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Executive Summary

Products derived from human tissue have been used as therapeutic products for more than a hundred years. In recent years, human tissue products have been increasingly linked with the developing field of regenerative medicine. Modern regenerative products include cellular treatments (e.g., stem cells), tissue grafts, and a wide variety of other products. As the U.S. Food and Drug Administration (FDA) stated in August 2017, regenerative therapies are “one of the most promising new fields of science and medicine,” but a “small number of unscrupulous actors” have “seized on the clinical promise of regenerative medicine” to “make deceptive and sometimes corrupt” claims “and, in some cases, dangerously dubious products.” Providing adequate assurances of safety and efficacy for regenerative products without stifling the practice and development of regenerative medicine poses a unique regulatory challenge for FDA and other stakeholders.

Historically, tissue products were not subject to active federal regulation. Instead, human tissue products were primarily regulated by voluntary quality assurance programs, particularly those established in 1976 by the American Association of Tissue Banks (AATB). Beginning in the mid-1980s, FDA began to assert authority over human tissue products on a case-by-case basis. FDA’s early efforts focused on categorizing specific human tissue products as medical devices, drugs, or biological products, thereby requiring premarket review under the Federal Food, Drug, and Cosmetic Act (FDCA) and/or the Public Health Services Act (PHSA). In the 1990s, however, FDA announced that it would create a comprehensive, risk-based framework to regulate the donation, handling, processing, and marketing of human cells, tissues, and tissue-based products (HCT/Ps). FDA began with the publication of an Interim Final Rule in 1993, which it finalized in 1997. Establishing the framework took several years and multiple additional rulemakings, but, by 2005, FDA had completed the HCT/P regulations in 21 C.F.R., Parts 1270 and 1271.

The HCT/P regulations create a tiered, risk-based system in which the level of oversight varies depending on the source of the tissue, the degree to which it is processed, and the manufacturer’s claims for the final product. In broad strokes, the regulations categorize HCT/Ps into three tiers. The lowest tier consists of cell and tissue “products” harvested and reimplanted during surgical procedures (e.g., a vein harvested during a cardiac bypass) or reproductive cells or tissues donated by a sexually intimate partner of the recipient. Subject to important limitations, FDA exercises virtually no oversight over such products. At the other end of the spectrum, the highest tier includes tissue products that present safety and efficacy risks similar to those presented by conventional medical products. These products are required to comply with the preapproval requirements of the FDCA and/or PHSA, although FDA is exploring concepts to reduce the burden of seeking premarket clearance. Between those two extremes lies a “middle tier” of tissue products regulated solely as HCT/Ps under section 361 of the PHSA and the Part 1270 and 1271 regulations, which require registration and compliance with good tissue practice (GTP), but do not require formal premarket review.

The three risk-based tiers are not sharply defined, however, and it is sometimes difficult to know, in advance, how a given tissue product or regenerative technique will or should be regulated. Some of that confusion stems from the fact that FDA’s effort to balance risk and innovation is necessarily difficult. In lieu of developing a bright-line, preapproval scheme for all HCT/P products, FDA chose instead to limit premarket review requirements to those products that present the highest risk. This risk-based approach requires lines to be drawn, and some of

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the terms used to draw them are not always intuitive (e.g., “homologous use”) or easily defined (e.g., “minimally manipulated”). Further, firms in this space must decide in the first instance whether to bring products to market without preapproval based on FDA’s signals in preamble statements, product jurisdiction designations, enforcement activities, and related guidance documents. In several cases, this has led firms to reach different conclusions than FDA may have, and it has led to accusations that some have deliberately exploited the situation to put high-risk products on the market without the necessary FDA review. The confusion has been aggravated in the last decade by profound advances in science and technology and a rapid expansion of this market segment. These advances underscore the importance of determining how FDA’s risk-based scheme applies, or should apply, to new products and therapies. On one hand, overregulation and insistence on premarket review could serve as a barrier to important innovation. On the other, new products that are not tested or evaluated for safety and efficacy may carry risks that are not anticipated and cause grievous harm.¹

To address this confusion and the continuum of risk, FDA announced in August 2017 that it would re-examine the regulatory framework for HCT/Ps and other regenerative therapies. FDA stated its intent to increase enforcement activities against bad actors and revealed enforcement actions against two firms marketing stem cell treatments to cancer patients and those suffering from serious neurological and autoimmune diseases. At the same time, FDA acknowledged the confusion about “where the regulatory lines ... are drawn” and promised to “establish clearer lines” while also promising to establish “a way to more efficiently gain FDA approval” when premarket approval is required for a tissue product.

In November 2017, FDA announced the availability of four guidance documents, which FDA collectively described as a “comprehensive regenerative medicine policy framework” to modernize the regulation of cell- and tissue-based therapies. According to FDA, the guidance documents represent a “new” and “innovative” approach to the regulation of tissue products that will foster innovation while taking steps to protect patient safety. One stated goal was to establish “a clear, efficient pathway for product developers” while “clarifying the FDA’s authorities and enforcement priorities.” Accordingly, the guidance documents focus in large measure on clarifying the lines between the three tiers, especially the lines between those products regulated solely as HCT/Ps and those considered to be medical products subject to full premarket review.

As part of the November 2017 announcement, FDA explained it will provide a transition period for those HCT/Ps that require premarket review under the new guidances. FDA has stated that it will give manufacturers of HCT/Ps that do not present significant safety risks 36 months to determine whether premarket approval is required and, if so, to begin to prepare an appropriate premarket submission. This grant of enforcement discretion is significant in at least three respects. First, FDA’s exercise of enforcement discretion suggests its awareness that many HCT/Ps have been marketed for several years based on a good faith understanding that premarket review was not required. Second, the provision of enforcement discretion similarly may reflect recognition that the lines between the tiers in FDA’s framework had not been clearly or adequately drawn in the past. Finally, and most importantly, it suggests FDA’s belief that a great many products marketed today as HCT/Ps are in fact unapproved drugs, biological

¹ See, e.g., FDA Warns About Stem Cell Therapies (Nov. 2017) (warning of severe and unexpected adverse events, including blindness and tumors), <https://www.fda.gov/forconsumers/consumerupdates/ucm286155.htm>.

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products, or medical devices that will need to come into compliance with premarket approval requirements over the next three years.

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Background

Federal regulation of regenerative therapies, including human cell and tissue products, is a complex and evolving subject. Until quite recently, the principal federal statutes regulating medical products—the Federal Food, Drug, and Cosmetic Act (FDCA) and the Public Health Service Act (PHSA)—did not explicitly address these types of products. In the absence of direct Congressional action, the rules regarding human cell and tissue products developed at the administrative level, through a complicated set of regulations and sub-regulatory guidance documents promulgated by the U.S. Food and Drug Administration (FDA)². Those rules and the governing interpretations have shifted over time, as administrations (and FDA priorities) have changed. Even today, FDA is pursuing a new “comprehensive” initiative to strike a new balance between innovation on the one hand and the need to ensure the safety and efficacy of regenerative therapies on the other.³

I. Statutory framework

The FDCA regulates, among other products, the interstate manufacture and distribution of “drugs” and “medical devices.” See, e.g., 21 U.S.C. § 331(d). Both categories are defined primarily in terms of an intended therapeutic use: articles become drugs or medical devices when they are “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease” or are “intended to affect the structure or any function of the body.” *Id.* § 321(g)(1); see *id.* § 321(h)(2)-(3). Subject to relatively few exceptions, all “new” drugs and all “Class III” medical devices require preapproval from FDA prior to being marketed in the United States. See *id.* § 355(a); *id.* § 360e(a). To obtain FDA’s approval, the manufacturer of the new drug or Class III device must affirmatively prove, through adequate and well-controlled clinical trials, that its product will be both safe and effective. See *id.* § 355(d); *id.* § 360e(d).

Section 351 of the PHSA is the modern successor to the Biologics Control Act of 1902 and regulates the interstate sale of “biological products,” which include “proteins” and “analogous products” that are “applicable to the prevention, treatment, or cure of a disease or condition of human beings.” 42 U.S.C. § 262(i)(1). Biological products require a license from FDA before they may be introduced into interstate commerce. See *id.* § 262(a). To obtain a license from FDA, the manufacturer must affirmatively prove safety and efficacy pursuant to the same scientific standards that apply to new drugs and Class III devices.⁴

² “Subregulatory guidance” refers collectively to the many sources of guidance provided by an agency—including, without limitation, manuals, documents formally designated guidance, enforcement letters, and regulatory decisions—that are not codified in the Code of Federal Regulations and do not carry the force of law.

³ Please note this memorandum is current as of June 20, 2018, and Sidley assumes no obligation to revise or supplement it to reflect any changes in facts, law, or regulation. This memorandum is provided solely for your benefit for informational purposes and should not be construed as legal advice to any person other than The Pew Charitable Trusts. This memorandum may not be quoted, used, or relied on by any other person. Delivery of this memorandum to other persons is not intended to create, and receipt of it by any other person does not constitute, a lawyer-client relationship.

⁴ See FDA Modernization Act of 1997 (FDAMA), § 123(f), Pub. L. No. 105-115, 111 Stat.2296 (1997). Biological products generally also qualify as drugs or devices under the FDCA. Both statutes make clear that duplicate FDA approvals are not required. See, e.g., 42 U.S.C. § 262(j). However, biological products remain subject to many other FDCA requirements that apply to drugs and medical devices. This includes

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section 361 of the PHSa contains separate authority stemming from 19th century statutes establishing the federal quarantine power.⁵ See 42 U.S.C. § 264. It authorizes “the Surgeon General” to “make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases.” *Id.* § 264(a). Regulations promulgated under PHSa section 361 “may provide for ... inspection, fumigation, disinfection, sanitation, pest extermination, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection to human beings, and other measures.” *Id.* For roughly 20 years, PHSa section 361 has been a principal source of FDA regulation of regenerative therapies.

Most recently, the 21st Century Cures Act created a new expedited approval pathway for “regenerative medicine advanced therapies” (RMAT).⁶ As defined in the statute, RMATs include regenerative therapies that are drugs; are not regulated solely under PHSa section 361; are intended to treat, modify, reverse, or cure a serious disease or condition; and have shown potential to address unmet medical needs. See 21 U.S.C. § 356(g).

II. Regulatory history

A. Pre-1993: Case-by-case enforcement

Historically, tissue products were not subject to active federal regulation. Instead, human tissue products were primarily regulated by voluntary quality assurance programs, such as the standards established and maintained by the AATB. A small minority of states also regulated tissue bank operations. See, e.g., N.Y. Pub. Health Law Art. 43-B. FDA began asserting its authority over human tissue products during the late 1980s in the wake of several events, including the 1979 death of a woman who contracted rabies after receiving a corneal transplant, the 1987 death of another woman from Creutzfeldt-Jakob disease following a dura mater transplant, and the mounting AIDS crisis.⁷

Despite the fact that these events involved the transmission of communicable diseases, FDA did not seek to impose controls on human tissue products through PHSa section 361. Instead, FDA took the position that such articles were medical devices subject to regulation under the FDCA. Thus, in 1986, FDA asserted that corneal lenticules were Class III medical devices and requested that a company manufacturing them submit a Premarket Approval

facility registration and product listing, good manufacturing practice (GMP) requirements, and ongoing reporting obligations. See, e.g., 21 C.F.R. § 601.20(a).

⁵ E.g., *Joint Resolution Respecting Quarantine and Health Laws*, No. 42, 14 Stat. 357 (May 28, 1866); *An Act to Prevent the Introduction of Contagious or Infectious Diseases Into the United States*, ch. 66, 20 Stat. 37 (Apr. 29, 1878); *An Act to Prevent the Introduction of Contagious Diseases From One State to Another and for the Punishment of Certain Offenses*, ch. 51, 26 Stat. 31 (March 27, 1890); *An Act Granting Additional Quarantine Powers and Imposing Additional Duties Upon the Marine-Hospital Service*, ch. 114, 27 Stat. 449 (Feb. 15, 1893).

⁶ Pub. L. No. 114-255, 130 Stat. 1033 (Dec. 13, 2016).

⁷ See Stuart Nightingale, associate commissioner for health affairs, FDA, Remarks on FDA Regulatory Philosophy at FDLI Program, “The Regulation of Human Tissue and Organs” (July 10, 1990) in 46 *Food Drug Cosmetics Law Journal* (special issue), 4, 4-6 (1991).

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(PMA) application.⁸ The following year, FDA declared imported human dura allografts to be adulterated devices because they were not “process[ed] and handle[d] . . . according to guidelines such as those of the [AATB].”⁹ In 1991, FDA announced that it would regulate human heart valves intended for transplantation as Class III devices,¹⁰ taking the position that these valves were already subject to an existing regulatory classification for “replacement heart valves”¹¹ even though the regulation in question had previously been applied only to artificial and porcine valves.

This piecemeal approach to regulation prompted judicial challenge and led to rulings from both the U.S. District Court for the District of Maryland and the Seventh Circuit suggesting that FDA had violated the Administrative Procedure Act (APA) by attempting to regulate tissue products without notice and comment.¹²

B. 1993-1997: Establishment of the Part 1270 regulations

In the early 1990s, Congress held several hearings regarding FDA’s approach to human tissue products. The general tone of the hearings was that FDA should increase its oversight but that regulation of tissue products as medical devices was not appropriate.¹³ Beginning in October 1993, FDA sought to develop a more comprehensive regulatory approach to human tissue products. That effort, which lasted more than a decade, began with a statement of policy asserting that FDA had jurisdiction over human cells intended for use as somatic cell therapy, defined as “the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries in humans by the administration of autologous, allogenic, or xenogenic cells that have been manipulated or altered ex vivo.”¹⁴ In the policy statement, FDA said that it would regulate such therapies pursuant to its authority over biological products and drugs.

In 1993, FDA published an interim final regulation imposing new requirements for donor testing, recordkeeping, inspections, and recalls for human tissue products, which are now codified in Title 21, Part 1270.¹⁵ The promulgation of the Part 1270 regulations represented a significant shift in FDA’s approach to the regulation of human tissue products because the rules

⁸ See *Allergan’s Kerato-Lens, Kerato-Patch Cornea Implants for Treatment of Adult, Pediatric Aphakia Win Panel Approval Recommendation with Conditions*, The Gray Sheet, Jan. 25, 1988.

⁹ FDA Import Alert 84-03 (quoting FDA Safety Alert, *Possibly Contaminated Dura Mater* (April 28, 1987)), <http://1.usa.gov/1G9Gz9h>.

¹⁰ See 56 Fed. Reg. 29177 (June 16, 1991).

¹¹ 21 C.F.R. §870.3925.

¹² See *Northwest Tissue Ctr. v. Shalala*, 1 F.3d 522, 527, 536 (7th Cir. 1993); Preliminary Injunction Order, Docket No. 13, in *Biodynamics Int’l Inc. v. Shalala*, No. 95-919 (D. Md.) (filed April 19, 1995). The agency subsequently settled both cases. See 62 Fed. Reg. 40429, 40430 (July 29, 1997).

¹³ See, e.g., *Regulation of Human Tissue Transplantation: Hearing Before the S. Comm. on Labor and Human Resources*, 102d Cong. (1992); *Regulation of Human Tissue Banks: Hearing Before the Subcomm. on Regulation, Business Opportunities, and Technology of the H. Comm. on Small Business*, 103d Cong. (1993); Human Tissue for Transplantation Act of 1993, S. 1702, 103d Cong. (1993); Human Tissue for Transplantation Act of 1993, H.R. 3547, 103d Cong. (1993).

¹⁴ 58 Fed. Reg. 53248, 53250 (Oct. 14, 1993).

¹⁵ See 58 Fed. Reg. 65514 (Dec. 14, 1993).

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were promulgated pursuant to section 361 of the PHSA.¹⁶ Thus, they were intended “to prevent the transmission of communicable disease,” and were made effective immediately in light of the “immediate need to protect the public health from the transmission of HIV and hepatitis infection through transplantation of tissue.”¹⁷

C. 1997-2005: Establishment of the Part 1271 regulations

While the Part 1270 regulations were being developed, the agency attempted to regulate certain categories of human tissue products as drugs and biological products through a series of subregulatory announcements.¹⁸ FDA’s reliance on sub-regulatory guidelines in that era was controversial,¹⁹ and Congress responded in 1996 by introducing legislation to exempt human tissue from FDA regulation.²⁰

Taking the hint, the Clinton Administration announced in 1997 that it would develop a “new regulatory framework for cells and tissues that would protect the public health without imposing unnecessary government oversight.”²¹ The new framework was intended to “provide adequate protection of public health ... while enabling investigators to develop new therapies and products with as little regulatory burden as possible.”²²

A proposed rulemaking regarding facility registration and product listing was published in 1998.²³ FDA’s preamble made clear that qualifying products would be regulated “solely” under section 361 of the PHSA and would not be subject to premarket clearance or approval, while

¹⁶ 42 U.S.C. § 264; see 58 Fed. Reg. at 65516.

¹⁷ See 58 Fed. Reg. at 65516. The Part 1270 regulations were eventually finalized after substantial public input, including three public meetings, in July of 1997. See 62 Fed. Reg. at 40430.

¹⁸ See, e.g., FDA, Guidance on Applications for Products Comprised of Living Autologous Cells Manipulated Ex Vivo and Intended for Structural Repair or Reconstruction (May 1996); FDA, Draft Document Concerning the Regulation of Placental/Umbilical Cord Blood Stem Cell Products Intended for Transplantation or Further Manufacture into Injectable Products (Dec. 1995); FDA, Draft Document Concerning the Regulation of Peripheral Blood Hematopoietic Stem Cell Products Intended for Transplantation or Further Manufacture into Injectable Products (Feb. 1996).

¹⁹ FDAMA contained provisions requiring FDA to codify into regulations a recently-released Good Guidance Practices policy document. As explained in the legislative history of FDAMA, “FDA’s increasing reliance on policy statement has produced several problems. ... FDA has maintained no compilations of these documents. The regulated industries and the public were often not aware that they existed ... there was no systematic process for their adoption or amendment. There may or may not have been an opportunity for interested individuals ... to have any input into their formulation ... [and] there was inconsistency among FDA personnel in the use of these documents. Some FDA employees insisted that industry strictly follow them, and others did not.” H.R. Rep. No. 105-43 (1997).

²⁰ See, e.g., Human Tissues Safety Act of 1996, S. 2195, 104th Cong. (1996).

²¹ President Bill Clinton, Vice President Al Gore, *Reinventing the Regulation of Human Tissue*, National Performance Review, Executive Summary (Feb. 1997), <http://1.usa.gov/1IMAxSk>; accord FDA, *Proposed Approach to Regulation of Cellular and Tissue-Based Products* (Feb. 28, 1997), <http://1.usa.gov/1frdukF> (Proposed Approach).

²² 62 Fed. Reg. 9721, 9721 (March 4, 1997).

²³ 63 Fed. Reg. at 26744.

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others would be subject to full preapproval requirements.²⁴ The registration and listing rules were finalized as Part 1271 in January 2001.²⁵ Additional rules regarding donor eligibility²⁶ and good tissue practices²⁷ were soon added. Together, these rules form a “comprehensive” system intended to encourage “significant innovation,” but provided key public health safeguards as well.²⁸

Over time, the Part 1271 regulations have been perceived by stakeholders as creating three “tiers” or “buckets” of tissue products, two of which are subject to virtually no FDA oversight. First, when an establishment recovers reproductive cells or tissues for immediate transfer into an intimate partner of the donor, the establishment need not comply with either the Part 1271 regulations or the preapproval requirements of the FDCA or PHSA.²⁹ Similarly, establishments that remove HCT/Ps from an individual and implant them “into the same individual during the same surgical procedure” also are exempt from both the Part 1271 regulations and the statutory preapproval requirements.³⁰ FDA justified a hands-off approach for these HCT/Ps based on its determination that the communicable disease risks, as well as the safety and effectiveness risks, in these two scenarios did not warrant additional regulation.³¹

Second, some HCT/Ps are regulated pursuant to PHSA section 361 and the Part 1271 regulations but are exempt from the preapproval requirements that apply to drugs, biological products, and Class III medical devices. These products are often labeled “361 HCT/Ps” to distinguish them from products that fall into the lower or higher tiers of regulation. The linchpin of this “middle tier” is 21 C.F.R. § 1271.10(a), which sets out four requirements that must be met. To qualify for regulation as a 361 HCT/P, the product:

- (1) must be “minimally manipulated”;
- (2) must be “intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer’s objective intent”;
- (3) must be manufactured through processes that do not “involve the combination of the cells or tissues with another article,” except for certain articles (e.g., water) that do not “raise new clinical safety concerns”; and

²⁴ *Id.* at 26747.

²⁵ 66 Fed. Reg. 5447 (Jan. 19, 2001).

²⁶ 69 Fed. Reg. 29786 (May 25, 2004); see 64 Fed. Reg. 52696 (Sept. 30, 1999) (proposed rule).

²⁷ 69 Fed. Reg. 68612 (Nov. 24, 2004); see 66 Fed. Reg. 1508 (Jan. 8, 2001) (proposed rule).

²⁸ 69 Fed. Reg. at 68612.

²⁹ 21 C.F.R. § 1271.15(e).

³⁰ 21 C.F.R. § 1271.15(b).

³¹ See Proposed Approach at 12.

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- (4) either (i) “does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function”; or (ii) is for autologous use, allogenic use in a first- or second-degree relative, or reproductive use.³²

A significant body of law has developed regarding the interpretation and application of the above requirements. Some of the terms used (e.g., “minimal manipulation” and “homologous use”) are further defined in the regulations. FDA has added additional interpretive gloss through the preambles to the regulation, guidance documents, *ad hoc* product designations, individual enforcement actions, and other interactions with regulated industry.

Finally, those tissue products that are not exempt from Part 1271 and do not meet the requirements set out in 21 C.F.R. § 1271.10(a) are subject to regulation under *both* section 361 of the PHSA *and* the full panoply of regulatory requirements that apply to new drugs, biological products and/or Class III medical devices. This “highest risk” tier includes a number of much-publicized regenerative therapies, including many stem cell therapies and adoptive cell transfer technologies, such as CAR-T cell therapy. To date, a number of HCT/Ps have obtained FDA approval as drugs, biological products, or medical devices.³³

D. 2013-2015: Increased enforcement activity

When FDA announced its intention to create the Part 1271 framework in 1997, it also established an internal working group, known as the Tissue Reference Group (TRG), to provide guidance on which products qualified for regulation solely under Part 1271 and section 361 of the PHSA.³⁴ The TRG is composed of representatives from both CBER and CDRH and makes recommendations with respect to specific HCT/Ps in response to requests from industry.³⁵ In addition, the Office of Combination Products (OCP) accepts Requests for Designation (RFDs) to determine whether products qualify as HCT/Ps.³⁶

For several years after the Part 1271 rules were proposed and finalized, RFD decisions from the OCP and TRG recommendations provided the primary source of guidance as to how FDA would interpret and apply the HCT/P regulations, including the criteria set out in 21 C.F.R. § 1271.10. Beginning in 2013, however, FDA began to issue an increasing number of enforcement letters to HCT/P manufacturers. These letters alleged that the manufacturers’

³² 21 C.F.R. § 1271.10(a). The fourth criteria, that the HCT/P not have a systemic effect or rely on living cells for its purpose, has exceptions for HCT/Ps intended for autologous use, allogenic use in a close relative, or reproductive use. *Id.* §1271.10(a)(4)(ii).

³³ See A.S. Mao & D.J. Mooney, Regenerative Medicine: Current Therapies and Future Directions, Proceedings of the National Academy of Sciences, 112(47):14452-14459 (2015) (available at: <http://www.pnas.org/content/112/47/14452.full>).

³⁴ Proposed Approach at 16.

³⁵ See FDA, Tissue Reference Group (<http://bit.ly/2xaP4bb>). Between 1998 and 2017, these recommendations were published in an annual report on FDA’s website; in November 2017 the agency announced that while the TRG would continue to provide recommendations, it would no longer post them. FDA explained that it had received feedback from stakeholders who observed that, because the public reports were stated in general terms to protect proprietary information, they were not helpful. See 82 Fed. Reg. 54290, 54292 (Nov. 17, 2017); see also FN54 *supra*.

³⁶ See 21 C.F.R. § 3.7.

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products were more than minimally manipulated, intended for non-homologous use, or both. According to FDA, the products targeted by these letters were not solely regulated under section 361 of the PHSa (i.e., did not qualify to the exemptions necessary for regulation solely under 21 CFR Part 1271) and instead were either devices or biological products that required premarket approval from the agency.³⁷

During this period, FDA also sought to narrow (or, depending on one's point of view, clarify) the scope of the "middle tier" and limit the types of products that could be marketed as "361 HCT/Ps." Between October 2014 and October 2015, FDA issued a series of draft guidance documents addressing (1) the "same surgical procedure" exemption,³⁸ (2) specific considerations for HCT/Ps derived from adipose (i.e., fat) tissue,³⁹ (3) minimal manipulation,⁴⁰ and (4) homologous use.⁴¹ Taken together, the draft guidances suggested that FDA had concluded many products marketed as section 361 HCT/Ps in fact posed risks akin to drugs, devices, and biologics and should have been subject to premarket review. The drafts thus signaled to industry that FDA intended to require premarket review for many additional products, including many processed and manufactured from amniotic membrane, adipose, and other types of tissues, that some in industry had been marketing for several years as section 361 HCT/Ps. Predictably, the drafts provoked a strongly negative reaction from many industry stakeholders. Commenters objected to FDA's proposal to use a "main function" test to determine whether source tissue should be classified as structural or non-structural.⁴² Commenters similarly objected to FDA's proposal to use that binary classification to limit the types of processing considered to be minimal manipulation or the types of uses considered to be homologous.⁴³

³⁷ See, e.g., FDA, Warning Letter to US Stem Cell Clinic (Aug. 24, 2017); FDA, Untitled Letter to Darwin Life, Inc. (Aug. 4, 2017); FDA, Untitled Letter to Pinnacle Transplant Techs., LLC (Oct. 27, 2016); FDA, Untitled Letter to BioDlogics, LLC (June 22, 2015); FDA, Untitled Letter to Osiris Therapeutics, Inc. (Sept. 26, 2013); FDA, Untitled Letter to Surgical Biologics (Aug. 28, 2013).

³⁸ FDA, Draft Guidance for Industry: Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception (Oct. 2014) (Draft Same Surgical Procedure Guidance).

³⁹ FDA, Draft Guidance for Industry: Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations (Dec. 2014) (Draft Adipose Tissue Guidance).

⁴⁰ FDA, Draft Guidance for Industry and FDA Staff: Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (Dec. 2014) (Draft Minimal Manipulation Guidance).

⁴¹ FDA, Draft Guidance for Industry and FDA Staff: Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products (Oct. 2015) (Draft Homologous Use Guidance).

⁴² See, e.g., American Association of Tissue Banks, Comments to Docket No. FDA-2014-D-1696 at 8-11 (Feb. 23, 2015) (AATB Comments); American Society of Plastic Surgeons, Comments to Docket No. FDA-2014-D-1696 at 2 (Feb. 23, 2015) (ASPS Comments).

⁴³ See, e.g., AATB Comments at 16-20; ASPS Comments at 2. Very few comments appear to have been submitted in support of the draft guidances. One notable comment in support was submitted by a manufacturer of an approved medical device that faced competition from products marketed as section 361 HCT/Ps. See Organogenesis, Inc., Comments to Docket No. FDA-2014-D-1696 (Feb. 22, 2015). Comments like this underscore the ways in which a scheme like Part 1271 can impact competition and the incentives to develop new products. Companies that go through an expensive preapproval process for biologics, drugs, or devices are understandably aggrieved if forced to compete in the marketplace

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E. Current initiatives

In October 2015, FDA announced a public hearing to discuss all four draft guidances and, more generally, the scope of the HCT/P regulatory framework.⁴⁴ The hearing was held Sept. 12-13, 2016. The vast majority of the more than 90 presenters⁴⁵ were critical of FDA's approach in the draft guidance documents and in its recent enforcement posture. In general, the presenters argued that FDA's guidances were inconsistent with the Part 1271 regulations, were inconsistent with the policies embodied by those regulations, and were based on overly simplified or incorrect scientific assumptions. For example, several presenters took issue with FDA's determination that adipose tissue is structural or that its "main function" is cushioning and support.⁴⁶ Presenters also expressed skepticism concerning FDA's determination that amniotic membrane is a structural tissue and, as such, can serve only as a protective barrier.⁴⁷

FDA activity regarding HCT/Ps has continued under the Trump Administration. On Aug. 28, 2017, FDA Commissioner Scott Gottlieb released a public position paper describing a new "comprehensive policy" to "establish clearer lines around when these regenerative medicine products have sufficient complexity to fall under the agency's current authority, and then define an efficient process for how these products should be evaluated for safety and effectiveness." The goal, it appeared, was to help bring clarity to the increasingly difficult questions surrounding which tissue products would be considered 361 HCT/Ps and which would require premarket review. In addition, the commissioner seemed to contemplate steps to reduce the significant burdens of seeking premarket approval. On its face, the language seemed moderate and conciliatory, intended no doubt to signal FDA's interest in balancing innovation and regulation.

against similar or identical products that did not navigate such barriers. This concern is amplified when a company that has secured FDA approval believes its competitor has avoided those hurdles through a misapplication of the rules in Part 1271. Further, companies may be less inclined over time to invest in new therapies that are subject to a costly preapproval process if they believe they may have to compete directly against similar products manufactured by other companies that do not have to shoulder the same burden.

⁴⁴ See 80 Fed. Reg. 66845 (Oct. 30, 2015).

⁴⁵ The hearing date was delayed by several months in order to accommodate the high number of requests to speak; FDA had originally planned only for a one-day hearing in a smaller facility. See 81 Fed. Reg. 23661 (Apr. 22, 2016). In addition to the significant interest in the hearing, nearly 7,000 comments were posted to the public docket.

⁴⁶ See, e.g., Hearing transcript, Day 1, 77-78, Steven Brody ("Now, adipose tissue contains cell types with nonstructural functions. We mustn't think of fat tissue as just adipocytes. It's monocytes, parasites, granulocytes, and most important, the stem and progeny cells which have the capability of repair and regeneration. ... The most important thing is that fat isn't even meant to be structural in the human body. It's a repository of energy in times of caloric scarcity.")

⁴⁷ See, e.g., Hearing Transcript, Day 2, 93. Rebecca Baergen, M.D. ("It is my opinion that the premises underlying the proposed regulatory scheme are scientifically flawed. The amniotic membrane has multiple functions in vivo, both structural and nonstructural, and one is not more important than the other. In addition to the functions listed in the draft guidance documents the amniotic membrane also produces bioactive factors and molecules, including growth factors, cytokines, leukotrienes, interleukins, and a number of enzymes, chemokines, and related regulatory proteins, including anti-inflammatory proteins. It secretes extracellular matrix, it serves as a substrate for supporting growth of epithelial cells and modulates inflammation, and serves as an anti-scarring agent.")

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On Nov. 16, 2017, FDA announced “a comprehensive new policy approach to facilitating the development of innovative regenerative health products.”⁴⁸ Once again, the “new” approach was set forth in guidance documents. The agency released a final combined guidance regarding minimal manipulation and homologous use.⁴⁹ The agency also issued a final guidance regarding the same surgical procedure exception and withdrew the prior draft guidance regarding adipose tissue.⁵⁰ In general, the two final guidances are substantively similar to the drafts proposed in 2014 and 2015.

FDA also issued two new draft guidances focusing on the RMAT designation process created by the 21st Century Cures Act. The first, which is titled “Expedited Programs for Regenerative Medicine Therapies for Serious Conditions,” describes the expedited programs available to sponsors of regenerative medicine therapies and the RMAT designation process.⁵¹ The second addresses how FDA intends to apply its regulatory requirements to devices used in the recovery, isolation, and delivery of RMATs.⁵² In addition, FDA announced that it is seeking to develop innovative trial designs that would allow individual investigators to follow the same manufacturing protocols and share combined clinical trial data in support of FDA approval.⁵³ These efforts to reduce the burdens associated with premarket approval are arguably the “newest” and most innovative aspect of FDA’s announcement and underscore the agency’s interest in creating an approval process that will allow safe and effective regenerative medicines to reach the market. As Commissioner Gottlieb explained, FDA needs “to provide a clear, efficient pathway for product developers, while making sure that we meet our obligation to help ensure the safety and efficacy of these medical products so that patients can benefit from these novel therapies.”⁵⁴

However, the most significant aspect of the November 2017 announcement is not substantive but procedural. As part of its initiative, FDA agreed to extend enforcement discretion to some regenerative therapies that are already on the market. Specifically, FDA stated that “in light of [the] new guidance,” it will not enforce the premarket review requirements of the FDCA and PHSa against HCT/Ps that do not pose a potential significant safety concern in order to

⁴⁸ FDA News Release, FDA Announces Comprehensive Regenerative Medicine Policy Framework (Nov. 16, 2017).

⁴⁹ FDA, Guidance for Industry and FDA Staff: Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use (November 2017) (Regulatory Considerations Guidance).

⁵⁰ FDA, Guidance for Industry: Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception (November 2017) (Same Surgical Procedure Guidance); *Id.* at 1 (“These materials, together with the material related to adipose tissue included in the [Regulatory Considerations Guidance] supersedes the Adipose Draft Guidance. Accordingly, we do not intend to finalize the Adipose Draft Guidance which is withdrawn.”)

⁵¹ FDA, Draft Guidance for Industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions (November 2017).

⁵² FDA, Draft Guidance for Industry: Evaluation of Devices Used with Regenerative Medicine Advanced Therapies (November 2017).

⁵³ See Statement from FDA Commissioner Scott Gottlieb, M.D., on FDA’s Comprehensive Regenerative Medicine Policy Framework (Nov. 16, 2017).

⁵⁴ *Id.*

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allow their manufacturers to determine whether they are subject to preapproval requirements and, if so, to begin the process of seeking FDA approval.⁵⁵ This “transition” period recognizes that many products that have long been marketed as 361 HCT/Ps now fall outside the scope of 21 C.F.R. § 1271.10(a).⁵⁶

Analysis

Understanding how FDA will regulate a regenerative therapy is largely an exercise of product classification. As discussed above, FDA has used regulations and guidance to sort human cell and tissue products into three “tiers” based on FDA’s evaluation of the likely safety, efficacy, and communicable disease risks posed by the product. Under the scheme, there are two tiers that FDA has judged to be of sufficiently low risk that significant federal regulation is not warranted. The first is exempted from Part 1271 altogether. The second, or “middle tier,” is regulated solely under FDA’s communicable disease authority set out in PHSA section 361 and the regulations in 21 C.F.R., Parts 1270 and 1271. Any products that do not fit within the first two tiers fall into the “highest tier” and are subject to full regulation as medical products under the FDCA and PHSA, including applicable premarket review requirements.

Below, we describe each of FDA’s risk-based “tiers” in more detail, particularly the requirements that must be met to qualify for regulation in the first and second tiers. Before turning to those tiers, however, we first address the common but likely misplaced question of whether FDA’s regulation of regenerative therapies constitutes impermissible federal regulation of the practice of medicine.

I. Practice of medicine

That the FDCA does not regulate the “practice of medicine” is an ingrained principle derived from the legislative history of the original statute and certain provisions that have been included in amendments since 1938.⁵⁷ In application, however, the “practice of medicine” exception is extremely narrow and unlikely to apply to regenerative therapies.

FDA received several comments during the Part 1271 rulemaking expressing concern that the regulations would interfere with the practice of medicine.⁵⁸ The agency has generally responded to such concerns by distinguishing the *practice* of medicine from the *products* used in such in practice—according to FDA, the FDCA regulates only the latter. Thus, the agency

⁵⁵ See Regulatory Considerations Guidance at 21-22.

⁵⁶ FDA also announced that it will no longer post TRG decisions on its website. FDA, [Regulatory Considerations Guidance]; Availability, 82 Fed. Reg. 54290, 54292 (Nov. 17, 2017). That announcement has generated little attention or fanfare, but it seems at odds with FDA’s commitment in recent years to enhanced transparency in its decision-making.

⁵⁷ See <https://dash.harvard.edu/bitstream/handle/1/8846812/cberry.html?sequence=2>; see also, e.g., 21 U.S.C. §396 (“Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.”). Support for the notion that the FDCA was not intended to regulate the practice of medicine also can be derived from the fact that the statute generally only prohibits acts in interstate commerce. See 21 U.S.C. § 331(a)-(d), (o).

⁵⁸ See 66 Fed. Reg. at 5452, 5454, 5458; 69 Fed. Reg. at 29800.

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stated that it is “not attempting to govern practitioners’ use of HCT/Ps, but rather to ensure that HCT/Ps ... used by practitioners in their treatment of patients [comply] with applicable regulations, including regulations designed to prevent the transmission or spread of communicable disease.”⁵⁹ On this view, FDA’s regulation of HCT/Ps will not intrude upon the practice of medicine as long as the therapy or treatment in question results in the creation of an identifiable product derived from human cells or tissues.⁶⁰

The most significant claim that the HCT/P regulations impermissibly interfere with the practice of medicine was brought by Regenerative Sciences, LLC after it received an Untitled Letter from FDA alleging that its stem cell therapies were more than minimally manipulated and thus constituted unapproved drugs.⁶¹ The company sued FDA, and in court filings argued that FDA lacked the authority to regulate a medical procedure that occurred wholly within the state of Colorado.⁶² The procedure—called Regenexx—consisted of drawing bone marrow from a patient, isolating and culturing stem cells from the marrow at the company’s lab, combining them with doxycycline (an antibiotic), and injecting the cells back into the original patient to treat orthopedic and muscular injuries.

In 2012, a U.S. District Court granted FDA’s motion for summary judgment, a decision that was upheld by the U.S. Court of Appeals for the D.C. Circuit in 2014.⁶³ Both courts followed the same general framework in agreeing with FDA that the agency’s HCT/P regulations did not infringe on Regenerative Sciences’ physicians’ ability to practice medicine. Specifically, the courts explained, (1) the stem cells in question fit within the FDCA definition of a “drug”; (2) the stem cells were more than minimally manipulated because, among other things, they were cultured, and (3) FDA’s jurisdiction extended to the stem cell mixture because the antibiotic that was mixed with the stem cells prior to injection had previously traveled in interstate commerce.⁶⁴ FDA’s ability to regulate a drug, according to the D.C. Circuit, has little to do with practice of medicine concerns. As the court explained, an argument premised on FDA’s ability to regulate the practice of medicine “misapprehends what this case is about. Notwithstanding appellants’ attempt to characterize this case as an effort by FDA to ‘restrict the use of an autologous stem cell procedure,’ the focus of the FDA’s regulation is the mixture. That is, the FDA does not claim that the procedures used to administer the Mixture are unsafe; it claims that the Mixture itself is

⁵⁹ 66 Fed. Reg. at 5452.

⁶⁰ One question that does implicate the practice of medicine is *how* a product is used once it is lawfully on the market. FDA historically has not objected to uses of lawful medical products that differ from their approved conditions of use. Thus, practitioners are free to use drugs or medical devices “off-label,” even if manufacturers face restrictions on their ability to advertise or promote the unapproved use. See 37 Fed. Reg. 16503, 16504 (Aug. 15, 1972). The same reasoning applies to HCT/Ps. FDA has stated that it will not look to health care providers’ “actual use” of HCT/Ps to determine the intended use of the product. See 66 Fed. Reg. at 5458-59.

⁶¹ FDA, Untitled Letter to Regenerative Sciences, Inc. (July 25, 2008).

⁶² Related to the notion that FDA may not regulate the practice of medicine.

⁶³ *United States v. Regenerative Sciences, LLC*, 741 F.3d 1314 (D.C. Cir. 2014); *United States v. Regenerative Sciences, LLC*, 878 F. Supp. 2d 248 (D.D.C. 2012).

⁶⁴ *United States v. Regenerative Sciences, LLC*, 741 F.3d at 1319.

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unsafe. Appellants' arguments about the practice-of-medicine exemption are therefore wide of the mark."⁶⁵

Other federal courts may soon have an opportunity to weigh in on this issue. In May 2018, FDA filed two lawsuits seeking injunctions against stem cell clinics in California and Florida in order to prevent the clinics from marketing and performing procedures involving autologous stem cells without FDA approval.⁶⁶ The defendant in one case has announced that it intends to "vigorously defend [the] lawsuit" and the "medical freedom of Americans."⁶⁷ The defendant in the other case has stated that it would "fight the injunction to the Supreme Court if necessary."⁶⁸

II. Lowest-tier products

In broad strokes, the Part 1271 regulations impose facility registration, product listing, donor eligibility, and tissue practice requirements on entities engaged in interstate commerce involving HCT/Ps. When it established the Part 1271 regulations, FDA created exceptions for certain types of entities. For instance, institutions that use HCT/Ps "solely for nonclinical scientific or educational purpose[s]" are exempt from regulation.⁶⁹ Entities involved only in the transport or storage of HCT/Ps are likewise exempt.⁷⁰

The two most noteworthy exemptions are for entities that "recover reproductive cells or tissue and immediately transfer them into a sexually intimate partner of the cell or tissue donor" and those that "remove HCT/Ps from an individual and implant such HCT/Ps into the same individual during the same surgical procedure."⁷¹ The "same surgical procedure" exception is particularly relevant for stem cell procedures and many other regenerative therapies currently available in the marketplace. It was the subject of draft guidance in 2014 and is covered by a final guidance issued in November 2017.

⁶⁵ *Id.* The *Regenerative Sciences* opinions also served to further validate an additional position long-taken by FDA: that if even one component of a medical product has been introduced into interstate commerce, the agency may properly regulate the entire product. The agency's "component jurisdiction" over such products has particular implications for HCT/Ps, where—as with *Regenerative Sciences*—the products in question may be harvested, processed, and used entirely within a single institution.

⁶⁶ See *United States v. California Stem Cell Treatment Center, Inc. et al.*, No. 5:18-cv-01005 (C.D. Ca. Filed May 9, 2018); *United States v. US Stem Cell Clinic, LLC et al.*, No. 0:18-cv-61047 (S.D. Fl. Filed May 9, 2018).

⁶⁷ U.S. Stem Cell, Inc., Press Release, U.S. Department of Justice Files Lawsuit at Request of FDA to stop U.S. Stem Cell Clinic from Performing Autologous Stem Cell Procedure (May 9, 2018).

⁶⁸ William Wan, Laurie McGinley, *FDA seeks injunction to stop two stem cell companies after patients blinded*, *The Washington Post*, May 9, 2018.

⁶⁹ 21 C.F.R. § 1271.15(a).

⁷⁰ 21 C.F.R. § 1271.15(c), (d). Entities under contract with a registered establishment do not have to independently register but must otherwise comply with the Part 1271 regulations. *Id.* § 1271.15(f).

⁷¹ 21 C.F.R. § 1271.15(b), (e).

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The final guidance explicitly states that the same surgical procedure exemption was intended to be “a narrow exception to regulation under Part 1271.”⁷² The guidance explains that the exception turns on three requirements. First, the exception applies only to what is known as “autologous use,” which means that the same individual must be both the donor and recipient of the HCT/P. Second, the treatment or therapy must be considered a single surgical procedure. Third, the HCT/P must remain in its “original form,” *i.e.*, it must remain “such HCT/P,” as that phrase is used in the regulation.⁷³ The first of those three requirements (autologous use) is relatively straightforward, but the other two requirements (single procedure and “such HCT/P”) both present the potential for controversy.

FDA’s guidance regarding the single procedure requirement is particularly nuanced. FDA states that it generally will *not* consider procedures consisting of more than a single operation to be the same surgical procedure. At the same time, FDA states that removal and implantation may occur “a number of days apart.” FDA observes, for example, that craniotomies or craniectomies with subsequent implantation of the bone flap to reverse the cranial defect and parathyroidectomies with subsequent implantation of a portion of the tissue to preserve the parathyroid function may occur as multiple operations yet still qualify for the exception.⁷⁴ It is unclear whether these examples are intended to be illustrative or exhaustive.

In addition, the guidance states that FDA generally requires removal and implantation of the HCT/P to occur in the same establishment because transportation “raises safety concerns, such as contamination and cross-contamination, beyond those typically associated with surgery.” At the same time, FDA has stated that it will not object to shipping the removed bone flap or parathyroid tissue to a different medical facility to “accommodate the medical needs of an individual patient” if precautions are “taken to protect the HCT/P from contamination and cross-contamination.”⁷⁵ Once again, it is unclear whether these examples are intended to be exhaustive.

FDA’s guidance regarding “such HCT/P” also raises important questions. The guidance explains that only very limited handling is permissible and states that allowable processing includes only rinsing, cleansing, sizing, shaping, labeling, and storage. Further processing typically will preclude the exception from applying, even if the processing would be considered “minimal manipulation” for 361 HCT/Ps (discussed below).⁷⁶ For instance, centrifugation or filtration are permissible if done “solely to remove debris” but are impermissible if intended to accomplish “cell isolation, cell expansion, cell activation, or enzymatic digestion.”⁷⁷ Examples of

⁷² Same Surgical Procedure Guidance at 3; see also *Regenerative Sciences, LLC*, 741 F.3d at 1319-20 (explaining that regulatory exceptions are, as a rule, narrowly construed).

⁷³ Same Surgical Procedure Guidance at 4.

⁷⁴ *Id.* at 5-6.

⁷⁵ *Id.* at 6.

⁷⁶ *Id.* at 5-6. FDA’s rationale for imposing this limitation was partially explained in a 2001 preamble, in which the agency distinguished between activity that constitutes “manufacturing,” and thus requires FDA registration and compliance with Part 1271, and activity that is not manufacturing and thus does not present risks that are different from those typically associated with surgery. 66 Fed. Reg. 5447, 5460 (Jan. 19, 2001).

⁷⁷ *Id.* at 7.

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permissible sizing and shaping include dilatation of a vascular graft in a coronary bypass procedure, cutting parathyroid tissue into appropriately sized pieces, and meshing skin grafts to facilitate coverage of cutaneous burn wounds.⁷⁸

The guidance also includes a specific discussion of adipose tissue. It explains that the exemption generally covers the recovery of adipose tissue by tumescent liposuction, cleansing by centrifuge, and re-implantation in dermatologic or plastic surgery procedures.⁷⁹ In contrast, processing to isolate cellular components from adipose tissue (e.g., stromal vascular fraction), including the creation of adipose-derived stromal/stem cells, is not within the scope of the exception; according to the guidance, the resulting cells have been processed to such an extent that they no longer constituted “such HCT/P” that was originally taken from the patient.⁸⁰

III. The middle tier: Section 361 HCT/Ps

Historically, most of the uncertainty regarding HCT/Ps has centered on the lines between “361 HCT/Ps,” which are regulated solely under Part 1271 and PHSA section 361 and those HCT/Ps that are subject to regulation as medical products (drug, biological products, or medical devices). Those lines are drawn in 21 C.F.R. § 1271.10 and involve key variables such as “minimal manipulation,” “homologous use,” and “systemic effect.” The proper understanding of such terms is not intuitive and has been controversial since FDA first promulgated the tissue regulations in 2004.

As discussed above, FDA has devoted a significant amount of effort to narrowing (or clarifying) the scope of “minimal manipulation” and “homologous use,” which will likely necessitate premarket review of existing categories of 361 HCT/Ps. Most recently, FDA finalized a single guidance that covers both terms. As discussed below, the final guidance differs from the earlier drafts in several meaningful respects, likely due in part to comments and testimony from stakeholders. As FDA noted in the press release announcing the final guidance, there remain many unanswered questions “and it will take time for product developers to determine whether their products will require FDA approval.” This admission, combined with FDA’s decision to extend enforcement discretion, signals that FDA is aware of the confusion that has surrounded these criteria in the past and the need to level set expectations moving forward.

A. Minimal manipulation

Under 21 CFR 1271.10(a)(1), an HCT/P must be “minimally manipulated” to qualify for regulation solely under Part 1271 and PHSA section 361. The term “minimally manipulated” is defined differently for “structural” and “nonstructural” tissue, respectively.⁸¹ Neither the regulations nor their preambles define the terms structural or nonstructural or explain how to draw the distinction.⁸² FDA’s 2014 draft guidance attempted to fill that gap by stating that each

⁷⁸ *Id.* at 8.

⁷⁹ *Id.* at 7 & n.15.

⁸⁰ *Id.* at 7-8.

⁸¹ 21 C.F.R. § 1271.3(f)(1)-(2).

⁸² Some insight can be gleaned from FDA’s original 1997 announcement of the Proposed Approach, in which FDA stated that for HCT/Ps requiring premarket review, “structural tissues ... would generally be reviewed in accordance with requirements ... that apply to devices, while tissues used for metabolic or

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tissue has a “main function ... in the donor” that “determines which definition of minimal manipulation applies.”⁸³ This proposed definition drew criticism from industry stakeholders who noted that some tissues in the body serve multiple functions; that the potential uses of the tissue should not be arbitrarily constrained by a “main function” test; that the more important issue is the intended use of the finished HCT/P in the recipient; and that the draft guidance represented a significant change in FDA’s historical position.⁸⁴

In its final guidance, FDA acknowledged that tissues often have multiple functions and dropped the “main function” test. Nevertheless, FDA insists that the structural versus nonstructural distinction remains a binary question to be assessed based on the characteristics of the tissue in the donor without reference to the intended use in the recipient. Thus, structural tissues include bone, skin, amniotic membrane, umbilical cord, adipose tissue, articular cartilage, non-articular cartilage, tendons, and ligaments because they “physically support or serve as a barrier or conduit, or connect, cover or cushion in the donor.”⁸⁵ Nonstructural tissues include reproductive cells, hematopoietic stem/progenitor cells, lymph nodes, thymus, peripheral nerves, parathyroid glands, bone marrow, and pancreatic tissue because they “serve metabolic or other biochemical roles in the body such as hematopoietic, immune, and endocrine functions.”⁸⁶ The guidance largely assigned tissues into categories without discussion or analysis. For example, the guidance did not address why amnion should always be regarded as a structural tissue. The guidance did discuss the specific case of adipose tissue and took the position that it is “predominantly composed” of tissue that provides support and cushioning.⁸⁷

The category into which FDA assigns a tissue is significant because it determines how FDA must assess minimal manipulation. For structural tissue, minimal manipulation includes “processing that does not alter the *original relevant* characteristics of the tissue relating to the tissue’s utility for reconstruction, repair, or replacement.”⁸⁸ For cells or nonstructural tissues, minimal manipulation includes “processing that does not alter the *relevant* biological characteristics of cells or tissues.”⁸⁹ Thus, the minimal manipulation test for structural tissues includes additional limiting language regarding the “original” characteristics of the tissue and

reproductive functions would be subject to the kind of requirements that apply to licensed biologics.” FDA, *Reinventing the Regulation of Human Tissue* at 7 (Feb. 1997).

⁸³ Draft Minimal Manipulation Guidance at 4.

⁸⁴ See, e.g., AATB Comments). Prior FDA announcements had indicated that a tissue could have multiple and varied functions in the donor. For example, in 2001, the OCP wrote that amniotic membrane has several functions in utero. According to that decision; while the tissue does act as a physical barrier, it also acts an anti-scarring agent, an anti-inflammatory agent, and an antiangiogenic agent. Letter from FDA to Bio-Tissue, Inc. (Nov. 26, 2001). In enforcement actions, FDA had indicated that the structural or nonstructural status of a tissue product did not turn on the function of the tissue in the donor at all but rather on the intended use of the product *in the recipient*. For example, in 2005, the agency sent a warning letter construing amniotic tissue membrane to be nonstructural when “used for wound repair and wound healing.” Letter from FDA to OKTOS Surgical Corp. (June 23, 2005), <http://1.usa.gov/1CAAmll>.

⁸⁵ Regulatory Considerations Guidance at 7.

⁸⁶ *Id.* at 13.

⁸⁷ *Id.* at 8.

⁸⁸ 21 C.F.R. § 1271.3(f)(1) (emphasis added).

⁸⁹ 21 C.F.R. § 1271.3(f)(2) (emphasis added).

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arguably defines and limits the “relevant” characteristics to those “relating to ... utility for reconstruction, repair, or replacement.” Categorizing as many tissue types as possible as structural arguably allows FDA to use the narrower definition of minimal manipulation, which in turn subjects more types of HCT/Ps to premarket review.

1. As applied to structural tissue

The final guidance explains a tissue characteristic is “original” if it is present in the tissue in the donor, and that it is “relevant” if it could have a meaningful bearing on the tissue’s utility for reconstruction, repair, or replacement.⁹⁰ Examples of relevant characteristics for structural tissues include strength, flexibility, cushioning, covering, compressibility, and response to friction or shear.⁹¹ Thus, activities like grinding or cutting the tissue could render it more than minimally manipulated because the activity affects characteristics like tensile strength. This appears to be a departure from the original regulations. In the preamble to the final registration rule in 2001, FDA stated that it would consider the following procedures to be examples of minimal manipulation: “Density gradient separation; selective removal of B-cells, T-cells, malignant cells, red blood cells, or platelets; centrifugation; cutting, grinding, or shaping; soaking in antibiotic solution; sterilization by ethylene oxide treatment or irradiation; cell separation; lyophilization; cryopreservation; or freezing.”⁹² This list of examples was not expressly limited to any specific type of products and, therefore, was viewed by many in the industry to be broadly applicable to all HCT/Ps.

Some of the lines drawn also could be viewed as inconsistent or arbitrary. For example, the guidance states that cutting amniotic tissue into sheets or processing it to remove chorion or other cells does not alter the tissue’s original relevant characteristics as a barrier. But it also concludes that grinding or lyophilizing the amnion is more than minimal manipulation because the processing alters the tissue’s ability to function as a barrier.⁹³ In the case of bone, the guidance states that shaping bone into dowels or screws is minimal manipulation because the processing does not alter the bone’s original characteristics relating to its utility to support the body.⁹⁴ Curiously, however, FDA has long held that grinding bone does not constitute more than minimal manipulation, despite the fact that the activity would seem to alter its capacity to support the body.⁹⁵ The guidance does not address or change this longstanding position, nor does it explain the incongruity between its treatment of amnion and bone under the new criteria.

The guidance also provides a number of examples involving adipose tissue. FDA asserts that adipose is a structural tissue whose original relevant characteristics include cushioning and support.⁹⁶ This means that an establishment that processes adipose tissue by

⁹⁰ *Id.* at 9.

⁹¹ *Id.* at 9.

⁹² 66 Fed. Reg. at 5457.

⁹³ *Id.* at 10. The guidance draws the same distinctions with fascia lata and skin, noting that grinding or cutting them into particles is more than minimal manipulation because the processing alters their utility as a covering for muscles and a protective barrier, respectively. *Id.*

⁹⁴ *Id.* at 9.

⁹⁵ See 66 Fed. Reg. at 5457 (“We consider cutting, shaping and grinding of bone minimal manipulation.”).

⁹⁶ *Id.* at 11.

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removing its cells and leaving the decellularized extracellular matrix portion of the HCT/P is engaged in more than minimal manipulation because the processing alters its utility to provide support.⁹⁷ Similarly, an establishment that engages in stromal vascular fraction to source stem cells from adipose is deemed to be engaged in more than minimal manipulation because the processing breaks down and eliminates the adipocytes and the surrounding structural components that provide cushioning.⁹⁸ Practically speaking, these examples could have a significant impact on the development of stem cell therapies. Adipose tissue is an abundant and easily accessible source of adult stem cells. Large quantities of adipose-derived stem cells are “easily and repeatably harvested using minimally invasive techniques with low morbidity,”⁹⁹ especially as compared to other sources of adult stems cells, such as bone marrow. If harvesting and isolation of stem cells from adipose consists of more than minimal manipulation, stem cell therapies are likely be subject to the full set of requirements that apply to medical products, including the need to obtain premarket review. Some have expressed concern, arguing that too much oversight and expansion of the scope of products requiring preapproval will delay the development of potentially life-saving treatments and stifle innovation. Others have welcomed the approach, however, given the devastating adverse events associated with some unapproved stem cell products.

2. As applied to nonstructural tissues and cells

For cells or non-structural tissues, minimal manipulation includes “processing that does not alter the relevant biological characteristics of cells or tissues.”¹⁰⁰ The guidance explains that FDA understands “relevant biological characteristics” to include those properties that contribute to the tissue’s or cells’ function or functions in the donor. Examples include differentiation and activation state, proliferation potential, and metabolic activity. Processing that alters any of these characteristics generally would be considered more than minimal manipulation.¹⁰¹

As additional examples, FDA explains that performing cell selection on a mobilized peripheral blood apheresis product to obtain a higher concentration of hematopoietic stem/progenitor cells for transplantation would constitute minimal manipulation insofar as the cells are not altered with regard to their relevant biological characteristics to repopulate bone marrow.¹⁰² By contrast, a manufacturer that uses the same cells to produce terminally differentiated cells by culturing them would be engaged in more than minimal manipulation because the processing alters the cells’ relevant biological characteristics of multipotency and capacity for self-renewal.¹⁰³ Similarly, an establishment that incubates cord blood cells in a laboratory vessel containing culture media and growth factors more than minimally manipulates

⁹⁷ *Id.* at 11.

⁹⁸ *Id.* at 13.

⁹⁹ L. Frese et al., *Adipose Tissue-Derived Stem Cells in Regenerative Medicine*, *Transfusion Medicine and Hemotherapy* 2016; 43: 268–274.

¹⁰⁰ 21 C.F.R. § 1271.3(f)(2).

¹⁰¹ Regulatory Considerations Guidance at 14.

¹⁰² *Id.* at 14.

¹⁰³ *Id.* at 14.

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the cells because the processing affects the production of intracellular or cell-surface proteins.¹⁰⁴

B. Homologous use

Even if an HCT/P is minimally processed, it still will not qualify for regulation in the “middle tier” unless it is intended for homologous use only.¹⁰⁵ The term “homologous use” has only one definition in the regulations. It 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.”¹⁰⁶ On its face, the definition applies equally to nonstructural and structural tissue.¹⁰⁷

The final guidance posits a different approach using a new interpretation of the phrase “basic function or functions.” First, the guidance states that a tissue’s basic functions are limited to those “commonly attributed to the HCT/P as it exists in the donor.” The guidance explains that basic functions should be “well understood” and that “it should not be necessary to perform laboratory, preclinical, or clinical studies to demonstrate a basic function.” Next, the guidance posits that the “basic functions” of structural and non-structural tissues are different. It states that examples of basic functions of structural tissues are “to physically support or serve as a barrier or conduit, or connect, cover, or cushion,” while examples of basic functions for nonstructural tissues include “metabolic or biochemical function[s], such as hematopoietic, immune, and endocrine functions.”¹⁰⁸ The final guidance thus creates different understandings of homologous use for structural and non-structural tissues, even though FDA declined to do so when it established the Part 1271 regulations. This evolution is presumably informed by FDA’s experience with these products over the last decade and its goal of ensuring the scheme under Part 1271 properly calibrates risk.

The final guidance also explicitly reverses prior homologous use determinations. For instance, FDA had previously recognized that the permissible homologous uses of amniotic membrane include “ocular repair,”¹⁰⁹ “wound repair and wound healing,”¹¹⁰ and generally acting as an anti-scarring, anti-inflammatory, and anti-angiogenic agent.¹¹¹ The guidance, however, limits the “basic functions” of amniotic membrane to serving as a covering, protecting the fetus,

¹⁰⁴ *Id.* at 15.

¹⁰⁵ 21 C.F.R. § 1271.10(a)(2).

¹⁰⁶ *Id.* § 1271.3(c).

¹⁰⁷ Of note, FDA considered including different definitions but ultimately declined to do so in the face of significant public opposition. See 63 Fed. Reg. at 26749 (proposing separate definitions of “homologous use” for structural and nonstructural tissues); 66 Fed. Reg. at 5458 (“We have ... rewritten the definition of homologous use in response to the comments’ concerns. ... The rewording eliminates the distinction between, on the one hand, structural tissues and, on the other, nonstructural tissues and cells.”). Instead, the preamble to the Part 1271 regulations stated that FDA “intend[ed] to interpret ‘nonhomologous’ narrowly.” *Id.* at 5458.

¹⁰⁸ Regulatory Considerations Guidance at 16-17.

¹⁰⁹ 69 Fed. Reg. at 68643.

¹¹⁰ See Letter from FDA to OKTOS Surgical Corp. (June 23, 2005), <http://1.usa.gov/1CAAmll>.

¹¹¹ See Letter from FDA to Bio-Tissue, Inc. (Nov. 26, 2001), <http://1.usa.gov/1Db2q5l>.

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and serving as a selective barrier for the movement of nutrients.”¹¹² In a footnote, the guidance also says that “reducing scarring, angiogenesis, and inflammation are potential clinical effects” of amniotic tissue “but are not basic functions.”¹¹³ This means those prior sanctioned uses for amnion no longer qualify for the HCT/P safe harbor under Part 1271.

The final guidance also specifically addresses the homologous uses of adipose tissue. The guidance states that the use of adipose tissue to cosmetically fill voids in the subcutaneous space is a homologous use. This means adipose used in breast reconstruction procedures is considered homologous, which is a retreat from the contrary position that FDA proposed in the draft guidance on adipose tissues.¹¹⁴ But the use of adipose to treat a degenerative, inflammatory, or demyelinating disorder is not considered homologous.¹¹⁵ Indeed, FDA offers a general warning that any HCT/P intended for use as an unproven treatment for different diseases or conditions is likely not intended for homologous use.¹¹⁶

IV. Everything else: Premarket review

Any HCT/Ps that do not qualify for one the exemptions described in 21 C.F.R. § 1271.15 or for regulation as 361 HCT/Ps are subject to the full panoply of applicable authorities under the FDCA and the PHSa. Most importantly, such products must go through premarket review as a medical device, drug, and/or biological product.

FDA’s November 2017 announcement of a new framework for regenerative medicine acknowledges that many (if not most) cell- and tissue-based therapies will fall into this group and require premarket review. The agency issued two draft guidances on the regulation of regenerative therapies subject to full FDA review. The first addresses how FDA intends to regulate devices used in the recovery, isolation, and delivery of regenerative medicine advanced therapies (RMATs), a designation created by the 21st Century Cures Act,¹¹⁷ passed in December 2016. The second describes the programs that may be available to sponsors of regenerative medicine therapies to expedite development as well as the therapies that may be eligible for RMAT designation.¹¹⁸ Both are championed by FDA as efforts to simplify and reduce regulatory burdens, and FDA made similar commitments to explore innovative clinical trial design for these products.

These guidances reflect FDA’s effort to keep pace with the technological and scientific innovations associated with regenerative treatments like gene therapies that have long been subject to the highest-risk tier of full agency pre-review through the BLA or NDA pathways. Recent innovations present new complexities for FDA reviewers, and gene therapy has long

¹¹² Regulatory Considerations Guidance at 18.

¹¹³ Regulatory Considerations Guidance at 18.

¹¹⁴ See FDA, Draft Guidance for Industry: HCT/Ps from Adipose Tissue: Regulatory Considerations at 5 (December 2014) (withdrawn).

¹¹⁵ *Id.*

¹¹⁶ *Id.* at 15. See also “Human Cells, Tissues, and Cellular and Tissue Based Product; Establishment Registration and Listing,” 66 FR 5447 at 5457 (Jan. 19, 2001).

¹¹⁷ Pub. L. No. 114-255.

¹¹⁸ FDA Announces comprehensive regenerative medicine policy framework, at 3.

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been the subject of its own separate rulemakings and guidances. On July 7, 2017, FDA Commissioner Scott Gottlieb announced FDA's commitment to implementing those sections of the 21st Century Cures Act that apply to RMATs and the need for appropriate and flexible regulation by FDA.¹¹⁹ This Commissioner has also made known his belief in, and support of, the promise of properly regulated stem cell therapies. An analysis of technological innovations at the heart of these BLAs is beyond the scope of this memorandum, but it will be interesting to see how FDA's experience with these new technologies and its premarket review of them informs its evolving views of Part 1271.

Next Steps

FDA has now finalized key guidance documents drawing the clearest lines to date between the tiers discussed above, and has provided a three-year period of enforcement discretion to allow manufacturers to self-sort into those tiers based on the guidance. It is perhaps unrealistic to expect, however, an orderly three-year transition period during which all developers of stem cell therapies and others who—under the clear terms of the guidance—now find themselves subject to full FDA regulation as drugs and/or biological products will simply concede the point and begin to comply with FDA's premarket requirements. Instead, it is likely that many such developers will use these three years to push for regulatory, or even statutory, changes to the lines of demarcation FDA has drawn.

At the same time, FDA will almost certainly continue its efforts to crack down on manufacturers and products the agency views as unsafe or unscrupulous. At the same time Commissioner Gottlieb announced a new policy approach to regenerative medicine in August 2017, he also announced a warning letter issued to a stem cell clinic in Florida and a product seizure action taken against another clinic in California.

¹¹⁹ See Commissioner Gottlieb's statement available at <https://blogs.fda.gov/fdavoices/index.php/2017/07/how-fda-plans-to-help-consumers-capitalize-on-advances-in-science/>.