MAYO CLINIC

COMMENTARY

Federal Regulatory Oversight of US Clinics Marketing Adipose-Derived Autologous Stem Cell Interventions: Insights From 3 New FDA Draft Guidance Documents

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Clinics advertising adipose-derived autologous stem cell "treatments" are rapidly spreading across the United States.[1] Some of these businesses promote cosmetic procedures such as "stem cell facelifts" and "stem cell breast augmentation."[2] Other facilities market adipose-derived stem cell "therapies" for amyotrophic lateral sclerosis, spinal cord injuries, Parkinson disease, multiple sclerosis, Alzheimer disease, muscular dystrophy, and other diseases and injuries. Once regarded as a country that residents had to leave if they wished to access unproven and unlicensed stem cell interventions, the United States now has many businesses that promote procedures more commonly associated with "stem cell tourism" to clinics and hospitals in China, India, Mexico, Panama, Ukraine, and other destinations.[3] The phenomenon prompts concerns about patient safety, direct-to-consumer marketing of unproven interventions, and the extent to which patients undergoing procedures at these businesses are being given all the information required to make informed choices.[4] Two individuals suffered complications and died after undergoing autologous stem cell procedures at a clinic in Florida; there are reports of injured patients; and US companies marketing adipose-derived stem cell interventions have been the subjects of litigation.[5-7]

Many US stem cell clinics advertise what they describe as adipose-derived autologous adult stem cell treatments.[8,9] (Because such businesses typically do not make public their clinical protocols or publish peer-reviewed data, little is usually known about exactly what types of cells these clinics administer to patients. Nonetheless, when making marketing claims, these businesses use the rhetoric of "stem cell therapies," even though many researchers question whether patients are administered actual stem cells.) Although concentrated bone marrow aspirate and peripheral blood are sometimes used as sources of autologous stem cells, particularly by orthopedic clinics and sports medicine facilities, it is increasingly common for US businesses to promote adipose-derived autologous mesenchymal stem cell interventions.[10] At these facilities, liposuction is performed to obtain fat tissue.[11] Next, enzymatic digestion, ultrasonic cavitation, or other processing techniques are used, and the stromal vascular fraction (SVF) is obtained from lipoaspirate. Stromal vascular fraction contains a heterogeneous mixture of adipocytes, fibroblasts, blood cells, endothelial progenitor cells, mesenchymal stromal cells, pericytes, and other cells.[12] Stromal vascular fraction is then injected, infused, or otherwise administered to patients. Patients are charged anywhere from thousands to tens of thousands of dollars for such interventions.

21 CFR 1271 and the Same Surgical Procedure Exception

To date, the Food and Drug Administration (FDA) has not approved any adipose-derived stem cell medical products for the US marketplace. Many physicians advertising such interventions claim they are performing innovative surgical procedures that fall within the scope of a regulatory exception identified in 21 CFR 1271, the federal regulation governing human cells, tissues, and cellular-and-tissue–based products (HCT/Ps). They claim they are engaged in the practice of medicine, and the FDA does not directly regulate the practice of medicine.[13] It is also common for such physicians to emphasize patient choice, assert that adipose-derived autologous stem cell interventions are already known to be safe and

efficacious, and claim that the FDA's bureaucratic approach to regulating clinical research is impeding the rapid development of stem cell therapies. When making such statements, physicians marketing autologous adipose-derived stem cell interventions often refer to 21 CFR 1271.15(b). This passage contains an important exception to the various standards described elsewhere in 21 CFR 1271. It 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."[14]

Numerous US businesses advertising adipose-derived stem cell interventions claim that they fall within this regulatory exception. For example, StemGenex, a California-based clinic that advertises adipose stem cell therapy for "Alzheimer's and Parkinson's Disease, Diabetes Type II, Rheumatoid and Osteoarthritis Arthritis, Multiple Sclerosis, Autoimmune Diseases, COPD, Pulmonary Fibrosis, Chronic Bronchitis, Stroke, Crohn's Ulcerative Coilitis [sic], skin conditions, and HIV" states: "Our procedure is in compliance with CFR 21 Part 1271 (1271.15.b)."[15] Cell Surgical Network, an association of approximately 50 clinics that market adipose-derived autologous stem cell procedures for more than 30 diseases and injuries, states: "[T]he Cell Surgical Network's surgical procedures fall under the category of physician's practice of medicine, wherein the physician and patient are free to consider their chosen course of treatment. The FDA does have guidelines about treatment and manipulation of a patient's own tissues. At CSN we meet these guidelines by providing same day treatment with the patient's own cells that undergo no manipulation and are inserted during the same procedure."[16]

Despite what such clinics claim, the procedures they market do not appear to fall within the same surgical procedure exception identified in 21 CFR 1271. In the case of autologous SVF, the FDA's interpretation of 21 CFR 1271 is that "such HCT/P's" are not removed and returned. Rather, cells removed from processed fat tissue and then returned to the body are not "such HCT/P's" and SVF does not fall within the same surgical procedure regulatory exception.

New Draft Guidance from the FDA: Same Surgical Procedure Exception

A new "Draft Guidance for Industry" issued by the FDA, titled "Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception," addresses what actions clinicians can perform while remaining within the scope of the exception.[17] For the exception in 21 CFR 1271.15(b) to apply, 3 criteria must be met. First, establishments must "[r]emove and implant the HCT/Ps into the same individual from whom they were removed (autologous use)." Second, establishments must "implant the HCT/Ps within the same surgical procedure." Third, the HCT/Ps must "remain 'such HCT/Ps;' they are in their original form." The guidance document identifies "rinsing, cleansing, or sizing" and "shaping" as acceptable actions. Other processing steps, "even manufacturing steps considered minimal manipulation" elsewhere within 21 CFR 1271(a), will typically cause the HCT/P to no longer be "such HCT/P."

The interpretation of 1271.15(b) provided in the draft guidance resembles previous responses provided by the FDA's Tissue Reference Group when asked whether the production of SVF falls within the scope of the exception.[18,19] Although businesses can contest the FDA's interpretation of 21 CFR 1271, warning letters, informal responses by the Tissue Reference Group, and this new draft guidance document all indicate that the FDA does not regard the production and administration of SVF as falling within the same surgical procedure exemption. Physicians who market and administer adipose-derived autologous "stem cell" interventions while claiming they are at liberty to engage in the "practice of medicine" without having to comply with the requirements of 21 CFR 1271 appear to be incorrect.

The draft guidance, though it does "not establish legally enforceable responsibilities," clarifies the FDA's interpretation of the exception identified in 21 CFR 1271.15(b). The FDA has made it clear that it "considers the same surgical procedure exception to be a narrow exception to regulation under Part 1271."

In addition to failing to operate within the exception identified in 21 CFR 1271.14(b), clinics advertising adipose-derived stem cell therapies do not appear to meet the standard for what are often referred to as "361 products."

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Such cells, tissues, and cellular-and-tissue–based interventions must comply with 21 CFR 1271 and section 361 of the Public Health Service Act (Section 361 of the Public Health Service Act authorizes the FDA to develop regulations intended to prevent the spread of communicable diseases.) However, they do not require premarketing review and approval by the FDA. In contrast, "section 351 products" fall under the scope of section 351 of the Public Health Service Act; are regulated as drugs, biologic products, or medical devices; and require premarketing approval by the FDA. Two additional new draft guidance documents help distinguish stem cell interventions requiring premarketing approval by the FDA from HCT/Ps that do not need to go through the premarketing approval process.

21 CFR 1271.10 and 1271.20

According to 21 CFR 1271.10, autologous HCT/Ps are "regulated solely under section 361 of the PHS Act" and applicable components of 21 CFR 1271 only if they are "minimally manipulated," "intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;" and "[t]he manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent," provided that the addition of such agents "does not raise new clinical safety concerns with respect to the HCT/P."[14] However, in several warning letters, the FDA has stated that it regards the processing steps used to produce SVF from lipoaspirate as falling outside the minimal manipulation standard as it is defined in 21 CFR 1271.[20-22] These letters also state that clinics fail to comply with the "homologous use" standard when they market "adipose-derived stem cell treatments" for such clinical indications as multiple sclerosis and Parkinson disease.

Autologous HCT/Ps that do not comply with the minimal manipulation, homologous use, and combination standards are, 21 CFR 1271.20 states, "regulated as a drug, device, and/or biological product." Clinics wishing to market such drugs, devices, or biological products cannot simply begin advertising stem cell therapies. Rather, they must submit Investigational New Drug or Investigational Device Exemption applications to the FDA and conduct safety and efficacy trials before seeking premarketing approval. Companies conducting clinical studies under FDA-cleared Investigational New Drugs or Investigational Device Exemptions cannot remain compliant with federal regulations while also advertising and profiting from the sale of investigational agents of unknown safety and efficacy.

"Minimal Manipulation": A Second New Draft Guidance Document Addressing the Regulation of HCT/Ps

In December 2014, the FDA released a draft guidance document titled "Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products."[23] The draft guidance clarifies the FDA's interpretation of what constitutes "minimal manipulation" of HCT/Ps and addresses the question of what definition of minimal manipulation applies when a cellular therapy product is produced from cells isolated from structural tissue. (21 CFR 1271 states that in the case of structural tissue, minimal manipulation is "processing that does not alter the original relevant characteristics of the tissue related to the tissue's utility for reconstruction, repair, or replacement.") According to the draft guidance: "If you isolate cells from structural tissue, you should apply the definition of minimal manipulation for structural tissue." Providing an example of how the definition is applied, the draft guidance adds:

> Original relevant characteristics of adipose tissue, a structural tissue, to pad and cushion against shocks generally includes its bulk and lipid storage capacity. A manufacturer recovers adipose tissue by tumescent liposuction and processes the adipose tissue to isolate cellular components, commonly referred to as stromal vascular fraction, which is considered a potential source of adipose-derived stromal/stem cells. The HCT/P is generally considered more than minimally manipulated because the processing breaks down and eliminates the structural components that provide cushioning and support, thereby altering the original relevant characteristics of the HCT/P relating to its utility for reconstruction, repair, or replacement.

This draft guidance document states that SVF produced from processed fat tissue does not meet the definition of minimally manipulated structural tissue because the "original relevant characteristics" of fat tissue are changed when lipoaspirate is processed and its cellular components are isolated in the form of SVF. As a result, autologous SVF is classified as an HCT/P "regulated as a drug, device, and/or biological product" and requiring premarketing approval by the FDA.

HCT/Ps from Adipose Tissue: A Third New Draft Guidance

After the release of the 2 preceding guidance documents, in late December 2014 the FDA issued a third draft guidance document concerning HCT/Ps. This document titled "Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations" also states that when the FDA applies 21 CFR 1271 to processing of fat tissue, "[p]rocessing to isolate non-adipocyte or nonstructural components from adipose tissue (with or without subsequent cell culture or expansion) is generally considered more than minimal manipulation."[24] The draft guidance proceeds to offer numerous examples concerning how the FDA proposes to regulate HCT/Ps obtained from adipose tissue. Physicians, patients, stem cell researchers, and other parties interested in better understanding the FDA's classification scheme for regulating HCT/Ps obtained from fat tissue should familiarize themselves with the entire draft guidance. Although many key regulatory concerns related to SVF were already addressed in the 2 previously released draft guidances, this draft guidance provides the most detailed account to date of how the FDA proposes to regulate HCT/Ps processed from fat tissue. Individuals interested in submitting comments on this draft guidance or the preceding 2014 draft guidances related to HCT/Ps can provide feedback at http://www.regulations.gov.

Conclusion: Enforcing Compliance with Federal Regulations

Despite federal regulations that require approved biologic product, new drug, or medical device applications for adipose-derived autologous mesenchymal stem cell interventions intended for the treatment of particular clinical indications, a substantial number of US clinics are marketing adipose-derived autologous stem cell treatments. These clinics do not appear to operate in compliance with federal regulations. By failing to establish the safety and efficacy of their stem cell–based medical products in FDA-cleared and institutional review board–approved clinical trials, they are exposing their patients to unnecessary risks and charging substantial fees for medical products that are not approved by the FDA.

Given the significant revenues that can be generated from direct-to-consumer marketing of putative stem cell treatments, clinics engaging in such commercial activity are unlikely to cease operating simply because the FDA has released 3 new draft guidances or proceeds to issue final guidance documents. Even before the release of these draft guidances, such businesses were advertising cell-based interventions that put them at risk of being inspected and possibly subjected to regulatory action by the FDA. Although useful, the draft guidance documents alone are unlikely to have a meaningful deterrent effect. Instead, the FDA must now proceed to the challenging task of enforcing regulatory compliance in a rapidly expanding marketplace where many businesses appear to operate in noncompliance with federal regulations while profiting from the sale of unproven and unlicensed cell-based interventions. Given the number of US clinics now marketing adipose-derived autologous "stem cell treatments," it is going to require considerable effort by the FDA to promote improved regulatory compliance.

Abbreviations and Acronyms: **FDA** = United States Food and Drug Administration; **HCT/Ps** = human cells, tissues, and cellular and tissue-based products; **SVF** = stromal vascular fraction

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