



FDA's Framework for Regulating Regenerative Medicine Will Improve Oversight

Further action needed to facilitate development of safe, effective treatments

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This report benefited from the insights and expertise of two external peer reviewers: Douglas Sipp, researcher, the RIKEN Center for Biosystems Dynamics Research in Kobe, Japan, and visiting professor, Keio University School of Medicine in Tokyo; and Zubin Master, associate professor, Biomedical Ethics Research Program and the Center for Regenerative Medicine, Mayo Clinic. The team would also like to thank the offices of Sidley Austin LLP, which conducted the legal analysis that informed our report findings. Finally, we would like to thank Dana Trevas, a contracted writer who assisted in the data collection and provided an initial draft of this report. Although they have reviewed the report, neither they nor their organizations necessarily endorse its findings or conclusions.

Acknowledgments

We would like to thank the following current and former Pew colleagues for their contributions: Casey Ehrlich, Alan van der Hilst, Heather Creek, Sean Dickson, Andrew Whitacre, Henry Watson, and Colton Naval for their review of the proposal for this research; Laurie Boeder, Sara Brinda, Kimberly Burge, Tami Holzman, Matt Mulkey, and Liz Visser for their editorial input; and Cara Bahniuk and Sarah Tompkins for their work preparing this report for publication.

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Overview

Over the last two decades, cell therapies (which involve the transplantation of whole cells into a patient), gene therapies (which use genetic material to manipulate a patient's cells), and other medical treatments intended to repair or replace damaged, diseased, or dysfunctional cells, tissues, and organs have generated increasing public interest. Such treatments, which together make up the field of regenerative medicine, may have the potential to treat a range of problems such as organ failure, traumatic injuries, and serious diseases.

The increase in public interest has been accompanied by substantial private-sector financial investments in the development of regenerative treatments. Relatively few such treatments have been approved by the Food and Drug Administration (FDA) for use in the United States, but many more are in clinical development, and the number of approved products is expected to grow over the next several years.

But interventions that are marketed as regenerative therapies but have not been reviewed or approved by FDA are widely available, sometimes through clinics that provide these procedures exclusively, though some hospitals or other providers offer them as part of their broader medical services. Most of these businesses or providers offer stem cell therapies derived from a variety of sources—often the patient's own body—and maintain that these products can be used for a broad array of applications, from cosmetic procedures to treating multiple sclerosis and other serious conditions. In many cases, there is little or no reliable evidence to support the claims behind these potentially unsafe and usually expensive treatments, which are normally not covered by the patient's health insurance.

These businesses have emerged against the backdrop of limited regulatory oversight and enforcement from either state or federal authorities. In the rapidly evolving field of regenerative medicine, it has not always been clear where the responsibility for regulation lies. This lack of clarity has created opportunities for some unscrupulous businesses to market products that have not been fully evaluated for safety and effectiveness.

FDA has recognized the promise of the field of regenerative medicine and the growing risks posed by the proliferation of clinics offering unapproved therapies. In November 2017, the agency released four guidance documents that together constitute its regulatory framework for regenerative medicine, which aims to:

- Clarify the distinctions between products that are subject to the agency's full drug approval requirements and those that are not.
- Streamline the review process for new therapies and reduce some of the regulatory requirements on product developers.

The agency also pledged to increase its enforcement efforts against providers offering high-risk, unapproved interventions.

This report is drawn from a commissioned legal analysis; interviews with experts from the legal, scientific, clinical, bioethics, and advocacy fields; and a review of the related literature, which included peer-reviewed scientific publications, federal guidance documents and regulations, and media articles. It provides an overview of that regulatory framework and outlines key remaining areas of uncertainty and controversy, as identified by select stakeholders in the field. Among the key findings:

- Stakeholders generally believe that FDA's framework provides important clarity on how the agency will regulate regenerative therapies and—by clarifying which products must undergo FDA review before being introduced to the market—will have a significant impact on the trajectory of the field. Moving forward, it would be helpful for the agency to create or finalize any other guidance documents that are essential to supporting the development of safe and effective regenerative therapies, including guidances related

to manufacturing standards, the use of real-world evidence, and determining market exclusivity for regenerative therapies.

- Some areas of ambiguity, as well as controversy, persist, especially over whether FDA has appropriately defined the fundamental concepts that determine whether a product will be regulated as a drug and/or a device. The agency can address these ambiguities over time by clearly communicating its decisions regarding product classification and, when appropriate, by updating the four guidance documents that make up the regenerative medicine framework to reflect those decisions. Providing additional examples of how different products are regulated under the framework will help to clarify the agency's thinking.
- The regenerative medicine advanced therapy (RMAT) designation—an expedited development pathway established by FDA under the 21st Century Cures Act that may allow regenerative therapy developers to conduct smaller, shorter trials—increases the burden on the agency to enforce post-approval study requirements to confirm that products are safe and effective. The agency has historically struggled to meet this responsibility. It will be important for FDA to evaluate the RMAT designation and other processes that facilitate regenerative therapy development to ensure that its efforts to speed development and approval do not come at the cost of approving unsafe therapies.
- Nearly all stakeholders expressed doubts over whether the agency has the resources to fully enforce the framework, particularly regarding the hundreds of clinics that market unapproved stem cell interventions. The agency has pledged to expand its enforcement activities starting in 2020, and it will be important to follow through on that promise.
- Other public health stakeholders at the national and state levels—including the Federal Trade Commission, National Institutes of Health (NIH), state legislatures, state attorneys general, state medical boards, and other public health and professional organizations—can play a key role in limiting the ability of businesses to market unapproved interventions to patients and providing the public with accurate, reliable information about the field.

Background

Defining regenerative medicine

The term regenerative medicine covers a range of treatments intended to repair or replace damaged cells, tissues, or organs. These treatments include cell therapies, bioengineered tissue products, and gene therapies.¹ Regenerative techniques such as bone marrow or organ transplantation have been used for decades,² but the field began receiving increased attention in the late 1990s when scientists developed methods to isolate and grow cells from embryonic tissue that can differentiate into almost any kind of cell (known as pluripotent stem cells). Over the next decade, scientists succeeded in genetically engineering such differentiation in adult stem cells as well.³ More recently, technologies that allow for the editing and transfer of genetic material have offered new hope for treating inherited disorders and other serious conditions. The field of regenerative medicine has attracted significant enthusiasm, investment, and media attention for its potential to generate cures—rather than just treatments that alleviate symptoms or slow disease progression—as well as its focus on noncommunicable chronic diseases, which are primary drivers of overall morbidity and mortality.⁴

Despite this enthusiasm and investment, FDA has approved relatively few regenerative therapies. Most of those have been umbilical cord-derived stem cell therapies used to treat certain blood cancers and other diseases involving the immune system.⁵ The agency has also approved three gene therapies: two that treat cancer and one for a genetic form of blindness.⁶ Many more treatments are under development in clinical trials around the world. But it is challenging to establish a reliable estimate of the field's size, owing to variations in how different

regulatory authorities, researchers, and professional and trade organizations define the term regenerative therapy and the concept of regenerative medicine more broadly. According to one analysis by an industry trade association, 906 regenerative medicine companies exist globally, primarily in the United States (484), Europe and Israel (241), and Asia (142).⁷ These companies include both large pharmaceutical corporations and small biotechnology firms that are developing therapies to treat a range of conditions. As of 2018, overall global financing for regenerative medicine amounted to \$13.3 billion. Cell therapy alone accounted for \$7.6 billion.⁸

However, interventions marketed as regenerative therapies that have not been submitted to FDA for review are also widely available in the commercial market. These unapproved treatments have been a source of growing concern for public health officials and many others working in the field.⁹

Glossary

Regenerative medicine is a field comprising medical treatments that are intended to repair or replace damaged cells, tissues, or organs. Regenerative interventions produce living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects. Examples include stem cell therapies, bioengineered tissue therapies, gene therapies, and bone marrow and organ transplantation.

Key terms used in the oversight of regenerative medicine include the following:

Allogeneic cells or tissues are taken from a different individual than the patient receiving the treatment and thus differ genetically from the patient.

Autologous cells or tissues are obtained from the individual receiving the treatment.

Bioengineered tissue products are functional therapeutic tissues that are grown or constructed using a variety of techniques and materials.

Biologic drugs include any therapeutic product derived from a biological (rather than chemical) source, such as vaccines or monoclonal antibodies.

Biologics license applications are the formal requests that sponsors must submit to FDA for permission to introduce a biologic drug into interstate commerce.

Cell therapies involve the transplantation of whole cells into a patient for therapeutic purposes.

Gene therapies use genetic material to manipulate a patient's cells for therapeutic purposes.

HCT/P refers to human cells, tissues, or human cell- or tissue-based products.

Homologous use is defined by FDA as the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function(s) in the recipient as in the donor. **Nonhomologous use** describes situations in which the product is used in ways that deviate from its original function.

Investigational new drug applications are formal requests that sponsors must submit to FDA for authorization to administer an investigational drug to human patients.

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Minimal manipulation for structural tissue is processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement.

Minimal manipulation of cells or nonstructural tissues is processing that does not alter the relevant biological characteristics of cells or tissues.

Part 1271 regulations define FDA requirements related to facility registration; product listing; organ, tissue, and blood donor eligibility; and tissue handling.

Premarket review is a process through which manufacturers seek FDA approval to market a product by demonstrating that it is safe and effective for its intended use.

Regenerative medicine advanced therapy (RMAT) is an FDA designation that a regenerative medicine product or device has potential to address unmet medical needs. RMAT designation allows a sponsor to take advantage of expedited and alternative pathways to FDA licensure.

Stem cells are cells capable of dividing and differentiating into other types of cells to repair or replenish tissues. **Pluripotent stem cells** can differentiate into almost any kind of cell.

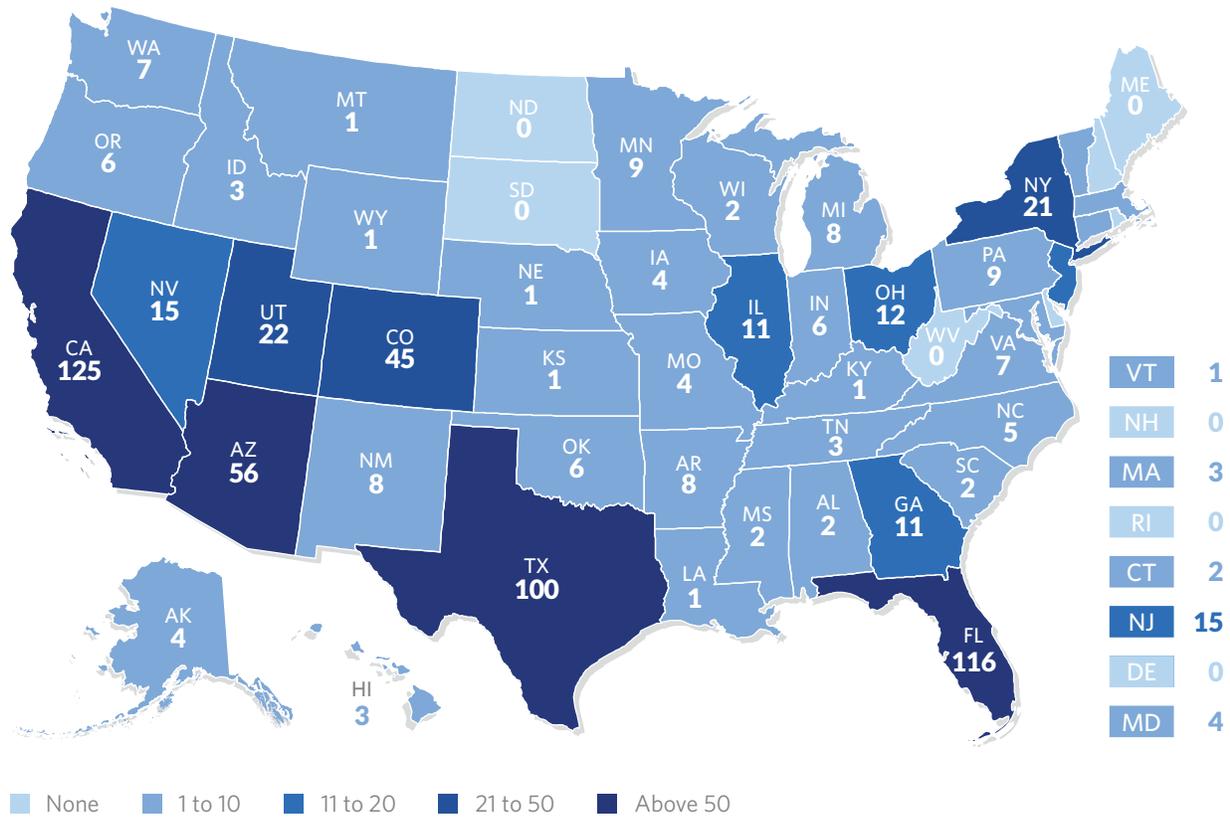
Warning letters are sent by FDA to identify violations of the agency's regulations and specify corrective actions the recipient must take to avoid enforcement action. **Untitled letters** cite violations that do not merit a warning letter. Both are distinct from **Form 483**, which is issued after an inspection and identifies conditions that may violate FDA regulations but draws no conclusion regarding whether a violation has occurred.

The growing commercial market

A substantial direct-to-consumer market exists for regenerative therapies, particularly those derived from stem cells. This industry has proliferated rapidly, first in low- and middle-income countries (catering largely to “medical tourists”) and subsequently in Europe, Japan, and the United States.¹⁰ A recent study of the global distribution of stem cell businesses found that the market was highly concentrated in a handful of countries, with the largest number operating in the U.S.¹¹

This complex industry encompasses a variety of businesses. Some companies, for example, act as recruitment agencies that link patients to providers offering these interventions, while others function as cell or tissue banking facilities that may partner with or sell directly to providers who administer them. Some are clinics that may operate independently, sourcing their interventions directly from the patients' own fat tissue or bone marrow.¹² As of May 2017, at least 716 clinics in the U.S. offered stem cell therapies, with nearly half in three states: California (125), Florida (116), and Texas (100).¹³ (See Figure 1.) This number has probably grown, given the rapid expansion of the market. A retrospective study published in early 2018 found that the number of new U.S. stem cell businesses with websites doubled on average every year between 2009 and 2014 and that up to 100 new websites appeared each year between 2014 and 2016.¹⁴

Figure 1
Stem Cell Clinics Operating in the United States, May 2017



Note: The map omits 43 clinics for which the source datasets did not include geographic locations. The data shown reflect revised counts published in 2018 for Arizona, California, Colorado, Florida, and Texas and 2019 for New Mexico, Nevada, and Utah.

Sources: L. Turner, "The U.S. Direct-to-Consumer Marketplace for Autologous Stem Cell Interventions," *Perspectives in Biology and Medicine* 61, no. 1 (2018): 7-24, <https://muse.jhu.edu/article/694817>; P.S. Knoepfler and L.G. Turner, "The FDA and the U.S. Direct-to-Consumer Marketplace for Stem Cell Interventions: A Temporal Analysis," *Regenerative Medicine* 13, no. 1 (2018): 19-27, <https://dx.doi.org/10.2217/rme-2017-0115>; E. Frow et al. "Characterizing Direct-to-Consumer Stem Cell Businesses in the Southwest United States," *Stem Cell Reports* 13 (2019): 1-7, <https://doi.org/10.1016/j.stemcr.2019.07.001>.

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These businesses advertise their treatments for a broad array of diseases and conditions, from cosmetic issues and orthopedic complaints such as arthritis to severe neurological diseases such as multiple sclerosis. While licensed medical providers offer most of these interventions, they may also be administered by complementary or alternative medicine practitioners (such as chiropractors, acupuncturists, or naturopaths), sometimes in conjunction with physicians.¹⁵ However, some of these physicians may be treating conditions that fall outside their particular specialty, which can increase the risk to patients.¹⁶ A recent study of stem cell businesses operating in three states found that nearly half of those clinics employed physicians who were operating outside the scope of their training.¹⁷ Most offer autologous interventions, in which stem cells are harvested from the patient who will receive the treatment, typically from adipose (fat) tissue or bone marrow. However, some companies also advertise allogeneic interventions, which are sourced from a donor and may be derived from amniotic, placental, or umbilical cord tissues.¹⁸

Patients may seek out these treatments for several reasons. Some may have exhausted conventional treatment options and are willing to accept the risks involved. Others may be searching for alternative therapies because they mistrust conventional medicine or government authorities that attempt to limit their access to treatment, even if unproved.¹⁹ Overly optimistic or positive media portrayals of stem cell treatments may also contribute to patient willingness to pursue these interventions.²⁰

In many cases, there is little reliable evidence to support claims that these so-called stem cell treatments will have any effect—or indeed that they contain stem cells at all, despite the claims made about them.²¹ There is also ongoing scientific debate over whether stem cells derived from fat tissue in particular—which are commonly referred to as mesenchymal stem cells and are used widely in stem cell clinics or businesses—should be classified as stem cells.²² Given the lack of evidence to support their use, the potential risk of harm to patients could outweigh the benefits.

One review of scientific literature and media reports found 35 serious adverse events related to unproven stem cell interventions—including loss of vision, tumor growth, and death—and many others have been reported since that publication.²³ (See Appendix B for a list of adverse events identified by Pew.) Adverse events are probably significantly underreported, as these businesses may not track patients after treatment and patients may not know how to notify authorities about what has occurred after they receive these types of interventions. An analysis of case reports published in scientific journals about patients who received stem cell treatments for eye disorders—all of whom were reported to have had either positive outcomes or no improvement—found that the clinics providing these results did not include patients with poor outcomes.²⁴ It is difficult to know how many patients experience adverse outcomes because many cases settle before court proceedings. However, in 2018, researchers identified nine cases involving 19 plaintiffs who sued providers of stem cell interventions claiming negligence, false advertising, medical malpractice, and harms arising from their treatment, among other allegations.²⁵

The cost for these treatments varies widely, with reported prices ranging from \$2,500 to more than \$50,000, though some patients say they received treatment free of charge.²⁶ For the most part, these costs are borne entirely by patients, as insurers generally do not cover unapproved interventions.²⁷ Some clinics encourage patients to take out loans or use crowdfunding websites to cover the costs.²⁸ A 2017 search of GoFundMe and YouCaring, two top crowdfunding sites, turned up more than 400 campaigns seeking funds for stem cell therapies, raising concerns that some businesses are financially exploiting vulnerable patients with chronic or life-threatening illnesses.²⁹ Beyond the potential physical, psychological, and financial harm to patients, the widespread availability of these unproven treatments could negatively affect the entire field of regenerative medicine by undermining the commercial incentive for those who develop therapies to invest in rigorous clinical trials and by damaging the field's reputation among patients, clinicians, and investors.

There has been relatively little regulatory scrutiny of businesses offering unproven regenerative treatments; many have operated under the apparent assumption that they are exempt from FDA regulations. Some in the field argue that federal authorities should not regulate human cells in this way, particularly in cases where a patient's own cells are being harvested, processed, and reimplanted.³⁰

History of FDA oversight of regenerative therapies

The field of regenerative medicine is complex and rapidly evolving, and the limits of FDA jurisdiction over therapies have not always been clear. The agency is primarily responsible for regulating medical products but has no direct authority over the practice of medicine, which is overseen mainly by state medical boards. In regenerative medicine, the products being used (i.e., cells and tissues) are closely connected to the care provided, so the distinction between product and practice is not always easy to determine.

Furthermore, human cells and tissues do not conform neatly to the traditional product categories that FDA uses to determine which regulations apply. For some FDA-regulated products, such as blood or its components, the regulatory focus is on establishing purity and potency, while others are regulated as drugs, devices, or drug-device combinations, which requires that manufacturers demonstrate both safety and effectiveness. These regulatory categories are governed by different requirements for review and approval, which further complicates the picture for product developers.

Regulation of human cell and tissue products (HCT/Ps) has evolved substantially over the last 30 years in response to medical advances and public health needs. HCT/Ps were first regulated primarily by states and through voluntary quality assurance programs. Beginning in the mid-1980s, however, FDA began to assert its regulatory authority on a case-by-case basis, largely in response to several events, including the 1979 death of a woman who contracted rabies after receiving a corneal transplant and the 1987 death of a woman from Creutzfeldt-Jakob disease following a spinal membrane transplant, as well as broader concerns about the AIDS epidemic and its impact on the national blood supply.³¹

FDA's initial efforts focused on categorizing specific human tissue products as medical devices, drugs, or biological products requiring premarket review under the federal Food, Drug, and Cosmetic Act and/or the Public Health Services Act (PHSA). In 1993, the agency began to create a comprehensive, risk-based framework to regulate the donation, handling, processing, and marketing of HCT/Ps. At the same time, it began establishing new requirements for donor testing, record-keeping, inspections, and recalls for HCT/Ps.³² Beginning in 1998, FDA also developed new rules establishing how human cell and tissue products would be regulated. Under these rules, products that met certain criteria established under Section 361 of the PHSA would not be subject to premarket clearance or approval, while those that did not meet the criteria would be regulated like any other drug or device, in line with regulations established under Section 351 of the PHSA.³³ By 2005, these regulations had been finalized in the Code of Federal Regulations under Title 21, parts 1270 and 1271.³⁴

Key FDA Authorizing Legislation

- **Federal Food, Drug, and Cosmetic Act:** Regulates drugs and medical devices “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease” or “intended to affect the structure or any function of the body.”³⁵ With few exceptions, drugs and medical devices are subject to Food and Drug Administration premarket review before they can be sold in the United States.³⁶ This means manufacturers must demonstrate that the product is safe and effective on the basis of adequate and well-controlled clinical trials.³⁷
- **Public Health Service Act (PHSA), Section 351:** Regulates the interstate sale of biologic products, which include vaccines, therapeutic proteins, and similar products that are used to prevent, treat, or cure a disease or condition.³⁸ Biologic products are subject to the same standards of safety and effectiveness as drugs and medical devices, and are approved by the agency under a biologics license application.
- **PHSA, Section 361:** Authorizes FDA to make and enforce regulations “to prevent the introduction, transmission, or spread of communicable diseases.”³⁹ Many human cell and tissue products are subject to Section 361 regulations, but not Section 351.

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- **21st Century Cures Act:** Among many provisions aimed at promoting innovation and reducing barriers to medical product development and approval, this legislation directed FDA to create an expedited process for evaluating regenerative medicine advanced therapies, known as the RMAT designation, and to consider the use of alternative forms of evidence for such evaluation.⁴⁰

Over time, the Part 1271 regulations have been interpreted in the field as establishing three tiers, or categories, of cell and tissue products; two of them are subject to virtually no FDA oversight, while the third is subject to the same requirements for licensure as a drug, medical device, or biological product.⁴¹

Manufacturers developing a regenerative product can seek input on which regulatory tier it will fall into by requesting a formal designation decision from FDA—made either by the Tissue Reference Group (composed of representatives of FDA’s Center for Biologics Evaluation and Research and Center for Devices and Radiological Health); or by the agency’s Office of Combination Products.⁴² For several years after the Part 1271 rules were proposed and finalized, these two groups’ responses to requests for designation were the primary source of guidance on how FDA would interpret and apply the HCT/P regulations.⁴³

In 2013, FDA began to narrow the scope of products that were exempt from regulation and started issuing more enforcement letters to manufacturers that it felt were improperly claiming such exemptions.⁴⁴ In 2014, it published several draft guidance documents intended to clarify its regulations, defining key concepts that govern how FDA classifies these products.⁴⁵ Taken together, the guidance documents signaled the agency’s intent to require premarket review for a broader range of HCT/Ps, including some that had been on the market for several years.⁴⁶ In response to the subsequent comments and feedback from industry, FDA convened a public hearing in September 2016 to discuss these documents and its overall framework for regulating HCT/Ps.

The December 2016 passage of the 21st Century Cures Act added further impetus to FDA’s efforts. In addition to authorizing \$30 million in NIH funding for regenerative medicine research,⁴⁷ the legislation also directed FDA to establish a new program—now known as the RMAT designation—that would facilitate development, review, and approval of these products.

FDA’s framework for regenerative medicine

After the public consultation process in 2016 and enactment of the 21st Century Cures Act, FDA published four guidance documents in November 2017 that supplement existing statutes and together form its regenerative medicine regulatory framework.

Key Guidances for Regenerative Therapies

The Food and Drug Administration’s guidance documents (known as guidances) do not establish legally enforceable responsibilities. Rather, they describe the agency’s current thinking and recommendations on a topic and, importantly to industries under the agency’s jurisdiction, indicate how it will enforce the law. Though product manufacturers are strongly encouraged to consult and comply with guidances, they are not required to do so. These four guidances outline key parameters of FDA’s regulatory framework for regenerative medicine.

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Table 1

Regulatory Framework Parameters

Guidance	Key features
Same Surgical Procedure Exception Under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception—Final^a	<p>Describes the exception from Food and Drug Administration oversight that applies to “same surgical procedures,” as described in the Code of Federal Regulations, Title 21, Part 1271. It includes:</p> <ul style="list-style-type: none"> • The types of interventions that generally meet the agency’s definition of “the same” procedure. • The ways that products can be processed and still meet the exception.
Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use—Final^b	<p>Provides FDA’s definition of key regulatory terms; namely, minimal manipulation and homologous use.</p> <p>Provides information on how to apply these definitions to a human cell or tissue product.</p> <p>Articulates FDA’s compliance and enforcement policy for human cell and tissue products.</p>
Evaluation of Devices Used With Regenerative Medicine Advanced Therapies—Final^c	<p>Describes how FDA will approach the evaluation of devices used in the recovery, isolation, or delivery of regenerative medicine advanced therapies (RMATs).</p>
Expedited Programs for Regenerative Medicine Therapies for Serious Conditions—Final^d	<p>Describes the expedited development program available for qualifying regenerative therapies, known as RMAT designation.</p> <p>Outlines a collaborative development model for RMAT products.</p>

a U.S. Food and Drug Administration, “Same Surgical Procedure Exception Under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception: Guidance for Industry” (2017), <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM419926.pdf>.

b U.S. Food and Drug Administration, “Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use: Guidance for Industry and FDA Staff” (2017), <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585403.pdf>.

c U.S. Food and Drug Administration, “Evaluation of Devices Used With Regenerative Medicine Advanced Therapies: Guidance for Industry” (2019), https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585417.pdf?utm_campaign=021519_FIB_FDA%20finalizes%20two%20guidances%20as%20part%20of%20regenerative%20medicine%20policy%20framework&utm_medium=email&utm_source=Eloqua.

d U.S. Food and Drug Administration. “Expedited Programs for Regenerative Medicine Therapies for Serious Conditions: Guidance for Industry” (2019), https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585414.pdf?utm_campaign=021519_FIB_FDA%20finalizes%20two%20guidances%20as%20part%20of%20regenerative%20medicine%20policy%20framework&utm_medium=email&utm_source=Eloqua.

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With these guidance documents, FDA sought to clarify the distinctions between products that are subject to full drug approval requirements and those that are not, while also streamlining the review process and reducing some of the regulatory requirements on product developers.⁴⁸ The agency's overall stated goal is to balance the expedient development of innovative therapies with ensuring that the therapies are sufficiently safe and effective.⁴⁹ In developing the four guidances that make up the framework, the agency says it considered how to prevent the transmission of communicable diseases between donors and recipients, the processing controls necessary to prevent contamination and preserve tissue integrity and function, and how to ensure clinical safety and effectiveness.⁵⁰

Regulators Focus on Unscrupulous Providers

The Food and Drug Administration has acknowledged the need for stricter enforcement in the regenerative medicine field. In a statement accompanying new guidance documents in November 2017, then-Commissioner Scott Gottlieb noted:

[T]he rapid growth and promise of this field has increasingly sowed the ground for the entry of some unscrupulous actors, who have opportunistically seized on the clinical potential of regenerative medicine to make deceptive claims to patients about unproven and, in some cases, dangerous products. ... This underscores the importance of having a clear regulatory framework for developers and ensuring that those who skirt these regulations are held accountable.⁵¹

November 2017 also marked the beginning of a three-year transition period, during which FDA would selectively target its enforcement efforts regarding products already on the market.⁵² While treatments that the agency considers to be of lower risk will not be subject to immediate enforcement, those that are higher risk will be. In May 2018, the agency followed through on this announcement, seeking permanent injunctions against two stem cell clinics for marketing unapproved stem cell interventions and violating regulatory standards for product manufacturing.⁵³ Both clinics have promised to challenge the injunction.⁵⁴ However, as the courts have historically sided with FDA in its efforts to regulate HCT/Ps, it is unlikely that these regenerative therapies would be deemed exempt from FDA oversight.⁵⁵ The agency has also issued warning letters to several other stem cell businesses.⁵⁶

Risk-based regulatory tiers for regenerative therapies

Under the FDA framework, regenerative therapies will continue to be regulated through a risk-based approach. Products will still be grouped into three general tiers, with therapies posing the least risk to patients placed in the lowest regulatory tier, and products posing the greatest risk in the highest tier and subject to the full premarket approval process.

The key changes introduced by the framework relate to how the agency has defined the boundaries of the tiers. These distinctions have significant consequences for the developers of regenerative therapies, as the premarket approval process may take many years and cost a great deal of money.

Lowest-tier products

HCT/Ps in the lowest regulatory tier include cases in which cells and tissues are transplanted as part of fertility treatments involving intimate partners, or are harvested and reimplanted within the same patient during the same surgical procedure, known as the "same surgical procedure exception."⁵⁷ These products are exempt from regulations governing FDA requirements for facility registration, product listing, donor eligibility, and tissue

handling—a group of rules known collectively as Part 1271 regulations. These regulations are generally aimed at preventing disease transmission and contamination.

The same surgical procedure exception hinges on three requirements:

1. The exemption applies only to autologous use—that is, the HCT/Ps must come from the patients themselves.
2. The treatment or therapy must be considered a single surgical procedure.
3. The HCT/P must remain in its original form.⁵⁸

Though some handling and processing of the HCT/P is permitted, FDA limits these activities to sizing, shaping, cleaning, and rinsing. Beyond this, the product is no longer considered to be in its original form.

Middle-tier products

To qualify for the middle tier, the product must meet four qualifications:⁵⁹

1. **Be minimally manipulated (see “Definitions: Minimal manipulation” below).**
2. Be intended for “**homologous use**”—that is, for a similar use in the recipient as in the donor.
3. Not be combined with other substances, except in limited, specific circumstances.
4. Not have a systemwide effect or depend on the metabolic function of living donor cells in order to function as intended, unless the product is for a patient’s own use, is being donated to a first- or second-degree relative, or is for reproductive use.

Middle-tier therapies are exempt from the premarket approval requirements that apply to highest-tier products, but unlike products in the lowest tier they must meet the Part 1271 requirements regarding infection and contamination prevention.

Much of the uncertainty and resulting controversy over whether a therapy belongs in the middle or the top tier stems from FDA’s interpretation of the terms “minimal manipulation” and “homologous use.” These concepts are not intuitive, and the consequences of failing to qualify for the middle tier—and thus landing in the top, most stringent tier of regulation—are substantial for product developers, and by extension for the patients who might receive those treatments. A more stringent level of review helps to ensure that products are truly safe and effective. This is important, as these products can pose significant risks to patients. However, a heavy regulatory burden can also slow the pace of innovation and potentially keep effective therapies from reaching the market.

Definitions

Minimal manipulation

The Food and Drug Administration’s threshold for determining if a product has been minimally manipulated depends on whether the human cell and tissue product (HCT/P) is considered a structural tissue or nonstructural cells or tissue.⁶⁰ Structural tissues, according to the agency, provide physical support or serve as a barrier, cover, cushion, or conduit in the donor. Examples include bone, skin, and adipose tissue (fat). (See Table 2.)

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To meet the definition of minimally manipulated, a structural tissue must not be processed in a way that affects key characteristics such as strength, flexibility, cushioning, or covering. Processing can include testing, sterilizing, preserving, cutting, grinding, and other steps. For example, grinding or shaping bone into screws is considered minimal manipulation because such processing does not alter the bone’s ability to serve as support for the body. Processing adipose tissue to extract stem cells, however, does not meet the definition of minimal manipulation because this process eliminates the components in the tissue that allow it to serve its structural function as fat.⁶¹

Nonstructural cells and tissues, by contrast, primarily serve metabolic or biochemical roles in the body. Examples include reproductive cells, blood stem cells, and bone marrow. For these products, any processing that alters a key biologic characteristic that would affect its function in the donor (such as changing a tissue’s metabolic activity or the ability of cells to divide) could be classified as more than minimal manipulation. Thus, processing blood to obtain a higher concentration of stem cells meets the definition of minimal manipulation because it has not altered the stem cells’ ability to repopulate bone marrow after being administered to the recipient. However, altering those same cells by making them grow into a specific type of cell goes beyond minimal manipulation.⁶²

Table 2
Structural Versus Nonstructural Cells, Tissues

Structural tissues	Nonstructural cells and tissues
Bone	Reproductive cells
Skin	Blood stem cells or blood progenitor cells
Amniotic membrane	Lymph nodes
Umbilical cord	Thymus
Adipose tissue	Peripheral nerves
Cartilage	Parathyroid and thyroid glands
Tendons	Bone marrow
Ligaments	Pancreatic tissue

Source: U.S. Food and Drug Administration, “Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use” (2017), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal>

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Homologous use

In addition to being minimally processed, a product in the middle tier must also be intended for homologous use, which is defined as the repair, reconstruction, replacement, or supplementation of cells or tissues with an HCT/P that performs the same basic function in the recipient as it does in the donor.⁶³

Under this definition, adipose tissue could be used as part of breast reconstruction procedures but could not be used as part of a treatment for a degenerative or inflammatory disorder. Similarly, amnion,

Continued on next page.

the membrane that covers an embryo, could be used as a cover or selective barrier for the passage of nutrients, but could not be used to reduce scarring or inflammation as part of wound repair.⁶⁴ By defining a cell or tissue's basic function more strictly, FDA further narrows the scope of HCT/Ps that fall into the middle tier, thereby classifying a broader range of products in the top tier.

Highest-tier products requiring full premarket approval

Regenerative therapies that do not meet the criteria for the low or middle tier are subject to the same premarketing requirements as any other drug or device, including the requirement that the manufacturer conduct clinical studies to demonstrate safety and efficacy. As part of its stated goal of encouraging the development of new regenerative therapies, FDA has also taken steps to reduce regulatory barriers and simplify the path to market without lowering standards for safety and efficacy.

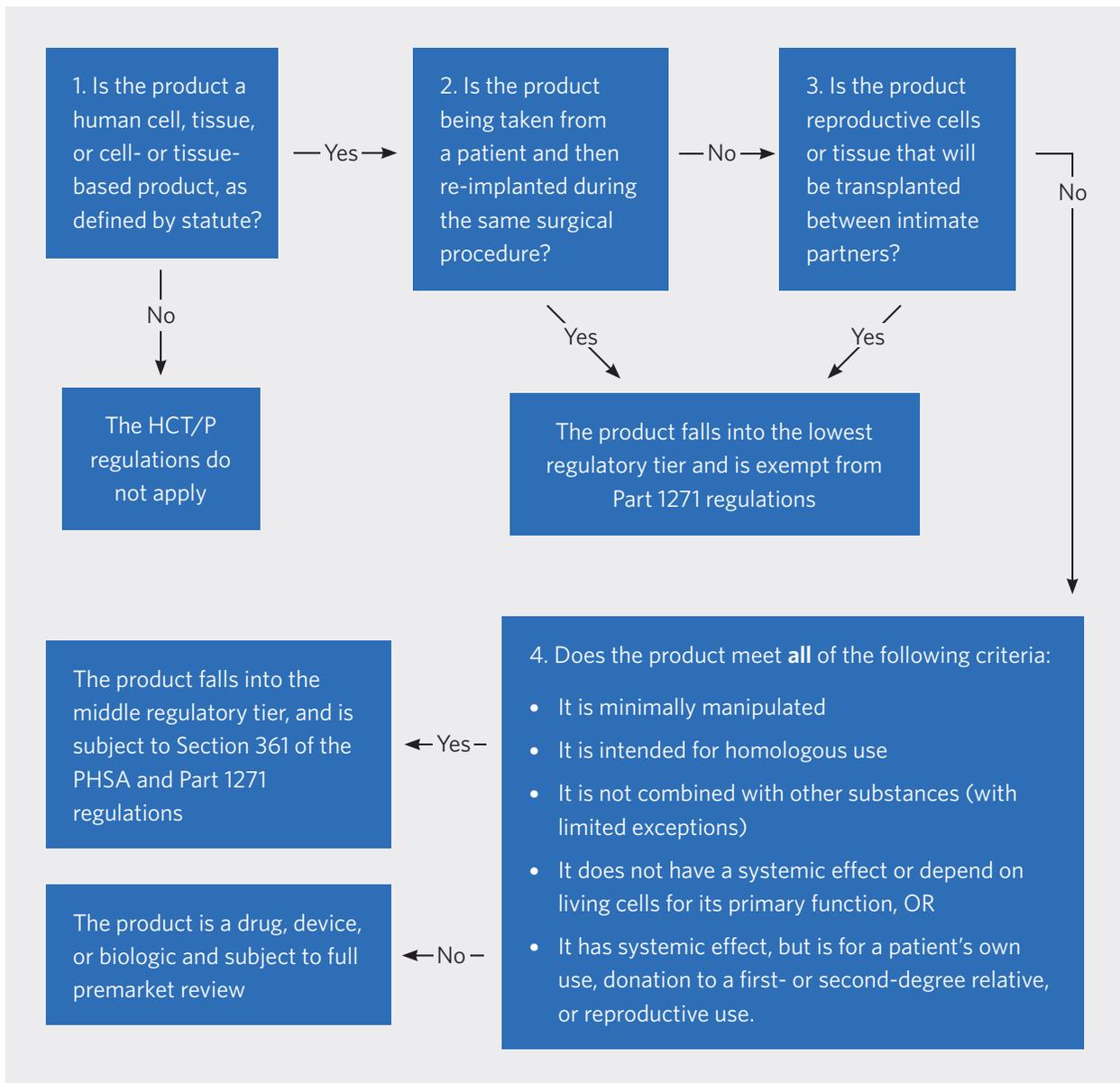
One of those steps was establishment of the RMAT designation, an expedited regulatory pathway authorized under the 21st Century Cures Act. For products that qualify, FDA can take actions to ease the path to market, including conducting a rolling review of application components and providing intensive guidance to developers throughout the process. The agency released two draft guidance documents related to this designation as part of its framework⁶⁵ that were finalized in February 2019.

In addition to the RMAT-related guidance documents, FDA has also pledged to adopt new regulatory concepts that would make the preapproval process more manageable, including collaborative development models that would allow multiple small-scale investigators or manufacturers to work together.⁶⁶ FDA is also implementing a program of informal meetings called INTERACT (short for Initial Targeted Engagement for Regulatory Advice on CBER products; CBER is the FDA's Center for Biologics Evaluation and Research), which will enable potential sponsors to communicate their questions and concerns at an early stage in the development process.⁶⁷



Figure 2

How FDA Determines Regulation of a Regenerative Therapy



Source: U.S. Food and Drug Administration, "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use" (2017), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal>

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Expedited and alternative paths to licensure

FDA maintains five expedited development and review programs for drugs and biologics, all of which are intended to shorten the time to market for products that treat serious conditions. (See Appendix C for a comparison of the expedited pathways.) These programs include breakthrough therapy designation, fast-track designation, priority review, accelerated approval, and RMAT designation. A therapy can qualify for RMAT if it meets three criteria:⁶⁸

1. It is a cell therapy, therapeutic tissue-engineering product, HCT/P, gene therapy, or combination product using any such therapy.
2. It is intended to treat, modify, reverse, or cure a serious condition.
3. Preliminary clinical evidence indicates that the therapy has the potential to address unmet medical needs for such condition.

The guidance also states that RMAT designation does not require data from controlled clinical trials. Rather, the necessary preliminary evidence can include studies with less rigorous designs, such as trials with historical controls (where the treatment group is compared to a control group from a prior study), clinical case series (a collection of individual case studies), and retrospective studies (in which investigators examine data collected previously from a group of subjects, unlike more rigorous prospective studies in which investigators collect data on subjects for pre-specified outcomes).⁶⁹ In practice, it is likely that the type and amount of evidence submitted in support of RMAT designation will vary, depending on the disease context (for example, a rare genetic disease with no available treatments versus a more prevalent condition with several therapeutic options) and where the product is in the development process. RMAT-designated products may also be eligible for other expedited pathways if they meet the associated criteria. RMAT designation can be rescinded if subsequent evidence reveals that the treatment no longer meets the qualification. Receiving a designation is also no guarantee that the product will be approved.

As FDA commissioner, Gottlieb said the agency intended to make maximum use of accelerated approval, especially for cell and gene therapies.⁷⁰ This would allow such treatments to be approved based on outcomes that could be measured at an earlier stage, provided that the product sponsor conducted follow-up studies to confirm the treatment's safety and effectiveness. RMAT-designated products that also receive accelerated approval may be able to rely on alternative forms of evidence to fulfill post-approval commitments that FDA also imposes, including patient registries or other sources of real-world evidence.

Since 2017, the agency has received at least 97 RMAT requests and granted at least 33. The remaining requests have been either denied (53), withdrawn by the sponsor (five), or are pending (six).⁷¹ (See Appendix D for a list of RMAT designations that have been announced by developers.)

Findings and potential next steps

This section outlines the findings that emerged from the Pew-commissioned legal analysis, key stakeholder interviews, and the literature, and highlights potential next steps that FDA and others can take to help ensure the safety and effectiveness of the regenerative therapies on the market.

Stakeholders say FDA framework provides important clarity

Overall, stakeholders reported that FDA's framework provides clarity for regenerative medicine and will have a significant impact on the field's trajectory. Most stakeholders also generally thought the framework constitutes an efficient, risk-based approach to regulating the industry, though not all shared this view. Nevertheless, the

majority viewed the agency's focus on regenerative therapies as a net positive, arguing that tighter control over the industry at this stage would lend legitimacy to the field and provide regulatory certainty, both of which are essential for developers seeking investment, as well as for payers that will eventually make insurance coverage decisions for these new treatments.

Stakeholders particularly welcomed the clarification around how the agency will define fundamental terms like "minimal manipulation," "homologous use," and "such HCT/Ps" for particular types of products. Most perceived this clarity to be important in ensuring that products are developed and regulated appropriately. The main areas of disagreement among interviewed stakeholders centered on where the agency had drawn its distinctions, with two stakeholders criticizing what they perceived to be an unnecessary broadening of the category of products now subject to full premarket review. The final guidances will be particularly disruptive to businesses that depend on adipose- or amnion-derived stem cells, which have already been the subject of FDA litigation as the agency has declared those products to be drugs. Many of these businesses have operated for years under a model that assumed their products were not subject to premarket review and approval.

The majority agreed that the framework is well-rooted in scientific and public health principles and that it was developed through a transparent process that included substantial stakeholder input. While some have suggested that FDA did not sufficiently explain the rationale behind its decisions,⁷² one former regulator noted that the agency has deeper insight into what is being developed than it can reveal, including into potential abuses of regulatory flexibility or enforcement discretion. Guidance may be influenced by FDA's experience with other types of products or by knowledge of work that is underway but that it cannot cite publicly.

Areas of ambiguity and controversy

Though all stakeholders generally agreed that the framework provided additional clarity, there were several areas they felt remained uncertain, as well as areas in which they disagreed with FDA decisions. To a certain extent, ambiguity and scientific disagreement will be unavoidable, particularly given the complexity and diversity of this relatively new field. Stakeholders involved in product development noted that the guidance documents serve as a useful starting point for conversation between FDA and industry, rather than a final decision about how a product will be classified.

Defining the same surgical procedure exception

Some stakeholders felt that the same surgical procedures exception—whereby HCT/Ps that remain in their "original form" and are transplanted within the same patient during the same surgical procedure are grouped into the lowest regulatory tier—may still be ambiguous in certain circumstances. Under the current guidance, the same surgical procedure exception may fail to address nonhomologous use: that is, cases in which the product is used in ways that deviate from its original function. If, for example, a patient's own bone marrow stem cells are isolated and only minimally manipulated before being reimplanted, the exception may apply even if those cells are used to treat, for instance, a neurological condition. This ambiguity regarding nonhomologous use may create a loophole for entities to evade appropriate regulatory scrutiny.

Determining what is—and is not—minimal manipulation

As previously noted, the threshold for determining whether a product is minimally manipulated—and thus avoids the requirement for premarket review—depends in part on whether it is defined as a structural or nonstructural tissue. This binary distinction is somewhat controversial, as human tissues often serve more than one function. While there may be different safety and effectiveness considerations for structural versus nonstructural tissues, the guidance largely does not explain why it has assigned tissues into these two categories.⁷³ Furthermore, this

distinction is made based on the cell or tissue's role in the donor, and some developers have argued that the more important issue is how the product will be used in the recipient.⁷⁴

The classification of adipose tissue as structural is particularly important, as many regenerative products under development or already offered as unapproved interventions are stem cell treatments that rely on adipose-derived stem cells. Under FDA's classification, many of these therapies are considered drug products and thus subject to the full approval process. Most stakeholders supported FDA's decision to classify adipose tissue as structural, citing the newness of the field and the inherent risks associated with unapproved products. Two were more skeptical, either from a belief that it would shut the door on innovation or because they objected to FDA's attempt to legally define a cell or tissue's basic function.

According to one analysis, some of FDA's examples of minimal manipulation may seem inconsistent or arbitrary.⁷⁵ For example, its guidance on this subject states that cutting amniotic tissue into sheets or processing it to remove certain cells does not alter its original relevant characteristics as a barrier; but the agency says grinding or freeze-drying would qualify as more than minimal manipulation because those processes would affect its ability to function as a barrier.⁷⁶ However, the agency has previously held that grinding bone does *not* constitute more than minimal manipulation, even though grinding would change the bone's ability to support the body (in other words, would affect a key characteristic of bone).⁷⁷ The guidance does not address the incongruity between FDA's treatment of amnion and bone under the new criteria. However, while grinding bone to shape it may affect its overall strength, the grinding would not necessarily alter its ability to function as a supportive structure within the body.

Moving forward, it would be helpful for the agency to clearly communicate decisions regarding how it will classify human cell and tissue products and, as appropriate, update the four guidance documents of the regenerative medicine framework to reflect those decisions. Providing additional examples of how different products are regulated under the framework might help to clarify the agency's thinking, and resolve these remaining areas of ambiguity.

Balancing innovation and patient safety in the RMAT-designation process

Several stakeholders, particularly those involved in product development, voiced strong support for the RMAT-designation program, with two praising the effect it has already had by allowing sponsors more frequent interactions with FDA to discuss appropriate endpoints, trial design, and data collection strategies. Others noted that it is too early to determine the impact of the RMAT-designation process on either the field of regenerative medicine or overall public health. As of December 2018, the agency had granted RMAT designation to at least 25 products, though none had been approved.⁷⁸

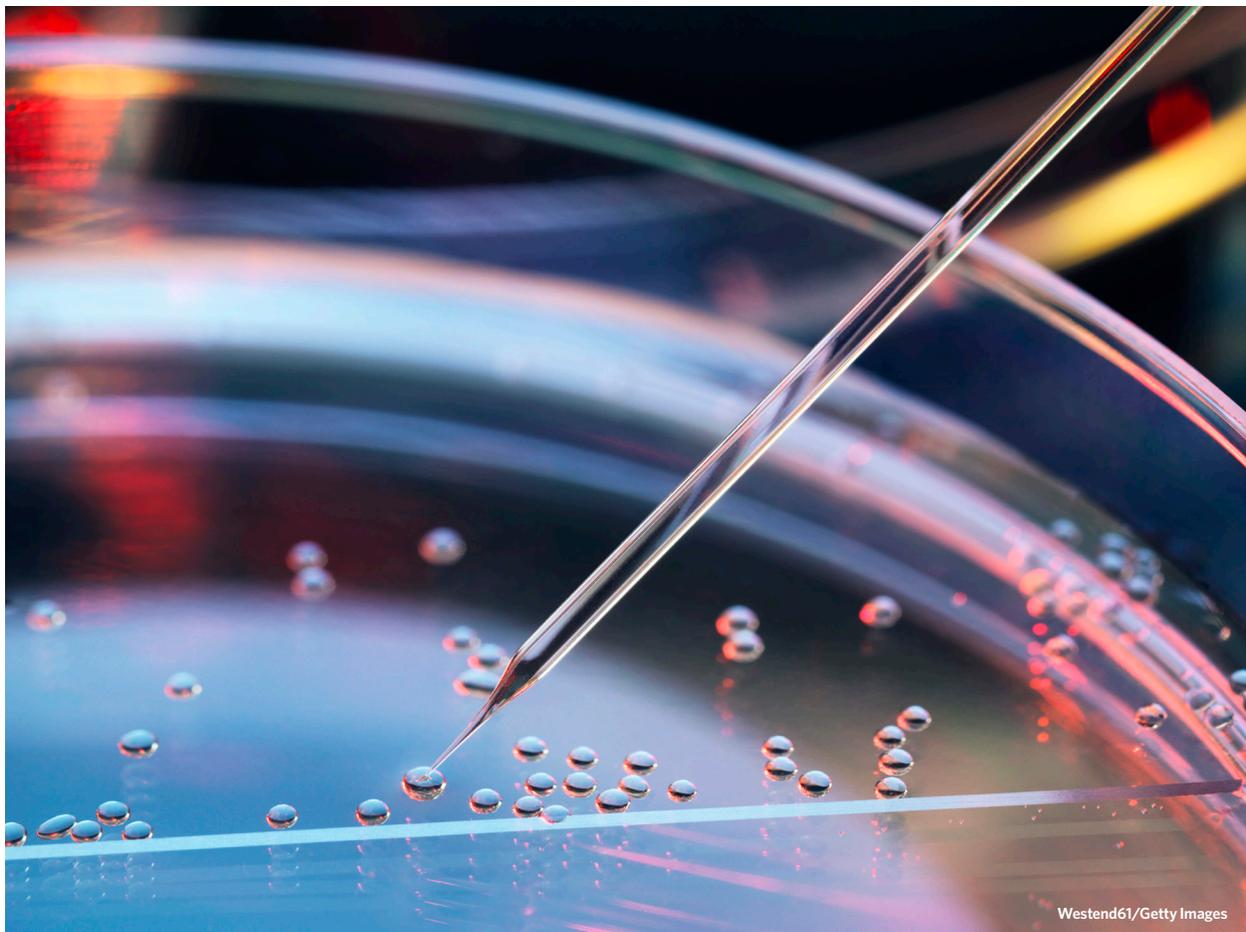
The RMAT designation differs from other expedited programs in terms of the type and level of evidence required to qualify. To be designated as a breakthrough therapy, for example, a treatment must show preliminary clinical evidence that it represents a substantial improvement over other available therapies, while an RMAT must demonstrate only that it could meet an unmet medical need, with no specific requirement that it offer advantages over other treatments. Though RMAT-designated products will need to meet the same evidentiary standard for approval as other therapies, some observers have voiced concern that the designation could increase the chances that regenerative therapies would be approved before they had been adequately tested.⁷⁹ A similar critique has been applied to the other expedited pathways that the agency maintains.⁸⁰ These concerns are not without merit: Drugs approved under expedited pathways may reach the market on the basis of fewer or smaller studies and are significantly more likely to require postmarket revisions to safety-related labeling, a pattern indicating that adverse events emerge only after the drug is on the market.⁸¹ RMAT therapies may, once approved, present similar challenges. However, like any expedited program, RMAT designation is intended for products that treat

serious conditions, sometimes with unmet medical need. In such cases, the higher risks may be acceptable and in line with patient preferences.

Over the last two decades, a greater proportion of new drug approvals has been associated with at least one expedited pathway, and some researchers have questioned whether these designations are being applied too widely.⁸² As more therapies, regenerative or otherwise, are approved based on smaller or shorter trials that rely on surrogate outcomes, the importance of adequate postmarket safety surveillance and completion of post-approval studies increases. However, the existing system for monitoring drug safety has well-known gaps that make it challenging to identify emerging problems, and the agency continues to struggle with enforcing postmarket study requirements for approved products, which are essential in establishing safety and effectiveness.⁸³ As the agency gains experience with the RMAT designation, it will be important for FDA to formally evaluate the program to ensure its efforts to facilitate the development and review process do not come at the cost of approving unsafe therapies.

Longer-term challenges and priorities for FDA

Looking ahead, stakeholders identified longer-term challenges for the still-emerging field of regenerative medicine, as well as specific recommendations that could help FDA achieve its stated regulatory goals of supporting innovation in the field while adequately ensuring patient safety.



Westend61/Getty Images

FDA capacity and resources for enforcement

While most stakeholders agreed that FDA guidance documents constitute an important step in the evolution of the regenerative medicine field, nearly all expressed concern about the agency's capacity to adequately implement them. It is particularly unclear whether and how FDA's efforts will affect the existing commercial market for unapproved stem cell treatments. Though stakeholders supported the agency's recent enforcement actions, nearly all noted that FDA lacks the resources to pursue every clinic that offers unapproved treatments. Two also noted that the cases the agency does take up may be of such high risk that providers of less invasive or more common procedures will continue to consider themselves exempt or come to believe that the agency is tolerant of noncompliance.

One academic researcher raised concerns that clinics may simply decamp to countries with fewer or no regulations. A U.S.-based clinician, they said, could attempt to sidestep the guidance by recruiting patients in the United States and then sending them to another country for the administration of the therapy. Though this has occurred, it is not clear how widespread the practice might be.⁸⁴

The agency has acknowledged the challenge of providing oversight and enforcement for so many businesses and has attempted to address the issue by prioritizing for enforcement those businesses that offer high-risk products.⁸⁵ (Lower-risk products are still within the initial three-year deferral period FDA announced in November 2017 and will not be subject to enforcement until after that.) Enforcement can take different forms, including inspections, warning letters, and—when warning letters are insufficient—legal injunction. However, FDA cannot bring legal actions by itself; the Department of Justice prosecutes such cases at the agency's request.

In May 2018, the federal government filed injunctions against two stem cell firms (one of which has approximately 100 affiliated clinics).⁸⁶ A little over a year later, the U.S. District Court for the Southern District of Florida ruled in one of these cases, affirming that the clinic's stem cell treatments are subject to agency jurisdiction.⁸⁷ However, these types of cases may take years to resolve in court while companies continue to operate. FDA's recent high-profile enforcement actions could have a broader impact on the conduct of other companies, particularly if the two firms at issue are ultimately shut down or given large fines. Such a win for the agency would signal to other providers the risks of offering unapproved interventions. However, this message would be more effective when coupled with additional enforcement activities that target a broader range of providers. For example, the agency issued two additional warning letters in 2018—to a clinic operating in California and a company that manufactures umbilical cord blood stem cells.⁸⁸ Such actions are an encouraging step. Gottlieb, then FDA commissioner, also noted in December 2018 that "time [was] running out for firms to come into compliance during [FDA's] period of enforcement discretion" and said that the agency would increase its oversight, in line with its framework.⁸⁹

As with any regulatory function, enforcement activities require adequate staffing and funding, as well as effective allocation of existing resources by the agency. Though FDA cannot address every business offering unapproved interventions, it can do more to target those that pose a high risk of harm to patients.

In addition to the financial resources needed to assess compliance and to bring the relevant enforcement actions against existing providers, the agency will also need adequately trained reviewers to evaluate applications and support the implementation of the RMAT designation. Attracting and retaining this staff—particularly in a cutting-edge field that is evolving rapidly—may be challenging. Congress sought to address staffing needs within FDA through provisions included in the 21st Century Cures Act. Specifically, the law provided the agency with new hiring authorities designed to improve its ability to draw experienced professionals, including the flexibility to offer salaries outside of the traditional federal pay schedule. Though FDA has recently announced a campaign to improve recruitment and retention, hundreds of vacancies across the agency need to be filled.⁹⁰

And though Congress provided the agency with flexibility in hiring, it did not supplement that authority with additional resources. Peter Marks, research director of FDA's Center for Biologics Evaluation and Research, noted that as of November 2018, the agency had seen an influx of investigational new drug applications—approximately 700.⁹¹ In light of this, Gottlieb articulated the need for 60 additional reviewers and would seek an increase of \$50 million in the agency budget to address this need.⁹² Adequate congressional support for FDA review and oversight activities will be essential to the full implementation of the agency's framework.

Additional guidance needs

Stakeholders engaged in product development also cited a longer-term need for additional guidance, particularly as more regenerative therapies reach the later stages of development and are approved. This includes more direction on the manufacturing of products, development and use of real-world evidence (RWE), and how market exclusivity will apply to regenerative products.

Manufacturing and distribution

Regenerative products present unique manufacturing challenges, largely because they rely on living cells and tissues for source materials, which can be difficult to characterize adequately or to reproduce consistently, particularly at a commercial scale. The field has not yet established consensus standards on how to source raw materials, manufacture products of consistent high quality, or deliver them safely and efficiently to patients.⁹³ The 21st Century Cures Act recognized the longer-term need for such standards and directed FDA to coordinate and prioritize their development, in collaboration with the National Institute of Standards and Technology and other stakeholders.⁹⁴

As part of this effort, the agency is working with the Standards Coordinating Body for Gene, Cell, and Regenerative Medicines and Cell-Based Drug Discovery to advance development and adoption of key standards related to raw materials, testing methodologies, product quality, supply chain logistics, preclinical studies, and clinical trials.⁹⁵ FDA also released updated guidance on chemistry, manufacturing, and control for gene therapies, though not for cell therapies.⁹⁶ Though these are necessary and positive steps, stakeholders noted that regulating the manufacturing and distribution of regenerative therapies will continue to be a challenge for the agency. Additional guidances—or updates and modifications to relevant existing guidances—will be helpful as more regenerative therapies near approval and reach the market.

Harnessing real-world evidence

Under the 21st Century Cures Act, FDA is required to explore the use of RWE for new indication approvals as well as post-approval study requirements, including specifically for RMAT-designated products. According to Gottlieb's statements, many RMAT-designated therapies are likely to be approved under the accelerated approval program⁹⁷—particularly for rare disease treatments—and may require extensive post-approval monitoring to confirm long-term safety and clinical benefit.

According to FDA's definition, RWE refers to clinical evidence that is derived not from randomized clinical trials but from analyzing data that is routinely collected throughout the health care system. This includes electronic medical records, claims, registries, and patient-generated data, among other sources. Such evidence has the potential to inform a variety of regulatory evaluations, including postmarketing surveillance, new uses of approved products, and even premarket approvals. FDA guidance on the use of RWE for satisfying postmarket evidentiary requirements will be helpful. And FDA oversight to ensure that this evidence is robust and reliable will also help address concerns that RMAT-designated products could be approved before they have been adequately tested.

Market exclusivity

Once approved, a regenerative therapy will, like other medical products, be eligible to receive market exclusivity for a defined period, during which it is protected from competition from functionally analogous products. For regenerative therapies and other drug products, the period for market exclusivity varies, depending on the drug and its indication, and could range from six months (if it is a product previously approved in adults that has been subsequently studied and labeled for pediatric use) to seven years (if it is intended to treat a condition that has attracted limited commercial investment). These defined periods of monopoly are intended to give companies a financial incentive to develop new therapies and bring them to market.

Exclusivity can serve public health interests by bringing new therapies to patients but can also delay generic competition and thus raise the price patients and their insurers must pay. However, one industry representative noted that it may be difficult to determine or enforce market exclusivity for some regenerative products. This is partly because many of the therapies under development are highly complex, even compared with other biologics. Because they are largely derived from living cells, they are also subject to variability. In this context, it can be challenging to determine—from scientific and legal standpoints—when a competing product is “the same” as the original product and therefore violating exclusivity provisions.

The challenge of determining exclusivity may also extend to regenerative products that are developed under an alternative model articulated by Gottlieb and Marks.⁹⁸ Under the traditional product development process, a single sponsor manufactures and distributes an investigational product to multiple research sites, collects the data, and submits that data in support of product approval under a single biologics license application (BLA). However, under FDA’s proposed collaborative model, multiple sponsors might collaborate in developing their respective therapies, manufacturing and testing the product at separate sites using common manufacturing and clinical trial protocols. The resulting data would be pooled and submitted as part of separate BLAs. It is unclear how exclusivity would be determined or applied under this model. In FDA’s latest guidance on RMAT, the agency advises potential collaborators to address these concerns upfront but offers no additional information on how this might be done.⁹⁹

The role of other stakeholders in safeguarding public health

While FDA plays a central role in regulating regenerative therapies, other entities can support the agency’s efforts to ensure patient safety and protect the legitimacy of the field more broadly. This section highlights several of these potential interventions, identified through stakeholder interviews and published literature.

Federal interventions

FDA is not the sole federal body with the authority and duty to provide industry oversight or ensure patient safety. The Federal Trade Commission and NIH also have potential roles, particularly in curbing unscrupulous practices.

Federal Trade Commission

The FTC is charged with protecting consumers by stopping unfair, deceptive, or fraudulent practices, including false or misleading advertising. Since 1971, when FDA and the FTC signed a memorandum of understanding,¹⁰⁰ the latter agency has had primary jurisdiction over advertising for foods, nonprescription drugs, devices, and cosmetics. FDA maintains primary jurisdiction over advertising for prescription drug products. However, the jurisdictional boundaries between the two agencies are less clear when it comes to internet claims and advertising related to unapproved drug products.

Companies offering unapproved stem cell products have used widespread advertising campaigns to reach patients, often online, including through social media platforms. Evaluations of the claims made in some of these ads have found many to be inaccurate or misleading about the known benefits or risks of the products, or the strength of the evidence supporting the treatment.¹⁰¹ This has caused substantial concern among researchers and clinicians in the field, as it likely would increase the number of patients seeking unproven, potentially harmful treatments and contributes to undermining the legitimacy of the field.¹⁰² There is substantial scope for the FTC, in cooperation with FDA, to take additional action to combat misleading advertising.

The FTC recently took encouraging steps in this direction. In October 2018, it announced that it had settled charges of deceptive advertising made by a California-based practice that had claimed, among other things, that stem cell therapy could treat Parkinson’s disease, multiple sclerosis, cerebral palsy, macular degeneration, osteoarthritis, strokes, and chronic kidney disease.¹⁰³ Under the terms of the settlement, the provider is prohibited from making future claims that misrepresent the effectiveness of stem cell treatments and will be fined \$3.31 million, which is the amount the practice earned from selling stem cell treatments between 2014 and 2017. (This fine will be partially suspended if the provider pays \$525,000 to the FTC, which may use the money to refund his former patients.)¹⁰⁴

However, the commission faces funding constraints of its own that may limit its ability to pursue individual clinics. It has expansive authority, which includes protecting consumers and maintaining healthy competition across the U.S. economy. The FTC employs roughly 1,100 full-time employees for this work (in comparison, FDA employs more than 17,000), and its budget has declined by more than 8 percent since 2010, adjusted for inflation.¹⁰⁵ Expanding the scope of the FTC’s enforcement against stem cell businesses and others that make misleading claims about their products may require additional appropriations.

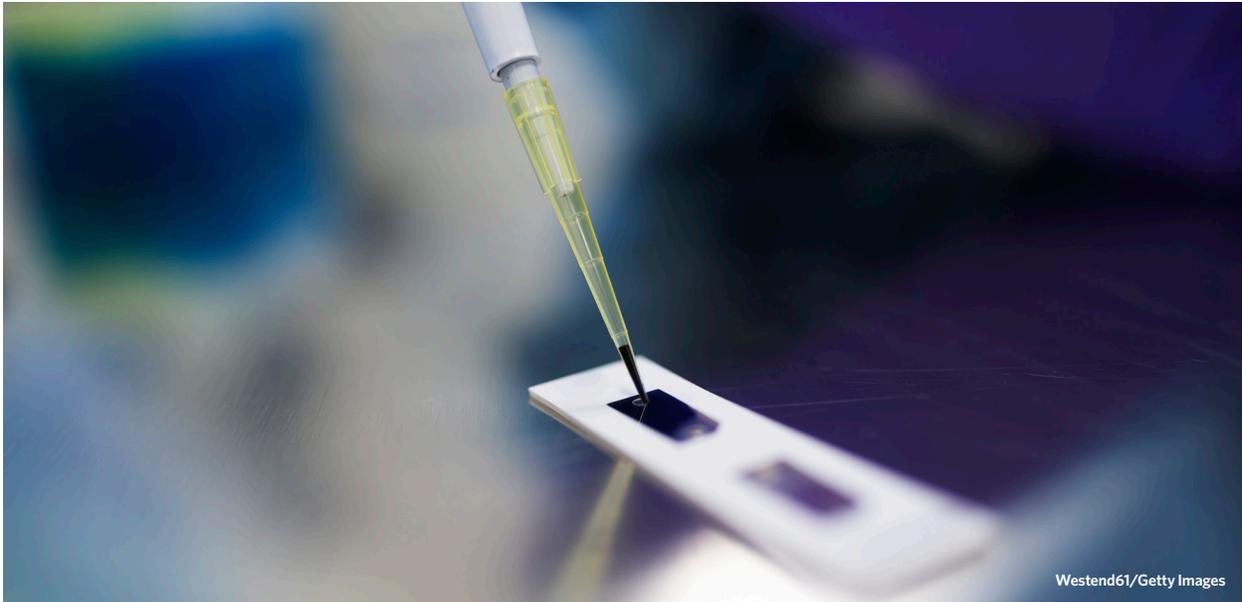
National Institutes of Health (clinicaltrials.gov)

Clinicaltrials.gov, a publicly searchable federal database maintained by NIH, includes information on all studies that are part of an FDA-reviewed product development program—as well as many trials that are not—and is an important resource for patients seeking information on experimental therapies.¹⁰⁶ Companies offering unapproved stem cell interventions will sometimes register on clinicaltrials.gov to recruit patients, who must then pay to participate in what the business is advertising as research.¹⁰⁷ One analysis found at least 18 stem cell studies registered on the website that were charging patients to participate; only seven of these noted participation charges. None listed the prices that those patients would pay.¹⁰⁸ Profiting from trial participants does not conform to conventional clinical research practice and raises significant ethical concerns, including the possibility for patient exploitation.¹⁰⁹

While NIH has added language to the website disclaiming endorsement of listed trials, some researchers have proposed additional safeguards that could help to protect patients and prevent companies from using the database to generate income from unapproved interventions.¹¹⁰ These recommendations include screening clinical studies before they are registered to determine whether they require FDA review and clearance to proceed, whether they intend to charge participants and how much, and whether they have been cleared by FDA to do so. Such trials could be flagged through an automated screening process for additional review before listing to ensure that those requiring FDA clearance have obtained it and that information on whether and how much a sponsor is charging is available to patients using the website.

State-level action

Though the federal government has primary jurisdiction over medical products and clinical research, state governments also play a meaningful role in protecting patients. At least six states have passed or introduced legislation intended to affect the delivery of these treatments, though it is unclear if any best practices have



emerged, and not all state actions have been geared toward stricter patient protections. (See Appendix E for an overview of sample state legislation.) California, Florida, and Washington have introduced or passed legislation that requires providers to alert patients during the informed consent process that the treatment is not approved by FDA. Florida has also sought to require clinics offering such therapies to register with the state, comply with FDA manufacturing standards, and submit to annual state inspections.

By contrast, lawmakers in Texas passed legislation in 2017 that allows patients to access unapproved stem cell therapies outside the FDA regulatory process, and Alabama introduced comparable legislation in 2018. Such laws may not withstand challenge in court as they conflict with federal statute.

In addition, some researchers have called for state attorneys general to take action against businesses providing unproven therapies.¹¹¹ In North Dakota, the state's Consumer Protection Division targeted a clinic's misleading claims, ultimately shutting down the stem cell injection practice and securing refunds for patients in 2018.¹¹² (In spring 2019, however, journalists at *The New Yorker* and ProPublica reported that the clinic's website said it would resume offering stem cell treatments "soon" and that the attorney general's office was reviewing the matter.)¹¹³ And in 2019, New York Attorney General Letitia James filed a lawsuit against a Manhattan clinic and its managing doctor for allegedly engaging in misleading advertising.¹¹⁴ Whether such actions could be a model for other states depends on several factors, including their resources, competing priorities, the number of consumers who are directly affected or the amount of compensation that could be won on their behalf, and the potential for the case to have a broader impact.

One potential limitation to state action is the pre-emptive authority of the federal government to regulate medical products. States may be more reluctant to intervene in cases where they perceive FDA has an established interest and is taking action. However, FDA cannot reasonably be expected to handle every case; adequate coordination and communication between state agencies and FDA can help to address any duplication of effort.

Some researchers have also proposed reforms, where necessary, of the regulations governing medical liability claims and imposition of a "strict liability" standard on clinics or affiliated businesses selling or administering stem cell or similar unapproved interventions.¹¹⁵ Such a standard would hold the clinician or clinic liable for any harm caused by use of the product, without reference to whether the provider in question was negligent in their actions. With a change in the standard for liability claims, companies would have a greater challenge finding

insurers that would cover them for performing such procedures. It would also allow patients to more easily seek redress for any harms arising from the treatments they received.

The role of state medical boards

In addition to action by state government officials, several stakeholders noted that state medical licensing boards could play a more prominent role in ensuring that clinics operate safely and that patients are adequately protected from fraud. The Federation of State Medical Boards published recommendations on regenerative and stem cell therapy treatments in May 2018, outlining best practices for physicians as well as actions that state boards can take to ensure that providers in their jurisdictions are not offering unduly risky treatments to patients.¹¹⁶

It is not clear to what extent those recommendations will be implemented by members or whether state boards will take increased action against providers offering unapproved stem cell therapies. A 2017 survey of all 51 medical boards found that 17 had investigated complaints against physicians related to regenerative medicine or stem cell therapy and eight had taken disciplinary actions as a result, though the nature of this action is not public.¹¹⁷ In November 2018, the California medical board announced the formation of a task force on stem cell and regenerative medicine, which is to investigate the claims made by stem cell providers in the state.¹¹⁸ The timeline and potential outcomes of this process is unclear, though the findings could be used to inform subsequent legislation or other regulatory actions.

State medical boards do not typically conduct proactive investigations of clinician practices, though they do investigate in response to formal complaints, and may conduct background checks to see if a provider has been the target of malpractice suits or other disciplinary or regulatory actions. There are a variety of sources for this information, including the National Practitioner Data Bank (NPDB), maintained by the federal Health Resources and Service Administration; and the Physician Data Center, which is overseen by the Federation of State Medical Boards.¹¹⁹ However, a recent investigation found that state medical boards vary substantially on how often they consult these data sources and that few state or territorial medical boards (12 of 63) are subscribed to receive regular updates on the providers they license.¹²⁰ Furthermore, neither database includes FDA warning letters, so boards may not always be aware when the agency has raised concerns about a provider's practices.

Under current statute, FDA is required to report certain enforcement actions to the federal NPDB, including injunctions, civil or criminal cases that the agency has successfully brought against a provider, and cases in which the agency has debarred or disqualified a clinical investigator from conducting research. Though warning letters are not considered enforcement actions, they are public documents and are posted on the agency website. FDA could institute a policy of sending such letters directly to the boards that license the targeted provider. Including these letters in the NPDB and the Physician Data Center would also be useful to state medical boards that are conducting investigations or background checks on providers.

Cross-cutting interventions

Improved communication to patients and consumers

Stakeholders generally agreed that the public needs more education on regenerative medicine to counter misleading advertising claims and media coverage surrounding the field. Some organizations, including some professional societies, already provide information and education about regenerative medicine—both its current capabilities and limitations—and offer guidance on how patients can evaluate the claims of stem cell providers.¹²¹ Professional societies can also play a role in educating providers on how to communicate, to help ensure that patients make informed decisions about their care.¹²² One 2014 study, however, found that educational materials for stem cell treatments were limited in their availability and comprehensiveness.¹²³ And while scientific societies

could further develop and disseminate information, patients might not absorb it, particularly if they were already disinclined to trust medical authorities.

Some stakeholders further suggested that companies like Google and Facebook should do more to scrutinize their advertisers and remove ads marketing unapproved medical therapies, which would help to reduce the spread of misinformation. These companies have policies regarding the sale of illegal products and could take steps to better police—and remove, where necessary—ads that promote these treatments. These firms (and the website GoFundMe, which hosts many patients' fundraising campaigns for these interventions) may be able to improve their responsiveness to specific complaints about an advertisement and could implement algorithms that search for and eliminate ads that violate their terms of service. But some stakeholders have raised concerns that these companies are not equipped to proactively distinguish between legitimate medical treatments and unapproved interventions.¹²⁴ Nevertheless, there is substantial opportunity for them to develop and implement policies that would prevent their platforms from being used to advertise illegal or unapproved medical interventions.

Several stakeholders noted the need for better informed consent practices in the clinical context (as distinct from the informed consent documents that patients sign as part of their participation in research). This is not specific to regenerative medicine; patients are often misinformed or inadequately informed about the benefits and risks of medical procedures and are infrequently provided with enough information to make informed decisions about their health. The International Society for Stem Cell Research recently published a set of standards aimed at stem-cell based interventions, which if widely adopted could help to ensure patients understand the potential benefits and risks of these treatments.¹²⁵ The broad acceptance of such standards would also provide a foundation for subsequent legal action if providers failed to secure adequate informed consent.

Systematic data collection

Multiple stakeholders noted that systematic, comprehensive data collection on regenerative therapies, including those that are not subject to premarket review, will be of critical importance in establishing their safety, effectiveness, and ultimate value. In addition to findings generated from randomized controlled trials, reliable and robust evidence derived from real world data sources—such as electronic health records and registries—would be highly relevant for a range of audiences. These include FDA as well as clinicians, patients, and the payers who will be making coverage and reimbursement decisions for regenerative therapies. The Centers for Medicare & Medicaid Services (CMS), for example, announced in early 2019 that it would cover chimeric antigen receptor T-cell (CAR-T) therapies for treating cancer in Medicare patients if the treatments were offered as part of a CMS-approved registry or clinical study that tracked patient outcomes for at least two years.¹²⁶ As more regenerative products are developed and approved, the need for robust postmarket data collection systems will grow. Such systems would be especially important for RMAT-designated products, which may be approved based on relatively smaller trials and would likely require many years of follow-up to confirm their safety and efficacy.

Several stakeholders supported the idea of a national, centralized patient registry to document the types of cells being used, key information about their manufacturing process, the indications they are applied in, their method of administration, and the resulting patient outcomes. One strategy, advanced by the Bipartisan Policy Center, would entail expanding the existing Stem Cell Therapeutic Outcomes Database, which is administered by the Health Resources and Services Administration.¹²⁷ However, this registry currently includes products already known to be safe and effective, which have clearly defined clinical outcomes that can be readily interpreted using standardized criteria. Expanding it to include unapproved interventions that carry no such assurance of safety and effectiveness and that may have outcomes that are not well-defined or standardized would pose significant, if not insurmountable, technical challenges and could undermine the integrity and usefulness of the registry.

Additionally, including outcomes from unapproved cell therapies in a government-funded registry could lend an imprimatur of legitimacy to what may constitute illegal activity by businesses operating outside of FDA oversight. Such an expansion would also require legislative action and significant additional funding. The Department of Health and Human Services (HHS) conducted a formal review to determine whether to expand the database in this way, and in August 2019 recommended against doing so.

More broadly, there is a need for agreement on and standardization of the common data elements that should be gathered as part of any data collection effort moving forward. This would greatly facilitate the development of real-world evidence on the safety and effectiveness of regenerative therapies and would ease data sharing and aggregation. Federal support for and coordination of such an initiative—involving NIH and other agencies within HHS—could help to achieve broad stakeholder buy-in and ensure adoption of these standards.

Conclusion

FDA's framework for regenerative medicine marks an important step in the agency's efforts to encourage the development of new therapies while also protecting patients from dangerous unapproved interventions. While the agency has made progress on implementing its various components, its impact on the regenerative medicine industry—and on the successful development of safe, effective, and innovative new therapies—remains to be seen. As FDA moves forward with implementation, clear and timely communication will be key to ensuring success. This includes communicating its decisions regarding how it will classify human cell and tissue products and, as appropriate, updating or finalizing the relevant guidance documents (those that make up the regenerative medicine framework as well as guidance on manufacturing, the use of real-world evidence, and determinations around market exclusivity). It will also be important for the agency to evaluate the impact of the framework's components—such as the RMAT designation and other agency efforts to facilitate development and review—to ensure they are having the desired effects, and adjust its approach as necessary.

While the agency's recent efforts to increase enforcement actions are encouraging, there are still hundreds of providers offering unapproved stem cell interventions in the U.S., and FDA must take further action if it wishes to reduce and eventually eliminate this practice. These enforcement activities could include warning letters and, where necessary, injunctions and product seizures. Direct communication with state regulators—for example, sending FDA enforcement letters to the boards that license the targeted provider—might also encourage boards to investigate and, where appropriate, censure providers or revoke their medical licenses for administering unapproved products.

More broadly, other stakeholders at both the federal and state levels—including the NIH, the FTC, state legislators, medical boards, and state attorneys general—also have a role to play in protecting patients from dangerous or ineffective stem cell interventions. Given the size of the current market for these products, addressing the problem will likely require a combination of different interventions.

Appendix A

Methodology

To better understand the regulatory landscape around regenerative medicine, Pew reviewed relevant literature and commissioned the law firm Sidley Austin LLP to detail the regulatory environment for regenerative therapies, evaluate relevant FDA guidance documents, and identify remaining areas of regulatory uncertainty as well as areas of potential concern or controversy.

Pew also conducted a series of semistructured interviews with 11 expert stakeholders (see below) to obtain a broad range of perspectives on the FDA framework. Interview subjects were selected using a purposive sampling

approach, drawing individuals from across academic research institutions, medical centers, policy and advocacy organizations, a small biotech company, and a research funding organization. Businesses that market unapproved stem cell interventions were not interviewed as part of this process, though the research team did interview two clinicians conducting research on stem cell therapies.

The research team then reviewed interview transcripts to identify broad themes and areas of agreement or disagreement. These findings were combined with the legal analysis provided by Sidley Austin, as well as reviews of the literature. A contracted writer, Dana Trevas, assisted in this process by identifying relevant literature, participating in interviews, and developing a first draft.

Stakeholders interviewed

Eric Anthony, *director of policy, International Society for Stem Cell Research.*

Alta Charo, J.D., *Warren P. Knowles professor of law and bioethicist, University of Wisconsin, Madison.*

Mary Ann Chirba, J.D., *professor of law, Boston College.*

Maria Millan, M.D., *president and CEO, California Institute for Regenerative Medicine.*

Anne-Virginie Eggimann, *vice president, regulatory science, Bluebird Bio Inc.*

Henry Klassen, M.D., *professor and director, Stem Cell & Retinal Regeneration Program, Ophthalmology, University of California, Irvine School of Medicine.*

Marc Scheineson, J.D., *partner, Alston & Bird*

Shane Shapiro, M.D., *medical director, Regenerative Medicine Therapeutics Program, Mayo Clinic.*

Jay Siegel, M.D., *retired chief biotechnology officer and head of scientific strategy and policy, Johnson & Johnson.*

Paul Knoepfler, Ph.D., *professor, department of cell biology and human anatomy, the Genome Center, and the Comprehensive Cancer Center, University of California, Davis School of Medicine.*

Michael Werner, J.D., *partner, Holland & Knight, and executive director, Alliance for Regenerative Medicine.*

Interview guide: Regenerative medicine report

1. FDA announced its new regulatory framework for regenerative medicine in November 2017. Overall, what is your impression/opinion of this framework?
2. What do you think are the primary goals of regulatory oversight for regenerative therapies? What do you think they should be?
3. What do you think are the most important changes/developments?
4. What types of businesses/practices will be most affected by this framework (e.g., is it giving greater clarity to those companies that always knew they were under FDA's authority, or is this really bringing new players into the fold?).
5. Are there any key gaps that have yet to be addressed? If so, what are they and how do you think those gaps should be addressed?
6. Where do you see the main areas of conflict/controversy with respect to this framework?
7. What impact do you think these changes will have on:
 - a. The field of regenerative medicine?
 - b. Patient safety?
8. Outside of FDA regulation, what steps should the broader public health community be taking to ensure that regen therapies are safe and effective?
 - a. Who/what groups should be engaged as part of this broader effort?

Examples of adverse events associated with unapproved stem cell treatments

Year	Reported cases	Reported deaths	Patient country of origin	Location of intervention	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Notes
2004 ^a	5		Not reported	China	Spinal cord injury	Olfactory ensheathing fetal cells	Spinal injection	Meningitis, CSF pleocytosis, ^b gastrointestinal bleeding, pneumonia, fever, headache ^c	
2005 ^d	1		Israel	Russia	Ataxia telangiectasia ^a	Fetal neural stem cells (SCs)	Direct injection into brain, spine	Tumors in brain, spine originating from donor fetal neural stem cells	
2006 ^f	1		Not reported	Egypt	Acute inflammation of spinal cord segments	Mesenchymal SCs (MSCs), embryonic, and fetal neural SCs	Spinal injection	Acute inflammation of brain, spinal cord that damaged myelin sheath protecting nerve fibers	
2006 ^g	1		Thailand	Thailand	Kidney inflammation due to lupus	Hematopoietic SCs	Injection into renal regions (no ultrasound guidance)	Multiple lesions in kidney, liver, adrenal gland	
2009 ^h	1		U.S.	U.S. (California)	Face-lift	Adipose-derived stromal cells	Injections around eye	Bone-like growth in eyelid	

Continued on next page.

Year	Reported cases	Reported deaths	Patient country of origin	Location of intervention	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Notes
2010 ¹	3	2	Italy; Azerbaijan; U.S. (Ohio)	Germany	Unspecified neurological conditions	Bone marrow-derived SCs	Direct injection into brain	Brain hemorrhage; death	Though the treating clinic in Germany was shut down, provider subsequently opened a similar clinic in Lebanon
2010-12 ¹	2	2	U.S. (Indiana, Florida)	U.S. (Florida)	Leg numbness, difficulty walking after cancer treatment; pulmonary hypertension	Grossly filtered bone marrow aspirate; adipose-derived stromal cells	Different methods of administration	Stroke; cardiac arrest; death in both cases	Provider was subsequently barred from practicing medicine in Florida but continues to treat patients in the Dominican Republic ^k
2011 ¹	1	1	U.S.	U.S. (Nevada)	Spontaneous widening of bronchi (for unknown reasons)	Nonspecified SC intervention	Unknown	Death	

Continued on next page.

Year	Reported cases	Reported deaths	Patient country of origin	Location of intervention	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Notes
2012-14 ^m	At least 10	At least 7	Several countries, including U.S. (Illinois)	Italy; Spain; Russia; U.K.; Sweden; U.S.	Various conditions affecting trachea function	SC-coated plastic or cadaveric trachea	Surgical transplant	Pulmonary embolism, postoperative infection, transplant failure; death	Patients were treated by the same surgeon, who was found to have engaged in numerous instances of scientific misconduct
2012 ⁿ	1		Not reported	Japan	Chronic kidney failure	Adipose-derived MSCs	Intravenous infusion	Unspecified neurological event	
2013 ^o	3		Not reported	Not reported	Herniated intervertebral disc	Adipose-derived MSCs	Intravenous infusion	Pulmonary embolism	
2013 ^p	1	1	Australia	Australia	Dementia	Autologous adipose stromal cells	Unknown	Uncontrolled blood loss during liposuction procedure, shock, death	Patient was on anticoagulant medication, which caused uncontrolled bleeding
2014 ^q	6		Canada, U.S. (New York)	Germany	Not reported	Live cell therapy/fresh cell therapy ^r	Intramuscular injections	Q fever	

Continued on next page.

Year	Reported cases	Reported deaths	Patient country of origin	Location of intervention	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Notes
2016-17 ^s	At least 5		Not reported	U.S. (California, other locations not specified)	Various conditions including chronic obstructive pulmonary disease	Adipose-derived stromal cells	Infusion, direct injection into brain, knee, and eyes; inhalation	Loss of consciousness, headaches, confusion, inability to walk, infection, retinal detachment, hospitalization	These adverse events occurred at several affiliated clinics
2018 ^t	13		U.S.	U.S. (Texas, Florida, Arizona)	Various conditions causing joint and back pain	Umbilical cord blood-derived SCs	Injection or infusion	Acute bacterial infections of spine, bones, joints; abscesses; hospitalization	
2018 ^u	1		Not reported	U.S. (Florida)	Arthritis	Not reported	Injection	Vomiting, hospitalization, coma	
Not reported ^v	1		U.S.	Costa Rica	Multiple sclerosis	Allogeneic cord blood MSCs and autologous adipose-derived stromal cells	Spinal injection, intravenous infusion	Catastrophic demyelinating encephalomyelitis ^w	
Not reported ^x	1		U.S.	China, Argentina, Mexico	Ischemic stroke	MSCs, embryonic, fetal neural SCs	Spinal injections	Lesions in spinal cord and surrounding membranes causing lower-back pain, paraplegia, urinary incontinence	

Continued on next page.

Year	Reported cases	Reported deaths	Patient country of origin	Location of intervention	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Notes
Not reported ^y	1		U.S.	U.S.	Face-lift	Fatty aspirate from abdominal wall in a procedure called "stem cell face-lift"	Facial injection	Necrotizing ^z facial ulcerations	
Not reported ^{aa}	1		U.S.	Portugal ^{bb}	Spinal fracture, associated spinal cord injury	Olfactory mucosal cells	Intraspinal transplantation	Spinal mass consisting of large amounts of mucus	
Not reported ^{cc}	3		U.S.	U.S. (Florida)	Age-related macular degeneration	Adipose-derived stromal cells	Eye injections	Hemorrhage and possible retinal detachment in both eyes; one year after injection, patients were either completely blind in both eyes or had minimal vision remaining in one eye	
Not reported ^{dd}	1		Not reported	Not reported	Heart disease	Autologous "precursor" cells	Direct injection into heart	Ventricular fibrillation; unable to undergo heart transplantation; death	

Continued on next page.

Year	Reported cases	Reported deaths	Patient country of origin	Location of intervention	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Notes
Not reported ^{ee}	1		U.K.	Netherlands	Unknown	Umbilical cord blood-derived SCs	Unknown	Serious acute allergic reaction, hospitalization	
Not reported ^{ff}	2		Not reported	Japan, China	Different conditions	Adipose-derived stromal cells	Unknown	Pulmonary embolism; death	
Not reported ^{gg}	2		China	China	Disabilities from a minor stroke; late-stage liver cirrhosis	Allogenic SCs (not specified)	Spinal, intramuscular injections	Death	Patient with late-stage liver cirrhosis died as a result of being taken off of hepatitis B medication in order to undergo stem cell treatment
Not reported ^{hh}	1		Russia	Russia	Aging	Human embryonic SCs	Skin injection	Pea-size facial tumors	
Total	69	18							

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Appendix C

Comparing FDA’s expedited pathways^a

	Fast track	Breakthrough	RMAT	Accelerated approval	Priority review
Qualifying criteria	<p>Intended to treat a serious condition; and</p> <p>Nonclinical or clinical data demonstrates the potential to address an unmet medical need; or</p> <p>Meets the statutory definition of a qualified infectious disease product</p>	<p>Intended to treat a serious condition; and</p> <p>Preliminary clinical evidence indicates the drug may demonstrate substantial improvement over existing therapies in at least one clinically significant endpoint</p>	<p>Meets the definition of regenerative medicine therapy;</p> <p>Is intended to treat, modify, reverse, or cure a serious condition; and</p> <p>Preliminary clinical evidence indicates the drug has the potential to address unmet medical needs for such disease or condition</p>	<p>Intended to treat a serious condition;</p> <p>Provides a meaningful therapeutic advantage over available therapies;</p> <p>Demonstrates an effect on: (1) a surrogate endpoint that is reasonably likely to predict clinical benefit; or (2) a clinical endpoint that can be measured earlier than irreversible morbidity and mortality that is reasonably likely to predict benefit</p>	<p>An application (original or efficacy supplement) for a drug that:</p> <ul style="list-style-type: none"> • Treats a serious condition; and • If approved, would provide a significant improvement in safety or effectiveness; or <p>An application for a drug that is:</p> <ul style="list-style-type: none"> • Submitted under a priority review voucher; • Designated as a qualified infectious disease product; or • Receiving an additional approval for use in children
Benefits	<p>Actions to facilitate development and expedite review (i.e., possibility of rolling review)</p>	<p>Actions to expedite development and review (e.g., rolling review)</p> <p>Intensive guidance on efficient drug development</p> <p>FDA commitment involving senior managers</p>	<p>All breakthrough therapy designation features, including early interactions to discuss any potential surrogate or intermediate endpoints</p>	<p>Approval is based on an effect on a surrogate or intermediate clinical endpoint that is reasonably likely to predict a drug’s clinical benefit</p> <p>Post-approval confirmatory trials are required to verify the effects</p>	<p>Shorter review time of marketing application (goal of 6 months instead of the standard 10-month review)</p>

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Appendix D

Publicly announced products designated as RMATs

FDA does not publicly announce when it has granted RMAT designation for a product, though companies may publicize this information. This list includes companies that have announced their designation as of December 2018. The designated products range across several disease areas and include cell, tissue, and viral vector-based therapies.

Table D.1

Products With RMAT Designations

Company	Product name	Indication
Cardiology		
Caladrius	CD34+ cell therapy	Angina
Humacyte	Vascular Access	Hemodialysis
Mesoblast	MPC_150-IM	Heart failure
Vericel	Ixmyelocel-T	Advanced heart failure
Chromosomal abnormalities		
Abeona Therapeutics	ABO-102	Sanfilippo syndrome type A
Enzyvant	RVT-802	Digeorge syndrome
Dermatology		
Abeona Therapeutics	EB-101 Gene Therapy	Epidermolysis bullosa
Mallinckrodt	Stratagraft	Skin burns
Hematology/oncology		
Bluebird Bio	Lentiglobin	Sickle cell disease
Cellerant Therapeutics	Romyelocel-L	Infection prevention during neutropenia
Iovance	Lifileucel	Metastatic melanoma
Juno	JCAR017	Blood cancer
Kiadis Pharma	ATIR101	Blood cancer and other blood disorders
Poseida Therapeutics	P-BCMA-101	Multiple myeloma
Rocket Pharmaceuticals	RP-L102	Fanconi anemia
Musculoskeletal conditions		
Audentes	AT132	X-linked myotubular myopathy
Capricor	CAP1002	Duchenne muscular dystrophy
MiMedx Group	AmnioFix	Osteoarthritis
Neurology		
Athersys	MultiStem	Ischemic stroke
AxoGene	Avance	Nerve injuries
Asterias	AST-OPC1	Spinal cord injury
Fortress Biotech	Cellvation's CEVA101,	Traumatic brain injury
Voyager Therapeutics	VY-AADC	Parkinson's disease
Ophthalmology		
jCyte	jCell	Retinitis pigmentosa
NightStar	NSR-REP1	Choroideremia

Note: Listed companies announced their designation as of December 2018.

Source: Paul Knoepfler, "RMAT List 27," The Niche (blog), Knoepfler Lab Stem Cell Blog, <https://ipscell.com/rmat-list>

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Appendix E

Sample state legislation targeting stem cell businesses, procedures

State	Bill number	Introduced	Status (as of June 30, 2019)	Summary
AL	S.B. 16	Jan. 9, 2018	Referred to committee	<p>Seeks to allow for the provision of investigational adult stem cell therapies to patients with severe chronic or terminal diseases.</p> <p>Before receiving treatment, a patient's doctor must have exhausted other treatment options and the patient must sign an informed consent form.</p> <p>Treatment must be overseen by an institutional review board (IRB).</p> <p>The state medical board is prohibited from taking action against physicians providing treatment in compliance with the act.</p>
CA	S.B. 512	Feb. 16, 2017	Enacted	<p>Requires health care practitioners offering unapproved stem cell treatments to provide patients with information that will allow them to give informed consent.</p> <p>Providers must communicate in writing to their patients and in prominent signage at their offices that the practitioner provides unapproved interventions.</p> <p>Fines may be levied against providers in noncompliance and the state medical board must, in its annual report, include information related to complaints or actions taken against providers of stem cell therapies.</p>
CA	S.B. 1495	Feb. 28, 2018	Enacted	<p>Seeks to modify the informed consent requirements established under S.B. 512, which pertains to health care practitioners providing stem cell treatments that have not been approved by the Food and Drug Administration.</p> <p>Limits the informed consent requirements to providers offering unapproved treatments that are subject to FDA regulation.</p> <p>Excludes treatments that are subject to FDA oversight under an investigational new drug or investigational device exemption.</p>
FL	S.B. 1508/ H.B. 1185	Jan. 3, 2018	Failed to pass committee	<p>Seeks to require the registration of facilities in which stem cell treatments are provided.</p> <p>Would require physicians offering such treatments to comply with quality standards called current good manufacturing practices for human cells, tissues, or human cell- or tissue-based products and would require annual state inspections.</p> <p>Would require the adoption of rules regarding advertising, adverse event reporting, and informed consent guidelines, and would impose fines on providers and businesses for noncompliance.</p>

Continued on next page.

State	Bill number	Introduced	Status (as of June 30, 2019)	Summary
FL	H.B. 65	Nov. 29, 2018	Failed to pass committee	<p>Establishes patient eligibility criteria and requirements relating to access and use of investigational stem cell treatments.</p> <p>Requires Department of Health to adopt rules for administering the legislation.</p> <p>Prohibits governmental interference in such treatments.</p> <p>Requires IRBs to oversee treatments, keep records, and submit reports.</p> <p>Prohibits purchase or sale of stem cells and provides penalties for violations.</p>
GA	S.R. 1059	Feb. 24, 2016	Enacted	<p>Establishes a Senate Study Committee on Nonembryonic and Nonfetal Cell Therapy to study issues related to the provision of stem cell therapies, including disciplinary action taken against the providers of such therapies.</p> <p>Committee was not appointed, and no findings were produced.</p>
TX	H.B. 810	Jan. 3, 2017	Enacted	<p>Permits the use of investigational adult stem cell treatments in patients with chronic or terminal diseases.</p> <p>Investigational treatments are defined as being stem cell treatments that are being administered to patients as part of a clinical trial.</p> <p>Providers are required to consider all other FDA-approved treatment options and patients are required to sign an informed consent form.</p> <p>Treatments must be provided by certified physicians at registered facilities overseen by an IRB.</p> <p>Prohibits state medical board action against physicians providing treatment under this act.</p>
WA	H.B. 2356	Jan. 3, 2018	Enacted	<p>As part of the informed consent process, requires providers of unapproved stem cell therapies to include written notice of the therapy's unapproved status, anticipated results, alternative treatments, and potential risks and benefits associated with the treatment.</p> <p>Requires inclusion of such a notice in any advertisements for the unapproved therapy.</p>

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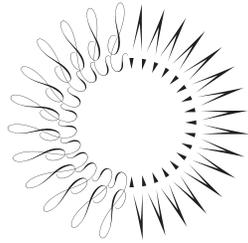
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