

FDA Regulation of Stem Cell Therapies: Using a Stem Cell Fraud Strike Force to Separate Fact from Fiction

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ABSTRACT

In recent years, growth in the U.S. stem cell industry has surged through online marketing of unproven cell therapies to treat everything from multiple sclerosis and dementia to autism. This Article focuses most closely on adipose (fat) derived stem cell therapies because of their prevalence in the market and the U.S. Food and Drug Administration's (FDA's) problems in regulating them. The discussion explains why FDA has stumbled to date and faces even greater problems going forward, and offers a more effective and efficient strategy of using an Federal Trade Commission (FTC)-led inter-agency collaboration to target clinics for false advertising rather than arguing about the intricacies of stem cell biology.

I. INTRODUCTION

What we're playing now is a game of Whac-a-Mole. . . . [W]e've got a major issue here and we have to triage somewhat. . . . [I]t will be incredibly hard to keep track of [stem cell clinics] because they keep changing products. . . . [T]rying to keep track of the clinics is nearly impossible anyway because whether it's 500, a thousand . . . they're entities that come and go very quickly. . . . There's nothing more that we would like to do than take more enforcement actions. It is a slow and deliberate process because we actually have to work through the process of law.¹

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¹ Peter Marks, *Stem Cells: How to Separate the Promising from the Questionable*, HEALTH JOURNALISM 2019 CONFERENCE (May 4, 2019), recorded in *Bad Batch*, WONDERY (Nov. 13, 2019), <https://wonderly.com/shows/bad-batch/#> [<https://perma.cc/N7XV-HTAS>].

One of the most powerful—and tragic—examples of therapies gone viral is direct-to-consumer (DTC) internet marketing by stem cell clinics, especially when it targets patients with serious conditions and few treatment options. Stem cell therapies and the clinics that offer them have surged in recent years as stem cells have become easier to find, harvest, and use while the internet has made them easier to promote. Two decades ago, the mere mention of “stem cells” would set off alarms about creating and destroying embryos. Today’s treatments do not carry the same ethical concerns or technical challenges that attend embryonic stem cells (ESCs) because they use adult stem cells (or more technically, adult mesenchymal stem cells or MSCs). Like ESCs, MSCs are undifferentiated and self-renewing (and thus “stem cells”); but only “multipotent” because they can differentiate into many but not all cell types (unlike “pluripotent” ESCs).²

A major advance in stem cell therapeutics occurred less than twenty years ago with the realization that MSCs are abundant in adipose tissue and readily harvested through liposuction.³ The comparative ease of extracting and using adipose-derived MSCs has catalyzed industry growth. Today, a quick web search can find a stem cell treatment for just about every condition with a diagnostic code, ranging from balding and impotence to cardiomyopathy, stroke, multiple sclerosis, and more. Glowing patient testimonials abound; references to “university research” in “FDA approved labs” with “Institutional Review Board” (IRB) approval are equally common while any mention of potential risks is largely absent. News headlines and court dockets nevertheless reveal what these websites often omit. For some, adult stem cell therapies delivered dramatic improvements after standard treatments fell short, but for others, they delivered little beyond high costs payable in dollars, permanent disability, or worse.⁴ These risks might not be apparent to the public, but they have not escaped FDA’s attention.

In November 2017, FDA announced “a comprehensive policy framework for the development and oversight of regenerative medicine products, including novel cellular therapies.”⁵ This consisted of: (1) a series of Draft and Final Guidance materials; (2)

² U.S. DEPT. HEALTH & HUMAN SERVS., NAT’L INSTS. OF HEALTH, *Stem Cell Basics*, <https://stemcells.nih.gov/info/basics.htm> [<https://perma.cc/TZ7G-X8YQ>] (last updated Mar. 13, 2020).

³ See, e.g., Peter H. Ashjian, Daniel De Ugarte, Adam Katz & Marc Hedrick, *Lipoplasty: From Body Contouring to Tissue Engineering*, 22 *AESTHETIC SURGERY J.* 121 (2002); Patricia A. Zuk, Min Zhu, Hiroshi Mizuno, Jerry Huang, J. William Futrell, Adam J. Katz, Prosper Benhaim, H. Peter Lorenz & Marc H. Hedrick, *Multilineage Cells from Human Adipose Tissue: Implications for Cell-Based Therapies*, 7 *TISSUE ENGINEERING* 211 (2001); see also Sunil S. Tholpady, Ramon Lull, Roy C. Ogle, J. Peter Rubin, J. William Futrell & Adam J. Katz, *Adipose Tissue: Stem Cells and Beyond*, 33 *CLINICS PLASTIC SURGERY* 55–57 (2006).

⁴ See, e.g., Katie LaGrone & Matthew Scott Apthorp, *New Lawsuit Against US Stem Cell After Patient Loses Vision; Family Ties Called into Question*, ABC ACTION NEWS (June 18, 2018), <https://www.abcactionnews.com/news/local-news/i-team-investigates/new-lawsuit-against-us-stem-cell-after-patient-loses-vision-family-ties-called-into-question> [<https://perma.cc/ZA5N-5RHR>] (reporting on three lawsuits against U.S. Stem Cell Clinic, each filed by a woman who was treated for age-related macular degeneration and lost all vision shortly thereafter; all eventually settled).

⁵ *FDA Announces Comprehensive Regenerative Medicine Policy Framework; Framework Aims to Spur Innovation, Efficient Access to Potentially Transformative Products, While Ensuring Safety and Efficacy*, U.S. FOOD & DRUG ADMIN. (Nov. 15, 2017), <https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regenerative-medicine-policy-framework> [<https://perma.cc/8GA3-8Y38>].

a three year period of enforcement discretion to encourage developers to consult FDA on the need for premarket review; and (3) risk-based regulation based on product type, method, and mode of delivery.⁶ Since then, FDA has sent dozens of Warning Letters (many have been ignored) and filed a small handful of lawsuits (results have been mixed). Thus, despite its scope and ambitions, this comprehensive approach has not kept pace with the rapidly growing and constantly evolving adult stem cell industry.⁷ CBER Director Peter Marks conceded as much when he described FDA's enforcement efforts as a frustrating game of Whac-a-Mole.⁸ Although more staff and money might help,⁹ they will never suffice because FDA is playing the wrong game, especially when it comes to adipose.¹⁰

Curiously, FDA has shown itself to be far more effective in controlling similar claims and promotional practices for unproven COVID-19 therapies. Even before coronavirus became a national emergency in mid-March 2020, FDA sent more warnings and obtained more settlements and court orders than it had in the previous years of pursuing stem cell clinics. The risks of adult stem cell therapies might pale in comparison with the threat of a global pandemic, but the striking similarities in therapeutic claims and promotional techniques (with some clinics promoting stem cells to treat COVID-19) make it hard to understand why FDA has been so efficient in one context and so sluggish in the other. There must be a way for FDA to replicate its COVID-19 successes in the stem cell sector. This Article offers a game plan.

Part II summarizes FDA's three-tiered framework for regulating human cell and tissue therapies based on product risk. Part III analyzes why FDA's enforcement of these regulations has often been self-defeating due to the regulations' heavy reliance on a stem cell product's "form" and "function" in determining regulatory status, and the agency's factually inaccurate determinations of form and function for adipose and its component cells. Part IV explains FDA's current use of protracted, clinic-by-clinic litigation to debate the complexities of what cells do pre- and post-implantation instead of targeting what providers do in promoting them to vulnerable patients. This section also shows why, in addition to being inherently inefficient, FDA's enforcement strategy became even more problematic when the U.S. Supreme Court pulled back on deference to agency interpretations in *Kisor v. Wilkie*.¹¹ Part V evaluates and ultimately endorses a simpler approach, one which FDA already knows well. As it has done in curtailing online marketing of bogus COVID-19 treatments, FDA should

⁶ *Id.*

⁷ The U.S. House Committee on Energy and Commerce has described "the slower than expected progress of manufacturers and providers . . . to come into compliance with premarket approval requirements" as especially concerning "given the high stakes for patients" and the insistence of many clinics that "their products are not subject to FDA review." Letter from House Comm. on Energy and Commerce to Acting Comm'r Norman E. Sharpless, (July 25, 2020), <https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/FDA.2019.7.25.pdf> [<https://perma.cc/S5CC-2RLN>].

⁸ *See supra* note 1 and accompanying text.

⁹ THE PEW CHARITABLE TRUSTS, FDA'S FRAMEWORK FOR REGULATING REGENERATIVE MEDICINE WILL IMPROVE OVERSIGHT (2019), https://www.pewtrusts.org/-/media/assets/2019/10/fdasframeworkforregulatingregenerativemedicine_v2.pdf [<https://perma.cc/49DW-58HJ>].

¹⁰ *Id.*

¹¹ *Kisor v. Wilkie*, 139 S. Ct. 2400 (2019).

collaborate with FTC to charge providers under the Federal Trade Commission Act (FTCA) for false and deceptive online marketing of unproven stem cell treatments.¹² The players, products, and claims are the same, but as Part IV will show, FTC is better equipped to make real gains in preventing clinics from placing patients at risk.

Finally, Part VI proposes its own comprehensive framework for overseeing regenerative medicine. This one is designed to replace FDA's losing Whac-a-Mole battle with a new and hopefully winnable game. It urges FDA to: (1) align current regulations and interpretive Guidance with accurate science; (2) reframe enforcement efforts to focus less on the biological form and functions of stem cells and more on the marketing practices of clinics that use them; (3) expand FDA's successful COVID-19 collaboration with FTC and U.S. Department of Justice to include unproven stem cell treatments;¹³ and (4) fortify this collaboration by enlisting state regulators, law enforcement, and professional licensing authorities to form an ongoing Stem Cell Strike Force. This four-step program is genuinely comprehensive and, as already demonstrated by collaboration against deceptive marketing of COVID-19 products, this game plan can accelerate the pace of protecting patients from unsafe stem cell therapies.

II. FDA REGULATION OF HUMAN CELL AND TISSUE PRODUCTS

Stem cell therapies are a form of regenerative medicine, a rapidly evolving area of medicine that involves “replacing, engineering, or regenerating human cells, tissues, or organs to establish, restore, or enhance normal function.”¹⁴ Regenerative products include “cell therapies, therapeutic tissue-engineering products, human cell and tissue products, and certain combination products involving cells and devices, such as scaffolds upon which cells can grow.”¹⁵

One of the most common and persistent criticisms of FDA regulation of cell therapies is that the government attempts to regulate the body's own cells as if they were drugs. This seems like an obvious concern given the differences between a person's own naturally produced stem cells and the chemically synthesized and mass-

¹² See 15 U.S.C. §§ 45, 52 (2006). In addition to combining forces in February 2020 to tackle DTC marketing of unproven coronavirus treatments, the two agencies are collaborating to prevent anti-competitive practices in the emerging biosimilars market. U.S. FOOD & DRUG ADMIN. & U.S. FED. TRADE COMM'N, *Joint Statement of the Food & Drug Administration and the Federal Trade Commission Regarding a Collaboration to Advance Competition in the Biologic Marketplace* (Feb. 3, 2020), <https://www.fda.gov/media/134864/download> [<https://perma.cc/2P2Z-43HR>].

¹³ For example, in mid-April 2020, FDA and FTC sent a joint Warning Letter to Genesis II Church of Health and Healing, calling for the immediate halt of promotion and sale of the company's “Mineral Miracle Solution” industrial strength bleach product as a COVID-19 treatment. The letter provided forty-eight hours for reply and when the manufacturer indicated its intent not to comply, the two agencies immediately obtained a preliminary injunction. The entire process took ten days. Press Release, U.S. Dept. of Justice, *Justice Department Seeks to End Illegal Online Sale of Industrial Bleach Marketed as “Miracle” Treatment for COVID-19* (Apr. 17, 2020), <https://www.justice.gov/opa/pr/justice-department-seeks-end-illegal-online-sale-industrial-bleach-marketed-miracle-treatment> [<https://perma.cc/L6SZ-TTEZ>].

¹⁴ Peter Marks & Scott Gottlieb, *Balancing Safety and Innovation for Cell-Based Regenerative Medicine*, 378 NEW ENG. J. MED. 954, 954 (2018).

¹⁵ *Id.*

produced medical drugs purchased at the local drug store. Human cells and tissue, and cell- and tissue-related products (HCT/P's), nevertheless qualify as both “drugs” and “biological products” as defined by, respectively, the Federal Food, Drug, and Cosmetic Act (FDCA)¹⁶ and the Public Health Service Act (PHSA).¹⁷ The FDCA defines a “drug” to include articles that are “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and . . . intended to affect the structure or any function of the body of man or other animal. . . .”¹⁸ Section 351 of the PHSA defines a biological product as a “virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.”¹⁹ Under the FDCA, an HCT/P as a drug must be sufficiently “safe” and “effective”²⁰ and, as a biological product under the PHSA, “pure and potent” before it can be marketed to the public.²¹

Although human cell and tissue products satisfy the statutory definitions of both drugs and biological products, they differ from conventional drugs and biologics in significant respects. For this reason, in 1997, FDA proposed a new approach to regulating cell and tissue products that would “enable the agency to provide only that level of oversight relevant to each of the individual areas of concern.”²² In 2005, the agency finalized rulemaking to create a separate framework that regulates HCT/P's as biologic products under sections 361 and 351 of the PHSA.²³ With the goal of tailoring the nature and extent of regulation to a product's risk of infection or transmission of a communicable disease, the framework consists of three levels of increasing requirements: (1) no oversight for exempt products;²⁴ (2) minimal oversight under PHSA section 361 (e.g., registration and listing);²⁵ and (3) full premarket review, current Good Manufacturing Practices (cGMPs), and associated requirements under PHSA section 351 (although compliance with current Good Tissue Practices or

¹⁶ 21 U.S.C. § 321(g)(1) (2018).

¹⁷ 42 U.S.C. § 262(i)(1) (2019).

¹⁸ 21 U.S.C. § 321(g)(1)(B), (C) (2018).

¹⁹ 42 U.S.C. § 262(i)(1) (2019).

²⁰ 21 U.S.C. § 355(b)(1) (2018).

²¹ 42 U.S.C. § 262(a)(2)(C)(i)(I) (2010). Although beyond the scope of this discussion, an HCT/P may also qualify as a medical device, defined by 21 U.S.C. § 321(h)(2)–(3) (2018) to include an:

implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or . . . intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

²² Proposed Approach to Regulation of Cellular and Tissue-Based Products; Availability and Public Meeting, 62 Fed. Reg. 9721, 9722 (Mar. 4, 1997).

²³ 21 C.F.R. Part 1271 (first effective May 25, 2005). Compare 42 U.S.C. § 262 (2019), and *Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing*, 66 Fed. Reg. 5447 (Jan. 19, 2001) (setting forth the regulatory framework for HCT/P products), with 21 U.S.C. § 360 (2018), and 21 C.F.R. § 207 (2019) (presenting the regulatory framework for drugs, devices, and non-§ 351 biologics).

²⁴ 21 C.F.R. § 1271.3(d) (2019).

²⁵ 21 C.F.R. §§ 1271.10(a)(1)–(4)(ii) (2019).

“cGTPs” still pertains).²⁶ Before examining each tier in detail, it is worth clarifying basic concepts.

A. Key Terms

The following definitions are critical to understanding the HCT/P framework’s operation and, for the purpose of this discussion, its impact on regulating adipose products.

- Autologous use “means the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered.”²⁷
- Homologous use “means 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.”²⁸
- Human cells, tissues, or cellular or tissue-based products (HCT/P’s) “means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.”²⁹
- Minimal manipulation “means:
 - For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue’s utility for reconstruction, repair, or replacement; and
 - For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.”³⁰
- Processing “means any activity performed on an HCT/P, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage.”³¹

B. The HCT/P Framework: A Closer Look

FDA’s purpose for using three risk-based, graduating levels of oversight is to “prevent the introduction, transmission, and spread of communicable diseases by HCT/P’s.”³² Products falling on the lower or middle tier of, respectively, no or

²⁶ 21 C.F.R. § 1271.20 (2019) (stating that HCT/P’s that do not fall under either of the first two tiers are regulated under Section 351 of the PHSA).

²⁷ 21 C.F.R. § 1271.3(a).

²⁸ *Id.* § 1271.3(c).

²⁹ *Id.* § 1271.3(d).

³⁰ *Id.* § 1271.3(f)(1)–(2).

³¹ *Id.* § 1271.3(ff).

³² *Id.* § 1271.1(a).

minimal oversight represent fewer safety concerns (at least in FDA’s assessment) than do higher-tiered products that warrant costly and time-consuming premarket review.

1. Tier 1: Exempt from HCT/P Oversight

The regulatory definition of an HCT/P expressly exempts from sections 361 and 351 oversight of certain products that in terms of their biological make-up and function, might otherwise fall within that definition. That certain articles “are not considered HCT/Ps” is, more accurately, regulatory parlance for FDA simply deciding not to regulate them as HCT/P’s.³³ Products “not considered HCT/Ps” include vascularized human organs for transplantation, whole blood and blood components, “[s]ecreted or extracted human products” such as milk or collagen, and “[m]inimally manipulated bone marrow for homologous use and not combined with another article[.]”³⁴

2. Tier 2: Minimal Section 361 Oversight

HCT/P’s in this category are subject to minimal oversight under section 361 of the PHSA, including registration, listing, and cGTPs, but need not undergo premarket review or employ cGMPs as required by section 351.³⁵ For section 361’s minimal oversight to apply, an HCT/P must be: (1) no more than minimally manipulated;³⁶ (2) intended for homologous use only;³⁷ (3) not combined with “another article;”³⁸ and (4) have no systemic effect or dependence on “the metabolic activity of living cells for its primary function” or, if it does, be intended either for autologous use or for allogenic use in a first-degree or second-degree blood, or for reproductive use.³⁹

3. Tier 3: Extensive Section 351 Oversight (Including Premarket Approval)

Failing one or more of section 361’s criteria signals greater safety risks that warrant premarket review and approval and additional protections required by section 351.⁴⁰ Unless the product falls within an exception to section 351⁴¹ or qualifies for some version of expedited approval,⁴² a section 351 product’s sponsor—including a single

³³ *Id.* § 1271.3(d).

³⁴ *Id.* § 1271.3(d)(1)–(4). Exclusion from HCT/P oversight does not exempt such products from other forms of federal regulation.

³⁵ See generally Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products, 63 Fed. Reg. 26744, 26745 (proposed May 14, 1998 and codified at 21 C.F.R. Pts. 207, 807, and 1271).

³⁶ 21 C.F.R. § 1271.3 (f) (2019).

³⁷ *Id.* § 1271.3(c).

³⁸ *Id.* § 1271.3(d)(4); however, combination is permitted with “water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the HCT/P.” *Id.*

³⁹ *Id.* § 1271.10(a)(4).

⁴⁰ 42 U.S.C. § 262 (2019); 21 C.F.R. § 1271.20 (2019) (stating that HCT/P’s that do not fall under either of the first two tiers are regulated under Section 351 of the PHSA).

⁴¹ See, e.g., *infra* notes 48–54 and accompanying text (discussing section 351’s Same Surgical Procedure exception).

⁴² Since the December 2016 enactment of the 21st Century Cures Act, FDA has taken a number of steps to improve the process of drug development and approval in general and regenerative products in

clinician treating a single patient with her own cells—must follow the same regulatory pathway traveled by a large pharmaceutical company bringing a new drug or biologic to the mass market.⁴³ Consequently, a clinician may need to file an investigational new drug application (IND)⁴⁴ and conduct three-phased clinical trials for the purpose of establishing the treatment’s safety, purity, potency, efficacy, and stability.⁴⁵ In addition, pursuant to the Prescription Drug User Fee Act,⁴⁶ payment of a sizeable user fee may be required for FDA to review the product, whether or not it ultimately approves a Biological License Application (BLA)⁴⁷ or a New Drug Application (NDA).⁴⁸ A “manufacturer”⁴⁹ engaged in recovering, screening, testing, processing, storing, labeling, packaging, or distributing would also bear the costs of following cGMPs.⁵⁰ All of these would pertain even when the treatment at issue consists of using the patient’s cells to treat that patient. For providers and their patients, the line between section 361 and section 351 classification can erect financial and logistical barriers to access that, in many instances, may prove insurmountable.⁵¹

4. *The “Same Surgical Procedure” Exception to Section 351 Oversight*

Recognizing that some clinical applications of an HCT/P may pose no greater risk of contamination and transmission of disease than those typically associated with surgery, FDA carved out a narrow “Same Surgical Procedure” (SSP) exception to

specific, particularly for serious conditions and unmet needs. Pub. L. No. 114-255, 130 Stat 1033 (2016) (codified as amended). These include designation as a breakthrough therapy or regenerative medicine advanced therapy (RMAT); designation for fast-track or priority review; an accelerated approval pathway; and innovative methods for clinical investigation such as multi-center design, use of real world evidence, surrogate endpoints, biomarkers, and more. A detailed examination of these measures exceeds the scope of this Article. For additional information, see U.S. FOOD & DRUG ADMIN., 21ST CENTURY CURES ACT, <https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act> [<https://perma.cc/5B4V-EXKC>] (last visited May 25, 2020).

⁴³ See 42 U.S.C. § 262(a) (2019).

⁴⁴ See 21 U.S.C. § 355(i) (2018). An approved IND permits limited distribution and clinical use of an unapproved drug for the purpose of human testing. *Id.* In applying for an IND, an investigator must submit detailed information about the drug, the proposed study design, protocols and location, and proposed measures for ensuring the safety of study participants. *Id.*; see also 21 C.F.R. § 312.23 (2019).

⁴⁵ 42 U.S.C. § 262(k) (2019) (outlining the process for licensure of biological products).

⁴⁶ The Prescription Drug User Fee Act of 1992, Pub. L. 102-571, (“PDUFA I”) permits FDA to impose fees for review of a New Drug Application for an FDCA § 505(b) drug or a Biological License Application for a PHSA § 351 biological product. FDA Reauthorization Act of 2017, Pub. L. No. 115-52 (FDARA) reauthorized PDUFA through fiscal year 2022 (“PDUFA VI”). In August 2020, FDA announced its 2021 user fee rates, which, depending on product type, can approach \$2.9 million. U.S. FOOD & DRUG ADMIN., PRESCRIPTION DRUG USER FEE RATES OF 2021, 85 Fed. Reg. 46651, 46652 (Aug. 3, 2020).

⁴⁷ See 42 U.S.C. § 262(a) (2019) (detailing need for a biologic license).

⁴⁸ See 21 U.S.C. § 355(a)–(b) (2018), 21 C.F.R. § 312.23 (2019) (requiring an NDA to provide extensive information on its active ingredient(s), the chemical means of delivering this ingredient, the manufacturing and packaging procedures, suggested labeling, and clinical trial data establishing the drug to be both safe and effective).

⁴⁹ 21 C.F.R. § 1271.3(e) (2019).

⁵⁰ *Id.* § 207.3(a)(8).

⁵¹ See Alastair J.J. Wood, *A Proposal for Radical Changes in the Drug-Approval Process*, 355 NEW ENG. J. MED. 618 (2006) (describing the expense and risk associated with new drug approvals that make the process prohibitive to all but the biggest companies).

section 351 oversight.⁵² A section 351 HCT/P can be used without fulfilling section 351's requirements of premarket approval and cGMPs if that HCT/P is removed from the patient and implanted back into that same patient (demonstrating autologous use) "during the same surgical procedure."⁵³ To qualify for the SSP exception, an HCT/P must remain in its "original form," as the Final SSP Guidance explains,⁵⁴ and undergo no "intervening processing steps beyond rinsing, cleansing, sizing, or shaping."⁵⁵

Under the section 351 SSP exception, the "same surgical procedure" often consists of a single surgery done at one time, or at least on the same day.⁵⁶ Harvest and return can also occur on separate dates and still qualify as the same surgical procedure if the HCT/P undergoes nothing beyond being "rinsed or cleaned and temporarily stored after being labeled, pending implantation . . . provided no other processing steps and no other manufacturing steps beyond labeling and storage are performed."⁵⁷ Whether the same surgical procedure takes place on a single day or spans several, the HCT/P must maintain its "original form," meaning that even minimal manipulation may involve too much processing to stay within section 351's narrow SSP exception.⁵⁸ Should its original form change, the HCT/P will need to qualify as a section 361 product or meet section 351's requirements, including obtaining premarket approval and employing cGMPs.

III. THE IMPORTANCE OF "FORM" AND "FUNCTION" IN REGULATING HCT/PS

Given the difficulties and costs of obtaining premarket approval and complying with section 351's other requirements, those using HCT/P's in a clinical setting typically want their product to qualify for either the section 351 SSP exception or minimal oversight under section 361. The section 351 SSP exception focuses on maintaining the HCT/P's original *form* as it existed in the donor.⁵⁹ Section 361's minimal manipulation requirement, original relevant characteristics, essentially

⁵² 21 C.F.R. § 1271.15(b); *see also* Proposed Approach to Regulation of Cellular and Tissue-Based Products, 62 Fed. Reg. 9721 (Mar. 4, 1997), <https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/tissue/ucm0626.pdf> [<https://perma.cc/SZJ7-TZS8>]. In addition to the SSP exception, section 351 requirements will not apply to "an establishment that uses HCT/P's solely for nonclinical scientific or educational purposes," 21 C.F.R. § 1271.15(a); "a carrier who accepts, receives, carries, or delivers HCT/P's in the usual course of business as a carrier," *id.* § 1271.15(c); or "an establishment that only recovers reproductive cells or tissue and immediately transfers them into a sexually intimate partner of the cell or tissue donor," *id.* § 1271.15(e).

⁵³ *Id.* § 1271.15(b).

⁵⁴ U.S. FOOD & DRUG ADMIN., SAME SURGICAL PROCEDURE EXCEPTION: QUESTIONS AND ANSWERS REGARDING THE SCOPE OF THE EXCEPTION: GUIDANCE FOR INDUSTRY 4 (Nov. 2017) [hereinafter FINAL SSP GUIDANCE].

⁵⁵ *Id.* at 3.

⁵⁶ *Id.* at 5.

⁵⁷ *Id.* at 6. Examples of procedures entailing more than a single operation on separate days that qualify for section 351's SSP exception include "[c]raniotomy or craniectomy with subsequent implantation of the bone flap to reverse the cranial defect" and "[p]arathyroidectomy with subsequent implantation of a portion of the tissue to preserve parathyroid function." *Id.* at 6.

⁵⁸ *Id.* at 5.

⁵⁹ *See* 21 C.F.R. § 1271.15(b) (2019).

focuses on form, too,⁶⁰ whereas section 361's criterion of homologous use requires maintaining the HCT/P's original *function* in the donor.⁶¹ For developers and clinicians, understanding the roles of "original form" in the section 351 SSP exception and "basic function" for section 361 are obviously essential in assessing whether to pursue premarket review under section 351. Making this determination is difficult due to the complex technicalities of these regulations.

A. *The Four Draft HCT/P Guidances*

With the goal of clarifying the labyrinthine HCT/P framework, FDA released a suite of four interrelated Draft Guidances on: (1) section 351's same surgical procedure exception (October 2014);⁶² (2) section 361's minimal manipulation (December 2014);⁶³ (3) homologous use (October 2015) requirements;⁶⁴ and (4) particular issues specific to adipose tissue (December 2014).⁶⁵ While commendable for their attempt, the Draft Guidances were neither clear in explaining regulations nor accurate in dealing with adipose.

To explain "basic function," the Draft Minimal Manipulation Guidance introduced the brand new concept of "main function":

The main function of the HCT/P, in the donor, determines which definition of minimal manipulation applies. For example, tissues that physically support or serve as a barrier or conduit, or connect, cover, or cushion are generally considered structural tissues for the purpose of applying the regulatory framework. Structural tissue is composed of structural components and cells, and those cells are part of the structural tissue for the purposes of determining which definition of minimal manipulation applies. . . . Cells or nonstructural tissues are generally those that serve predominantly metabolic or other biochemical roles in the body such as hematopoietic, immune, and endocrine functions.⁶⁶

The Draft Adipose Guidance does not mention the new and unexplained concept of "main function," but instead describes adipose as having solely structural functions.⁶⁷ FDA reasons as follows:

⁶⁰ *Id.* § 1271.3(f).

⁶¹ *Id.* § 1271.3(c).

⁶² U.S. FOOD & DRUG ADMIN., SAME SURGICAL PROCEDURE EXCEPTION: QUESTIONS AND ANSWERS REGARDING THE SCOPE OF THE EXCEPTION: DRAFT GUIDANCE FOR INDUSTRY (2014) [hereinafter DRAFT SSP GUIDANCE].

⁶³ U.S. FOOD & DRUG ADMIN., MANIPULATION OF HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS: DRAFT GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF (2014) [hereinafter DRAFT MINIMAL MANIPULATION GUIDANCE].

⁶⁴ U.S. FOOD & DRUG ADMIN., HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS FROM ADIPOSE TISSUE: REGULATORY CONSIDERATIONS: DRAFT GUIDANCE FOR INDUSTRY (2015) [hereinafter DRAFT ADIPOSE GUIDANCE].

⁶⁵ U.S. FOOD & DRUG ADMIN., HOMOLOGOUS USE OF HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS: DRAFT GUIDANCE FOR INDUSTRY AND FDA STAFF (2015) [hereinafter DRAFT HOMOLOGOUS USE GUIDANCE].

⁶⁶ DRAFT MINIMAL MANIPULATION GUIDANCE, *supra* note 63, at 7.

⁶⁷ DRAFT ADIPOSE GUIDANCE, *supra* note 64, at 3.

HCT/P's include adipose tissue and cells obtained from adipose tissue. Adipose tissue is typically defined as a connective tissue that stores energy in the form of lipids, insulates the body, and provides cushioning and support for subcutaneous tissues and internal organs. It is composed of clusters of cells (adipocytes) surrounded by a reticular fiber network and interspersed small blood vessels, divided into lobes and lobules by connective tissue septa. Additionally, adipose tissue contains other cells, including preadipocytes, fibroblasts, vascular endothelial cells, and a variety of immune cells. Because connective tissue provides structure and support to the body, FDA considers connective tissue, including adipose tissue, to be a structural tissue.⁶⁸

Because the basic function of all adipose HCT/P's is structural (at least according to the Draft Guidance), any nonstructural application automatically fails section 361's requirements of minimal manipulation⁶⁹ and homologous use.⁷⁰ For instance, "[p]rocessing to isolate non-adipocyte or non-structural components from adipose tissue . . . is generally considered more than minimal manipulation" because separating adipose's "connective tissue and structural components" from "non-adipocyte or non-structural isolates" changes the original characteristics that are relevant to adipose's structural function, i.e., its "utility for reconstruction, repair, or replacement."⁷¹ Similarly, because adipose is solely structural, anything beyond "the repair, reconstruction, replacement, supplementation of a recipient's cells or tissues" would not be homologous use because it would not perform "the same basic function or functions in the recipient as in the donor."⁷² It is difficult to follow the logic in stating that adipose is solely structural because it is a connective tissue, even though it performs the nonstructural function of storing energy. Equally unsettling is FDA's willingness to acknowledge that adipose contains immune cells without conceding that immune cells have basic functions, none of which are structural.

B. Criticisms of the Draft Guidances as Applied to Adipose

After releasing the Draft Guidances and inviting public comments, the agency seemed to be caught off guard by the amount and tenor of critical feedback, particularly with regard to the agency's treatment of adipose.⁷³ Angry patients cried

⁶⁸ *Id.* at 1–2.

⁶⁹ *Id.* at 3 (explaining that processing adipose tissue to isolate cells needed to perform adipose's nonstructural functions would be more than minimal manipulation since it would alter the original characteristics relevant to adipose's structural functions of providing cushioning and support—despite the fact that the cells and functions of interest have nothing to do with cushioning and support and focus instead on one or more of adipose's predominantly nonstructural functions).

⁷⁰ *Id.* at 4–5. In giving examples of homologous use of adipose tissue based on the HCT/P's basic function or functions in the donor, the Draft Adipose Guidance refuses to consider anything other than structural functions such as cushioning, support, and "the repair, reconstruction, replacement, or supplementation of a subcutaneous adipose tissue defect." *Id.* at 5.

⁷¹ *Id.* at 3.

⁷² *Id.* at 4.

⁷³ Following publication of the last of the four Draft Guidance documents (on homologous use) in October 2015, FDA extended comments until April 26, 2016 and scheduled a one-day public meeting in the middle of that month. 80 Fed. Reg. 66845 (Oct. 30, 2015). When that hearing was quickly over-subscribed,

foul on what they viewed as FDA's "immoral and disgusting" deprivation of their right to use their own cells, whether derived from adipose or elsewhere.⁷⁴ Exasperated experts warned that by relying on factual inaccuracies in terms of what adipose is and does, the Draft Guidances had managed to be unduly aggressive in regulating adipose therapies that are safe while foreclosing any meaningful evaluation of the benefits and risks of adipose's nonstructural clinical applications.⁷⁵

The Musculoskeletal Therapy Foundation (MTF), for example, charged FDA with ignoring facts (by treating adipose as solely structural with "no support" and "no scientific basis") as well as law (by circumventing formal rulemaking requirements to impose new regulatory obligations). The MTF explained:

[D]espite the fact that MSCs, whether they are derived from cord blood, peripheral blood, adipose, amnion, or other sources are (by definition) the same, FDA's interpretation is that the extraction of cell components from adipose tissue (because those are classified solely as structural tissues) results in a more than minimally manipulated MSC product, while extraction of those same MSCs from peripheral blood (which are classified solely as nonstructural tissues) results in a potentially minimally manipulated product. *For reasons which are scientifically unclear, FDA seems to be creating a regulatory hurdle for adipose-derived MSCs* (requiring them to be regulated as more than 361 HCT/P's), while simultaneously allowing peripheral blood derived MSCs (at least under certain conditions) to be regulated as 361 HCT/Ps. *It is unclear* as to why FDA believes that, from a regulatory standpoint, the source of the MSCs

FDA extended comments for another six months and scheduled a two-day public hearing with an additional scientific workshop in September 2016. 81 Fed. Reg. 23661, 23664, 23708 (Apr. 2016).

⁷⁴ Representative examples include: "Absolutely immoral and disgusting. ALL human beings deserve absolute and unconditional rights to all the cells in their body." Comment from Alberta Kovatcheva, Proposed Rule: Human Cells, Tissues, and Cellular and Tissue-Based Products From Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry; Reopening of the Comment Period (Apr. 4, 2016), <https://www.regulations.gov/document?D=FDA-2014-D-1856-0175> [<https://perma.cc/WM5Z-SM7F>]; "My stem cells are mine! How dare you attempt to regulate what is mine and how I use it to save my own life or someone else's [sic]." Comment from Laura Cotter, Proposed Rule: Human Cells, Tissues, and Cellular and Tissue-Based Products From Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry; Reopening of the Comment Period (Feb. 28, 2017), <https://www.regulations.gov/document?D=FDA-2014-D-1856-0172> [<https://perma.cc/SZT7-X9DK>]; "This is absolutely asinine[sic]!! . . . How dare you!! You a bureaucratic imbecile!!! . . . You have no idea of what you are doing . . . don't tell me what's best for me when you have no idea of what you are talking about!!!! IDOITS [sic]!!!!" Comment from Deborah Graham, Proposed Rule: Human Cells, Tissues, and Cellular and Tissue-Based Products From Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry; Reopening of the Comment Period (Oct. 19, 2016), <https://www.regulations.gov/document?D=FDA-2014-D-1856-0122> [<https://perma.cc/2DXW-8QDS>].

⁷⁵ See, e.g., Testimony of Ricardo L. Rodriguez MD, at 33 (Sept. 13, 2013), <https://www.fda.gov/media/101901/download> [<https://perma.cc/349G-UXQ9>]. Adipose was not the only HCT/P to trigger criticism; amnion and dermis were among the other kinds of HCT/P's that engendered similar concerns. See, e.g., U.S. FOOD & DRUG ADMIN., MUSCULOSKELETAL TRANSPLANT FOUNDATION COMMENTS 8-9 (Feb. 23, 2015), <https://www.regulations.gov/document?D=FDA-2014-D-1856-0039> [<https://perma.cc/K2GG-7CV6>] [hereinafter MTF COMMENTS]. The particulars of those criticisms are beyond the scope of this analysis, but their existence underscores the problem with FDA's decision to act as final arbiter of a particular HCT/P's basic function.

is most important, rather than the “relevant biological characteristics” (the key regulatory requirement for nonstructural tissues).⁷⁶

The MTF further claimed that categorizing adipose as solely structural would be “an additional, significant departure from agency practice” that “may dramatically affect current medical practice” particularly since it would effectively disregard “the ‘relevant biological characteristics’ (the key regulatory requirement for nonstructural tissues).”⁷⁷ This “wholly new regulatory concept” would add “an entirely new limitation [] to the regulations that should not be implemented via a guidance document”⁷⁸—especially because the reasons for doing so “are unclear from a scientific perspective[.]”⁷⁹ The American Association of Tissue Banks (AATB) concurred, finding the treatment of adipose as solely structural to be “unduly narrow[.]”⁸⁰ The American Academy of Orthopaedic Surgeons (AAOS) similarly criticized the Draft Guidances for employing “new” concepts and “arbitrary categorizations” that “ignor[e] the reality that some tissues fulfill both [structural and nonstructural] functions”—all of which would “chang[e] the established regulation of products without rulemaking.”⁸¹

The International Federation of Adipose Therapeutics and Science (IFATS) which, as its name suggests, focuses on the physiology, structure, function, and clinical uses of adipose-derived adult/mesenchymal stem cells, emphasized the need to correct the agency’s “factually inaccurate and logically flawed” structural mantra.⁸² This was particularly necessary because FDA’s entire support for its solely structural determination consisted of one cite to a single medical textbook.⁸³ It was not the dearth of support for FDA’s exclusively structural focus that concerned IFATS; it was its complete absence. This was not the typical battle of highly specialized experts defending conflicting but reasonable interpretations of scientific facts. This was simply reading what FDA’s chosen authority says.

Junqueira’s Basic Histology: Text & Atlas—the Draft Adipose Guidance’s sole cited authority for its insistence on viewing adipose as solely *structural*⁸⁴—expressly states that adipose “is now recognized as an important [nonstructural] endocrine tissue.”⁸⁵ Thus, FDA was relying on one medical textbook as authority for a

⁷⁶ *Id.* at 9 (emphasis added).

⁷⁷ *Id.* at 1, 3, 9.

⁷⁸ *Id.* at 4, 11.

⁷⁹ *Id.* at 9.

⁸⁰ AMERICAN ASSOCIATION OF TISSUE BANKS, COMMENT 2 (Feb. 23, 2015), <https://www.aatb.org/sites/default/files/sites/default/files/private/FDA%20Adipose%20FINAL%2002235.pdf> [<https://perma.cc/23D4-FMXA>] [hereinafter AATB COMMENTS].

⁸¹ AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS, COMMENT 1–2 (Mar. 31, 2017), <https://www.regulations.gov/document?D=FDA-2014-D-1856-0173> [<https://perma.cc/W3ST-N93J>] [hereinafter AAOS COMMENTS].

⁸² INTERNATIONAL FEDERATION OF ADIPOSE THERAPEUTICS AND SCIENCE, COMMENT 7 <https://www.regulations.gov/document?D=FDA-2014-D-1856-0164> [<https://perma.cc/DG5W-R56N>] [hereinafter IFATS COMMENTS].

⁸³ *Id.* at 6–7.

⁸⁴ DRAFT ADIPOSE GUIDANCE, *supra* note 64, at 2.

⁸⁵ See Anthony L. Mescher, JUNQUEIRA’S BASIC HISTOLOGY: TEXT & ATLAS, Chapter 6. Adipose Tissue 124 (13th ed. 2013) [hereinafter JUNQUEIRA] (emphasis added).

proposition that the book directly contradicts. IFATS cited an additional ninety-eight articles and detailed twenty-six nonstructural and seventeen combined nonstructural-structural functions to highlight the century-long “scientific consensus” that adipose is neither exclusively nor predominantly structural. Adipose is instead a predominantly “nonstructural metabolic and endocrine organ with secretory properties.”⁸⁶

IFATS further explained that adipose’s “basic” functions include “secret[ing] proteins” which systemically affect “hematopoietic, reproductive, metabolic, and other cells and tissues.”⁸⁷ These have nothing to do with providing structural cushioning and support. Adipose also performs paracrine functions such as secreting cytokines involved in angiogenesis and hematopoiesis and cytokine factors for neurogenesis.⁸⁸ Brown and beige fat are critical to thermogenesis; white fat stores energy.⁸⁹ The prevalence of adipose in breast tissue does far more than cushion and support. It is critical to lactation because it provides energy and nutrients to breast epithelial cells.⁹⁰ Adipose’s multipotent progenitor cells “repair and regenerate damaged tissues,” including “repairing irradiated skin, alleviating fibrotic changes, [and] improving mobility and vitality.”⁹¹ The same cells can “repair and regenerat[e] [] ischemic damage induced by acute myocardial infarction” and promote “vascular network formation and vascular structures.”⁹²

Like MTF, IFATS pointed out FDA’s inconsistency in treating the extraction of pre-adipocyte mesenchymal stem cells from fat-laden bone marrow as minimal manipulation while characterizing the even simpler extraction of the same cell types from subcutaneous adipose as more than minimal manipulation. Once liberated from their source, the cells go on to perform the same nonstructural functions, underscoring once again how FDA’s solely structural contrivance makes little sense given basic anatomy and physiology. Finally, as further evidence that adipose cannot be evaluated as solely structural, IFATS showed how structural ASCs often perform nonstructural functions at the same time, such as treating radiation damage, post-mastectomy pain, neuroma, thermal injury, pressure sores, scleroderma, systemic sclerosis, Raynaud’s disease, Dupuytren’s disease, tendon adherence, vocal fold paralysis, and more.⁹³

⁸⁶ IFATS COMMENTS, *supra* note 82, at 6.

⁸⁷ *Id.*

⁸⁸ *Id.* at 7.

⁸⁹ *Id.*

⁹⁰ *Id.* at 8.

⁹¹ *Id.*

⁹² *Id.* at 8. Anyone who disputes *Junqueira’s* categorization of adipose as primarily nonstructural must nevertheless concede that it simply does not support the proposition for which it is cited in the Draft Adipose Guidance. The agency’s inaccurate attribution was brought to the agency’s attention in both PART 15 ADIPOSE HEARING, Ricardo L. Rodriguez MD Testimony 33 (Sept. 13, 2016), <https://www.fda.gov/media/101901/download> [<https://perma.cc/7HAN-MPEG>] (emphasis added) and Anthony L. Mescher, *JUNQUEIRA’S BASIC HISTOLOGY: TEXT & ATLAS*, Chapter 6. Adipose Tissue (14th ed. 2015). For reasons unexplained, FDA never changed the original and now outdated 13th edition of the *JUNQUEIRA* text that opposed FDA’s solely structural view of adipose when first cited and continues to do so in later editions. U.S. FOOD & DRUG ADMIN., *REGULATORY CONSIDERATIONS FOR HUMAN CELLS, TISSUES, & CELLULAR & TISSUE-BASED PRODUCTS: MINIMAL MANIPULATION & HOMOLOGOUS USE GUIDANCE FOR INDUSTRY & FOOD & DRUG ADMIN. STAFF 8* (2017) (emphasis added) [hereinafter *FINAL MM/HU GUIDANCE*].

⁹³ IFATS COMMENTS, *supra* note 82, at 6–9.

In the assessment of IFATS and other scientific and medical associations steeped in stem cell science and clinical translation, FDA needed to reverse the Draft Adipose Guidance's erroneous determination that the basic function of adipose is solely structural. FDA should respect biology, regulate based on factual accuracy, and thus evaluate adipose for either its structural or nonstructural functions depending on its intended structural or nonstructural use in the recipient patient.

C. *Criticisms of the Draft Guidances on the "Basic Function" of Breast Tissue*

These critics also pointed out that the Draft Adipose Guidance had also erred in deciding that using adipose for breast reconstruction would be nonhomologous. After describing the breast as "composed of lobes of glandular tissue and branching ducts, interspersed with fat and ligaments that support the breast and give it shape; and nerves, blood vessels, and lymphatic tissues," the Draft Adipose Guidance announced that "[t]he basic function of breast tissue is to produce milk (lactation) after childbirth."⁹⁴ The document then reasoned that using adipose to reconstruct the breast would be nonhomologous because adipose's basic nonstructural cushioning and support functions would not restore the breast's basic function of lactation.⁹⁵ This reasoning was neither opaque nor counterintuitive; it was simply wrong.

Although FDA eventually reversed this position in finalizing the Draft Guidance documents,⁹⁶ it is important to understand just how badly the agency erred in taking this position in the first place. Determining the breast's basic function to be lactation is disturbing for many reasons, with the simplest being its overt disregard for elementary anatomy and physiology. Roughly half of the people with breasts are completely incapable of lactating for the very simple reason that they are men. And while they cannot lactate, they can develop breast cancer and will typically need or want reconstructive surgery.⁹⁷ Predicating homologous use on serving the same basic function of a tissue that the host's tissue never served—and was never even capable of performing—obviously makes no sense.

Determining that the breast's basic function is lactation was equally irrational as applied to women. Yes, women can lactate, but many never do and when lactation does occur, it is time-limited.⁹⁸ That post-menopausal women cannot lactate does not deprive their breasts of function. Rather, throughout a female's adolescence and adulthood, the breast's basic function is that of a secondary sex organ. Beyond misunderstanding the breast's basic function, FDA completely ignored breast

⁹⁴ DRAFT ADIPOSE GUIDANCE, *supra* note 64, at 5.

⁹⁵ *Id.*

⁹⁶ FINAL MM/HU GUIDANCE, *supra* note 92, at 19.

⁹⁷ Tarik Al-Kalla & Ewa Komorowska-Timek, *Total Male Breast Reconstruction with Fat Grafting*, 2 J. PLASTIC & RECONSTRUCTIVE SURGERY 257, 257 (2014) (estimating that 2,360 men were newly diagnosed with breast cancer in 2014 and reporting that following the standard treatment of radical mastectomy, using fat grafting for breast reconstruction offers superior results over alternative reconstructive approaches).

⁹⁸ Press Release, Ctrs. for Disease Control & Prevention, Breastfeeding Report Card United States 2018, at 2 (noting that 83.2% of the four million babies born in 2015 breastfed exclusively after birth but within six months had dropped to 57.6% with only 25% relying on breastfeeding exclusively), <https://www.cdc.gov/media/releases/2018/p0820-breastfeeding-report-card.html> [<https://perma.cc/5JDA-FW66>].

anatomy. Fat makes up a significant portion of healthy breast tissue, and using fat to reconstruct a breast is, to a large extent, replacing the patient's fat with his or her own fat.⁹⁹ In addition to replacing lost tissue, adipose can correct radiation damage and reduce the pain that often goes with it.¹⁰⁰

Speaking as a representative of the American Society of Plastic Surgeons at FDA's September 2016 public hearing, Peter Rubin, MD stated:

Seventy percent of U.S. plastic surgeons have used fat grafting techniques for breast operations, and 88% of those plastic surgeons said they use fat grafting for breast reconstruction techniques and often apply fat grafting along with implants or flap procedures. Fat grafting is a key option for treating other post-mastectomy conditions, including reversing damage caused by therapeutic radiation . . . and reducing implant breast pain and postmastectomy pain. . . . [F]at grafting to the breast is most certainly a homologous use. Adipose tissue, which is naturally present in breast tissue is a structural component. As a structural component is injected to the breast to preserve the structure and function of the secondary sex organ and, as such should be considered homologous use.¹⁰¹

In written comments, IFATS underscored that “[m]astectomy removes more than the ability to lactate. It removes size, shape and form by removing the breast mound, which is predominantly adipose. *Consequently, applying adipose tissue for the structural purpose of restoring form and shape is homologous use.*”¹⁰² In addition, “[b]y classifying adipose based tissues as nonhomologous when applied to the breast, an entire class of Centers for Medicare & Medicaid Services (CMS) approved breast reconstruction procedures would be at risk for not complying with the same surgical procedure exception.”¹⁰³ These would include one of the oldest and most common procedures known as autologous “free flap” reconstruction. IFATS continued:

Removing these and other reconstructive methods from clinical application has nothing to do with risk. It is instead a perverse outcome of insisting that breast reconstruction be evaluated for its ability to restore the breast's minor and episodic function of lactation despite fat's ability to restore the breast's size, shape and function as a secondary sex organ.

*For these reasons, IFATS respectfully requests FDA to revise the draft HCT/P guidance documents to recognize that as applied to the breast, adipose tissue is homologous use because it performs the structural functions of restoring, repairing or reforming size, form and shape.*¹⁰⁴

⁹⁹ IFATS COMMENTS, *supra* note 82, at 11.

¹⁰⁰ *Id.* at 12.

¹⁰¹ PART 15 ADIPOSE HEARING, *supra* note 2, Peter Rubin, MD testimony at 235–36, (Sept. 12, 2016), <https://www.fda.gov/media/101978/download> [<https://perma.cc/2ATL-46L6>].

¹⁰² IFATS Comments, *supra* note 82, at 11.

¹⁰³ *Id.*

¹⁰⁴ *Id.* at 10.

IFATS, MTF, and the many other scientific organizations, medical researchers, and clinicians to weigh in on the four Draft Guidances found so many problems that they are worth summarizing at this point. The experts' criticisms can be distilled into three basic problems:

- (1) FDA had improperly categorized adipose as a solely structural HCT/P when, based on FDA's own regulations that define structural and nonstructural functions, adipose clearly serves both.
- (2) FDA erred in declaring that the nonstructural function of lactation is the breast's basic function, and further erred in deciding that using adipose for structural cushioning and support during breast reconstruction was nonhomologous because it would not restore the breast's basic function of lactation.
- (3) More generally, FDA's decision to serve as the sole and final arbiter of an HCT/P's basic function was obviously problematic given the Draft Guidance's biological imprecision in determining the basic functions of the breast, adipose, and other types of HCT/Ps.¹⁰⁵

C. Final Guidance Provides a Partial Fix, but Basic Problems Remain

FDA finalized the four Draft Guidances in the form of two Final Guidances, one dealing with both Minimal Manipulation and Homologous Use (MM/HU)¹⁰⁶ and the second addressing the section 351 Same Surgical Procedure exception.¹⁰⁷ The Final MM/HU Guidance quickly disposes of the lactation as a breast's basic function controversy by reversing course. Using adipose for breast reconstruction or augmentation now qualifies as homologous use "because providing cushioning and support, is a basic function of adipose tissue."¹⁰⁸ In addition, "[s]ome breast reconstruction or augmentation procedures involving re-implantation of autologous adipose tissue that is only rinsed or cleansed" may fall within the SSP exception to section 351.¹⁰⁹

¹⁰⁵ See *supra* notes 80–90 and accompanying text. Although adipose is the focus of this discussion, it was not the only source of concern for experts weighing in on the Draft Guidances. The AATB, for example, criticized FDA for its determination that the basic function of amnion is solely structural (in this instance, as a covering), instead of recognizing it for what it is: a complex tissue that serves both structural and nonstructural (anti-scarring and anti-inflammation) functions. "Inappropriately narrowing the function or functions of an HCT/P to only one function" was, in the AATB's opinion, factually incorrect and, as such, legally unsupportable in terms of regulatory process. AATB COMMENTS, *supra* note 80, at 3. The MTF expressed similar concerns about FDA's determination of the basic function of skin without recognizing the separate basic functions of epidermis and dermis. MTF COMMENTS, *supra* note 75, at 14.

¹⁰⁶ FINAL MM/HU GUIDANCE, *supra* note 92, at 16–17.

¹⁰⁷ FINAL SSP GUIDANCE, *supra* note 54, at 3.

¹⁰⁸ FINAL MM/HU GUIDANCE, *supra* note 92, at 19.

¹⁰⁹ *Id.* at 19 n.27

1. *The Basic Problem with Final Guidance on the General Concept of Basic Function*

Responding to criticisms that its earlier use of “main function” to clarify “basic function” had only added to the confusion, FDA dropped “main function” from the Final MM/HU Guidance, offering the following in its place:

The basic function of an HCT/P is what it does from a biological/physiological point of view, or is capable of doing when in its native state.[] By “basic” we mean the function or functions that are commonly attributed to the HCT/P as it exists in the donor. *Basic functions are well understood*; it should not be necessary to perform laboratory, pre-clinical, or clinical studies to demonstrate a basic function or functions for the purpose of applying the HCT/P regulatory framework. Also, clinical effects of the HCT/P in the recipient that are not basic function or functions of the HCT/P in the donor would generally not be considered basic function or functions of the HCT/P for the purpose of applying the definition of homologous use.¹¹⁰

This version is also problematic for at least three reasons. First, simply declaring basic functions to be “well understood” stands in stark contrast to then-FDA Commissioner Scott Gottlieb and CBER Director Peter Marks’ statement that stem cell products are “remarkably complex biologic entities,”¹¹¹ and more complex than the traditional medical products that the agency has regulated for decades.¹¹² Second, declaring basic functions to be “well understood” does not make them so, and ignores the heated debate in written comments and public testimony concerning the Draft Guidances’ treatment of basic functions for certain types of HCT/P’s, particularly those involving adipose.¹¹³ Third, clarification is needed given the Final MM/HU Guidance’s repeated references to “basic function or functions,” “basic functions,” and “multiple functions” for “applying the HCT/P regulatory framework” in general and, more specifically, defining homologous use and determining the basic function of certain HCT/P’s, including adipose.¹¹⁴ The Final MM/HU Guidance’s dismissive assertion that the basic functions of complex biologics are “well understood” jeopardizes the agency’s interpretation and enforcement of the HCT/P framework, especially as applied to adipose-derived stem cell products.¹¹⁵

2. *The Basic Problem with Final Guidance on the Basic Function of Adipose*

Despite receiving an abundance of testimony and written comments with copious references to scientific studies proving that adipose is multifunctional and, if anything,

¹¹⁰ *Id.* at 16–17 (emphasis added).

¹¹¹ Peter Marks & Scott Gottlieb, *Balancing Safety and Innovation for Cell-Based Regenerative Medicine*, 378 NEW ENG. J. MED. 954, 954 (2018).

¹¹² *Id.* at 956.

¹¹³ *See supra* note 69 and accompanying text.

¹¹⁴ FINAL MM/HU GUIDANCE, *supra* note 92, at 7, 15, 16.

¹¹⁵ *Id.* at 16.

is predominantly nonstructural in function, FDA holds firm in its solely structural categorization in Final MM/HU Guidance.¹¹⁶ Structural tissues “physically support or serve as a barrier or conduit, or connect, cover, or cushion in the donor are generally considered structural tissues for the purposes of determining the applicable regulatory definition.”¹¹⁷ The Final MM/HU Guidance places adipose in this category because:

Adipose tissue is typically defined as a connective tissue composed of clusters of cells (adipocytes) surrounded by a reticular fiber network and interspersed small blood vessels, divided into lobes and lobules by connective tissue septa.[] Additionally, adipose tissue contains other cells, including preadipocytes, fibroblasts, vascular endothelial cells, and macrophages.[] Adipose tissue provides cushioning and support for other tissues, including the skin and internal organs, stores energy in the form of lipids, and insulates the body, among other functions. *While adipose tissue has multiple functions, because it is predominantly composed of adipocytes and surrounding connective tissues that provide cushioning and support to the body, FDA considers adipose tissue to be a structural tissue for the purpose of applying the HCT/P regulatory framework.*¹¹⁸

FDA apparently views the prevalence of adipocytes enmeshed in a reticular network to be the signature feature of fat’s structural function of providing cushioning and support. Adipocytes, however, are not mere droplets of fat that simply fill space. They are metabolically active in storing energy and regulating temperature, and even more important in secreting hormones, growth factors, and cytokines (so-called adipokines).¹¹⁹ Logically then, if the Final MM/HU Guidance is correct in describing adipose as “*predominantly composed of adipocytes and surrounding connective tissues*,”¹²⁰ adipose is not predominantly structural as FDA contends, but instead functions predominantly as an endocrine organ with systemic, metabolic nonstructural functions.¹²¹ By squeezing “storing energy in the form of lipids” and “providing cushioning and support” into the same sentence that purports to identify “[t]he basic functions of adipose,” the Final Guidance underemphasizes adipocytes as powerhouses of nonstructural activities.¹²² This might camouflage flawed logic, but it certainly does not cure it.

Evaluating adipose for its nonstructural functions would end Stromal Vascular Fraction’s (SVF) automatic failure of section 361’s requirements of minimal

¹¹⁶ *Id.* at 8.

¹¹⁷ *Id.* at 7.

¹¹⁸ *Id.* at 8 (emphasis added).

¹¹⁹ Adipocytes’ nonstructural functions include regulating lympho-hematopoiesis, erythropoiesis, synthesizing plasma membranes during blood cell development, homeostatic control of temperature, and overall energy metabolism. IFATS COMMENTS, *supra* note 82, at 8, citing ninety-eight medical references, at 15–19.

¹²⁰ FINAL MM/HU GUIDANCE, *supra* note 92, at 8 (emphasis added).

¹²¹ IFATS COMMENTS, *supra* note 82, at 8.

¹²² FINAL MM/HU GUIDANCE, *supra* note 92, at 8, 18.

manipulation¹²³ and homologous use¹²⁴ and make it possible for SVF to qualify as a section 361 HCT/P. Depending on the process, extracting nonstructural cells from lipoaspirate could qualify as minimal manipulation because it “does not alter the relevant biological characteristics of cells” in the remaining SVF.¹²⁵ The SVF could also qualify as intended for homologous use because it would be used for “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.”¹²⁶ FDA nevertheless persists in evaluating multifunction adipose as solely structural despite acknowledging adipose’s many (and the experts would say, predominant) nonstructural components and functions.¹²⁷ By clinging to this rigid either/or dichotomy instead of rethinking its approach, FDA has painted itself into a corner of defending the logically indefensible—which, recent and pending litigation suggests, is a curious enforcement strategy since it risks incentivizing the very practices it is trying to deter.¹²⁸

IV. THE BASIC PROBLEMS WITH FDA’S CURRENT ENFORCEMENT STRATEGY

A. *It’s Complicated . . .*

In announcing FDA’s comprehensive regenerative medicine framework in November 2017, then-Commissioner Scott Gottlieb stated FDA would observe a three-year period of enforcement discretion to encourage developers to seek input on the need for section 351 premarket approval.¹²⁹ In August 2017, Commissioner Gottlieb had emphasized the need for vigilant enforcement against the “small number of unscrupulous actors” pedaling “illegal” products carrying a potential “significant risk” to patient safety.¹³⁰ Since then, there have been numerous inspections and dozens of warnings, but very few lawsuits and no real progress. This creates its own risks by diluting any deterrent value that litigation might have.

Making matters worse is FDA’s reliance on factually inaccurate and illogical interpretations of its own regulations, especially as applied to adipose-derived cell products. The agency has apparently decided that regulating aggressively is necessary

¹²³ See 21 C.F.R. § 1271.3(f).

¹²⁴ See *id.* § 1271.3(c).

¹²⁵ *Id.* § 1271.3(f)(2) (defining minimal manipulation for cells or nonstructural tissues).

¹²⁶ *Id.* § 1271.3(c) (defining homologous use).

¹²⁷ FINAL MM/HU GUIDANCE, *supra* note 92, at 8.

¹²⁸ *Id.* at 6.

¹²⁹ U.S. FOOD & DRUG ADMIN, *Statement 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/newsevents/newsroom/pressannouncements/ucm585342.htm> [<https://perma.cc/Y2UW-AUZH>]. FDA recently announced a six-month extension of this period due to the COVID-19 pandemic.

¹³⁰ U.S. FOOD & DRUG ADMIN, *Statement on FDA’s New Policy Steps and Enforcement Efforts to Ensure Proper Oversight of Stem Cell Therapies and Regenerative Medicine* (Aug. 28, 2017), <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fdas-new-policy-steps-and-enforcement-efforts-ensure> [perma.cc/UA7U-G57X].

to protect patients from a shape-shifting stem cell industry. For adipose HCT/P therapies, however, rigid categorization built on biological inaccuracies does just the opposite. Instead of protecting patients, it forecloses any meaningful assessment of risk for recognized and emerging therapies that rely on adipose's predominantly nonstructural functions. Refusing to assess risk is no way to regulate it.

The agency's conceptual dilemma in regulating adipose has further complicated FDA's persistent concerns about stem cell clinics that promote adipose-derived stromal vascular fraction (SVF). For example, in an August 2017 Warning Letter, FDA informed U.S. Stem Cell Clinic, L.L.C. (U.S. Stem Cell) in Florida that promoting its adipose-derived SVF product to treat kidney and heart disease, neurodegenerative disorders, spinal injuries, and more required section 351 premarket review and an approved BLA.¹³¹ The letter explained:

Your SVF product does not meet the minimal manipulation criterion set forth in 21 CFR 1271.10(a)(1) and defined for structural tissue, such as adipose tissue, in 21 CFR 1271.3(f)(1) . . . because your processing alters the original relevant characteristics of the adipose tissue relating to the tissue's utility for reconstruction, repair, or replacement.

In addition, your SVF product fails to meet the 21 CFR 1271.10(a) (2) criterion that the HCT/P be "intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent." As noted above, the SVF product is intended for use in the treatment of a variety of diseases or conditions. Because the SVF product is not intended to perform the same basic function or functions of adipose tissue, such as cushioning the body, using the SVF product for treatment of these diseases or conditions is not homologous use as defined in 21 CFR 1271.3(c).¹³²

On the same day, FDA initiated parallel enforcement proceedings against the California Stem Cell Treatment Center.¹³³

¹³¹ Letter from FOOD & DRUG ADMIN., Warning Letter to U.S. Stem Cell Clinic OBPO 1 17-02 (Aug. 28, 2017), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/us-stem-cell-clinic-llc-524470-08242017> [<https://perma.cc/M3ES-7BMW>].

¹³² *Id.*

¹³³ When it released its Warning Letter to U.S. Stem Cell on August 28, 2017, FDA also announced enforcement proceedings against California Stem Cell Treatment Centers for its use of SVF as well as a combined SVF-smallpox product to treat cancer via intertumoral and intravenous injections. According to FDA, the SVF-smallpox mix posed a risk of myocarditis and pericarditis for potentially immunocompromised patients. It also threatened the general public especially "unvaccinated people who are pregnant, or have problems with their heart or immune system, or have skin problems like eczema, dermatitis, psoriasis and have close contact with a vaccine recipient [because they] are at an increased risk for inflammation and swelling of the heart and surrounding tissues if they become infected with the vaccine virus, either by being vaccinated or by being in close contact with a person who was vaccinated." Press Release, U.S. FOOD & DRUG ADMIN., Statement of Seizure of Small Pox from StemImmune (Aug. 28, 2017), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm573427.htm> [<https://perma.cc/KMD6-GQVZ>].

Eventually, FDA filed complaints against both clinics on May 9, 2018.¹³⁴ To date, both cases remain pending, albeit at different procedural stages. In Florida's *U.S. Stem Cell Clinic* case, the district court granted FDA's motion for summary judgment on briefs alone, and permanently enjoined the clinic's use of SVF; the matter remains pending before the U.S. Court of Appeals for the Eleventh Circuit.¹³⁵ In *U.S. v. California Stem Cell Treatment Center, Inc.*, the district court denied the government's motion for summary judgment and the parties are preparing for trial as of this writing.¹³⁶ A summary of the district courts' conflicting dispositions of FDA's highly similar summary judgment arguments follows.

In *U.S. v. U.S. Stem Cell Clinic, L.L.C.*, Judge Ursula Ungaro confirmed FDA's authority to regulate autologous stem cell therapies under the PHSA and FDCA,¹³⁷ and found that the clinic's SVF qualified as a drug.¹³⁸ However, the SVF could not qualify for the Same Surgical Procedure exception to section 351 oversight because the SVF process altered the original form of adipose post-harvest.¹³⁹ Moreover, the product did not qualify for section 361's reduced oversight because it was not intended for homologous use.¹⁴⁰ Therefore, the SVF fell within section 351 and needed an IND during development followed by premarket review, an approved BLA, and cGMPs.¹⁴¹ Failing these requirements rendered U.S. Stem Cell's version of SVF an adulterated and misbranded drug and warranted a permanent injunction of its promotion and use.¹⁴²

To reach this conclusion, the court undertook a painstaking analysis of the litigants' competing and equally complicated arguments about the applicability, meaning, and clarity of the section 351 and section 361 HCT/P regulatory framework and related guidance, as well as the biological complexities of adipose and the impact of the SVF process.¹⁴³ The major sticking point concerned 21 C.F.R. § 1215.15(b)'s requirement that "such HCT/P's" must maintain their original form between harvest and re-implantation to qualify for the section 351 SSP exception.¹⁴⁴ As applied to adipose, did this mean adipose as a freshly harvested and fully intact tissue or could it pertain instead to particular cells within that tissue? Both sides insisted that the term "such HCT/P's" is unambiguous despite proffering contradictory interpretations, at least as

¹³⁴ *U.S. v. Cal. Stem Cell Treatment Ctr., Inc.*, No. 5:18-cv-01005 (C.D. Cal. May 9, 2018); *U.S. v. U.S. Stem Cell Ctr., L.L.C.*, No. 18-CV-61047 (S.D. Fla. May 9, 2018).

¹³⁵ 403 F. Supp. 3d 1279 (S.D. Fla. 2019). When FDA initially sued, U.S. Stem Cell had recently settled several lawsuits by former patients, each of whom claimed to experience partial or total vision loss shortly after receiving bilateral intravitreal injections of autologous adipose-derived SVF to treat age-related macular degeneration. See, e.g., Sharon Begley, *Three Patients Blinded by Stem Cell Procedure, Physicians Say*, STATNEWS (Mar. 16, 2017), <https://www.statnews.com/2017/03/15/stem-cell-patients-blind-macular-degeneration/> [<https://perma.cc/VM4T-Y3LF>].

¹³⁶ No. EDCV 18-1005 JGB (KKx), at *9 (S.D. Fla. Jan. 27, 2020).

¹³⁷ 403 F. Supp. 3d at 1285–87.

¹³⁸ *Id.* at 1298–99.

¹³⁹ *Id.* at 1296.

¹⁴⁰ *Id.* at 1297–98.

¹⁴¹ *Id.* at 1298–1300.

¹⁴² *Id.* at 1299–1300.

¹⁴³ *Id.* at 1285–1300.

¹⁴⁴ *Id.* at 1287–88.

applied to SVF.¹⁴⁵ According to FDA, “such HCT/P’s” refers to intact adipose tissue as originally extracted from the patient subject only to “minor ‘rinsing, cleansing, sizing and shaping.’”¹⁴⁶ Defendants countered that the term “unambiguously means HCT/P’s that are ‘like or similar’ [to] the HCT/P’s removed from the patient,” including adipose’s cellular components because, although SVF does consist of disaggregated cells, the cells themselves do not change form following harvest.¹⁴⁷ Finding the regulation’s use of “such HCT/P’s” to be facially unclear, the court exercised so-called “*Auer* deference”—i.e., judicial deference to an agency’s interpretation of its own regulation—because the court found that FDA’s interpretation of the term “such HCT/P’s” was neither plainly erroneous nor inconsistent with the regulation.¹⁴⁸

In deferring to FDA’s reading of the HCT/P regulations, Judge Ungaro acknowledged that the U.S. Supreme Court would soon decide whether to invalidate *Auer* deference altogether in *Kisor v. Wilkie*, but stated: “until the Supreme Court overturns *Auer*, it remains binding precedent and the Court must apply it as such.”¹⁴⁹ Further, judicial deference is especially important where, as here, a regulator is administering “‘a complex and highly technical regulatory program’ in which the identification and classification of relevant ‘criteria necessarily require significant expertise and entail the exercise of judgment grounded in policy concerns.’”¹⁵⁰ Since creating the SSP exception to section 351 in 1997, FDA has consistently seen simple relocation of a person’s cells from one body part to another as presenting risks no greater than those typically associated with surgery.¹⁵¹ FDA has just as consistently viewed processing methods that change an HCT/P’s original form as posing risks in need of section 351 premarket review.¹⁵² In the court’s assessment, the agency overseeing this “complex and highly technical regulatory program” has the right to make this call.¹⁵³

Having rejected U.S. Stem Cell’s’ section 351 SSP exception defenses, the court considered whether the SVF product could nevertheless avoid premarket review as a section 361 product under 21 C.F.R. § 1271.10(a)(2).¹⁵⁴ Focusing solely on the “dispositive” issue of whether the SVF met section 361’s requirement of being solely

¹⁴⁵ *Id.* at 1288.

¹⁴⁶ *Id.*

¹⁴⁷ *Id.*

¹⁴⁸ *Id.* at 1296 (citing *Auer v. Robbins*, 519 U.S. 452, 461 (1997)).

¹⁴⁹ *Id.* at 1296 n.9.

¹⁵⁰ *Id.* at 1292 (quoting *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994) (quoting *Pauley v. BethEnergy Mines, Inc.*, 501 U.S. 680, 697 (1991))).

¹⁵¹ *Id.* at 1293.

¹⁵² *Id.* at 1292.

¹⁵³ *Id.* at 1293. In a separate line of argument, U.S. Stem Cell claimed that FDA’s interpretation and application of the section 351 SSP exception failed because it rested on Final Guidance that was effectively making substantive changes which necessitated formal notice and comment rulemaking. The court disagreed, explaining that Guidance is merely informative and the regulations themselves were more than adequate to support FDA’s action to prevent further marketing and use of SVF in this case. *Id.* at 1294–96.

¹⁵⁴ *Id.* at 1296–98.

intended for homologous use,¹⁵⁵ the court found itself revisiting the issue of whether the appropriate subject of analysis was adipose lipoaspirate or its SVF cellular components.¹⁵⁶ Ultimately, the court saw no need to choose because whether the appropriate unit of analysis was the tissue as harvested or its cellular components, intending it for a “regenerative” function failed as a matter of law to show that the product was “intended solely for homologous use” under 21 C.F.R. § 1271.10(a).¹⁵⁷ Given the SVF’s resulting need for formal premarket section 351 approval and U.S. Stem Cell’s failure to obtain it, the court permanently enjoined continued promotion and use of this product.¹⁵⁸

Using a similar rationale, FDA moved for summary judgment to permanently enjoin adipose-derived SVF therapies in *U.S. v. Calif. Stem Cell Treatment Ctr., Inc.*¹⁵⁹ FDA again argued that harvesting adipose tissue and returning an SVF derivative violated the section 351’s SSP exception’s requirement of retaining “such HCT/P” in its original form.¹⁶⁰ The California court agreed that “[i]ndisputably, SVF cells are not the same as adipose tissue: adipose tissue contains a cellular matrix that SVF cells do not and adipose tissue has properties that SVF cells lack.”¹⁶¹ However, the court also agreed with defendants that instead of focusing “on the largest system that was removed (i.e., adipose tissue),”¹⁶² section 351’s SSP exception “unambiguously demands” that its use of the term “such HCT/P” be understood to mean “the target of the removal—either the cell or the tissue—rather than the largest system removed.”¹⁶³ In essence, the *California Stem Cell* court created a two-step inquiry: (1) from the harvested substance, identify the HCT/P intended for return to the patient which, at least for this case, was SVF; and then (2) evaluate whether that SVF maintained its original form during the process of separating it from the harvested lipoaspirate.¹⁶⁴ With regard to the latter point of whether the SVF cells changed form during processing, the court found that the parties’ conflicting views create a question of fact and, accordingly, denied summary judgment and instructed the parties to prepare for trial.¹⁶⁵

Because the SSP exception to section 351 oversight does not require homologous use, the court did not consider how or why the SVF product would be used.¹⁶⁶ Should defendants prevail at trial in showing that the SVF process does not alter the original

¹⁵⁵ Because the absence of homologous use was “dispositive” of the SVF’s non-section 361 status, the court saw no need to consider whether it fulfilled section 361’s remaining requirements, including minimal manipulation. *Id.* at 1297.

¹⁵⁶ *Id.* at 1298.

¹⁵⁷ *Id.*

¹⁵⁸ *Id.* at 1300–01.

¹⁵⁹ No. EDCV 18-1005 JGB (KKx), 2020 WL 1289543 (C.D. Cal. Jan 27, 2020).

¹⁶⁰ *Id.* at *7.

¹⁶¹ *Id.*

¹⁶² *Id.*

¹⁶³ *Id.* at *8.

¹⁶⁴ *Id.* at *9.

¹⁶⁵ *Id.*

¹⁶⁶ See *United States v. U.S. Stem Cell Clinic, L.L.C.*, 403 F. Supp. 3d 1279, 1298 (S.D. Fla. 2019).

form of the cells themselves, it will be able to continue marketing the same therapies that initially flagged the case for FDA. Currently, the website of California Stem Cell Treatment Center’s co-defendant, Cell Surgical Network Corporation (Cell Surgical), describes its network of providers as “currently studying” and “investigating” the following “protocols” for using SVF to treat various conditions:

Cell Surgical Network Website: “Currently Studying” Available “Protocols”	
Condition	Treatment Protocol
Parkinson’s Disease	“Special measures are taken to optimize transport of SVF across the blood-brain barrier to improve central nervous system uptake.” ¹⁶⁷
Multiple Sclerosis	“[A] specific SVF deployment protocol that attempts to utilize the immunoregulatory and anti-inflammatory properties of SVF (rich in mesenchymal stem cells and growth factors). Special measures are taken to optimize transport of the SVF across the blood-brain barrier to improve central nervous system uptake.” ¹⁶⁸
Congestive Heart Failure; Cardiomyopathy	“We use a protocol designed by our interventional cardiologist that includes intravenous deployment.” ¹⁶⁹
Chronic Obstructive Pulmonary Disease	“Cell Surgical Network is investigating the effects of SVF (rich in mesenchymal stem cells and growth factors) on airway healing. We use a protocol that includes a combination of intravenous and nebulized SVF delivery.” ¹⁷⁰

¹⁶⁷ *Parkinson’s*, CELL SURGICAL NETWORK, <https://stemcellrevolution.com/currently-studying/neurology/parkinson/> [https://perma.cc/MF59-EQRB] (last visited May 28, 2020).

¹⁶⁸ *Multiple Sclerosis*, CELL SURGICAL NETWORK, <https://stemcellrevolution.com/currently-studying/neurology/multiple-sclerosi-and-regeneration/> [https://perma.cc/US9L-Y3AL] (last visited May 28, 2020).

¹⁶⁹ *Congestive Heart Failure (CHF) & Cardiomyopathy*, CELL SURGICAL NETWORK, <https://stemcellrevolution.com/currently-studying/pulmonary/cardiomyopathy/> [https://perma.cc/97Y3-L7N3] (last visited May 28, 2020).

¹⁷⁰ *Lung Disease*, CELL SURGICAL NETWORK, <https://stemcellrevolution.com/currently-studying/pulmonary/copd/> [https://perma.cc/9YHS-G4AZ] (last visited May 28, 2020).

Macular Degeneration; Diabetic Retinopathy	“[P]rotocols for visual loss conditions that emphasize safety and efficacy.” ¹⁷¹
Lupus	“[A] specific SVF deployment protocol that attempts to utilize the immunoregulatory and anti-inflammatory properties of SVF (rich in mesenchymal stem cells and growth factors) to mitigate the effects of Lupus. SVF is deployed systemically and may require repeat dosing.” ¹⁷²

Cell Surgical’s website concedes that its adipose-derived SVF “protocols” are not FDA approved. However, it also claims—incorrectly—that FDA approval is unnecessary because the SVF treatments “fall under the category of physician’s practice of medicine, wherein the physician and patient are free to consider their chosen course of treatment.”¹⁷³ First, state regulation of the practice of medicine in no way precludes federal regulation of the materials used—be it a chemically synthesized medication, medical device, or cell therapy—while practicing medicine.¹⁷⁴ According to FDA, this representation is not accurate or at most, remains strongly disputed as evidenced by FDA’s willingness to sue California Stem Cell Treatment Center, Cell Surgical, and U.S. Stem Cell for promoting SVF products subject to section 351’s premarket approval requirements.¹⁷⁵ Cell Surgical’s website further states that network providers meet FDA’s “guidelines about treatment and manipulation of a patient’s own tissues . . . by providing same day treatment with the patient’s own cells that undergo no manipulation and are inserted during the same procedure.” This passage obviously refers to the SSP exception. Upon learning that “we meet these guidelines,” the reader would have no idea that the Cell Surgical Network and its founding member, the California Treatment Center, are currently defending against FDA’s lawsuit for marketing unapproved SVF therapies.¹⁷⁶

Neither of the Florida and California cases tackled the core problem with FDA’s interpretation and application of its section 351 and section 361 frameworks to adipose-derived stem cell therapies. At their foundation, the HCT/P regulations and the legitimacy of the Final MM/HU and SSP Guidances turn on the validity of FDA’s determination of the original form and basic function or functions of adipose tissue and its component cells. FDA gets it wrong when it expressly acknowledges the structural and nonstructural functions of adipose and simultaneously refuses to

¹⁷¹ *Ophthalmology*, CELL SURGICAL NETWORK, <https://stemcellrevolution.com/currently-studying/ophthalmology/ophthalmology/> [<https://perma.cc/9Y6Q-FWYS>] (last visited May 28, 2020).

¹⁷² *Lupus*, CELL SURGICAL NETWORK, <https://stemcellrevolution.com/currently-studying/autoimmune-diseases/lupus-2/> [<https://perma.cc/X39L-HW3B>] (last visited May 28, 2020).

¹⁷³ FAQs, CELL SURGICAL NETWORK, <https://stemcellrevolution.com/about-us/faqs/> [<https://perma.cc/Z47C-78W4>] (last visited May 28, 2020).

¹⁷⁴ As one court observed, “[t]he fact that the practice of medicine is an area traditionally regulated by the states does not invalidate those provisions of the [FDCA] which may at times impinge on some aspect of a doctor’s practice.” *Pharm. Mfrs. Ass’n v. Food & Drug Admin.*, 484 F. Supp. 1179, 1188 (D. Del. 1980).

¹⁷⁵ See *supra* notes 129–32 and accompanying text.

¹⁷⁶ FAQs, *supra* note 173.

evaluate adipose as anything other than solely structural. FDA then compounds this error by highlighting the prevalence of adipocytes as indicative of adipose's structural features when its primary support, *Junqueira's* histology text, expressly contradicts the agency's position on this point.¹⁷⁷ Adipocytes release hormones and various other important substances, and adipose tissue is now recognized as an endocrine organ at the center of nutritional homeostasis.¹⁷⁸ According to the regulatory apparatus and definitions that FDA duly promulgated in formal rulemaking and explained in its Final MM/HU Final Guidance, "[b]asic functions of a cellular or nonstructural tissue would generally be a *metabolic or biochemical* function, such as, hematopoietic, immune, and *endocrine functions*."¹⁷⁹

Prior to June 2019, FDA might have justified this as an exercise of agency discretion in interpreting its own regulations, ones that are extremely technical and therefore deserving of strong judicial deference to an agency's interpretation of its regulations under *Auer*.¹⁸⁰ However, as explained below, the U.S. Supreme Court's June 2019 decision in *Kisor v. Wilkie* preserves but limits *Auer* deference meaning that, today, no agency should take it for granted.¹⁸¹

A. *Kisor v. Wilkie* and its Potential Impact on FDA Regulation of Adipose HCT/P's

In *Kisor v. Wilkie*, the U.S. Supreme Court rejected an effort to end so-called "*Auer* deference" or judicial deference to an agency's interpretation of its own regulations.¹⁸² The Court cautioned, however, that *Auer* deference must be exercised with care and firmly supported by a showing that: (1) "before concluding that a rule is genuinely ambiguous, [the court has exhausted] all the 'traditional tools' of construction[.]"¹⁸³ (2) the agency interpretation of that regulation is reasonable,¹⁸⁴ (3) the court independently determines that in addition to being reasonable, the "character and context of the agency interpretation entitles it to controlling weight" because it reflects the agency's "'authoritative' or 'official position,'" "substantive expertise," and "fair and considered judgment" rather than "'a convenient litigating position,'"¹⁸⁵ and (4) the agency interpretation does not "create[] 'unfair surprise' to regulated parties."¹⁸⁶

For the purpose of this discussion, *Kisor's* first three requirements are most salient. First, the regulation must be "genuinely ambiguous," and Justice Kagan admonished that "when we use that term, we mean it—*genuinely ambiguous*, even after a court has resorted to all the standard tools of interpretation."¹⁸⁷ This poses a serious problem for

¹⁷⁷ See *JUNQUEIRA*, *supra* note 85.

¹⁷⁸ *Id.*

¹⁷⁹ *Id.* (emphasis added).

¹⁸⁰ *Auer v. Robbins*, 519 U.S. 452, 461 (1997).

¹⁸¹ *Kisor v. Wilkie*, 139 S. Ct. 2400 (2019).

¹⁸² *Id.* at 2423–24.

¹⁸³ *Id.* at 2415.

¹⁸⁴ *Id.* at 2416 (citing *City of Arlington v. FCC*, 569 U.S. 290, 296 (2013)).

¹⁸⁵ *Id.* at 2414 (citing *Christopher v. SmithKline Beecham Corp.*, 567 U.S. 142, 155 (2012)); *Auer*, 519 U.S. at 462 (internal citations omitted).

¹⁸⁶ *Id.* at 2418 (quoting *Long Island Care at Home, Ltd. v. Coke*, 551 U.S. 158, 170 (2007)).

¹⁸⁷ *Id.* at 2414 (emphasis added).

FDA. As written, the HCT/P regulations define minimal manipulation and homologous use based on whether the product's basic function or basic functions fit the regulatory definitions for structural or nonstructural.¹⁸⁸ The regulations and their terminology might be technical and intertwined, but they are not ambiguous. According to *Kisor v. Wilkie*, any hope of obtaining *Auer* deference ends here.¹⁸⁹

Second, assuming for the sake of discussion that the HCT/P regulations are "genuinely ambiguous," FDA's interpretation of them must be reasonable¹⁹⁰ and, as applied to adipose, FDA's interpretation is not. No expertise is needed to spot the glaring illogic in the Final MM/HU Guidance's refusal to evaluate adipose as anything but solely structural while simultaneously acknowledging that adipose contains structural and nonstructural components and performs "multiple functions."¹⁹¹ This is facially unreasonable. FDA's solely structural categorization of adipose is even more confounding because it uses regulations that are supposed to facilitate the evaluation and reduction of risk to prevent the evaluation of whatever risks might inhere in therapies that rely on adipose's numerous (and many would say predominantly) nonstructural functions.

Third, *Kisor* bars deference to an agency's interpretation that "does not reflect an agency's authoritative, expertise-based, 'fair [or] considered judgment.'"¹⁹² FDA's factually inaccurate and logically unsound decision to treat adipose as solely structural is not "fair" and it is certainly not "expertise-based." The complexity of regulating stem cell products, particularly adipose, may explain why, in finalizing the MM/HU Guidance, FDA ignores overwhelming expert consensus and also misrepresents what its own cited authority, *Junqueira*, says about adipose being a nonstructural tissue.¹⁹³ Perhaps the agency concluded that it can choose to overlook inconvenient facts for the purpose of administrative expediency. However, a court cannot choose to "defer to a merely 'convenient litigating position' or 'post hoc rationalizatio[n] advanced' to 'defend past agency action against attack.'"¹⁹⁴ Rather, whether interpreting a statute or its own regulation, "the agency's reading must fall 'within the bounds of reasonable interpretation.'"¹⁹⁵ Justice Kagan practically scolded regulators and lower courts, adding, "[a]nd let there be no mistake: That is a requirement an agency can fail."¹⁹⁶ Post-*Kisor*, there is nothing convenient about reading the HCT/P regulations to evaluate adipose as solely structural. Regulating fat based on fiction rather than fact instead exceeds "the bounds of reasonable interpretation" and thus fails as legally unsupported.¹⁹⁷ As discussed *infra*, FDA's current strategy is also logistically unworkable.

¹⁸⁸ 21 C.F.R. § 1271.3(e) (defining homologous use) and § 1271.3 (f)(1)–(2) (defining minimal manipulation).

¹⁸⁹ See *Kisor*, 139 S. Ct. at 2415.

¹⁹⁰ *Id.* at 2415.

¹⁹¹ FINAL MM/HU GUIDANCE, *supra* note 92, at 8.

¹⁹² *Kisor*, 139 S. Ct. at 2414 (quoting Christopher, 567 U.S. at 155).

¹⁹³ See *supra* notes 92–99 and accompanying text.

¹⁹⁴ *Kisor*, 139 S. Ct. at 2414 (quoting Christopher, 567 U.S. at 155).

¹⁹⁵ *Id.* at 2416 (quoting City of Arlington, 569 U.S. at 296).

¹⁹⁶ *Id.* (emphasis added).

¹⁹⁷ See *supra* notes 86–101 and accompanying text.

B. *More Whac-a-Mole is a Losing Game*

Even before *Kisor v. Wilkie*, FDA's growing struggles to regulate the stem cell industry were captured by a series of statements that Scott Gottlieb, MD made before, during, and following his tenure as FDA Commissioner. Writing as a private citizen in 2012, Dr. Gottlieb cautioned that regulating adult stem cells as drugs "could put the brakes on one of the most promising areas of medical research."¹⁹⁸ In November 2017, Commissioner Gottlieb announced the agency's "comprehensive" and "innovative" framework to protect safety and promote innovation through the aforementioned blend of guidance with simultaneous enforcement discretion toward most clinics and aggressive enforcement against those deemed to pose especially high risks.¹⁹⁹ Shortly before leaving office in 2019, Commissioner Gottlieb joined CBER Director Peter Marks to express their frustration that after several years of pursuing this comprehensive strategy, the agency—and more importantly, the public—was still dealing with too many clinics that continued to promote unapproved stem cell treatments.²⁰⁰ The early enthusiasm of 2012 that had grown into a regulator's cautious optimism in 2017 now hardened into a sharp rebuke:

We've seen too many cases of sponsors claiming that cells aren't subject to FDA regulation just because the cells originated from the same patient to whom the eventual manufactured product is being given. And we've seen too many cases of companies making unsubstantiated claims that these treatments prevent, treat, cure or mitigate disease where the products have sometimes led to serious patient harm.

Patient safety is our first priority. These violative actions create a direct risk to patients. They also create indirect risks by potentially encouraging them to forgo otherwise effective, available treatments, and opt instead for purported treatments that create risks and offer no demonstrated benefits. These kinds of false claims and violative activities also do a tremendous disservice to innovators who are working to legitimately develop safe and effective stem cell therapies by casting doubt across the entire field.²⁰¹

The authors were correct in their call to identify, criticize, correct, and if needed, halt the operations of unscrupulous clinics making unsubstantiated claims. They were right to underscore that such actors hurt not only patients, but "do a tremendous disservice . . . to the entire field."²⁰² What the FDA Commissioner and Director of CBER did not acknowledge, though, and what FDA continues to ignore is the agency's

¹⁹⁸ Scott Gottlieb & Coleen Klasmeier, *The FDA Wants to Regulate Your Cells*, WALL ST. J. (Aug. 7, 2012), <https://www.wsj.com/articles/SB10000872396390444405804577558992030043820> [<https://perma.cc/9L3T>].

¹⁹⁹ *Id.* at 16; see also *Kisor*, 139 S. Ct. at 2400.

²⁰⁰ Press Release, U.S. FOOD & DRUG ADMIN., *Statement on FDA's Continued Efforts to Stop Stem Cell Clinics and Manufacturers From Marketing Unapproved Products That Put Patients at Risk* (April 19, 2019), <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-biologics-center-director-peter-marks-md-phd-fdas> [<https://perma.cc/2RJY-QRHX>].

²⁰¹ *Id.*

²⁰² *Id.*

role in perpetuating this “tremendous disservice” by rooting enforcement in logically flawed and factually incorrect readings of its own regulations. Anyone concerned about FDA’s enforcement strategy then should be even more alarmed post-*Kisor v. Wilkie*.

The mechanics and pace of FDA enforcement further hamper real progress. FDA filed the *U.S. Stem Cell* and *California Stem Cell Treatment Center/Cell Surgical Network* lawsuits after at least a year of multiple rounds of FDA inspections and communications informing the clinics that their respective stem cell therapies were illegal and needed to stop.²⁰³ This is cumbersome when FDA is suing a single clinic or network; industry-wide, it cannot work.²⁰⁴ Making the process even more daunting when taking on an entire industry is the diversity of stem cell products and protocols offered.²⁰⁵ FDA faces high stakes as it prepares to try *California Stem Cell* on the west coast and handle the *U.S. Stem Cell* appeal on the east. As applied to adipose products, FDA’s stance on adipose is likely to run afoul of *Kisor v. Wilkie*. More Whac-a-Mole post-*Kisor* (i.e., more rounds of pursuing one clinic at a time while other clinics multiply and perpetuate the same troubling practices) is making matters worse, not better. There’s got to be a better way.

Fortunately, there is one, and FDA already knows about it. FDA needs to retire from Whac-a-Mole and organize a team, with FTC as its captain.

V. FTC PLAYS A SIMPLER GAME

FTC’s authority to enforce the FTC Act’s prohibition of unfair or deceptive acts or practices in or affecting commerce²⁰⁶ and false advertising of drugs²⁰⁷ intersects with FDA’s role in reviewing labeling and related promotional materials for products that it labels.²⁰⁸ To “afford maximum protection to the consumer,” FDA and FTC signed a Memorandum of Understanding (MOU) in 1971 that delineates their respective roles in overseeing the “truth or falsity” of the advertisement and promotion of FDA-

²⁰³ See, e.g., Final MM/HU Guidance, *supra* note 92.

²⁰⁴ The total number of stem cell clinics in the United States is difficult to ascertain because clinics come and go—literally. Some exit the market, others reinvent their identity, and still others open multiple offices or join networks of affiliates. Stem cell scientist and industry watchdog Paul Knoepfler has described the industry as a “moving target” and estimates that from 2008 to 2017, the number of stem cell clinics in the U.S. grew from zero to approximately 715. Paul S. Knoepfler, *Rapid Change of a Cohort of 570 Unproven Stem Cell Clinics in the USA Over 3 Years*, 14 REGEN. MED. 735–38 (2019).

²⁰⁵ Extensive discussion of non-adipose products exceeds the scope of this Article, but a quick summary of one case underscores why FDA needs to rethink its approach to enforcement. In May 2019, FDA notified R3 Stem Cell, L.L.C. (R3), a processor and distributor rather than a healthcare provider, needed premarket approval of its umbilical and amniotic products. Although the company quickly declared its respect for FDA and promised to review its website, it continues to offer unapproved amniotic and umbilical products a year later, stating that, as biologics, they “are not required to be licensed or approved by FDA” and can instead “be used for conditions where physicians deem them to be safe and clinically useful.” David Greene, *Consumer Guide to Amniotic Umbilical Cord Stem Cell Therapy*, R3 STEM CELL 2–4, 10–11 (n.d.), https://www.omgfitnessmd.com/wp-content/uploads/Consumer_Guide_to_Amniotic_and_Umbilical_Cord_Stem_Cell_Therapy-3.pdf. These statements are incorrect.

²⁰⁶ 15 U.S.C. § 45(a) (2006).

²⁰⁷ *Id.* § 52.

²⁰⁸ Drugs and devices qualify as misbranded if their labeling is false or misleading. 21 U.S.C. § 352(a) (2018). Similarly, prescription drugs and restricted devices are deemed misbranded if their advertising is false or misleading in any particular respect. *Id.* § 352(n), (q)(1); 21 C.F.R. § 202.1(e)(5)(i) (2019).

regulated products.²⁰⁹ FDA would regulate labeling/branding of all food, drugs, devices, and cosmetics since these are already central to its general oversight responsibilities for these products. Consistent with FTC's overall mission of preserving fair and competitive markets, FTC would oversee advertising of all FDA-regulated products with the exception of prescription drugs; that responsibility stayed with FDA.²¹⁰ In the ensuing decades, section 351 cell and tissue products joined FDA's portfolio because of the need for premarket approval, giving FDA primary oversight over their online promotion.²¹¹

When the MOU took effect in 1971, the stem cell therapies that saturate today's internet did not exist; in fact, the internet itself did not exist. Products and their promotion have certainly changed since then, but the need "to afford maximum protection to the consumer" has not.²¹² To uphold its end of this commitment, FDA should reconsider and reduce its role in overseeing the promotion and marketing of stem cell products and allow FTC to lead the charge. Although both agencies are empowered to prevent clinics from promoting unproven stem cell treatments via the internet and other means, their respective statutory responsibilities and enforcement tools require them to pursue this shared end in very different ways. These differences give FTC a significant edge in achieving the common goal of stopping a clinic from promoting and using dangerous stem cell therapies. FDA enforcement of the HCT/P framework is too complicated and too time-consuming. A quick comparison reveals FTC's advantages.

Enforcing the section 351 and section 361 regulatory framework inevitably commits FDA to incorporating into all correspondence exhaustively detailed and hyper-technical descriptions of, and claims and arguments about, stem cell biology, laboratory handling, mechanical versus chemical processing, clinical applications, and more. In today's online world, however, establishing section 351 violations by peering through a microscope lens misses what clinics are doing on the web. For the purpose of section 351's SSP exception, perhaps mechanical separation and enzymatic digestion carry different risks, but for patients considering an unproven therapy, this

²⁰⁹Memorandum of Understanding Between Federal Trade Commission & the Food and Drug Administration, 36 Fed. Reg. 18539 (Sept. 16, 1971).

²¹⁰ *Id.*

²¹¹ Technically, HCT/Ps qualify as both drugs and biological products under the FDCA and PHSA, respectively, but are regulated as biological products under PHSA. *See supra* notes 19–22 and accompanying text. FDA's Center for Drug Evaluation and Research (CDER) oversees drugs, and the Center for Biologics Evaluation and Research (CBER) has primary authority for most biological products. In 2003, CBER formally "transferred" several categories of biologic products to CDER, giving it "regulatory responsibility, including premarket review and continuing oversight" of certain monoclonal antibodies, proteins (including cytokines), immunomodulators, and growth factors. CBER retained oversight of, *inter alia*, cell therapies, gene therapies, vaccines, and blood products. Drug and Biological Product Consolidation, 68 Fed. Reg. 38067 (June 26, 2003). Nested within CDER's Office of Medical Policy is the Office of Prescription Drug Promotion (OPDP), which helps to ensure that prescription drug information, including advertisements and online marketing "is truthful, balanced, and accurately communicated" through, *inter alia*, "comprehensive surveillance [and] compliance[.]" The Office of Prescription Drug Promotion (OPDP), U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-prescription-drug-promotion-opdp> [https://perma.cc/L55E-REHQ]. The OPDP has not been involved in overseeing the stem cell clinic industry, probably because its base is CDER rather than CBER, which regulates cell therapies.

²¹² Memorandum of Understanding Between Federal Trade Commission & the Food and Drug Administration, 36 Fed. Reg. at 18539.

is likely not material to their decision. FDA's enforcement process presents another hindrance. Pursuing a single clinic can take months if not years of conducting inspections, issuing warnings, filing extraordinarily complicated complaints, fielding requests for extensions of time, submitting to court-ordered mediation, waging discovery battles, preparing for trial, dealing with dueling experts, handling adverse rulings, and exhausting the appeals process. The scientific complexities of the issues involved make every step a slow and tortured one.

FTC is able to conduct a simpler inquiry into facts because it implements a simpler set of statutory and regulatory provisions which, in turn, creates a more straightforward and efficient enforcement strategy. The truth or falsity of a product's claims turns on the perspective of a reasonable consumer, not a highly specialized stem cell scientist.²¹³ Unlike the halting pace of FDA enforcement proceedings that need to enlist the U.S. Department of Justice (DOJ) to initiate litigation, FTC has the power to insist that a clinic respond within forty-eight hours of receiving an initial Warning Letter and to initiate a lawsuit on its own.²¹⁴

FTC Warning Letters may be simple, but they are powerful. Demonstrating their importance in enabling the agency to move aggressively to stop deceptive marketing of unproven COVID-19 treatments, FTC recently explained:

You might wonder: why send letters? Why not just sue the !*\$@&#? Fair question. But the letters are working. And, given the scope of the scams out there right now, we want to get the best and fastest results we can with the most efficient tool we have. Right now, for these Coronavirus-related issues, that's warning letters.

In general, here's how it goes:

- We spot someone advertising something with no proof that it works—and, in many cases, telling outright lies about its wonders.
- We send a letter pointing out the illegal things they're doing.
- They then have forty-eight hours to tell us what they've done to resolve the problems we've raised.

In nearly all cases so far, those who get the letters have stopped making the false claims or selling the scammy thing—whether cures from a product or earnings from a work-at-home scheme. Within 48 hours: no more lying to people, no more stealing people's money. During a crisis like this, we've prioritized stopping as many bad actors as we can, as

²¹³ Christine Varney, Former Comm'r, Fed. Trade Comm'n, Address at the 1996 International Consumer Product Health & Safety Organization Symposium: To Your Health: An FTC Review of Safety Related Marketing (Feb. 29, 1996), <https://www.ftc.gov/public-statements/1996/02/your-health-ftc-review-safety-related-marketing> [<https://perma.cc/D8LW-4JPT>].

²¹⁴ See, e.g., *supra* note 15.

quickly as we can. And when a warning letter will do that, we'll take that win.²¹⁵

FDA is entering year three of litigating against U.S. Stem Cell and California Stem Cell Treatment Center (with at least a year of inspection and warnings before filing the complaints). Results have been mixed and the final outcomes are anything but certain.

Should FTC file suit, it will skip FDA's detailed analyses of cell biology in favor of simple screenshots of the clinic website and social marketing materials.²¹⁶ Are the claims true or not? Misleading or accurate? A simple yes or no will suffice and as a consequence, results can be swift. A recent case demonstrates how this works.

On October 12, 2018, FTC filed a Complaint against Regenerative Medical Group, Inc. (RMG) for false and deceptive online promotion of unproven amniotic stem cell treatments.²¹⁷ But for the source of RMG's stem cells (amnion as opposed to adipose), the details of the case are remarkably similar to *U.S. Stem Cell* and *California Stem Cell Treatment Center* in terms of promotional methods, diseases targeted, therapeutic claims, and the absence of scientific evidence. Nevertheless, the legal allegations and, as a result, enforcement timelines and outcomes could not be more different.

FDA's Complaint against U.S. Stem Cell focuses less on marketing and more on the actual processing and use of the SVF product—as it needs to in order to enforce section 351 and the HCT/P regulations. As a result, the complaint details such matters as “the original relevant characteristics of the adipose tissue, including its extracellular matrix” and the impact of using “enzymatic digestion to break down the adipose tissue's extracellular matrix and isolate cellular components.”²¹⁸

FTC's RMG Complaint makes no mention of original relevant characteristics, extracellular matrices, isolated cellular components, for the simple reason that there is no need to do so. Instead, the RMG Complaint offers seventeen screenshots from RMG's website, YouTube channel, and Facebook pages displaying clear and unequivocal statements like “[s]tem cell treatment acts as a form of medical time machine, reversing the damage” to brain tissue following a stroke;²¹⁹ “[w]e can make blinded People see again!” and “[w]e can reverse Autism symptoms;”²²⁰ and “No More Fear Of a Heart Attack! We Repair Yours” (coupled with a “Fast Heart Repair Guarantee”).²²¹ The RMG Complaint allows RMG's promotional material to literally speak for itself, and then alleges quickly and concisely:

Defendants have not conducted any studies to assess the efficacy of amniotic stem cell therapy, including its ability to cure, treat, or mitigate

²¹⁵ Andrew Smith, *Fighting Coronavirus Scams: Taking Stock*, U.S. FED. TRADE COMM'N (May 8, 2020), <https://www.ftc.gov/news-events/blogs/business-blog/2020/05/fighting-coronavirus-scams-taking-stock> [<https://perma.cc/F785-EDH4>] (emphasis added).

²¹⁶ See, e.g., Complaint, Fed. Trade Comm'n v. Regenerative Medical Group, Inc., No.8:18-cv-01838 (C.D. Ca. Oct. 12, 2018).

²¹⁷ *Id.*

²¹⁸ See *supra* note 136, at para. 39–40.

²¹⁹ *Supra* note 215, at para. 16 Ex. B(15).

²²⁰ *Id.* at para. 16 Ex. B(4).

²²¹ *Id.* at Ex. C(1).

any disease or health condition. Moreover, there are no studies in the scientific literature establishing that amniotic stem cell therapy cures, treats, or mitigates diseases or health conditions in humans.²²²

That's it.

There are no extended explanations of the impact of processing on extracellular matrices, no meditations on the preservation of original form and basic function, and no debate about which HCT/P is the correct "such HCT/P" to run through this regulatory gauntlet. FTC's Complaint displays seventeen screenshots of RMG's therapeutic statements followed by a quick allegation of no scientific support, and pleads FTCA violations in the form of "unfair or deceptive acts or practices in or affecting commerce"²²³ and "false advertisement . . . in or affecting commerce for the purpose of inducing, or which is likely to induce, the purchase of food, drugs, devices, services, or cosmetics."²²⁴

In addition to enforcing a simpler statutory framework, FTC is able to hold targets to a compressed timeline. FTC filed the RMG Complaint on October 12, 2018, and within a week, RMG agreed to refrain permanently from any form of marketing amniotic stem cell therapies without "competent and reliable scientific evidence," repay the approximately three million dollars in profits derived from marketing amniotic treatments in the preceding three years (currently some \$525,000 returned to patients, with the balance suspended), and submit to compliance monitoring going forward.²²⁵ Of course, there is no guarantee that every FTC suit against every stem cell clinic for comparable practices will be resolved so quickly. Nevertheless, in statutory requirements, and enforcement options, FTC is better equipped to make real progress in reigning in the hundreds of clinics and companies promoting unproven stem cell therapies online.

VI. PLAYING TO WIN: EXCHANGING SOLO WHAC-A-MOLE FOR A TEAM SPORT

A. *It Takes a Village (or a Strike Force)*

The groundwork is already in place for FDA to collaborate with FTC in tackling online promotion of stem cells (with adipose as the most common type). FDA and FTC recently published a "Joint Statement" to announce a formal collaboration to prevent anticompetitive practices in the biosimilars market.²²⁶ FDA is currently working with FTC as well as DOJ to prevent fraudulent marketing of unproven COVID-19 treatments (a few of which involve adipose-derived SVF stem cell therapy).²²⁷ On June 2, 2020, DOJ's Civil Division announced the trio's rapid success in shuttering the operations of a seller whose website extolled its product's powers to

²²² *Id.* para. 17.

²²³ 15 U.S.C. § 45(a) (2006).

²²⁴ *Id.* § 52(a)(2).

²²⁵ [Proposed] Stipulated Order of Permanent Injunction and Monetary Judgment, Fed. Trade Comm'n v. Regenerative Medical Group, Inc., No. 8:18-cv-01838 (C.D. Ca. Oct. 12, 2018).

²²⁶ *Supra* note 13 and accompanying text.

²²⁷ *Supra* note 15 and accompanying text.

cure COVID-19. The seller: (1) sold the product to a special agent on May 5, 2020; (2) received a warning letter, dated May 14, 2020 from FDA, FTC, and DOJ jointly demanding immediate termination of all marketing and sales; (3) continued to promote and sell the product for the next two weeks; and (4) received a temporary restraining order on June 2, 2020. The seller's website promptly vanished from the internet. Start to finish, the entire process took less than one month.

As is typical for FTC but not for FDA when flying solo, the three-agency collaboration secured a fast and favorable resolution by focusing solely on false or unsubstantiated claims, allowing the seller's own statements to prove their case, issuing a prompt warning demanding an immediate and definitive response and, when business operations proceeded as usual, quickly following up with a court-ordered injunction. Unlike section 351 Whac-a-Mole, this game plan was methodical, efficient, and effective due in no small part to its reliance on FTCA basics instead of the complex technicalities of the FDCA or PHSa.

Comparing FDA's responsibilities, resources, and results with those of FTC demonstrates unequivocally that FDA needs to retire from Whac-a-Mole. In doing so, however, it need not abandon its November 2017 goal of exercising comprehensive oversight over adult stem cell therapies. The enforcement arm of the 2017 strategy fell short because the HCT/P framework is too convoluted for one agency to enforce when pursuing one clinic at a time. A truly comprehensive approach should employ an inter-agency strike force, an organizational model that has worked particularly well in targeting various forms of healthcare fraud. The Office of Inspector General (OIG) for Health and Human Services puts it this way:

These teams have a proven record of success in analyzing data and investigative intelligence to quickly identify fraud and bring prosecutions. The interagency collaboration also enhances the effectiveness of the Strike Force model. For example, OIG refers credible allegations of fraud to the Centers for Medicare & Medicaid Services (CMS) so that it can suspend payments to the suspected perpetrators, thereby immediately preventing losses from claims submitted by Strike Force targets.²²⁸

Strike Forces have shut down health care fraud schemes around the country, arrested more than a thousand providers and manufacturers, and recovered millions of taxpayer dollars. This model has worked so well for the Medicare Strike Force Program that there are now over a dozen regional Medicare Strike Forces operating throughout the country.²²⁹

Given the clear benefits of the strike force model and the successes of federal-state strike forces dedicated to preventing Medicare Fraud, Medicaid Fraud, Healthcare Fraud and Abuse, and the like, perhaps the time has come for a Stem Cell Fraud Strike

²²⁸ As of May 2019, the Medicare Strike Force Program was responsible for 2,208 criminal actions, 2,829 indictments, and \$3.48 billion in investigative receivables. *See, e.g., Medicare Fraud Strike Force*, U.S. DEPT. HEALTH & HUMAN SERVS. OFFICE OF INSPECTOR GEN., <https://oig.hhs.gov/fraud/strike-force/> [<https://perma.cc/Q9X9-98S6>]; *see also Strike Force Operations*, U.S. DEPT. OF JUSTICE, <https://www.justice.gov/criminal-fraud/strike-force-operations> [<https://perma.cc/4PSE-G2GU>] (describing the operations of the Department of Justice's Health Care Fraud Strike Force).

²²⁹ *Id.*

Force.²³⁰ At long last, real gains can be made if FDA takes the initiative to organize a federal and state interagency collaboration to coordinate enforcement of the FTCA and companion state laws to stop unfair and deceptive marketing of unproven stem cell therapies by health care providers, clinics, manufacturers, and distributors. From an enforcement standpoint, the landscape of stem cell clinics is just as fragmented and logistically daunting as that of Medicare fraudsters. Thus, strike force membership should include state regulators, law enforcement, and professional licensing authorities because beyond enforcing state analogs of the FTCA, several states have enacted legislation specific to stem cell clinics²³¹ or have initiated their own lawsuits to stop online stem cell marketing.²³²

Federal coordination with state officials offers efficiencies when federal and state laws overlap. It can also assist in circumventing defense challenges to FDA's basic authority to regulate stem cells based on improper federal intrusion into the state-regulated practice of medicine. Strike forces facilitate the collection and analysis of data and other evidence. Acting on its own, FDA faces an uphill battle in taking on wayward stem cell clinics, even with DOJ's support during litigation. Acting in concert with other federal agencies and state and local authorities can make FDA a force to be reckoned with, especially if it focuses on unproven marketing claims.

²³⁰ *Id.*

²³¹ For instance, California recently updated its professional licensing laws to require providers of unapproved stem cell therapies to inform patients in writing that the provider “performs one or more stem cell therapies that have not yet been approved by the United States Food and Drug Administration.” CAL. BUS. & PROF. CODE § 684 (2019). The law requires providers offering HCT/P therapies that are not FDA-approved and have no IND to display in the office and deliver to the patient the following statement: “THIS NOTICE MUST BE PROVIDED TO YOU UNDER CALIFORNIA LAW. This health care practitioner performs one or more stem cell therapies that have not yet been approved by the United States Food and Drug Administration.” *Id.* The medical licensing board will issue a warning only for a first violation, and subsequent violations will result in a citation and a fine of no more than \$1,000 per incident. *Id.* Texas has taken a different approach; it generally requires adult stem cell therapies to be FDA-approved or undergoing study in an FDA-approved clinical trial. TEX. HEALTH & SAFETY CODE ANN. §§ 1003.002, 1003.003 (West 2019). However, it partially relaxed this requirement in its 2017 “right to try law” which allows a patient with severe chronic disease or terminal illness to receive an investigational adult stem cell treatment (defined as being under investigation in a clinical trial but not yet approved by FDA; no mention is made of having an IND, NDA, or BLA on file with FDA) if the physician in consultation with the patient determines that “all other” FDA-approved treatment options have been considered and are “unavailable or unlikely to alleviate” the pain or impairment caused by the condition, and the physician provides a prescription of recommendation of “a specific class of investigational stem cell treatment.” *Id.* at §§ 1003.51–1003.53. Reactions have been mixed, with some praising the law's respect for the autonomy of patients struggling with serious illness, and others criticizing its indulgence of the private stem cell clinic industry. Andrew Joseph, *Texas on Track to Become First State to Explicitly Back Stem Cell Therapies*, STAT (May 30, 2017), <https://www.statnews.com/2017/05/30/stem-cell-therapies-texas/> [<https://perma.cc/XSJ3-YWLJ>].

²³² The ongoing matter of *New York v. Image Plastic Surgery, L.L.C.*, Complaint No. 450389 (Sup. Ct. New York Cnty. INDEX NO. 450389 (Apr. 3, 2019)) seeks permanently to enjoin Image Plastic Surgery, L.L.C. (Image), from promoting its amniotic cell product to treat everything from heart disease to stroke, claiming such practices demonstrate “repeated illegal acts or persistent illegality in the carrying on, conducting, or transaction of business” and “deceptive acts and practices in the conduct of any business” in violation of state law. As occurred in FTC's RMG Complaint, New York's complaint against Image relies heavily on material from screen captures of Image's website and Facebook page (comprising the majority of pages devoted to factual allegations).

B. Playing a Better Game with a Better Enforcement Plan

FDA must find a way to exercise effective oversight of online and other direct-to-consumer promotion. Challenging clinics that promote unsafe SVF and other stem cell products is the right thing to do, but proceeding for the wrong reasons undermines overall enforcement post-*Kisor v. Wilkie*. If FDA's comprehensive framework of litigation, enforcement discretion, advisory consultation, and interpretive guidance is to work, FDA needs to revise its current guidance and rethink its overall approach to regulating adipose. It needs more than a new game plan; it needs to play a new game. Becoming more efficient and effective in regulating online promotion of unproven stem cell therapies involves two phases that can be pursued contemporaneously. Phase I requires FDA to look within in order to improve its internal practices and update current Guidance. It must ground all interpretation and enforcement of HCT/P regulations in accurate biology. Phase II requires FDA to look beyond itself to organize a Stem Cell Fraud Strike Force.

Phase I: Improving FDA Interpretation and Implementation of HCT/P Regulations.

- (1) FDA must revise existing HCT/P guidance to correct factual inaccuracies and logical inconsistencies, especially for adipose-derived stem cell products.
 - a. For multifunction HCT/Ps, including those derived from or otherwise involving adipose, this will require FDA to expand its evaluation to consider both structural and nonstructural functions depending on the multifunction HCT/P's intended structural or nonstructural use (or, if relevant, both) for the specific clinical application. Both fact and law require this, and patients searching the internet for hope and health deserve nothing less.
- (2) FDA should be guided by extensive collaboration with experts, especially those with expertise in the specific HCT/P types that prompted controversy when finalizing current guidance (e.g., adipose and amniotic products). The goal should be a transparent, rational, and predictable system for evaluating an HCT/P's functions (whether structural, nonstructural, or both) based on its intended use for a particular clinical application.
- (3) Consistent procedures are needed for making these assessments at the levels of general categorization and specific clinical applications. How determinations will be made and who will make them warrants careful thought and extensive discussion among FDA and stakeholder representatives. Diverse opinions need not be adopted, but they should be taken seriously and considered carefully.
- (4) Because the determination of an HCT/P's basic function for an intended clinical application is central to a product's regulatory status under the HCT/P framework and need for section 351 approval, the determination must be accompanied in writing by a clearly articulated rationale grounded in scientific expertise, evidence, and biologically accurate facts. In this regard, explicit mechanisms and

processes must be established to accommodate scientific advances in understanding the form, functions, and other characteristics relevant to an HCT/P's intended use.

Phase II: Forming a Stem Cell Strike Force to Pursue False and Deceptive Online Marketing

Beyond repairing and refining FDA's interpretation and implementation of its own HCT/P regulations, *FDA's enforcement strategy must shift its focus from what HCT/P's do to what clinics do with them.* Toward this end, FDA should create an inter-agency and multidisciplinary Stem Cell Fraud Strike Force that would draw on federal, state, and local resources to identify, warn, and if needed, quickly sue and enjoin clinics and other actors engaged in online and other direct-to-consumer marketing of unproven stem cell therapies. FDA should build on its Phase I, in-house clean-up with these or similar measures:

- (5) FDA should formalize and expand its partnership with FTC, which has already demonstrated that it is willing and well-equipped to hold stem cell clinics accountable for offering unsafe therapies directly to consumers.²³³ FTC's involvement is critically important because, particularly when dealing with hundreds of clinics and providers, demonstrating false and misleading statements on a website is more feasible than litigating the inner workings of specific cells when subjected to specific processing methods and applications by separate clinics.
- (6) FDA should reach beyond FTC to develop the kind of inter-agency and multidisciplinary federal, state, and local collaborations that have enabled the Medicare Strike Force and other strike forces to pool data, streamline analytics, optimize investigative intelligence, and coordinate resources of regulators, law enforcement, and professional licensing authorities to their maximum effect.²³⁴

VII. CONCLUSION

FDA is losing its game of Whac-a-Mole, and stem cell clinics know this. Some are probably betting on it. More resources might help FDA, but it will take more than money and personnel to conquer an internet populated by growing numbers of shape-shifting stem cell clinics. Regulating the readily available, easy to use, and functionally versatile adipose products that dominate the market is especially difficult for reasons of FDA's own making. With the worthy goal of reigning in rogue clinics, the agency undermines enforcement by interpreting and applying the HCT/P regulations based on skewed biology and flawed rationales. Instead of reducing risk, this strategy

²³³ See, e.g., Press Release, U.S. FED. TRADE COMM'N, FTC Returns Almost \$515,000 to Consumers Who Bought Deceptively Marketed "Amniotic Stem Cell Therapy" Between 2014 and 2017 (Apr. 30, 2019), <https://www.ftc.gov/news-events/press-releases/2019/04/ftc-returns-almost-515000-consumers-who-bought-deceptively> [<https://perma.cc/U6ZL-KYTE>].

²³⁴ See *Strike Force Operations*, U.S. DEPT. OF JUSTICE, <https://www.justice.gov/criminal-fraud/strike-force-operations> [<https://perma.cc/4PSE-G2GU>].

exacerbates it by foreclosing meaningful evaluation of adipose's nonstructural components and functions.

Post *Kisor v. Wilkie*, this game plan poses more risks than ever. Regulating based on fake facts and faulty logic makes courts less likely to defer and clinics more likely to persist in marketing unproven and unsafe therapies. If FDA loses its bid to exclude adipose-derived SVF from section 351's SSP exception, clinics can continue to promote SVF to treat everything from autism to retinopathy. For unproven high-risk treatments (e.g., injecting SVF into both eyeballs at the same time), patients lose. Conversely, if FDA prevails in classifying adipose as solely structural, the agency can continue to regulate nonstructural risk by ignoring it while depriving patients of autologous therapies that might otherwise deserve the more moderate oversight and wider availability that section 361 provides. Patients lose again. Another downside of more Whac-a-Mole is that FDA's insistence on using complex interpretations of complex regulations to evaluate complex cell forms and functions too often leads to the agency being completely ignored or deeply consumed by complex litigation.

For the reasons explained in this Article, FDA should recruit a larger team in order to play a simpler game. It should start by recognizing the promotion of high risk, unproven cell therapies for what it is: healthcare fraud. After all, when a clinic's website says its product needs no FDA approval when in fact it does, or proffers studies that have "looked at" a treatment's effectiveness to imply that the treatment actually works, or represents a protocol as low risk when patient experience indicates the contrary—these are all models of fraudulent misrepresentations or at least unfair and deceptive trade practices. For SVF, it is not necessary to distort biology by pretending that the large majority of adipose's nonstructural cells have no significant functions. It makes no sense at all to weave a messy web of contrived concepts and skewed facts only to be entangled by it, particularly when FDA/FTC partnership has already proven itself to be more effective and efficient.

FDA must revamp its enforcement strategy and shift its focus from the prospect of HCT/P's behaving badly to the problem of clinics and other providers behaving badly. For the sake of patients, the general public, and the overall field of regenerative medicine, FDA should retire from Whac-a-Mole, rethink, reorganize, and recruit a Stem Cell Fraud Strike Force that focuses less on *what cells do* and more on *what providers do with them*.

In the end, the only way to start winning Whac-a-Mole is to stop playing it.