewed as a whole, before any significant processing, when determining whether the procedure involves the removal and implantation of the same HCT/Ps. Therefore, defendants' procedure involving the removal of fat tissue and the implantation of the stem cell mixture did not qualify for the SSP exception because the fat tissue and the stem cell mixture were not the same.

Considerations for Congress

The defendants have filed a petition for certiorari in the U.S. Supreme Court. If the Supreme Court grants the petition, it may decide whether the stem cells used in the procedure are "drugs" under the FDCA and, even if they are "drugs," whether the SSP exception applies. Such a ruling may provide clarity on how the SSP exception applies and what the correct comparator is for purposes of determining if HCT/Ps are the same. The Supreme Court may also decline to hear the dispute, which would leave the Ninth Circuit opinion intact.

Other courts have issued opinions on similar legal questions involving HCT/Ps. For example, in *United States v. U.S. Stem Cell Clinic*, the U.S. Court of Appeals for the Eleventh Circuit considered FDA's enforcement action against a clinic performing a procedure similar to the one considered in *California*

Stem Cell Treatment Center. The Eleventh Circuit determined that the HCT/P used in the procedure was a drug and that the SSP exception "unambiguously does not apply" to the clinic's HCT/Ps. In *United States v. Regenerative Services*, the U.S. Court of Appeals for the District of Columbia held that the HCT/Ps used in a different procedure involving the injection of a mixture containing a patient's stem cells and the antibiotic doxycycline were drugs or biologics.

FDA has recently indicated that it may consider revisiting the regulation of HCT/Ps in light of scientific advancements in this area. On February 5, 2025, the Office of Therapeutic Products (OTP) in FDA's Center for Biologics Evaluation and Research (CBER) held a workshop to "identify and discuss the current state of the science, development, and regulation for cellular therapies and tissue-based products." One industry approach outlined at this meeting suggested adding a low- and medium-risk category for HCT/Ps regulated as biologics, wherein the premarket requirements would differ, reflecting differences in evidentiary requirements needed to evaluate the products.

To the extent the industry approach outlined above is consistent with Congress's policy objectives, it may consider codifying the framework in statute. Congress could also amend federal law to exempt from the drug or biologic approval process certain HCT/Ps that otherwise do not qualify for a regulatory exception. Such legislation might require establishments using HCT/Ps to notify FDA before using them, to submit certain safety and effectiveness data, or to comply with other requirements that Congress deems appropriate. Congress could also reject FDA's tiered framework entirely and create a new framework. Congress may also decide not to amend the current framework.

Author Information

Dorothy C. Kafka
Legislative Attorney

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