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What comes out, must go back in: Court sides with FDA on "same surgical procedure" and "homologous use" definitions governing human cell and tissue products

FDA authority to crack down on illegally marketed stem cell treatments confirmed

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On 3 June a U.S. District Court in Florida issued a decisive blow against US Stem Cell Clinic LLC, granting the U.S. Food and Drug Administration's (FDA) motion for summary judgment, and stopping the clinic from offering its stem cell therapy to patients. The court found that the population of stromal and vascular cells in the clinic's therapy, known as stromal vascular fraction (SVF), constitutes a biological drug product that FDA must review and license before it can be commercially marketed. The court also found that the clinic's manufacturing procedures and its promotion violated statutory requirements, causing the clinic's cellular product to be adulterated and misbranded. Critically, the court rejected the clinic's argument that because its SVF procedure merely extracts and reinserts cells during the "same surgical procedure," it is exempt from FDA regulation. Instead, the court adopted FDA's view that the clinic's separation of stromal and vascular cells from surgically removed adipose (fat) tissue disqualified the procedure from this exception. The court held that the exception only applies to a procedure where the human cell, tissue, or cellular- or tissue-based product (HCT/P) that is implanted into a patient includes "all" of "the antecedent HCT/P removed from the patient in its original form." The case is a critical ruling supporting FDA's increasing enforcement against stem cell clinics. It also clarifies FDA's authority to regulate SVF therapies in particular, and bolsters FDA's effort to gain more control over the HCT/P field more broadly.

FDA has published regulations governing HCT/Ps under which certain of such products are subject to a standard generally lower than that applying to drugs and biological products. Specifically, if an HCT/P meets four criteria set forth in 21 Code of Federal Regulations § 1271.10(a), then it is deemed a "361 HCT/P," meaning that it is regulated solely under Section 361 of the Public Health Service Act (PHSA) and its implementing regulations in 21 Code of Federal Regulations Part 1271. Section 361 authorized FDA to issue regulations to prevent the transmission of communicable diseases. However, if the HCT/P does not meet all of those

criteria, the product is deemed a "351 HCT/P," meaning that it constitutes a "biological product" requiring FDA review and licensure under Section 351 of the PHSA. In that case, it is also a "drug" subject to regulation under the Federal Food, Drug, and Cosmetic Act (FDCA), as well as the PHSA.

Since 2015, FDA has been documenting violations of Current Good Manufacturing Practice (CGMP) for tissue products by US Stem Cell Clinic. The agency ultimately issued a warning letter to the company in August 2017, which we analyzed here. In response to the letter, the clinic claimed that FDA's CGMP regulations are not applicable because the clinic's SVF treatment falls under FDA's "same surgical procedure" exception to the HCT/P regulations. 21 Code of Federal Regulations § 1271.15(b). This provision states that FDA's regulation does not apply if "you are an establishment that removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure." Bringing this issue to court, FDA successfully asserted that the SVF implanted into the clinic's patients does not constitute "such HCT/P" removed from the patient due to the processing steps applied to the SVF, meaning the defendant was not covered by the exception.

US Stem Cell Clinic argued that an HCT/P reimplanted into a patient meets the regulatory definition of "such HCT/P" if it is "like or similar" to the HCT/P removed from the patient. The court disagreed. Instead, it adopted FDA's interpretation that "such HCT/P" refers to "the antecedent HCT/P removed from the patient in its original form." The clinic further asserted that in its procedures, the "unit of HCT/P", i.e., SVF cells implanted into the patient, "remain largely unchanged" from the SVF cells present in the adipose tissue extracted from the patient, fitting FDA's interpretation of "such HCT/P." The court again disagreed, deferring to FDA's view that "such HCT/P" implanted into the patient refers to "all of the HCT/P [in this case, the adipose tissue] removed from the patient in its original form." The court found that "FDA has historically interpreted the same surgical procedure exception as limited to those procedures in which the HCT/P removed from the patient is implanted back into that patient in its original form, with minimal processing."

In defense, the clinic also argued that FDA permits "such HCT/Ps" to be those that underwent "rinsing, cleansing, sizing, or shaping," asserting that this means that FDA historically has not required "such HCT/Ps" to be reimplanted in their original form in order for the "same surgical procedure" exception to apply. Yet, in a footnote, the court maintained that those processes "do not change the original form," but rather, constitute only "limited handling," as described by FDA guidance. In making this distinction, the court did not explain how resizing or reshaping a tissue preserves "all" of the extracted tissue in its original form. Instead, the court cited the risk of disease transmission as the agency's primary concern and its criterion for determining the scope of the exception. The court found that "FDA has consistently limited the same surgical procedure exception to procedures in which all such HCT/P removed from the patient is implanted back into the patient because the more a procedure modifies an HCT/P from its original form, the higher the risk of spreading communicable disease and the more regulation is required." Notably, although the court adopted the narrow interpretation that "all" of the tissue removed during the procedure must be reimplanted to satisfy the same surgical procedure exception, the court did not explain why implanting only a portion of the originally removed tissue necessarily increases the risk of disease transmission.

SVF therapy found not intended for homologous use

The court's assessment of whether SVF therapy is a 361 HCT/P turned on whether SVF was exclusively intended for homologous use, which is defined as "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." 21 Code of Federal Regulations § 1271.3(c). In making this determination, the court said it relied upon "the labeling, advertising, [and] other indications of the manufacturer's objective intent." Because the defendants had marketed their SVF therapy to treat an array of diseases, the court found the clinic could not argue the preprocedure SVF cells were intended to have performed the same function as the reimplanted SVF cells.

Court: FDA is not using guidance as a "Legislative Rule"

The clinic also argued that FDA was improperly enforcing its November 2017 final guidance, "Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception." The District Court spent considerable time dealing with this objection, emphasizing that FDA was not using guidance as a disguised legislative rule. Rather, the court concluded, the FDA guidance itself does not impose any obligations, but merely reflected FDA's long-standing, consistent, and permissible interpretation of the regulation. In reaching this conclusion, the court gave considerable deference to FDA's position that the guidance is not binding. Nevertheless, the court also expressed the view that even if the FDA considered the guidance to be legally binding, that position would be "irrelevant" to the disposition of the action.

Stem cell industry has been warned

The District Court's decision follows years of efforts by the government to reign in stem cell practices that it views as potentially dangerous. Below is a timeline showing the government's growing seriousness and commitment to policing stem cell therapies:

- **December 2015:** FDA cites US Stem Cell Clinic for significant deviations from CGMP discovered during investigations occurring between October and December 2015.
- **August 2017:** FDA announces new policy initiatives regarding stem cell therapies and regenerative medicine, anticipating stepped up enforcement in this area, which we analyzed here.
- **August 2017:** FDA issues warning letter against US Stem Cell Clinic, which we analyzed here.
- **August 2017:** FDA seizes five vials of a vaccine-stem cell admixture that were discovered during an FDA inspection at StemImmune Inc., as we discussed here.
- **November 2017:** FDA issues regenerative medicine policy framework consisting of four guidance documents that set forth a risk-based approach to driving advances in regenerative medicine (as previously discussed in our blog). FDA announced a limited period of enforcement discretion to give manufacturers time to assess whether they need to seek FDA approval, and to engage with FDA as needed. The enforcement discretion period will end in November 2020**.**
- **May 2018:** FDA announces that it filed two complaints in federal court seeking injunctions to stop marketing efforts of unapproved stem cell treatments by US Stem Cell Clinic and California Stem Cell Treatment Center, which we analyzed here.

- **October 2018:** The Federal Trade Commission (FTC) announces it settled charges against California-based Regenerative Medical Group, Telehealth Medical Group, and the founder of both companies, Dr. Bryn Jarald Henderson, based on deceptive stem cell therapy claims, as we discussed here.

- **November 2018:** FDA issues warning letter against Genetech Inc. in San Diego, California, over marketing "dangerous" unapproved stem cell products and for significant deviations from Current Good Tissue Practice (CGTP) and CGMP requirements, including some violations that may have led to microbial contamination, potentially causing serious blood infections in patients.

- **December 2018:** Former FDA Commissioner Scott Gottlieb, M.D. gives remarks at a December 2018 industry conference, in which he noted that FDA would be "stepping up actions" against stem cell clinics marketing unapproved new drugs and warned: "Expect to see brisk activity from the FDA when it comes to some rogue stem cell outfits that are putting patients at risk."

- **20 December 2018:** Following Dr. Gottlieb's warning, FDA sends letters to manufacturers, health care providers, and clinics that appear to be selling such stem cell treatments and urged them to contact the agency to discuss how to come into compliance (the "Stem Cell Letters").

- **March 2019:** FDA issues formal warning letter to Cord for Life Inc., located in Altamonte Springs, Florida, "for manufacturing unapproved umbilical cord blood products in violation of current good manufacturing practice (cGMP) requirements, including failing to validate processes to prevent bacterial contamination, raising potential significant safety concerns that put patients at risk."

- **April 2019:** FDA announces it sent 20 advisory letters to companies that may be selling unapproved stem cell products, including both manufacturers and health care providers.

- **May 2019**: FDA Chief Counsel Stacey Cline Amin gives speech highlighting stem cell products as an enforcement priority and decrying those "flouting the law and deceiving patients by illegally manufacturing or selling purported therapies, and falsely promoting their benefits."

- **3 June 2019**: *US Stem Cell* ruling, discussed above, which will likely spur the agency to take additional enforcement actions against other clinics that it views as endangering patients.

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The crackdown on illegally marketing unapproved stem cell treatments continues the stepped up enforcement by FDA, FTC, and the U.S. Department of Justice (previously summarized here). That enforcement has included actions against clinics in California, Florida, and New Jersey (previously summarized here). Monday's District Court opinion may increase the likelihood of other courts finding in favor of the agency's authority to regulate these types of therapies, including FDA's pending request for an injunction against California Stem Cell Treatment Center and Cell Surgical Network. We will continue to monitor how FDA is following through on its commitment to increasing oversight and enforcement in the regenerative medicine space, including criminal prosecutions, injunctions, seizure actions, and warning letters against other stem cell clinics.

For any questions relating to FDA's regenerative medicine policy framework, including engaging the agency on your product's classification and Biologic License Applications/Investigational New Drug requirements, feel free to contact any of the authors of this article or the Hogan Lovells lawyer with whom you regularly work.

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