

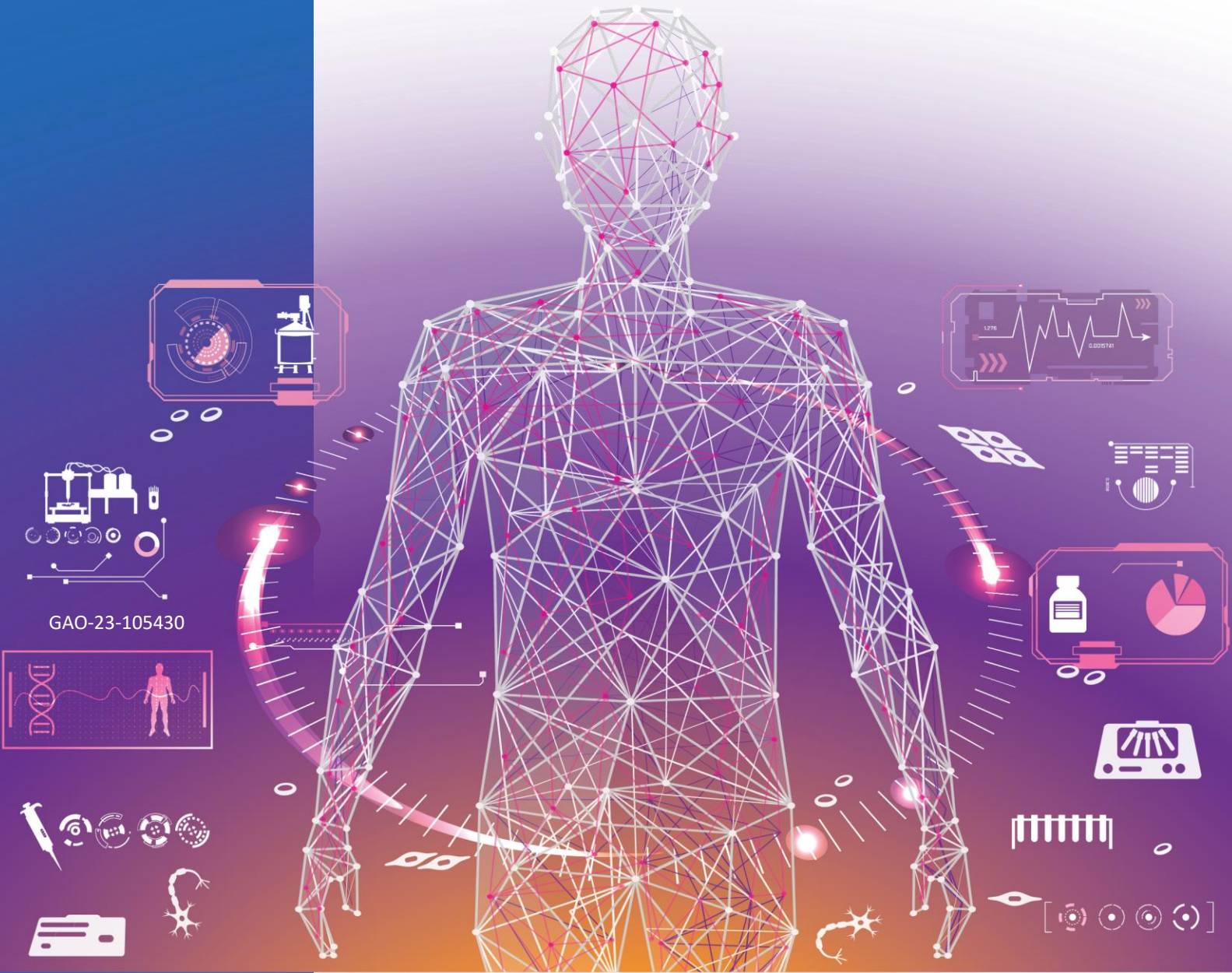
July 2023

## TECHNOLOGY ASSESSMENT

# Regenerative Medicine

### Therapeutic Applications, Challenges, and Policy Options

Accessible Version



GAO-23-105430

The cover image displays a stylized representation of a human body, circled by icons representing key regenerative medicine technologies.

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### Why GAO did this study

Regenerative medicine represents a paradigm shift in the medical field because it aims to restore or supplement function, rather than just treating symptoms, and opens the door for personalized therapies.

GAO conducted an assessment of current and emerging regenerative medicine technologies and therapeutic applications. This report examines (1) current and emerging regenerative medicine technologies and therapies and their potential benefits, (2) challenges that hinder their development and use, and (3) policy options that could help enhance benefits and mitigate challenges associated with these technologies and therapies.

GAO reviewed scientific and policy literature and other key reports; convened a 3-day expert meeting; and interviewed subject matter experts and stakeholder groups including government agencies, such as the Department of Health and Human Services, non-government organizations, industry, academia, end user groups such as patient groups. GAO is identifying policy options in this report.

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# Regenerative Medicine

## Therapeutic Applications, Challenges, and Policy Options

### What GAO found

Regenerative medicine offers the hope of being able to restore or replace cell, tissue, and organ functions affected by disease, injury, or aging. This may eventually help manage or cure many conditions that are currently considered chronic, untreatable, or terminal.

#### Examples of Diseases and Regenerative Medicine Therapies That Might Address Them

	<b>Cancer</b> CAR T cell therapy
	<b>Sickle cell disease</b> Genetically edited stem cell therapy
	<b>Age-related macular degeneration</b> Retinal pigment epithelial cell patch
	<b>Bone injuries</b> Bioprinted bone replacement
	<b>Diabetes</b> Pancreatic cell organoid implant

Source: GAO (analysis); Designcells/antoniotruzzi/firefightermontreal/sutthab/rfbsip/stock.adobe.com (images). | GAO-23-105430

GAO identified many challenges that may affect the development and use of regenerative medicine technologies and therapies including:

**Challenges related to standardization.** Standards are rules, conditions, guidelines, or agreed-upon practices that are adopted within an industry to provide developers with a common framework and promote consistency. Developing regenerative medicine standards is challenging because these technologies and therapies are complex and rapidly evolving. In addition, standards require consensus from stakeholders, which may be difficult to obtain.

**Challenges related to regulation.** The Food and Drug Administration (FDA) ensures the safety, efficacy, and security of human medical products in the U.S. through regulation. Regenerative medicine faces challenges related to regulation, including difficulty navigating a complex regulatory framework, uncertainty over which regulatory pathway is most appropriate for certain emerging technologies and therapies, and staffing shortages at FDA and collaborating agencies.

**Challenges related to manufacturing.** Manufacturing is the creation of products from starting materials, in a way that is generally consistent and reproducible. It is a key step for many emerging technologies and therapies, but the cells, tissues, and organs used for regenerative medicine are complex and difficult to manufacture at scale. Other challenges related to manufacturing include a lack of infrastructure and difficulty ensuring quality and consistency.

GAO developed 11 policy options that could help address the challenges or enhance the benefits of regenerative medicine. These policy options are provided to inform policymakers of potential actions to address the policy challenges identified in this technology assessment. They identify possible actions by policymakers, which include Congress, federal agencies, state and local governments, academic and research institutions, and industry. Policymakers would need to consider the impacts these new technologies will have on existing federal programs that are already strained. We suggested possible federal components for the policy options. See tables 1-3 for a full list of the policy options, potential implementation approaches, and opportunities and considerations.

**Selected Policy Options to Mitigate Challenges Associated with Regenerative Medicine Technologies and Therapies**

Selected policy option	Opportunities	Considerations
<p><b>Invest in standards development.</b> (report p. 25)</p> <p>This policy option could help address the challenge that standards require consensus.</p>	<ul style="list-style-type: none"> <li>• Could streamline standards development, which may, in turn, accelerate innovation, increase product safety and reliability, accelerate regulatory review, and decrease costs of regenerative medicine therapies.</li> </ul>	<ul style="list-style-type: none"> <li>• Existing organizations may not include all stakeholders, and stakeholders may hesitate to accept standards created without their input.</li> <li>• Industry stakeholders may hesitate to adopt standards if they perceive it will cost them a controlling position in the market.</li> <li>• Standards should be appropriately flexible to allow for innovation, while still being detailed and specific enough to support manufacturing of consistent, quality products.</li> </ul>
<p><b>Provide opportunities for increased interactions between regulatory experts (at FDA or in industry) and smaller companies, especially early in the development process</b> (report p. 31)</p> <p>This policy option could help address the lack of access to regulatory expertise.</p>	<ul style="list-style-type: none"> <li>• May provide more timely advice and avoid unnecessary delays or uncertainty by pursuing the wrong regulatory pathways or submitting data that do not meet regulatory requirements.</li> </ul>	<ul style="list-style-type: none"> <li>• May require additional resources to bolster the workforce of regulatory scientists at FDA or public-private partnerships.</li> <li>• FDA may be limited in its ability to advise companies early in the process so as not to create a conflict of interest.</li> </ul>
<p><b>Consider whether changes to the framework for evaluating combination products and medical devices to accommodate emerging technologies and therapies may be necessary.</b> (report p. 32)</p> <p>This policy option could help address whether current regulatory pathways are sufficient for emerging technologies and therapies.</p>	<ul style="list-style-type: none"> <li>• May encourage innovators, researchers, and developers of new products to provide valuable feedback to regulators.</li> </ul>	<ul style="list-style-type: none"> <li>• Coordinating among stakeholders to consider changes to regulatory pathways may be time- and resource-intensive.</li> <li>• If such consideration leads to recommended changes to the framework, statutory and regulatory changes may be necessary.</li> </ul>
<p><b>Provide more oversight and feedback to suppliers to increase consistency in starting materials</b> (report p. 39)</p> <p>This policy option could help address inconsistency in starting materials for manufacturing.</p>	<ul style="list-style-type: none"> <li>• May accelerate manufacturing by reducing variation in input materials.</li> <li>• May reduce the risk of failure during product development.</li> </ul>	<ul style="list-style-type: none"> <li>• Starting material suppliers may lack incentives to follow standards if they lead to higher costs.</li> </ul>

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## Abbreviations

AMD	age-related macular degeneration
CAR T Cell	chimeric antigen receptor T cell
CQA	critical quality attribute
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
FDA	Food and Drug Administration
NIST	National Institute of Standards and Technology
RMAT	regenerative medicine advanced therapy
SCB	Standards Coordinating Body for Gene, Cell, and Regenerative Medicines and Cell-Based Drug Discovery





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July 13, 2023

The Honorable Bernard Sanders  
Chair  
The Honorable Bill Cassidy, M.D.  
Ranking Member  
Committee on Health, Education, Labor, and Pensions  
United States Senate

The Honorable Frank D. Lucas  
Chair  
The Honorable Zoe Lofgren  
Ranking Member  
Committee on Science, Space, and Technology  
House of Representatives

Regenerative medicine technologies offer the hope of creating therapeutic products that restore cell, tissue, and organ functions affected by disease, injury, or aging. These technologies represent a paradigm shift in the medical field, away from developing therapies that treat symptoms and toward creating products that cure the underlying disease or restore function. They also open the door to personalized therapies that use an individual’s own genes or cells, sometimes engineered to replace or augment their functions. Currently, these technologies are being used to create life-saving therapies for broad categories of diseases, which may help Americans with diabetes (accounting for one-quarter of all U.S. health care costs), cancer (about 1.7 million new cases annually), non-fatal fall injuries (about 8 million cases in 2018), or age-related macular degeneration (AMD) (about 20 million cases overall as of 2019).<sup>1</sup> In addition, regenerative medicine may one day offer relief to the approximately 104,000 individuals in need of an organ transplant who are on a waiting list that far exceeds availability.<sup>2</sup>

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<sup>1</sup>Centers for Disease Control and Prevention, *Cancer Data and Statistics*, <https://www.cdc.gov/cancer/dcpc/data/>, accessed Mar. 17, 2023. Briana Moreland et al. Trends in Nonfatal Falls and Fall-Related Injuries Among Adults Aged ≥65 Years — United States, 2012–2018. *MMWR Morb Mortal Wkly Rep* 2020;69:875–881. <http://doi.org/10.15585/mmwr.mm6927a5>. Centers for Disease Control and Prevention, *Prevalence of Age-Related Macular Degeneration (AMD)*, <https://www.cdc.gov/visionhealth/vehss/estimates/amd-prevalence.html>, accessed Mar. 17, 2023.

<sup>2</sup>The Health Resources and Services Administration website shows 104,200 individuals were on the organ transplant waiting list as of March 2023. <https://www.organdonor.gov/learn/organ-donation-statistics>, accessed Mar. 28, 2023.

GAO has done prior work on funding streams, workforce, and education for regenerative medicine and the known problems within the organ transplant system.<sup>3</sup> We prepared this report under the authority of the Comptroller General in light of congressional interest in the potential of this field. This report examines:

- (1) current and emerging regenerative medicine technologies and therapies and their potential benefits,
- (2) challenges that hinder the development and use of regenerative medicine technologies and therapies, and
- (3) policy options that could help enhance benefits and mitigate challenges associated with these technologies and therapies.

To address these objectives, we conducted a literature search; interviewed officials and representatives from government, industry, academia, and end user groups such as patient groups; and convened a 3-day expert meeting. See appendix I for the full objectives, scope, and methodology used in this report and appendix II for the list of participants in our expert meeting.

We conducted our work from September 2021 through July 2023 in accordance with all sections of GAO's Quality Assurance Framework that are relevant to technology assessments. The framework requires that we plan and perform the engagement to obtain sufficient and appropriate evidence to meet our stated objectives and to discuss any limitations to our work. We believe that the information and data obtained, and the analysis conducted, provide a reasonable basis for the findings and conclusions in this product.

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<sup>3</sup>GAO, *Regenerative Medicine and Advanced Therapies: Information on Workforce and Education*, [GAO-23-106030](#) (Washington, D.C.: Mar. 23, 2023); *Organ Transplants: Changes in Allocation Policies for Donated Livers and Lungs*, [GAO-21-70](#) (Washington, D.C.: Oct. 16, 2020); *Regenerative Medicine: Federal Investment, Information Sharing, and Challenges in an Evolving Field*, [GAO-15-553](#) (Washington, D.C.: June 23, 2015).

# 1 Background

## 1.1 Definition

Regenerative medicine refers to a general approach to restore, replace, or recreate cells, tissues, or organs to treat or mitigate disease.<sup>4</sup> Under the Federal Food, Drug, and Cosmetic Act, the Food and Drug Administration (FDA) regulates regenerative medicine products, which include cell therapies, therapeutic tissue engineering products, combination products using such therapies or products, some gene therapy products, and certain human cell and tissue products.<sup>5</sup>

## 1.2 How regenerative medicine works

Regenerative medicine aims to develop new therapies that offer benefits beyond those offered by existing medical treatments. These therapies can be highly personalized and may eventually help manage or cure many conditions that are currently considered chronic, untreatable, or terminal. These include heart disease, diabetes, cancer, and sickle cell disease, as well as severe burns and certain types of bone fractures.

Regenerative medicine works by harnessing the body's own healing ability to restore lost function, to establish normal function

that was absent at birth, or to augment natural function to fight a disease. There is a wide range of technologies available in the field. For example, some researchers are using gene editing technology to correct genetic defects or introduce new healing capabilities for diseases such as sickle cell disease. Another tool is the use of implanted materials that, unlike existing medical implants, interact with the body to encourage healing. Yet another is tissue engineering, the practice of combining materials, cells, and biologically active molecules into functional tissues. These tools can often be used on or in combination with patients' own cells, which could bring additional benefits. For example, the use of a patient's own cells to create a personalized organ could transform organ transplantation by alleviating donor organ shortages and eliminating organ rejection—a reaction to foreign biological material that requires transplant patients to take immunosuppressive drugs for the rest of their lives.

## 1.3 The development and licensure process for biologics

Biologics, a category that includes regenerative medicine products, are a diverse group of products regulated by

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<sup>4</sup>See 21 U.S.C. § 356(g)(8).

<sup>5</sup>Certain regenerative medicine products may be eligible for regenerative medicine advanced therapy (RMAT)

designation, which provides drug sponsors with certain benefits, such as expedited review. See 21 U.S.C. § 356(g).

FDA.<sup>6</sup> FDA is responsible for the safety, efficacy, and security of human medical products marketed in the U.S., which for biologics, includes premarket review and approval of a biologics license application. Figure 1 shows the conventional process for developing and licensing regenerative medicine products.

Depending on the medical product type, different FDA centers may handle the review process: the Center for Drug Evaluation and Research (CDER) (which regulates drugs and certain biologics), the

Center for Biologics Evaluation and Research (CBER) (which regulates most biologics), and the Center for Devices and Radiological Health (CDRH) (which regulates devices). Agency officials told us that regenerative medicine products are generally under the purview of CBER. For combination products—such as those that combine two or more regulated products (e.g., a biologic and a device)—the center with primary jurisdiction over the product’s primary mode of action will review and regulate the product.<sup>7</sup>

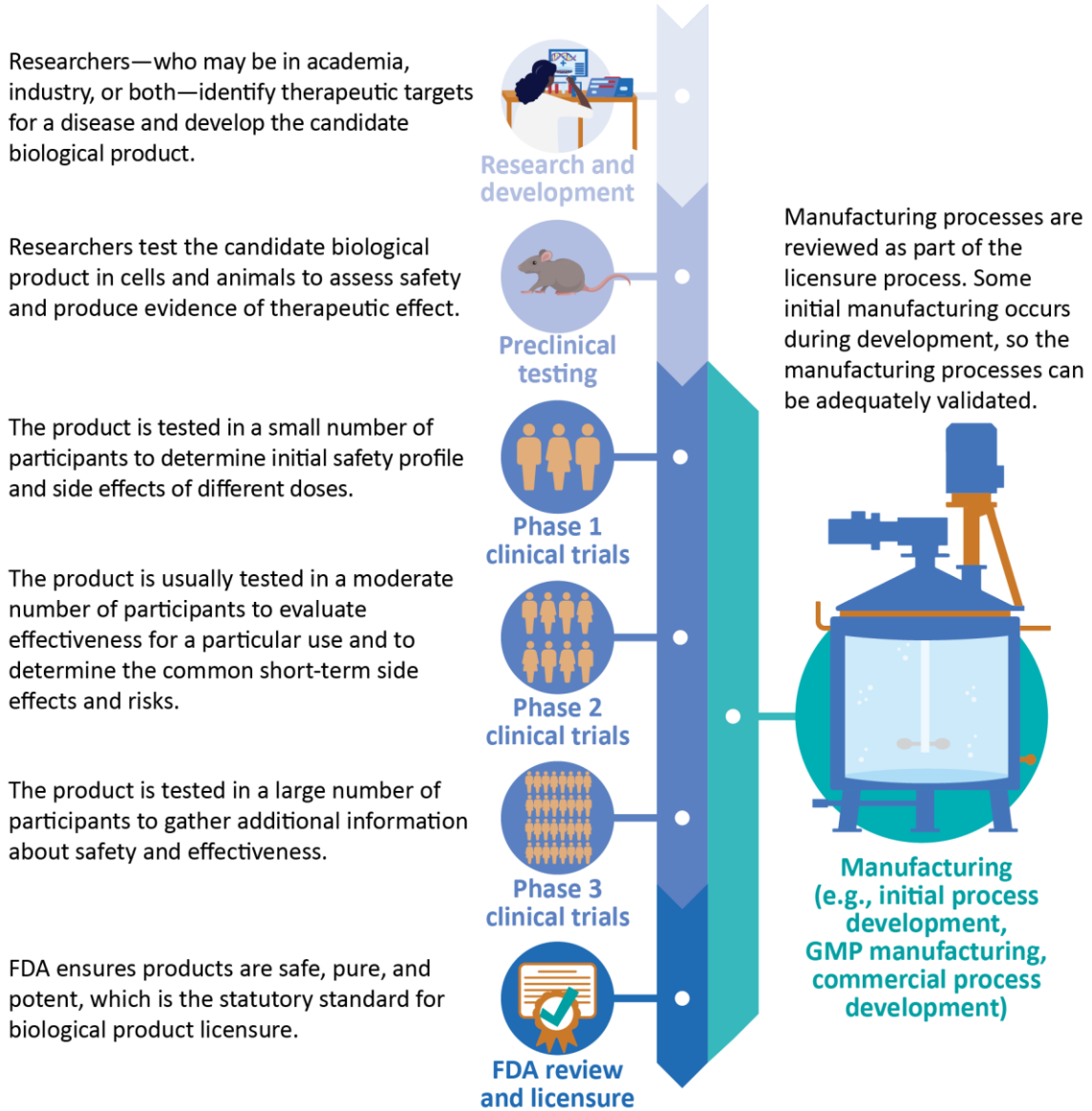
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<sup>6</sup>Biological products—which may also be called biologics—include vaccines and allergenic products, blood and blood components, and proteins applicable to the prevention, treatment, or cure of a disease or condition. 42 U.S.C. § 262(i)(1). Biologics are derived from living sources, such as humans, animals, and microorganisms. FDA licenses biologics that are safe, pure, and potent (i.e., safe and effective).

<sup>7</sup>The primary mode of action is the single mode of action of a combination product that provides the most important

therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effect of the combination product. 21 C.F.R. § 3.2(m) (2022). The Office of Combination Products assigns combination products to FDA’s medical product centers for review, and coordinates reviews involving more than one FDA center.

**Figure 1: Conventional development and licensure process for regenerative medicine products**



Source: GAO analysis of Food and Drug Administration (FDA) information (data); Barbulat/happypictures/microone/stock.adobe.com (images). | GAO-23-105430  
 Notes: The steps shown in the figure are not drawn to time scale, and the specific development steps for a given product may vary and may overlap. Interactions with FDA can begin at the preclinical testing stage of development and FDA oversight begins with clinical studies in human subjects.  
 Biological products—which may also be called biologics—include vaccines and allergenic products, blood and blood components, and proteins applicable to the prevention, treatment, or cure of a disease or condition. 42 U.S.C. § 262(i)(1). Biological products are derived from living sources, such as humans, animals, and microorganisms. FDA licensure: biologics that are safe, pure, and potent (i.e., safe and effective).

## 1.4 Advancements in regenerative medicine

FDA first licensed a tissue-engineered product in 1998—a skin graft for the treatment of a form of skin ulcers.<sup>8</sup> Since then, technological advances have increased steadily, and the number of investigational new drug applications for regenerative medicine products, as well as the number of products in clinical trials continues to grow.<sup>9</sup> These applications include cell therapy to cure blood cancers and gene therapy to cure sickle cell disease. Further, researchers have successfully grown whole organs such as livers and bladders.

Despite these advances, the number of regenerative medicine products licensed for use in humans remains small. Many regenerative medicine products are considered more complex than certain other biologics, such as monoclonal antibodies. Unlike drugs, cells and tissues are living, constantly changing, and variable

from person to person. This fact underpins many of the challenges in the field, which we describe in chapter 3.

Recent laws may help accelerate medical product development, bringing new innovations and advances to patients more quickly and efficiently. For example, the 21st Century Cures Act created an expedited process for FDA evaluation of certain regenerative medicine therapies, known as the regenerative medicine advanced therapeutic (RMAT) designation.<sup>10</sup>

Chapter 2 of this report discusses the current and emerging technologies in regenerative medicine, including cell, tissue, and organ technologies that may be used to develop therapeutic products. Chapter 3 discusses the challenges that researchers and developers face in developing and bringing regenerative medicine products to market. In chapter 3, we also present policy options that may help address these challenges.

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<sup>8</sup>FDA CDRH, Summary of Safety and Effectiveness Data, [https://www.accessdata.fda.gov/cdrh\\_docs/pdf/P950032S016b.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf/P950032S016b.pdf), 7, accessed Mar. 27, 2023.

<sup>9</sup>A drug sponsor may not conduct human clinical trials until it has submitted an investigational new drug application to FDA. Once submitted, the sponsor may begin clinical trials after 30 days unless FDA issues a clinical hold. See 21 C.F.R. § 312.40 (2022).

<sup>10</sup>Pub. L. No. 114-255, § 3036, 130 Stat. 1033, 1104 (2016) (codified at 21 U.S.C. § 356(g)). FDA is required to designate a drug as a regenerative medicine advanced therapy if (1) the drug is a cell therapy, therapeutic tissue engineering product, human cell or tissue product, or combination product (with certain exceptions); (2) the drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and (3) preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition. Once an RMAT designation has been made, FDA is required to facilitate an efficient development program for and expedite review of the drug. RMAT designation includes the benefits of certain other expedited programs, and early interactions with FDA may be used to discuss potential surrogate or intermediate endpoints to support accelerated approval. See 21 U.S.C. § 356(g).

## 2 Current and Emerging Technologies in Regenerative Medicine

Regenerative medicine technologies can be grouped in various ways including broad categories such as cells, tissues, and organs, which can be used to develop therapeutic products. These vary in complexity according to their level of structural organization.<sup>11</sup> A cell is a self-sustainable unit that can replicate itself and carry on all the metabolic processes essential for life. Tissues are groups of cells that function together as a unit. For example, epithelial tissue lines the various passages inside the body such as the intestinal lining, and also

makes up the skin. Organs are collections of several different tissues arranged to perform a special function in the body. The human heart, for example, contains cardiac muscle tissue, connective tissue (which holds the muscle tissue together), epithelial tissue (which creates the lining of the heart), nerve tissues, and specialized pacemaker cells, which coordinate the heartbeat. The level of structural organization increases moving from cells to tissues to organs, leading to technologies with increasing engineering complexity (see fig. 2).

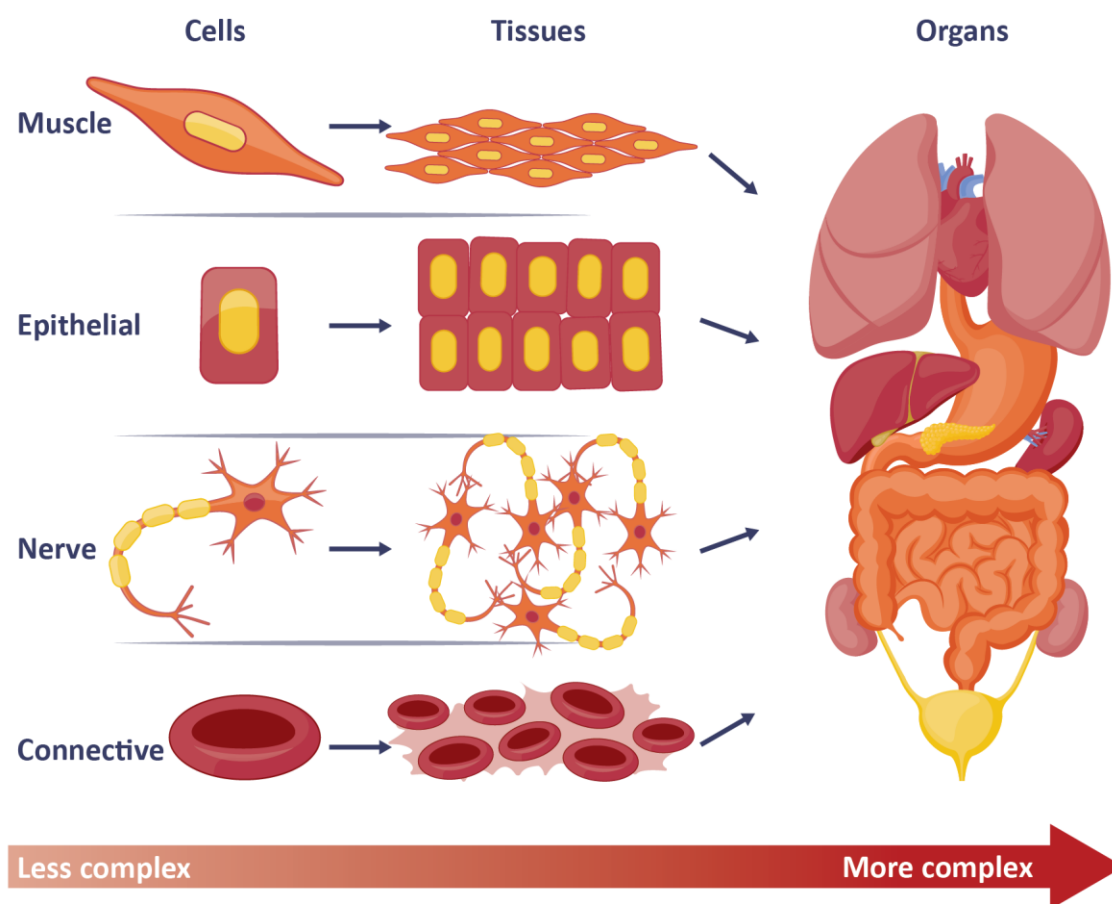
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<sup>11</sup>For the purposes of this report, technologies are grouped into broad categories that aim to regenerate or restore cells, tissues, and organs. FDA uses the term “cell and gene therapy products” to describe a wide range of products.

Gene therapy products are biologics, as the term is defined under 42 U.S.C. § 262(i)(1). While human gene therapy products may include ex vivo modified cells, FDA distinguishes between cellular and gene therapies.



**Figure 2: Levels of complexity in cells, tissues, and organs**



Source: GAO (analysis); Greenvector/winwin/stock.adobe.com (images). | GAO-23-105430

## 2.1 Cell technologies

Cells are the smallest units of life and make up all living organisms. Each cell has a full set of genetic material (i.e., a *genome*) that provides the instructions needed to perform essential processes and reproduce. Cell-based regenerative medicine technologies may be used to develop cures for a variety of diseases and can use either

cells from a patient’s own body or cells from a donor as the starting material for therapy. Regenerative medicine technologies may use specialized or unspecialized cells. Specialized cells are those that have undergone genetic changes to become a specific type of cell, such as a red or white blood cell.<sup>12</sup> Unspecialized cells, which are known as *stem cells* and found in both embryos and adults, have not yet undergone these changes and have the

<sup>12</sup>The process by which a cell becomes specialized in order to perform a specific function is called ‘differentiation.’ When cells differentiate, certain genes are turned on or off and this determines what type of cell will result.

ability to become different types of cells. Finally, regenerative medicine technologies may incorporate gene-editing techniques to produce gene-edited cells.

The following describes current and potential cell-based therapies. We group them into therapies based on stem cells and those based on gene-edited cells, although some therapies use stem cells that have also been gene-edited.

**Stem cell therapies.** Stem cells have been used to replace damaged cells and restore or improve bodily functions since the first bone marrow transplant more than 60 years ago (bone marrow makes stem cells). Today, there are several types of stem cell transplants. For example, hematopoietic stem cell transplants provide a person with a blood disorder, such as anemia or cancer, with an infusion of stem cells that restores their ability to produce blood cells.<sup>13</sup> Depending on the circumstances, the stem cells may be obtained from the patient or a donor and may be derived from bone marrow, peripheral blood, umbilical cord blood, or other sources. Stem cells have also been used in certain types of tissue grafts for patients with corneal eye diseases and skin grafts for burn victims.<sup>14</sup>

Stem cell therapies have the potential to cure numerous diseases and injuries. Initial

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<sup>13</sup>Hematopoiesis is the term for blood cell production. The body continually makes new blood cells to replace old ones to supply oxygen to the tissues (red blood cells), fight infection (white blood cells), and clot the blood after injury (platelets). Stem cell transplant for cancer may help to restore normal stem cells after chemotherapy or radiation, or it may act against cancers like leukemia or myeloma.

<sup>14</sup>For a more detailed explanation of how stem cells are used in tissue grafts for eye and skin regeneration, see de

research in the 1950s and 1960s used embryonic stem cells from mice, as they are more flexible and have the natural ability to turn into any type of cell. However, controversies around the use of human embryonic stem cells turned researchers' focus toward applying gene-editing techniques to specialized cells and adult stem cells (see text box).

#### Embryonic stem cell concerns and the discovery of induced pluripotent stem cells

Embryonic stem cells come from a human embryo and their use has raised ethical concerns. In January 1996, federal law prohibited the use of federal funds on research that created or destroyed human embryos.<sup>a</sup> This policy limited some research on embryonic stem cells, and led scientists to search for alternative stem cell sources.

In 2006, researchers identified conditions that allowed adult human cells to revert to a state similar to an embryonic stem cell. In 2007, researchers developed the first human cells of this kind, known as induced pluripotent stem cells.<sup>b</sup> Similar to embryonic stem cells, induced pluripotent stem cells can change into all types of cells in the body. These cells can provide a replacement for embryonic stem cells. They may be derived from a patient's own cells, offering the benefit of avoiding rejection by the host immune system.

Source: GAO. | GAO-23-105430

<sup>a</sup>Balanced Budget Downpayment Act, I, Pub. L. No. 104-99, § 128, 110 Stat. 26, 34 (1996). The parameters on fetal research, transplantation of fetal tissue, and prohibitions regarding fetal tissue are governed by the provisions of 42 U.S.C. §§ 289g-289g-2.

<sup>b</sup>See Kazutoshi Takahashi et al. "Induction of pluripotent stem cells from adult human fibroblasts by defined factors." *Cell*, vol. 131, 5 (2007): 861-72. <https://doi.org/10.1016/j.cell.2007.11.019>.

**Gene-edited cell therapies.** Gene-edited cells have been manipulated using a gene

Araujo, Aline Lütz, and José Álvaro Pereira Gomes. "Corneal stem cells and tissue engineering: Current advances and future perspectives." *World journal of stem cells*, vol. 7, 5 (2015): 806-14. <https://doi.org/10.4252/wjsc.v7.i5.806>. And Chen, Ming et al. "Stem cells for skin tissue engineering and wound healing." *Critical reviews in biomedical engineering*, vol. 37, 4-5 (2009): 399-421. <https://doi.org/10.1615/critrevbiomedeng.v37.i4-5.50>.

editing technology, such as CRISPR, to alter a gene that codes for a particular protein.<sup>15</sup>

These changes can restore cellular functions or give cells new functions, such as the potential to fight disease. Gene editing can be used on specialized cells or stem cells. For example, chimeric antigen receptor (CAR) T cells are gene-edited versions of a patient's own immune cells that target and kill certain types of cancer cells in their body (see vignette 1).<sup>16</sup>

Similarly, gene-edited stem cell therapies are being used to treat sickle cell disease, an inherited blood disorder that causes sickle-shaped red blood cells (see vignette

2). The combination of gene editing and stem cells could help researchers achieve therapy breakthroughs for a variety of diseases. This includes severe combined immunodeficiency, a group of hereditary diseases that severely compromises or destroys the immune system; leukodystrophies, which are rare, degenerative diseases of the nervous system; and junctional epidermolysis bullosa, a group of genetic conditions that cause the skin to be very fragile and to blister easily.

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<sup>15</sup>CRISPR and other gene editing technologies can delete, insert, replace, or modify parts of a cell's DNA. DNA is a molecule that stores hereditary information in humans and other organisms. For more information on gene editing technologies and CRISPR, see GAO, *Science & Tech Spotlight: CRISPR Gene Editing*. [GAO-20-478SP](#) (Washington, D.C.: Apr. 7, 2020).

<sup>16</sup>T cells, also known as T lymphocytes or thymocytes, are part of the immune system and develop from stem cells in the bone marrow. They help protect the body from infection and may help fight cancer. CAR T cells are modified versions of T cells.

# VIGNETTE 1

## CHIMERIC ANTIGEN RECEPTOR T CELLS AS A THERAPY FOR CANCER

Source: Design cells/solvod/stock.adobe.com (images). | GAO-23-105430

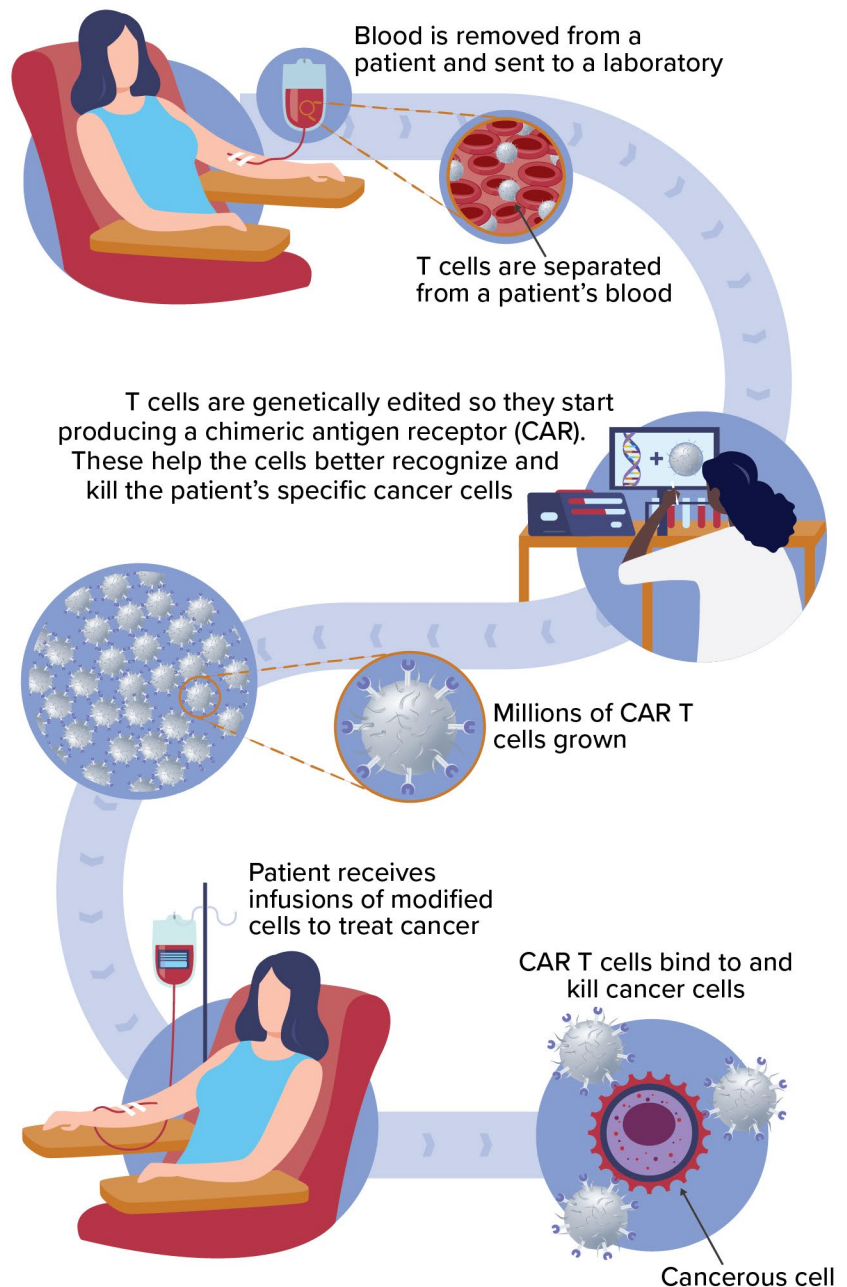
### WHAT IS IT?

Cancer occurs when cells grow uncontrollably. It is among the leading causes of death worldwide, and an estimated 1.7 million Americans are diagnosed with cancer every year—about 186,000 of them with leukemia, lymphoma, or myeloma. These blood cancers are caused by excessive production of white blood cells in the bone marrow. Patients undergoing treatment for cancer often receive chemotherapy or radiation, but recurrence is common. Chimeric antigen receptor (CAR) T cells are a therapy alternative for patients for whom standard treatment is not effective, or whose cancer returns after initial treatment.

### WHAT'S NEXT?

CAR T cell therapies have emerged as one of the major breakthroughs in cancer therapies over the last decade. The first CAR T cell therapy received FDA licensure in 2017. As of March 2022, there are at least six licensed therapies for various types of blood cancers. Researchers are developing new CAR T therapies for other types of cancers. For example, some early studies have shown that CAR T cells may be able to treat solid tumors, such as glioblastoma, which is an aggressive type of cancer that can occur in the brain or spinal cord. Researchers are also exploring the use of donor cells for CAR T therapies, which may enable larger-scale manufacturing.

#### A possible process for making CAR T cells.



Source: GAO (analysis); Designua/greenvector/microone/topvectors/stock.adobe.com (images). | GAO-23-105430



# VIGNETTE 2

## GENE-EDITED STEM CELLS AS A THERAPY FOR SICKLE CELL DISEASE

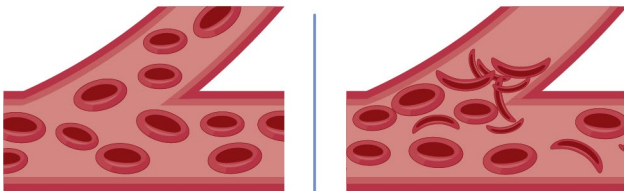
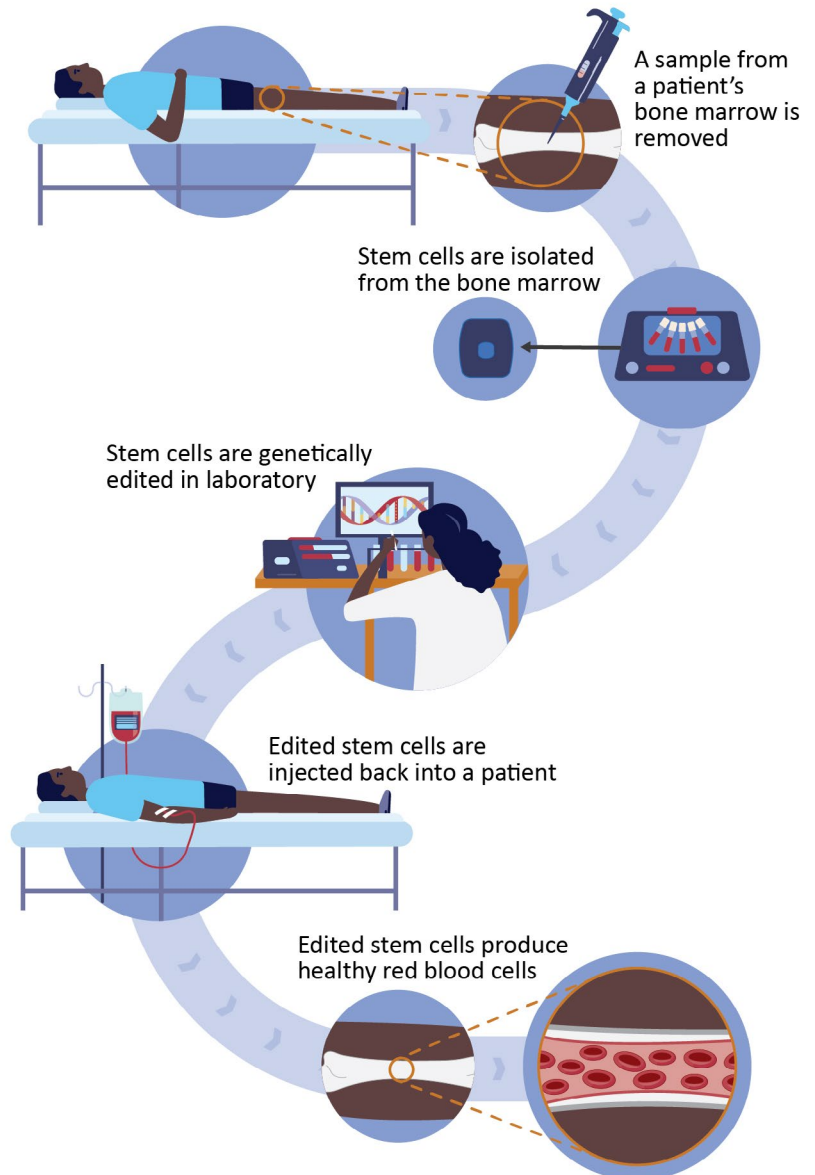
Source: tussika/solvod/stock.adobe.com (images). | GAO-23-105430

### WHAT IS IT?

Sickle cell disease is a group of inherited genetic disorders caused by an abnormal hemoglobin gene. This gene causes red blood cells to stick together and take on a rigid sickle shape rather than the flexible round shape found in healthy cells. Approximately 100,000 Americans are affected by sickle cell disease, including approximately one in 365 African Americans. Sickled cells can cause a broad range of symptoms, including pain, stroke, and organ damage. Current patient care is primarily limited to relieving symptoms rather than treating the disease. Some patients with sickle cell disease may receive blood transfusions or bone marrow transplants, but these therapies have risks. Red blood cells come from bone marrow stem cells, so genetically editing stem cells can correct a patient's hemoglobin gene and lead to the production of healthy red blood cells.

disorder called beta-thalassemia. Other applications of this technology—for sickle cell disease and other diseases, such as diabetes—are being studied in phase 1 and 2 clinical trials.

A possible process for genetically editing stem cells



Healthy red blood cells

Sickled red blood cells

Source: GAO. | GAO-23-105430

### WHAT'S NEXT?

Genetically edited stem cells have significant potential for treating hereditary and rare diseases, according to experts. In August 2022, FDA licensed the first gene-edited stem cell treatment for a related blood

GAO-23-105430

## 2.2 Tissue technologies

Tissue technologies for regenerative medicine combine cells and biocompatible materials into a single product. By combining these materials with cells, tissue technologies help cells stay at a specific location in the body, provide structural support, and enable more targeted therapeutic approaches.

The following describes two categories of tissue technologies that may have therapeutic applications:

**Biocompatible materials.** Biocompatible materials come from natural or artificial sources and serve as structural scaffolds. When implanted into a patient, they can be used to support or replace damaged tissues. Certain materials, such as metals, ceramics, plastic, or glass, have been used extensively as surgical implants and scaffolds because they replace the function of tissue and are not biologically active—meaning they typically do not actively interact with a patient’s body. Biomaterials under development for regenerative medicine technologies—such as hydrogels—differ from those currently used in surgical implants because they are not inert and are designed

for cells to attach or interact with them to actively facilitate healing responses. While these materials have the potential to significantly advance regenerative medicine, there are limitations. For example, new applications of biologically active or regenerative materials will require much closer monitoring and testing to ensure patient safety because they do not have the well-established performance records of inert materials.

**Combination products.** Combination products are products made up of two or more components regulated by FDA. For example, a tissue-engineered product containing both living cells and biocompatible materials is classified as a combination product because it has elements of both a biologic and device. Combination products may address certain age-related conditions that can cause structural and functional changes in the cells and tissues. For example, a retinal implant that combines a patient’s cells with a biodegradable scaffold to create a combination product may cure advanced dry age-related macular degeneration (AMD), an eye disease that can blur the central part of a person’s vision (see vignette 3).

# VIGNETTE 3

## RETINAL IMPLANTS AS A THERAPY FOR DRY AGE-RELATED MACULAR DEGENERATION

Source: Firefighter Montreal/solvod/stock.adobe.com (images). | GAO-23-105430

### WHAT IS IT?

Dry age-related macular degeneration (AMD) is an eye disease caused by damage to a person's retina as they age. Approximately 20 million Americans have AMD, more than 1.7 million of whom have an advanced form of the disease that results in vision loss. Such vision loss makes it hard to do everyday tasks, including seeing faces, reading, driving, or working around the house. There are currently no effective therapies. Retinal implants—a patch made from a patient's cells and a synthetic scaffold—are being developed with the hope of providing the first therapy for this type of vision loss.

Normal vision



Macular degeneration

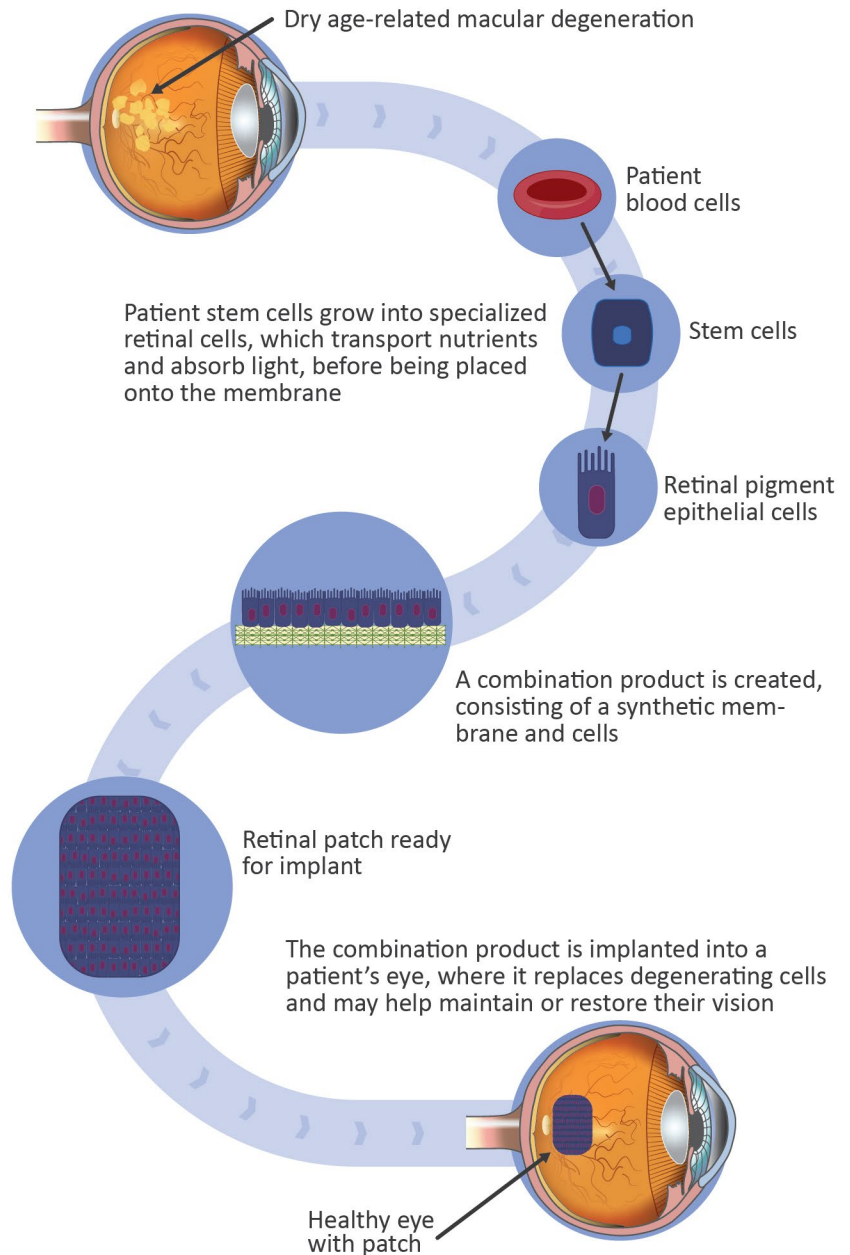


Source: GAO (analysis); GAO (image). | GAO-23-105430

### WHAT'S NEXT?

At least three different stem-cell-based therapies for AMD are in phase 1 and 2 clinical trials. Further developments in tissue engineering may pave the way for other combination products made from a patient's own cells. Researchers are exploring tissue engineering for other conditions, but it is difficult to predict the future direction of this technology given its early development stage.

### A possible process for making retinal implants.



Source: GAO (analysis); Greenvector/pattarawit/stock.adobe.com (images). | GAO-23-105430



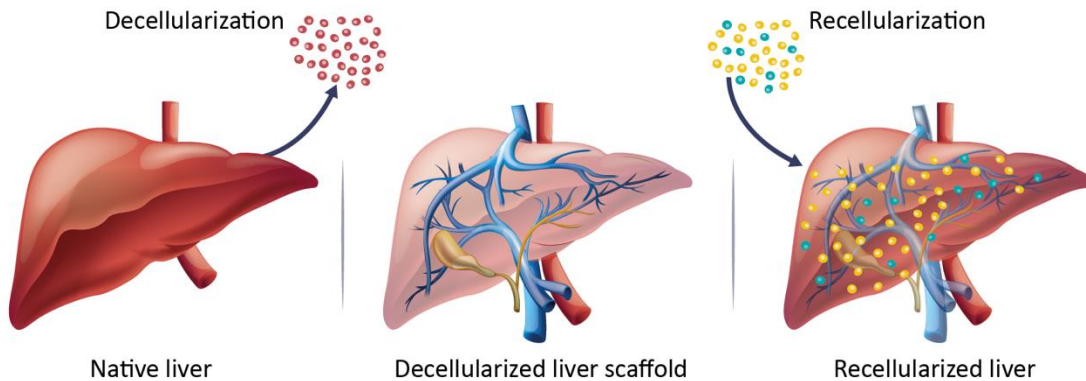
### 2.3 Organ technologies

Organ technologies, such as artificial hearts and kidneys, can have more complex structures and functions than cell or tissue technologies. They combine multiple cell and tissue types to create complex 3D structures. New strategies will be required to support these technologies.

Some technologies under development for potential therapeutic application include the following:

**Scaffold de- and recellularization.** Scaffold decellularization removes cells from tissues or organs and leaves behind the non-cellular portion of a tissue (i.e., scaffold) which mainly provides physical support. Recellularization adds new cells from a patient or other external source to the scaffold, where those cells will attach and grow. Patients needing organ transplants may benefit from the use of this technology once it is more developed. For example, a pig liver can be decellularized and the resulting scaffold may be repopulated with patient-derived cells, which makes it less likely that the new liver would be rejected (see fig. 3).

**Figure 3: Scaffold de- and recellularization of a liver**



Source: GAO (analysis); Blueringmedia/stock.adobe.com (images). | GAO-23-105430

**3D bioprinting.** 3D bioprinting uses 3D printing techniques to create implantable structures. The material used as ink for the 3D printer can contain cells, or cells can be added after printing is complete. Researchers have successfully implanted 3D printed bone and muscle structures into animals. Additionally, in June 2022, a human patient received a 3D printed ear implant as part of a clinical trial.<sup>17</sup>

These advances highlight the potential application of 3D bioprinted technologies, but applications that allow for the treatment of human disease are still under development. For example, researchers are pursuing 3D printed tissues to cure bone defects or injuries (see vignette 4).

<sup>17</sup>See [ClinicalTrials.gov](https://clinicaltrials.gov), *AuriNovo for Auricular Reconstruction*, <https://clinicaltrials.gov/ct2/show/NCT04399239>, accessed Mar. 28, 2023.

## BIOPRINTED BONE REPLACEMENTS AS A THERAPY FOR ACUTE BONE INJURIES

Source: Sutthab/solvod/stock.adobe.com (images). | GAO-23-105430

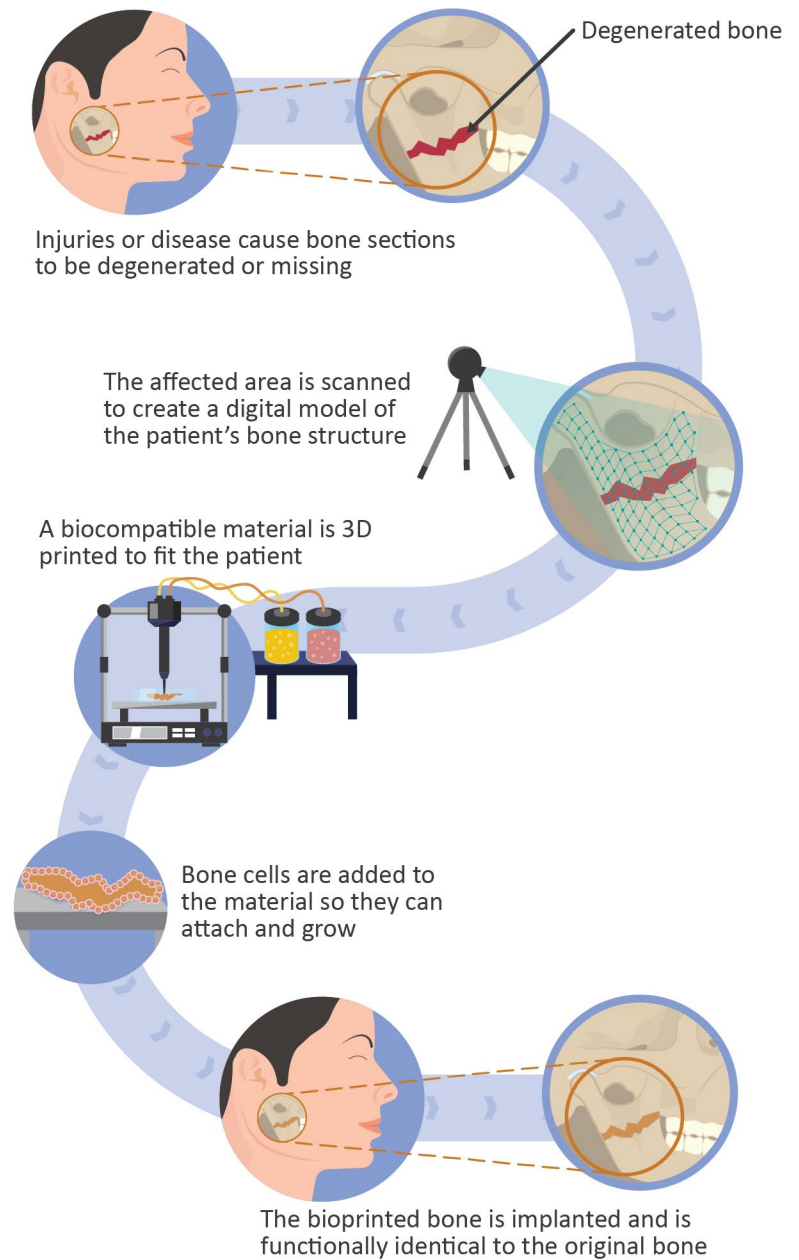
### WHAT IS IT?

Injuries and accidents can cause bone fractures. Between 11 million and 15 million bone fractures occur in the U.S. every year, of which more than 1 million fail to heal properly. Current therapies may use transplanted tissues or inorganic materials, but neither of these fully restores functionality. Bioprinted bones could combine a 3D printed biocompatible material with a patient's own bone cells to create customized replacements for damaged bone.

### WHAT'S NEXT?

3D bioprinted bone replacements are still in research and development. No bone construct has been made by combining tissue engineering and 3D bioprinting, but studies have been done in animals. Further progress requires research into creating blood vessels in implanted materials and developing stronger, more flexible materials, among other areas. Additionally, a report from the Pew Charitable Trusts published in July 2022 noted that current FDA guidance does not clearly explain how bioprinted products will be regulated, which may cause some companies to be hesitant about using new manufacturing technologies like 3D printing.

### A possible process for bioprinting bone material.



Source: GAO (Analysis). Derariad/rumruay/stock.adobe.com (images). | GAO-23-105430

**Organoids.** Organoids are small, artificially grown groups of cells or tissues that resemble an organ and mimic the original tissue architecture. Organoids can be grown from patient tissues, and have been successfully generated from several kinds of human tissues including heart, liver, brain, and kidney. Currently, organoids are being used

primarily for research and testing during multiple stages of the drug development process. However, researchers are also evaluating a variety of organoid technologies to determine whether they may be used to cure diseases such as diabetes—which affects how the body uses sugar (see vignette 5).

## PANCREATIC ISLET CELL ORGANOIDS AS A THERAPY FOR TYPE 1 DIABETES

Source: Rfbsip/solvod/stock.adobe.com (images). | GAO-23-105430

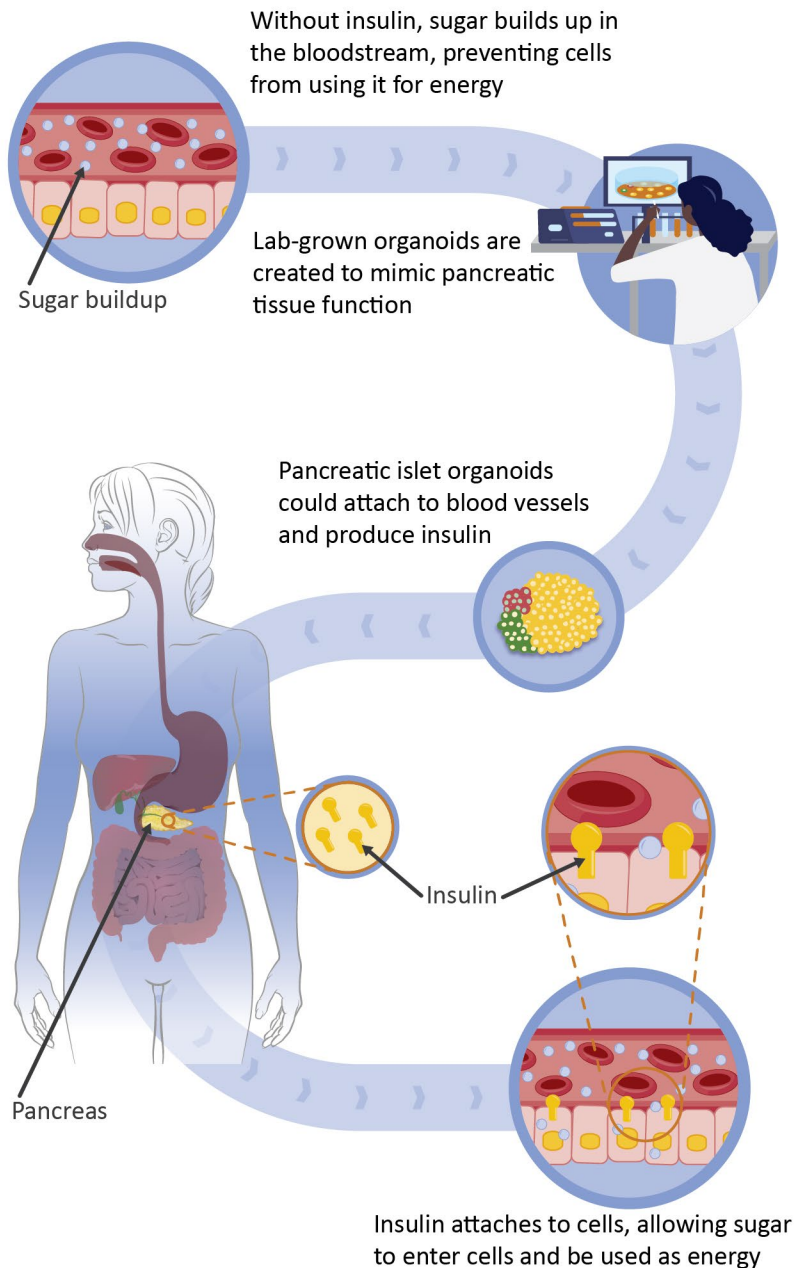
### WHAT IS IT?

Type 1 diabetes occurs when a person's immune cells attack pancreatic islet cells. This destroys the person's ability to produce insulin, an essential hormone needed to properly convert sugars to energy and control blood sugar levels in the human body. About 1.6 million Americans have type 1 diabetes and need daily insulin injections throughout their lives, a significant economic burden to the individual and the U.S. health care system. Pancreatic islet organoids offer the possibility of curing the disease by restoring a patient's ability to produce insulin.

### WHAT'S NEXT?

Pancreatic islet organoids are in phase 1 and 2 clinical trials in humans. Organoid technologies have significant potential to transform research and therapeutics. As a research technology, organoids may model human disease more accurately than animals and help drugs move from the laboratory to the clinic more quickly. As therapeutics, they may be capable of more complex functions than simple biological products. However, it is difficult to predict the future direction of this technology given its early development stage.

### A possible process for generating pancreatic organoids.



Source: GAO (analysis); Microone/christosgeorghiou/stock.adobe.com (images). | GAO-23-105430

**Full-size organs.** Whole organs can be engineered using the methods described above. However, full-size engineered organs for clinical use are still in the early research and development phase and face several technical limitations. In order to restore the function of an organ, all the relevant components need to be engineered. The vessels that carry blood and other cells throughout the body are important, as they allow oxygen, nutrients, and immune cells to reach every part of the body. These vessels are a fundamental feature of most complex organs, and researchers are studying how to engineer organs with vascular systems.

Researchers have successfully developed organs that have less engineering complexity

and used them to cure spina bifida-induced bladder damage.<sup>18</sup> Lab-grown bladders, developed from a small piece of a patient's bladder, have smooth muscle cells on the outside and specialized bladder-lining cells on the inside. Researchers grew both types of cells separately at first and layered them together onto a bladder-shaped, biodegradable scaffold. After further growth, the bladders were implanted into children whose spina bifida had damaged the neural connections that allow nerve cells to help signal a full bladder (see fig. 4). However, the use of engineered bladders to treat patients is currently advancing through clinical trials.

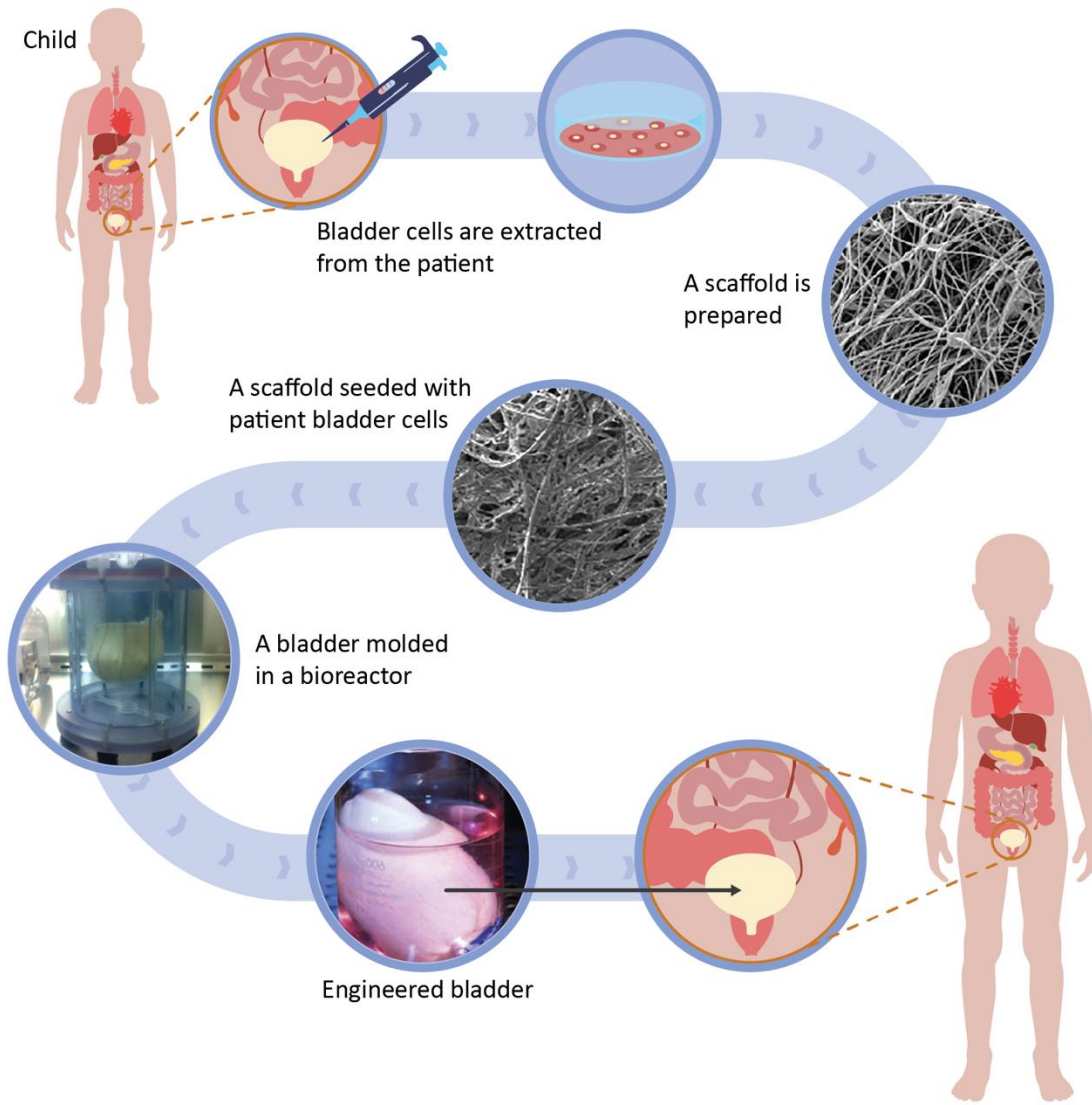
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<sup>18</sup>Anthony Atala et al. "Tissue-engineered autologous bladders for patients needing cystoplasty." *Lancet (London, England)*,

vol. 367, 9518 (2006): 1241-6. [https://doi.org/10.1016/S0140-6736\(06\)68438-9](https://doi.org/10.1016/S0140-6736(06)68438-9).



**Figure 4: An engineered bladder using a patient's cells and a biodegradable scaffold**



Source: GAO (analysis); Wake Forest Institute for Regenerative Medicine (photos); Mariia/pikovit/stock.adobe.com (vector images). | GAO-23-105430

### 3 Challenges and Policy Options for Regenerative Medicine Technologies and Therapies

Regenerative medicine technologies and therapies have potential benefits, but challenges may affect their development and use. We identified challenges including but not limited to: standardization, regulations, and manufacturing.<sup>19</sup>

GAO developed 11 policy options that could help address these challenges or enhance the benefits of regenerative medicine. These policy options are provided to inform policymakers of potential actions to address the policy challenges identified in this technology assessment. They identify possible actions by policymakers, which include Congress, federal agencies, state and local governments, academic and research institutions, and industry.

#### 3.1 Challenges related to standardization

Standardization can help promote more rapid and effective technology development, but relatively few standards exist for regenerative medicine technology. A 2020 FDA-commissioned report from the Nexight Group

and Standards Coordinating Body for Gene, Cell, and Regenerative Medicines and Cell-Based Drug Discovery (SCB) identified a strong need for more standards and outlined more than 250 needed standards relevant to regenerative medicine.<sup>20</sup> However, developing standards is challenging because these technologies are complex and rapidly evolving. Developing standards is also challenging because of the need to reach consensus across a range of stakeholders and the need for accurate, well-developed measurement science in the field.

Standards are rules, conditions, guidelines, or agreed-upon practices that are adopted within an industry.<sup>21</sup> They are created to provide researchers and developers with a common framework, which promotes consistency across product development, manufacturing, and other processes. Standards are generally developed outside of the federal government by independent organizations and are therefore distinct from federal statutory or regulatory requirements, unless the regulations are specifically tied to

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<sup>19</sup>We identified other challenges that may affect the development and use of regenerative medicine technologies including: Gaps in funding for translational research, market access and reimbursement, and potential difficulty in understanding safety of some therapies in the short-term.

<sup>20</sup>SCB is a nonprofit organization first established as an initiative by the Alliance for Regenerative Medicine, but is now an independent organization that engages industry, academic, and government stakeholders to accelerate the standards development process. SCB is also referred to as the Standards Coordinating Body. See SCB, *The Regenerative Medicine Standards Landscape* (Fall 2020), <https://static1.squarespace.com/static/58a331b0db29d63c7fb64528/t/5fc51dfc173fb5383b470452/1606753809117/LandscapeReportFall2020.pdf>, accessed Mar. 3, 2023.

<sup>21</sup>Standards include documentary standards, reference materials, and reference data. Documentary standards are written documents containing protocols, experimental methods, technical specifications, or terminologies. Reference materials are highly characterized substances with known properties, used to ensure consistency and quality of a product, calibrate equipment, serve as experimental controls, or aid in describing and evaluating qualitative and quantitative data. Reference data are critically evaluated quantitative data related to a measurable physical or chemical property of a substance.



such standards.<sup>22</sup> For example, the U.S. Pharmacopeial Convention, a nonprofit organization, publishes the U.S. Pharmacopeia: a continuously revised document that sets quality, purity, and strength standards for medicines, food ingredients, and dietary supplements. Small-molecule drug manufacturers test their products, which include over-the-counter drugs like aspirin, against the U.S. Pharmacopeia's published standards to help ensure safety and consistency.

However, regenerative medicine technologies and therapies are significantly more complex than small-molecule drugs, in part because they can be highly personalized and made of living cells. Currently, regenerative medicine has relatively few standards, which raised concerns with some experts we spoke with.<sup>23</sup> For example, a report from a leading advocacy organization said there is unclear guidance on how to ensure certain products

are sterile, even though such guidance could significantly reduce the potential for contamination.<sup>24</sup>

SCB also agreed that advancing the development and use of voluntary consensus standards in regenerative medicine may accelerate innovation, increase product safety and reliability, accelerate regulatory review, and decrease costs. The 21st Century Cures Act, enacted in 2016, required the Secretary of Health and Human Services, in consultation with the National Institute of Standards and Technology (NIST) to facilitate an effort to coordinate and prioritize the development of standards for regenerative medicine.<sup>25</sup> SCB's 2020 report stated that a lack of standards leaves researchers and manufacturers to independently solve the complex challenges of clinical translation and scaling of commercial products. The report also noted that a lack of standards may raise safety concerns (see text box) and prevent novel

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<sup>22</sup>The National Technology Transfer and Advancement Act of 1995, codified the existing policies in Office of Management and Budget Circular A-119, "Federal Participation in the Development and Use of Voluntary Consensus Standards and in Conformity Assessment Activities." The act states that the National Institute of Standards and Technology (NIST) should facilitate standards-related information sharing and cooperation between federal agencies and to coordinate the use by federal agencies of private sector standards emphasizing where possible, the use of standards developed by private, consensus organizations. Pub. L. No. 104-113, § 12, 110 Stat. 775, 782 (1996) (codified at 15 U.S.C. § 272(b)(3)). Similarly, the Office of Management and Budget guidance states that its policies are intended to encourage federal agencies to benefit from the expertise of the private sector, promote federal agency participation in standards bodies to support the creation of standards that are useable by federal agencies, and minimize reliance on government-unique standards where an existing standard would meet the federal government's objective. Office of Management and Budget, OMB Circular No. A-119, *Federal Participation in the Development and Use of Voluntary Consensus Standards and in Conformity Assessment Activities*, (originally issued Oct. 20, 1993, it was subsequently revised and replaced in 1998, and later revised Jan. 27, 2016).

<sup>23</sup>We interviewed experts from government, academia, industry, and the nonprofit sector, and convened an expert meeting to discuss the objective topics. See Objectives, Scope, and Methodology section for more details. The U.S. Pharmacopeia does not have the authority to create standards for regenerative medicine. According to the National Technology Transfer and Advancement Act of 1995 and the Office of Management and Budget Circular No. A-119, the federal government prefers the use of standards developed through a consensus-based process. Standards development organizations that follow a consensus-based process can be accredited by the American National Standards Institute and include organizations like the International Society of Automation and the International Organization for Standardization. The U.S. Pharmacopeia does not meet these requirements and is therefore not recognized as a consensus standards developing body.

<sup>24</sup>Alliance for Regenerative Medicine, *A-CELL: A case study-based approach to integrating QbD principles in Cell-based Therapy CMC programs*, <https://alliancerm.org/wp-content/uploads/2022/09/PROJECT-A-CELL-V2.pdf>, accessed Feb. 22, 2023.

<sup>25</sup>Pub. L. No. 114-255, § 3036, 130 Stat. at 1104 (codified at 21 U.S.C. § 356g).

regenerative medicine therapies from becoming commercially viable.

**Standards can help address safety concerns**

Viral vectors are commonly used as delivery vehicles for gene therapy products. The viral vectors insert a modified DNA sequence into patient’s cells, which can help cure a wide range of diseases and genetic disorders. However, according to the Standards Coordinating Body for Gene, Cell, and Regenerative Medicines and Cell-Based Drug Discovery (SCB), therapies using viral vectors can produce adverse and even life-threatening reactions in patients if administered at the wrong dose.<sup>3</sup> In 1999, a patient died due to a severe immune response during a gene therapy trial that used a viral vector. The field lacked a reference material that could help regulators to adequately evaluate the safety of such therapies.

In response to this incident, a working group of experts from industry, academia, and FDA created a standard reference material for that viral vector: a highly characterized sample containing a known concentration of viral vectors. This material, first released in 2002 and used until 2022, helped developers accurately determine viral vector concentrations in their products. While developers are not required to use a reference material, and FDA has additional processes to establish a product’s safety and effectiveness, SCB stated that this viral vector reference material helped address safety concerns and restore public confidence in gene therapies.

Source: GAO. | GAO-23-105340

<sup>3</sup>SCB, Standards Development in Action: Reference Material for Human Adenovirus 5, <https://www.standardscoordinatingbody.org/adenovirus>, accessed Mar. 14, 2023.

However, overly rigid standards may also cause problems. FDA officials cautioned that, at this time, standards for regenerative medicine should be optional and take a flexible approach that can account for the complexity of biological products. They said that imposing stringent, mandatory standards, such as those used for small-molecule drugs, may impede the development of innovative biologics and place unnecessary burdens on industry and on FDA reviewers.

In addition to the complexity of regenerative medicine technologies and therapies, we identified the following two challenges that

make it difficult to develop and establish standards in the field.

**Standards require consensus.** Standards are developed through a consensus-building process that requires participation from a range of stakeholders. Unlike regulations, standards can be voluntary and are not typically developed by government agencies, so broad buy-in is important for them to be accepted and used. However, even if stakeholders agree that a particular standard should exist, it can be difficult to reach agreement on the details. This is especially true if one or more companies have existing products or infrastructure that do not align with the proposed standard. For example, experts noted that companies that have already built unique data infrastructures are unlikely to adopt new data standards if switching would require significant time and money.

To overcome this barrier and accelerate the standards development process, SCB engages with various regenerative medicine stakeholders in industry, academia, and government. This engagement has helped identify, prioritize, and develop voluntary standards, including standards related to sterility testing and cell counting. However, SCB’s impact is limited by its current size and funding. According to an SCB representative, SCB receives the majority of its operating budget through FDA and NIST contracts, which facilitates federal participation in standards development but is not sufficient to address the current need for regenerative medicine standards. This representative stated that SCB is hesitant to collect membership fees because it could limit stakeholder participation in the standards development process and would be counter

to the consensus-based process supported by federal stakeholders.

Two federal agencies—NIST and FDA—have important roles in standards development. NIST engages with key stakeholders to develop consensus and helps ensure that standards do not conflict with or duplicate each other.<sup>26</sup> It currently runs laboratory programs to advance measurements needed for the characterization and testing of regenerative medicine manufacturing and leads multiple consortia to develop or support the development of documentary standards and reference materials for regenerative medicine.<sup>27</sup> Federal law and policy encourage agencies to use industry-developed standards whenever possible. NIST therefore works with appropriate standards development organizations to advance documentary standards for regenerative medicine. NIST also supports the development of reference materials made available through NIST or another entity.

FDA also has a role, as FDA officials review and recognize the voluntary standards that the agency can apply during its review of products for regulatory approval. Product sponsors can choose to follow a voluntary standard recognized by FDA, which may reduce the amount of supporting data and information they need to submit to FDA.<sup>28</sup> However, in response to draft guidance from

FDA, several organizations stated that the agency’s process for recognizing voluntary standards has not been clear for regenerative medicine, and stakeholders may therefore hesitate to commit resources to developing standards. FDA published draft guidance on the Voluntary Consensus Standards Recognition Program for Regenerative Medicine Therapies in June 2022, which the agency said can facilitate the development of safe and effective regenerative medicine products.<sup>29</sup> Agency officials told us that finalized guidance is anticipated to be published in calendar year 2023.

**Additional measurement science is needed.**

Measurement science ensures that measurements are reliable, comparable, and accurate. Reliable measurements are a key driver for emerging technologies, but often require dedicated research that is separate from technology development. For example, it took decades of measurement science research to directly connect the measurement of time to a fundamental physical constant—the vibration of a cesium atom. Once time could be measured consistently around the globe, new technologies that rely on highly accurate time measurements could start to emerge, like global positioning systems (GPS). Similarly, advancing measurement science in different areas of regenerative medicine can support

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<sup>26</sup>According to NIST officials, the agency’s role is to support research and development, translation, and manufacturing, including characterization and testing, as well as promoting the broader ecosystem.

<sup>27</sup>NIST leads multiple laboratory programs for regenerative medicine and has a contract with SCB to support standards development. NIST, *RMAT Laboratory Programs*, <https://www.nist.gov/regenerative-medicine>, accessed Apr. 5, 2023.

<sup>28</sup>A product sponsor or applicant means any person who submits or plans to submit an application to FDA for premarket review. 21 C.F.R. § 3.2(c) (2022).

<sup>29</sup>Food and Drug Administration, *Voluntary Consensus Standards Recognition Program for Regenerative Medicine Therapies* (June 16, 2022). Available from: <https://www.fda.gov/media/159237/download>, accessed June 16, 2022.

**Measurement science in regenerative medicine**

Sickle cell disease is a genetic condition caused by a one-letter mutation in the gene for hemoglobin, a protein in red blood cells. As a result of this genetic mutation, red blood cells change to a crescent (or sickle) shape and can cause significant pain. Gene therapies aim to cure sickle cell disease by changing the incorrect letter without altering any of the other 3 billion letters in the patient’s genome. However, it is difficult to measure whether a gene therapy has created any unintended changes.

DNA sequencing, a measurement technology used to observe the effects of gene therapies (among other uses), is imperfect and accuracy can vary depending on the technique being used. Even the most accurate existing methods will still take many inaccurate measurements across a person’s full genome, due to inherent errors in the process. This creates a critical measurement challenge, because it will not be clear whether an altered letter in the data was caused by the gene therapy or the sequencing method. Improved DNA sequencing technologies, standards, and reference materials could therefore increase confidence in gene therapies. Such improvements will require specific research on the methods used for sequencing and on new chemistry or data analysis techniques that could reduce error.

Source: GAO. | GAO-23-105340

standardization and technology development (see text box).

NIST officials told us that budgetary resources for regenerative medicine standards, which includes work on measurement science, have been limited and inconsistent. Agency officials also said that fluctuating resources may hinder efforts to support industry and advance regenerative medicine standards.

We identified three policy options to help address challenges in regenerative medicine standardization. Table 1 presents these options, along with potential opportunities and considerations.

**Table 1: Policy options for regenerative medicine standardization**

Policy options	Opportunities	Considerations
<ul style="list-style-type: none"> <li>Invest in standards development</li> </ul> <p><i>This policy option could help address the challenge that standards require consensus.</i></p> <p><i>Potential implementation approaches:</i></p> <p><i>Government agencies could support organizations that develop regenerative medicine consensus standards.</i></p> <p><i>Government agencies could support consensus-building activities between stakeholders, such as those conducted by the Standards Coordinating Body for Gene, Cell, and Regenerative Medicines and Cell-Based Drug Discovery.</i></p>	<ul style="list-style-type: none"> <li>Could streamline standards development, which may, in turn, accelerate innovation, increase product safety and reliability, accelerate regulatory review, and decrease costs of regenerative medicine therapies.</li> </ul>	<ul style="list-style-type: none"> <li>Existing organizations may not include all stakeholders, and stakeholders may hesitate to accept standards created without their input.</li> <li>Industry stakeholders may hesitate to adopt standards if they perceive it will cost them a controlling position in the market.</li> <li>Standards should be appropriately flexible to allow for innovation, while still being detailed and specific enough to support manufacturing of consistent, quality products.</li> </ul>

- Provide more consistent support for measurement science research.

*This policy option could help address the need for more measurement science.*

*Potential implementation approaches:*

*Government agencies (e.g., NIST, FDA) could dedicate specific funding for measurement science research.*

*Industry stakeholders could devote more resources to measurement science research initiatives.*

- Could enable more or faster development of regenerative medicine technologies, and could provide additional benefits outside of regenerative medicine.

- Additional federal spending on measurement science for regenerative medicine may shift resources that were supporting other emerging technologies.
- Private industry may not invest in measurement science since they may not receive a timely return on investment.

- Maintain the status quo.

- Standards may be developed without further intervention.
- Potential cost savings for federal agencies.
- Would avoid establishing standards too early, which can stifle innovation and competition.

- Technologies may be more likely to fail in development or during regulatory review due to a lack of standardization.
- Companies may need to spend more to meet safety requirements for FDA approval or licensure.
- Companies may not be willing to change their existing processes if standards are not established early enough.

Source: GAO. | GAO-23-105430

### 3.2 Challenges related to regulation

According to experts we interviewed, the field of regenerative medicine faces several challenges related to regulation, including:

- Lack of access to regulatory expertise.
- Difficulty navigating a complex regulatory framework.
- Current regulatory pathways may be insufficient for emerging technologies and therapies.

- Staffing shortages at FDA and collaborating agencies.
- Unlicensed stem cell products.

#### **Lack of access to regulatory expertise.**

Sponsors who develop regenerative medicine products need regulatory expertise throughout all stages of product development, including the stage where they submit a product for FDA review. Start-ups and other small companies or academic institutes that do not have designated in-house regulatory departments may be at a disadvantage due to lack of expertise on the

complex regulatory process. This lack of expertise could delay the product development process. For example, companies could spend time and resources generating data that do not meet FDA requirements. An expert told us that these companies need access to knowledgeable regulatory experts and adequate opportunities to interact with FDA reviewers.<sup>30</sup>

**Difficulty navigating a complex regulatory framework.** Clear and predictable regulations ensure that product developers are able to understand the data and other requirements needed for approval without unnecessary delays or uncertainty. Experts told us that it can be challenging for product sponsors to navigate the complex regulatory framework for regenerative medicine products, which may span multiple FDA centers and pathways to approval. Some regenerative medicine products are combination products (see sec. 2.2), and it can be difficult to understand what classification they fall under.<sup>31</sup> While some regenerative medicine products clearly fit in to a particular classification, others may be less clear. This can be challenging for technologies and therapies for which the primary mode of action may not be known or fully understood.

Another layer of complexity comes from the multiple FDA programs for which

regenerative medicine products may be eligible. Sponsors of regenerative medicine products can ask FDA to review their product under one or more of these programs if they meet the criteria. For example, they can request RMAT designation, which allows for accelerated approval of products with the potential to address unmet medical needs. In addition, regenerative medicine products may be eligible for other expedited programs, including fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation. Sponsors may receive more than one designation for a given product, but they must request each one separately.<sup>32</sup>

To understand which programs are available before submitting, product sponsors can get information in many ways including seeking advice from FDA. Experts told us that FDA was generally inclined to provide advice to sponsors who ask for it, but the agency does not always have the ability to respond as quickly as it would like. We also heard from experts that such advice, when provided to regenerative medicine product sponsors, is not always clear, leading sponsors to spend extra time seeking information. Experts also told us that sponsors could benefit from clear guidance documents and additional opportunity for interaction with FDA reviewers at various stages of product

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<sup>30</sup>In order to address the substantial growth in the development of novel products, CBER has established a new Office of Therapeutic Products. This reorganization is intended to create flexibility and capacity for future growth in the number of full-time employee positions and enhance the timeliness and consistency of the office's interactions with sponsors.

<sup>31</sup>Officials told us that the Office of Combination Products situated in FDA's Office of the Commissioner evaluates the classification and regulatory review jurisdiction of combination

products as well as other articles for which the classification as drug, device, and/or biologic is unclear. Officials told us that the Office of Combination Products has various mechanisms for stakeholders to obtain recommendations or determinations for their products.

<sup>32</sup>Priority review designation is determined for every product application, regardless of whether the product sponsor requested it.



development.<sup>33</sup> They said clarifying guidance to sponsors as early as possible in the product development process could save time and resources, potentially making therapies available to patients sooner.<sup>34</sup>

**Current regulatory pathways may be insufficient for emerging technologies.**

Emerging regenerative medicine technologies and therapies may blur the lines between drugs, biologics, and devices which could make their pathways to approval or licensure more uncertain. Participants in our expert meeting and other experts told us that the requirements for these types of products can unintentionally hinder the development of emerging technologies. To illustrate this, experts told us about medical devices made from materials that can promote cell growth or tissue healing. One such device is known as a tissue fixation implantable device which is used to attach soft tissue grafts to a fractured bone to promote healing. These experts told us that products made with such materials are regulated as devices, and FDA guidance does not allow sponsors to claim regenerative properties for products regulated solely as devices.<sup>35</sup> However, experts said there is a growing understanding that devices may be more effective if they are made from

materials that are biologically active and promote cell regeneration.

Another possible difficulty is that companies that develop novel products may lack examples of the same types of products previously going through the regulatory process. Experts said that this can lead to confusion about which regulatory pathway is most appropriate for their product.<sup>36</sup> We heard from experts that there is an opportunity for FDA to clarify regulatory pathways for regenerative medicine products and assess the need for alternative pathways. For example, experts said that a new pathway or amendments to current pathways could be proposed to allow for devices with regenerative properties.

**Staffing shortages at FDA and collaborating agencies.** FDA needs knowledgeable personnel to handle incoming applications, provide clear advice to product sponsors, and achieve the agency’s mission of advancing public health. Agencies that collaborate with FDA and fund regenerative medicine programs, like the National Institutes of Health, also need to have personnel

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<sup>33</sup>Sponsors can obtain early feedback from FDA through an Initial Targeted Engagement for Regulatory Advice on CBER/CDER Products (INTERACT), which is a meeting at a specific time early in product development.

<sup>34</sup>GAO previously reported similar challenges with existing FDA guidance related to advanced manufacturing for drugs. See GAO, *Drug Manufacturing: FDA Should Fully Assess Its Efforts to Encourage Innovation*, GAO-23-105650 (Washington, D.C.: Mar. 10, 2023).

<sup>35</sup>According to FDA, combination products can be eligible for RMAT designation when the biologic constituent part of the product is a regenerative medicine therapy and that therapy serves as the product’s primary mode of action.

<sup>36</sup>GAO previously reported that FDA is working to clarify and address similar challenges related to the agency’s review of drugs made using advanced manufacturing technology. For example, FDA has a website that has a list of technologies that have been accepted into CDER’s Emerging Technology Program, thus informing industry stakeholders about the type of technologies FDA has experience reviewing. In addition, CDER is implementing an initiative to examine its regulatory framework for advanced manufacturing to determine whether changes are needed to its statutory authorities, regulations, and guidance in order to facilitate the agency’s review of applications that use advanced manufacturing technologies. See GAO-23-105650.



knowledgeable in regulatory science.<sup>37</sup> We heard from experts that even when provided with a potentially sufficient number of positions, agencies have historically faced challenges meeting their medical product workforce needs, due in part to competition with the private sector. Experts we spoke with said that FDA continues to lack adequate capabilities, including the ability to recruit, train, and retain regulatory scientists. Without sufficient interdisciplinary training, FDA reviewers may be less familiar with novel and complex emerging regenerative medicine technologies.<sup>38</sup> Experts told us that this can lead to inconsistent or contradictory advice over the course of product development. Experts conveyed the importance of bolstering FDA's ability to hire and retain reviewers trained in evaluating emerging technologies and therapies. A recent GAO report recommended that FDA develop and implement an agency-wide strategic workforce plan with performance measures to ensure it can evaluate the effectiveness of its human capital efforts.<sup>39</sup>

**Unlicensed stem cell products.** Stem cells can be the basis for safe and effective treatments and FDA has licensed stem-cell products

derived from cord blood for limited use in patients with blood disorders. However, some U.S. clinics offer stem cell products that are not FDA licensed. Experts told us that such clinics are eroding public trust in regenerative medicine technologies and therapies, and are a threat to public health and safety. According to a study in 2021, more than 2,700 clinics were found selling purported stem cell treatments in the U.S.<sup>40</sup> In 2019, FDA issued a warning about stem cell treatments that are illegal and potentially harmful and asked patients to ensure any treatments they are considering are either FDA licensed or part of an FDA-approved study.<sup>41</sup> FDA stated that it "is increasing its oversight and enforcement to protect people from dishonest and unscrupulous stem cell clinics, while continuing to encourage innovation so that the medical industry can properly harness the potential of stem cell products."

Other government agencies and states are also taking action against clinics marketing certain unlicensed stem cell products. For example, in 2021, the Federal Trade Commission (FTC) and the Georgia Attorney General's Office sued the co-founders of the Stem Cell Institute of America for allegedly

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<sup>37</sup>Regulatory science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products. <https://www.fda.gov/science-research/science-and-research-special-topics/advancing-regulatory-science>, accessed July 6, 2023.

<sup>38</sup>FDA hosts the Centers of Excellence in Regulatory Science and Innovation (CERSI) program to foster robust and innovative approaches to advance regulatory science, and the goal is for the CERSIs to advance regulatory science individually and synergistically through collaborative interactions with FDA scientific experts and funding offices.

<sup>39</sup>GAO, *FDA Workforce: Agency-Wide Workforce Planning Needed to Ensure Medical Product Staff Meet Current and*

*Future Needs*, GAO-22-104791 (Washington, D.C.: Jan. 14, 2022).

In response, FDA stated in July 2022 that it was working to develop and implement an agency-wide strategic workforce plan to document human capital goals, and anticipates having a baseline version of this plan by the end of fiscal year 2024. GAO will continue to follow the agency's progress on this activity.

<sup>40</sup>Turner, Leigh. "The American stem cell sell in 2021: U.S. businesses selling unlicensed and unproven stem cell interventions." *Cell stem cell* vol. 28, 11 (2021): 1891-1895. <https://doi.org/10.1016/j.stem.2021.10.008>.

<sup>41</sup>Food and Drug Administration, *FDA Warns About Stem Cell Therapies* (Washington, D.C.: Sept. 3, 2019). <https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies>, accessed Mar. 28, 2023.

marketing stem cell therapy to seniors nationwide using “bogus claims” that it is effective in treating arthritis, joint pain, and a range of other orthopedic ailments.<sup>42</sup> FTC also issued a warning about false and misleading information about stem cell therapies, as a number of them have not been shown to be safe or effective.<sup>43</sup>

A recent report suggests that patients considering stem cell and regenerative medicine interventions do research online or by contacting friends, family, medical providers, and consultation services.<sup>44</sup> However, a 2021 study concluded that efforts should be directed at helping physicians

obtain information to inform themselves and their patients about unlicensed regenerative medicine therapies.<sup>45</sup> Experts warned that the public may be vulnerable to confusion and the spread of false information online, partially because of the novelty and complexity of these emerging technologies.

We identified five policy options to help address challenges related to the regulation of regenerative medicine products. Table 2 presents these options, along with the option of maintaining the status quo, and opportunities and considerations.

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<sup>42</sup>Federal Trade Commission et al v. Peyroux et al, 1:21-vc-03329 (N.D. Ga. Filed Aug. 16, 2021).

<sup>43</sup>FTC, Think Stem Cell Therapy Can Treat Your Ailments? It may pay to think twice (Aug. 17, 2021), <https://consumer.ftc.gov/consumer-alerts/2021/08/think-stem-cell-therapy-can-treat-your-ailments-it-may-pay-think-twice>, accessed on Mar. 26, 2023.

<sup>44</sup>Arthurs, Jennifer et al, “Patients seeking stem cell therapies—a prospective qualitative analysis from a

*Regenerative Medicine Consult Service*,” npj Regenerative Medicine (2022) 7:20. <https://doi.org/10.1038/s41536-022-00215-w>.

<sup>45</sup>Smith, Cambray et al, “Academic Physician Specialists’ Approaches to Counseling Patients Interested in Unproven Stem Cell and Regenerative Therapies - A Qualitative Analysis,” *Mayo Clinic Proceedings*, vol. 96, 12 (2021): 3086-3096. <https://doi.org/10.1016/j.mayocp.2021.06.026>.

**Table 2: Policy options for regenerative medicine regulation**

Policy options	Opportunities	Considerations
<ul style="list-style-type: none"> <li>• Provide opportunities for increased interactions between regulatory experts (at FDA or in industry) and smaller companies, especially early in the development process.</li> </ul> <p><i>This policy option could help address the lack of access to regulatory expertise.</i></p> <p><i>Potential implementation approaches:</i></p> <p><i>Policymakers could increase funding to existing public-private partnerships that can provide access to regulatory experts.</i></p> <p><i>Sponsors could devote more resources to sharing lessons learned from their regulatory submissions to help accelerate technology development across the field.</i></p>	<ul style="list-style-type: none"> <li>• May provide more timely advice and avoid unnecessary delays or uncertainty by pursuing the wrong regulatory pathways or submitting data that do not meet regulatory requirements.</li> </ul>	<ul style="list-style-type: none"> <li>• May require additional resources to bolster the workforce of regulatory scientists at FDA or public-private partnerships.</li> <li>• FDA may be limited in its ability to advise companies early in the process so as not to create a conflict of interest.</li> </ul>
<ul style="list-style-type: none"> <li>• Identify mechanisms for FDA to clearly communicate advice for regenerative medicine product classification and update guidance documents accordingly.</li> </ul> <p><i>This policy option could help address the challenge of navigating a complex regulatory framework.</i></p> <p><i>Potential implementation approaches:</i></p> <p><i>FDA could provide examples in guidance documents to further clarify product classifications. Examples could be provided for technologies and therapies that FDA has experience reviewing.</i></p> <p><i>FDA could provide mechanisms to ensure consistent advice across FDA reviewers when</i></p>	<ul style="list-style-type: none"> <li>• Could encourage new products and may speed up the review process.</li> <li>• Examples can further clarify product classifications.</li> </ul>	<ul style="list-style-type: none"> <li>• The rapidly changing field of regenerative medicine may necessitate more frequent updates to guidance documents.</li> <li>• Guidance that is too specific can be a constraint if there are multiple valid ways of doing things.</li> </ul>

Policy options	Opportunities	Considerations
<p><i>responding to product sponsor inquiries.</i></p> <ul style="list-style-type: none"> <li>Consider whether changes to the framework for evaluating combination products and medical devices to accommodate emerging technologies and therapies may be necessary.</li> </ul> <p><i>This policy option could help address whether current regulatory pathways are sufficient for emerging technologies and therapies.</i></p> <p><i>Potential implementation approaches:</i></p> <p><i>FDA could consult with other stakeholders to determine whether amendments to existing pathways or additional pathways are needed.</i></p> <p><i>The framework could allow products regulated solely as medical devices and made from materials that promote cell growth or tissue healing to claim regenerative properties.</i></p>	<ul style="list-style-type: none"> <li>May encourage innovators, researchers, and developers of new products to provide valuable feedback to regulators.</li> </ul>	<ul style="list-style-type: none"> <li>Coordinating among stakeholders to consider changes to regulatory pathways may be time- and resource-intensive.</li> <li>If such consideration leads to recommended changes to the framework, statutory and regulatory changes may be necessary.</li> </ul>
<ul style="list-style-type: none"> <li>Improve FDA’s ability to develop and maintain an appropriate interdisciplinary regulatory workforce.</li> </ul> <p><i>This policy option could help address the challenge of staffing shortages at agencies like FDA.</i></p> <p><i>Potential implementation approaches:</i></p> <p><i>FDA could continue to develop and implement an agency-wide strategic workforce plan.</i></p> <p><i>FDA could improve training for current staff on the latest technologies and therapies.</i></p>	<ul style="list-style-type: none"> <li>Could result in timely feedback to sponsors, enable increased interaction between reviewers and sponsors, and make therapies available to patients sooner.</li> </ul>	<ul style="list-style-type: none"> <li>Could require funding for FDA for additional positions.</li> <li>Salaries may need to be increased for FDA to compete with the private sector.</li> </ul>
<ul style="list-style-type: none"> <li>Support better and more effective information tools that</li> </ul>	<ul style="list-style-type: none"> <li>Combat false information and improve public trust.</li> <li>Help patients to evaluate the legitimacy of available therapies.</li> </ul>	<ul style="list-style-type: none"> <li>A public education campaign could require significant resources, and it is unclear how its effectiveness would be evaluated.</li> </ul>

Policy options	Opportunities	Considerations
<p>are publicly available to clinicians and patients.</p> <p><i>This policy option could help address the challenge of unlicensed stem cell products.</i></p> <p><i>Potential implementation approaches:</i></p> <p><i>Key stakeholders—such as councils or associations of governments or federal or state agencies—could coordinate strategic campaigns and partnerships between government health agencies and organizations that have broad public appeal (e.g., faith- or community-based organizations, sports, or patient advocacy groups).</i></p> <p><i>FDA and state health departments or medical boards could create and publicize a shared database of clinics offering unlicensed stem cell products.</i></p> <p><i>Federal agencies and organizations that help consumers gauge the value, quality, or authenticity of goods and services could create informational materials with strategies for consumers to evaluate medical claims and advertising.</i></p>	<ul style="list-style-type: none"> <li>• Help increase the diversity of clinical trial participants, which improves understanding of the safety and effectiveness of medical products for different populations.</li> </ul>	<ul style="list-style-type: none"> <li>• Even with more accurate information, patients ultimately decide what is best for their health based on their personal circumstances. For example, studies show that patient decisions on whether to undergo an unapproved or unlicensed intervention are complex and depend on the patient’s condition, consideration of medical risks, trust in research or medical institutions, and other factors.</li> </ul>
<ul style="list-style-type: none"> <li>• Maintain the status quo.</li> </ul>	<ul style="list-style-type: none"> <li>• Could allow current regulatory framework for evaluating regenerative products to remain unchanged.</li> <li>• Could save government or private sector resources for other priorities, including promising medical technologies and therapies other than regenerative medicine.</li> <li>• Would avoid making changes to regulatory framework that may not address the needs of technologies and therapies yet to be developed.</li> </ul>	<ul style="list-style-type: none"> <li>• Product developers may have difficulties advancing new technologies and therapies to the market.</li> <li>• Larger companies may continue to maintain advantage such as access to regulatory advisors over smaller companies.</li> <li>• Consumers may continue to fall prey to misleading marketing about unapproved or unlicensed stem cell products.</li> </ul>

Source: GAO. | GAO-23-105430

### 3.3 Challenges related to manufacturing

Manufacturing is the creation of new products from starting materials, in a way that is generally consistent and reproducible.<sup>46</sup> It is a key step for many emerging technologies and therapies, because it can help increase product consistency, decrease costs, and facilitate larger production volumes that make products more accessible and affordable.

Biologics, including cells, tissues, and organs used for regenerative medicine are difficult to manufacture at scale because they are far more complex than many other medical products, such as small-molecule drugs (see text box). This complexity also contributes to three challenges related to manufacturing in regenerative medicine: lack of infrastructure, ensuring quality, and workforce shortages. Currently, some components of certain regenerative medicine products can be reliably manufactured. For example, the DNA and viral vectors used to alter a cell's genome—a key part of gene and cell therapies—can be produced at large scales. However, producing complete products, such as CAR T cell that may cure certain types of cancer, currently requires technicians to perform many steps manually. Experts stated that regenerative medicine technologies and therapies will require increased levels of automation if they are to be widely accessible and affordable.

#### Biologics are significantly more complex than small-molecule drugs

Even though small-molecule drugs and biologics are often discussed in similar contexts, their complexity differs substantially. Aspirin is a drug that has 21 atoms. Monoclonal antibodies, which experts consider to be relatively simple biologics, have around 25,000 atoms. Thus, the difference in complexity between small-molecule drugs and monoclonal antibodies is similar to the difference between a bicycle and a commercial jet.

A human cell is far more complex than a single protein, like an antibody. An average cell is estimated to contain 42 million proteins, and the precise composition of these proteins is constantly changing as the cell uses energy and grows.<sup>a</sup>

Existing manufacturing technologies, even those used to manufacture simpler biologics, require significant adaptations and advances to manufacture the complex biologics needed for regenerative medicine.

Source: GAO analysis. | GAO-23-105430

<sup>a</sup>Brandon Ho et al. "Unification of Protein Abundance Datasets Yields a Quantitative *Saccharomyces cerevisiae* Proteome" *Cell Systems* vol. 6, 192–205 (2018). <https://doi.org/10.1016/j.cels.2017.12.004>.

We identified the following three challenges to the widespread and efficient manufacture of regenerative medicine products.

**Lack of infrastructure.** The cell, tissue, and organ products being developed for regenerative medicine will require more complex manufacturing facilities than are currently used to produce small-molecule drugs. For example, many existing pharmaceutical manufacturing lines are not entirely closed off from the external environment, because small-molecule drugs can be sterilized once manufacturing is complete, using tools like heat, chemicals, and radiation. Regenerative medicine products cannot be sterilized, because sterilization can damage or kill cells and tissues. Therefore, manufacturing facilities will need complex systems to prevent

<sup>46</sup>Starting or ancillary materials are materials used during the manufacturing of cell and tissue products that are not intended to be a part of the therapy itself.

contamination and keep products sterile throughout manufacturing. Additionally, manufacturing facilities will need to allow for some customization to individual patients, while also enabling some level of mass production to reduce costs.

Experts stated that standing up such facilities will be risky for private companies. The necessary complexity will require significant investment, regardless of whether the facilities are newly built or remodeled. Further, a company likely will not receive a return on this investment until FDA has licensed its product, a process that generally takes years and is difficult to predict early in product development, according to experts.

Some initiatives are underway to help companies develop their manufacturing processes at testbed facilities before building at larger scales. These facilities, sometimes operated as public-private partnerships, can help smaller companies pilot their manufacturing processes or begin scaling up production, before they engage with larger companies or contract manufacturers. For example, the Advanced Regenerative Manufacturing Institute (ARMI) has a shared

facility where member organizations can test and develop manufacturing processes for new products.<sup>47</sup> Similarly, the Wake Forest Institute for Regenerative Medicine has a manufacturing facility that helps researchers test manufacturing processes as they develop their technologies. Additionally, the California Institute for Regenerative Medicine is planning to build a California Cell and Gene Therapy Manufacturing Network that will address manufacturing bottlenecks and help advance regenerative medicine therapies to patients. However, industry experts, including those at ARMI, stated that more facilities may be needed to meet the demands of the regenerative medicine industry. In particular, patients receiving therapies that use their own cells or tissues could benefit from distributed manufacturing facilities to help increase production capacity and allow patients to receive therapies more quickly.<sup>48</sup> A greater and more widely distributed number of manufacturing facilities may be beneficial, because there are few existing facilities and patient cells must be flown to one of those facilities from hospitals around the country (see fig. 5).

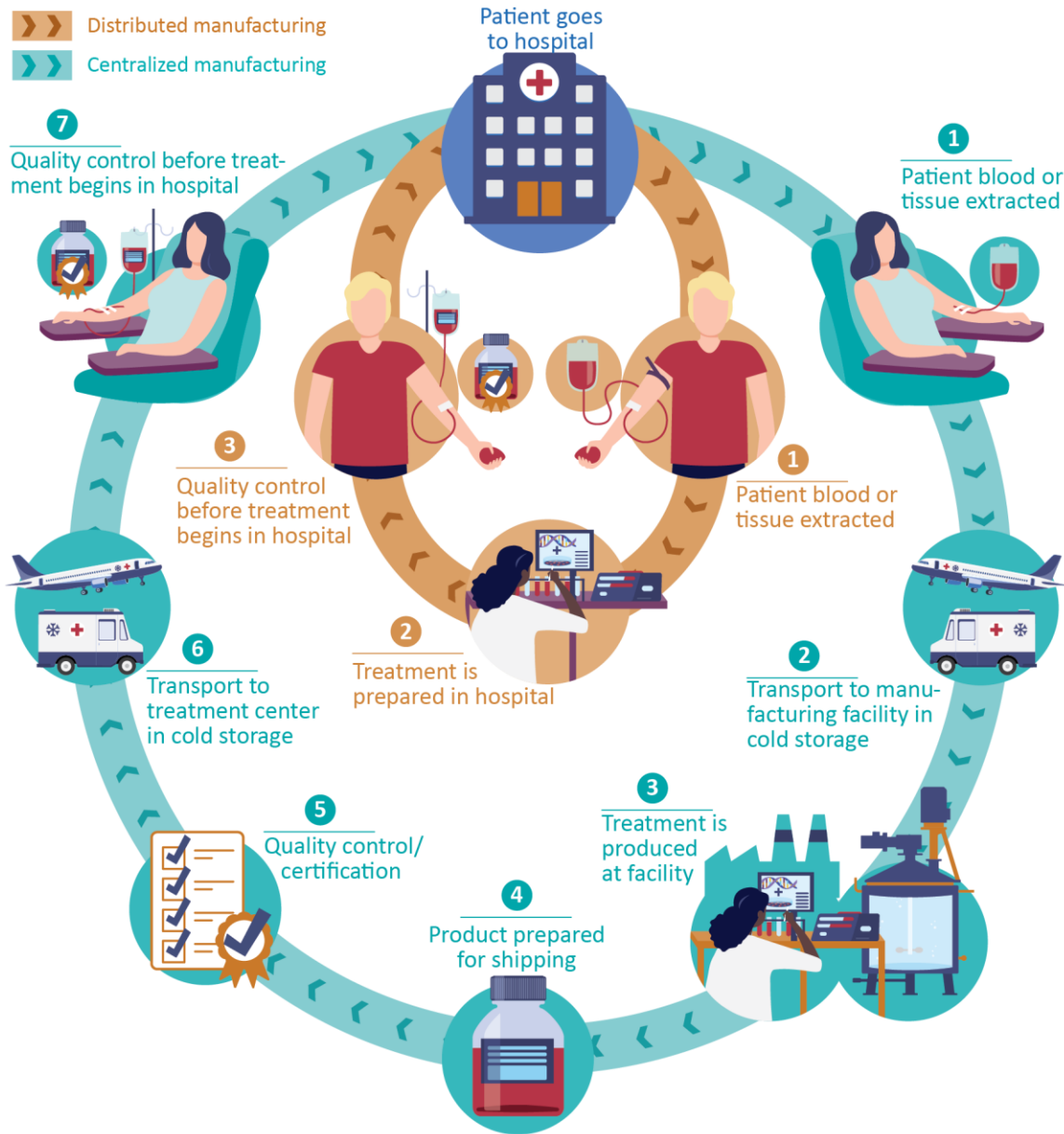
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<sup>47</sup>The Departments of Commerce, Defense, and Energy have established a network of innovation institutes—known as Manufacturing USA institutes—to promote research, development, and commercialization of advanced manufacturing technologies. ARMI is a non-profit organization administering BioFabUSA, a Manufacturing USA institute (also known as a Manufacturing Innovation Institute) founded in 2017 and funded by the Department of Defense. Its goal is to make practical the scalable, consistent, and cost-effective manufacturing of cells, tissues, and organs. The National Institute for Innovation in Manufacturing Biopharmaceuticals is another manufacturing innovation institute funded by NIST, whose mission is to accelerate biopharmaceutical innovation, including in the area of cell therapies. GAO is mandated to

regularly assess the operation of this network. See, for example, GAO, *Advanced Manufacturing: Innovation Institutes Report Technology Progress and Members Report Satisfaction with Their Involvement*, GAO-22-103979 (Washington, D.C.: Dec. 16, 2021).

<sup>48</sup>Distributed manufacturing is a decentralized manufacturing strategy in which portable manufacturing units may be deployed to multiple locations. Point-of-care manufacturing is a type of distributed manufacturing in which manufacturing units are deployed to places close to where patients may receive care, such as a health care facility. Point-of-care manufacturing could thus be used by health care facilities to meet specific patient needs.

**Figure 5: Comparison of potential centralized and distributed manufacturing models**



Source: GAO (analysis); Alena/barbulat/microone/oksana/topvector/stock.adobe.com (images). | GAO-23-105430

**Ensuring quality.** All medical products have defined properties or characteristics that help ensure quality, known as critical quality attributes (CQA). For example, the CQAs for a

small-molecule drug like aspirin might be the active ingredient’s concentration or the product’s purity. These properties can be measured by, for example, comparing them



to established standards.<sup>49</sup> A batch of a drug can be stored as a reference so future batches can be compared against it.

However, stakeholders often lack consensus on how to measure quality for regenerative medicine products. There are also few standardized reference materials that can be used to evaluate a finished product, making it difficult to identify CQAs. Furthermore, because regenerative medicine products contain living cells, they can change over time or with environmental conditions. For example, cells in a laboratory may function differently than the same cells in a patient. Instead of comparing their products to reference materials, many regenerative medicine manufacturers operate under the assumption that if their manufacturing processes are consistent, the final product will be high quality and consistent. FDA has issued several guidance documents to help product developers identify CQAs.<sup>50</sup> However, CQAs are often product-specific and may be challenging to identify during early clinical development. Therefore, additional studies may be needed later in development to

update CQAs for each regenerative medicine product and establish processes to measure them.

Keeping manufacturing consistent may also be difficult because the starting materials used in regenerative medicine are inherently variable in their composition. For example, in the area of stem cell therapies, starting materials include nutrients for growing cells and growth factors for triggering stem cells to grow into the specific type of cell needed for a therapy. Variation in these materials can reduce product consistency or cause contamination.<sup>51</sup> Product quality standards and oversight may reduce such variation, but according to experts we spoke with, few quality standards currently exist for these materials or even for the starting materials used to make them.<sup>52</sup>

**Workforce shortages.** According to industry experts, there is a shortage of skilled technical personnel who could work on regenerative medicine manufacturing lines. As demand for regenerative medicine products grows, workforce needs will also continue to grow.

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<sup>49</sup>Standards for manufacturing may include reference materials, or internal standards that a company establishes for their specific products and processes.

<sup>50</sup>Food and Drug Administration, *Human Gene Therapy Products Incorporating Human Genome Editing* (Mar. 2022), <https://www.fda.gov/media/156894/download>, accessed Apr. 11, 2023; *Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products* (Mar. 2022), <https://www.fda.gov/media/156896/download>, accessed Mar. 8, 2023; *Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)* (Jan. 2020), <https://www.fda.gov/media/113760/download>, accessed Mar. 8, 2023; and *Potency Tests for Cellular and Gene Therapy Products* (Jan. 2011), <https://www.fda.gov/media/79856/download>, accessed Apr. 11, 2023.

<sup>51</sup>Recent FDA draft guidance acknowledges that the safety and quality of starting and ancillary materials can vary widely

depending on factors such as source or vendors. They also note that lot-to-lot variability and stability of reagents can be problematic. Food and Drug Administration, *Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products*. (Mar. 2022).

<https://www.fda.gov/media/156896/download>, 9, accessed Mar. 13, 2023. Experts told us that, unlike sponsors, starting material suppliers are not required to follow current good manufacturing practice regulations if a material is not incorporated into a final product.

<sup>52</sup>The International Organization for Standardization has recently published a standard that gives guidance to suppliers and users of ancillary materials to improve the consistency and quality of ancillary materials used in the production of cellular therapeutic products and gene therapy products for human use. International Organization for Standardization, "ISO 20399:2022 Biotechnology – Ancillary materials present during the production of cellular therapeutic products and gene therapy products," December 2022. <https://www.iso.org/standard/79399.html>, accessed Mar. 13, 2023.

Additionally, manufacturing may need to be spread out geographically because some regenerative medicine products would be easier to produce near patient care centers. The industry may therefore need technical workers in many locations, not just cities that already have a large biomedical workforce.

A recent study noted that regenerative medicine manufacturing requires people to perform routine, repetitive processes with as much consistency as possible.<sup>53</sup> Experts also suggested that workers will need technical skills, such as the ability to accurately handle liquids and keep materials sterile, but they may not need significant theoretical background in biology. Experts said community and technical colleges may be best suited to train students for such careers, because they have robust workforce development programs. The National Science

Foundation Advanced Technical Education program is supporting some workforce development programs for biotechnology training, but an expert emphasized the need to expand to more campuses and increase awareness about regenerative medicine at the pre-college level.<sup>54</sup> We previously reported on the regenerative medicine workforce and found that, in addition to a shortage of existing skilled laboratory and manufacturing technicians, vocational and technical education is insufficient to meet both current and future workforce needs.<sup>55</sup>

We identified three policy options to help address these manufacturing challenges. Table 3 presents these options, along with the option of maintaining the status quo and opportunities and considerations.

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<sup>53</sup>Gary M. Green et al, "Recommendations for workforce development in regenerative medicine biomanufacturing," *Stem Cells Translational Medicine*, (2021) 10; 1365-1371. <https://doi.org/10.1002/sctm.21-0037>. FDA ensures the quality of drugs and biologics by monitoring manufacturers' compliance with its current good manufacturing practice regulations. 21 C.F.R. Parts 210, 211, 212, and 600 (2022).

<sup>54</sup>For more information about the National Science Foundation Advanced Technological Education (ATE), see

<https://beta.nsf.gov/funding/opportunities/advanced-technological-education-ate>, accessed Feb. 21, 2023.

<sup>55</sup>GAO, *Regenerative Medicine and Advanced Therapies: Information on Workforce and Education*, GAO-23-106030 (Washington, D.C.: Mar. 23, 2023). We also found that there were no nationally recognized regenerative medicine education curricula for various postsecondary degrees.

**Table 3: Policy options for regenerative medicine manufacturing**

Policy options	Opportunities	Considerations
<ul style="list-style-type: none"> <li>• Create more shared pilot- and mid-scale manufacturing facilities to help companies develop their manufacturing processes.</li> </ul> <p><i>This policy option could help address the lack of manufacturing infrastructure.</i></p> <p><i>Potential implementation approaches:</i></p> <p><i>Government agencies could support more public-private partnerships that can share costs for manufacturing facilities.</i></p> <p><i>Industry stakeholders could partner with academic researchers to increase manufacturing readiness of technologies and prepare them for commercialization.</i></p>	<ul style="list-style-type: none"> <li>• May accelerate product development.</li> <li>• May help companies de-risk their products by giving them opportunities to develop and confirm the effectiveness of automated and scalable manufacturing processes.</li> <li>• May save time and money by allowing companies to postpone building infrastructure until after their products and manufacturing processes are further along the development pipeline.</li> </ul>	<ul style="list-style-type: none"> <li>• It will be costly to build shared manufacturing infrastructure.</li> <li>• It is unclear which stakeholders should be responsible for funding and operating shared facilities.</li> <li>• Not all therapies require the same level of scale-up (e.g., therapies for rare diseases have smaller market sizes, so fewer doses will be needed).</li> <li>• Not all stakeholders agree that there should be a federal role and may, instead, prefer to maintain the current free-market model for developing regenerative medicine products.</li> <li>• Issues may arise when sponsors transition from development processes in one location to commercial processes in a second location.</li> <li>• Proprietary manufacturing processes may be a component of FDA licensure. If FDA were engaged with private companies in developing such processes, FDA would need to ensure there was no conflict of interest and that other companies had a level playing field.</li> </ul>
<ul style="list-style-type: none"> <li>• Provide more oversight and feedback to suppliers to increase consistency in starting materials.</li> </ul> <p><i>This policy option could help address inconsistency in starting materials for manufacturing.</i></p> <p><i>Potential implementation approaches:</i></p> <p><i>FDA could work with the Standards Coordinating Body for Gene, Cell, and Regenerative Medicines and Cell-Based Drug Discovery and manufacturers to establish quality standards for starting materials.</i></p>	<ul style="list-style-type: none"> <li>• May accelerate manufacturing by reducing variation in input materials.</li> <li>• May reduce the risk of failure during product development.</li> </ul>	<ul style="list-style-type: none"> <li>• Starting material suppliers may lack incentives to follow standards if they lead to higher costs.</li> </ul>

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*Starting material suppliers could commit to following starting material consensus standards, like those published by the International Organization for Standardization.*

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- Create hands-on training programs at community and technical colleges to address workforce shortages.

*This policy option could help address manufacturing workforce shortages.*

*Potential implementation approaches:*

*Academic stakeholders could use government-run pilot facilities to train students.*

*Academic stakeholders could create standardized training certifications to expand opportunities for both trainees and employers.*

- Could expand the regenerative medicine workforce and help students develop technical skills to meet existing and future needs.
- Could lead to increased domestic manufacturing, which can contribute to U.S. global competitiveness.
- Could create opportunities for high-paying jobs that do not require an advanced degree.

- Educational programs may need to be integrated with regenerative medicine research programs to ensure that trainees can stay up to date on techniques and technologies.
- Community and technical colleges may have limited access to training facilities.

- 
- Maintain the status quo.

- Could allow manufacturing to continue its current incremental development.
- Could save government or private sector resources for other priorities, including promising medical technologies other than regenerative medicine.

- Larger companies may continue to control manufacturing.
  - Product developers may have difficulty accessing manufacturing facilities during development, creating high potential for product failure once they begin manufacturing at scale.
- 

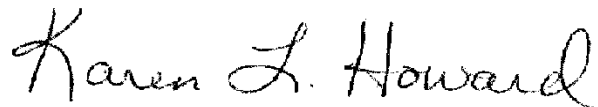
Source: GAO. | GAO-23-105430

## 4 Agency and Expert Comments

We provided a draft of this product to Department of Health and Human Services' FDA and National Institutes of Health, Department of Defense, and Department of Commerce's NIST for review. Department of Defense concurred without comment. The other agencies and some participants from our expert meeting provided technical comments, which we incorporated as appropriate.

We are sending copies of this report to the appropriate congressional committees and other interested parties. In addition, the report is available at no charge on the GAO website at <https://www.gao.gov>.

If you or your staff have any questions about this report, please contact me at (202) 512-6888 or [HowardK@gao.gov](mailto:HowardK@gao.gov). Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix III.

A handwritten signature in black ink that reads "Karen L. Howard". The signature is written in a cursive, flowing style.

Karen L. Howard, PhD  
Acting Chief Scientist and Director,  
Science, Technology Assessment, and Analytics

## Appendix I: Objectives, Scope, and Methodology

### Objectives

This report examines:

- (1) current and emerging regenerative medicine technologies and therapies and their potential benefits,
- (2) challenges that hinder the development and use of regenerative medicine technologies and therapies, and
- (3) policy options that could help enhance benefits and mitigate challenges associated with these technologies and therapies.

### Scope and methodology

To address all three of our objectives, we assessed available and developing regenerative medicine technologies and approaches that may restore cell, tissue, and organ functions lost to disease or injury. For all of our objectives, we reviewed peer-reviewed scientific literature and other documents describing current and developing technologies; interviewed federal agency officials and experts from government, academia, industry, the nonprofit sector, and end user groups such as patient groups; and convened a 3-day expert meeting with assistance from the National Academies of Sciences, Engineering, and Medicine (National Academies) to discuss the objective topics. We provide more details on these methodologies below. We also reviewed federal agency guidance on the development and deployment of relevant technologies, such as Food and Drug Administration

(FDA) guidance on the biologics license applications process.

### Limitations to scope

The list of key technologies discussed in this report is not intended to be exhaustive. Based on our review of the literature and discussions with federal agency officials and other experts, we selected technologies currently in use or under development by researchers to restore body functions that may be lost to disease or injury. We did not include technologies used for research purposes, testing, or diagnostics, such as organ-on-a-chip devices. Though regenerative medicine technologies may be developed or used internationally, the policy options we identified represent possible actions U.S. policymakers and stakeholders could take.

### Literature search

In the course of our review, we conducted a literature search of key technologies for curing human disease and restoring bodily functions using search terms including “regenerative medicine,” “bioprinting,” and “organs,” among other keywords relevant to technologies for regenerative medicine. We also conducted a broad search of materials published within the last 10 years, including scholarly articles and government reports. From these searches, we identified and selected relevant articles to include in our review. We used the results of our literature review to inform our findings as well as identify experts to interview or invite to participate in our expert meeting.



## Interviews

We interviewed federal agency officials and researchers as well as nonfederal experts with a diverse set of perspectives on the science and application of these technologies. The federal experts included individuals from FDA, the National Institutes of Health, Department of Defense, and National Institute of Standards and Technology (NIST). We also interviewed experts from technology companies, universities, and research institutes that use or develop regenerative medicine technologies and representatives from national advocacy organizations, such as the American Society of Gene and Cell Therapy and the Alliance for Regenerative Medicine.

## Expert meeting

To address all of our objectives, we also held a 3-day expert meeting on April 13, 19, and 22, 2022. This meeting was held with assistance from the National Academies and was divided into six sessions: (1) emerging regenerative medicine technologies; (2) regulatory challenges for new regenerative medicine technologies; (3) manufacturing and standardization challenges in regenerative medicine; (4) social, economic, and ethical implications of emerging regenerative medicine technologies; (5) translational hurdles for emerging regenerative medicine technologies; and (6) potential policy options that could help address technology limitations and other challenges.<sup>56</sup>

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<sup>56</sup>This meeting of experts was planned and convened with assistance from the National Academies to better ensure that a breadth of expertise was brought to bear in its preparation.

We selected meeting participants based on their expertise in at least one area related to our objectives. We provided the National Academies staff with descriptions of the expertise needed by expert meeting participants. From this information, the staff provided an initial list of potential participants for the expert meeting. We reviewed the list and provided an additional list of experts based on our review of the literature.

In addition to evaluating experts on the basis of their expertise, we evaluated them for any conflicts of interest. A conflict of interest was considered to be any current financial or other interest, such as an organizational position, that might conflict with the service of an individual because it could (1) impair objectivity or (2) create an unfair competitive advantage for any person or organization. Of the 18 experts who participated in the expert meeting, some were affiliated with companies, government agencies, universities, or public-private partnerships. We took these affiliations into consideration as potential conflicts of interest when conducting our analysis and preparing our report. We determined that these experts' affiliations were unlikely to bias our overall reporting.

## Policy options

Based on our research, we developed a series of policy options. These are not listed in any particular order, nor are they inclusive of all possible policy options. Policy options are intended to represent possible options policymakers can take to address a policy

However, all final decisions regarding meeting substance and expert participation were the responsibility of GAO.

objective. We consider policymakers to include Congress, federal agencies, state and local governments, academia, and industry. For each policy option, we discussed potential opportunities and considerations. We limited policy options to those that fit the objective and fell within the report scope.

To develop our policy options, we compiled a list of possible options over the course of our work based on review of the literature, interviews with experts, and our expert meeting. We further refined and assessed these options to ensure they were adequately supported by the evidence we collected, could be feasibly implemented, and fit into the overall scope of our work. We then analyzed the information we collected to identify potential benefits and considerations of implementing each policy option. The policy options and analyses were supported by documentary and testimonial evidence.

We conducted our work from September 2021 to July 2023 in accordance with all sections of GAO's Quality Assurance Framework that are relevant to technology assessments. The framework requires that we plan and perform the engagement to obtain sufficient and appropriate evidence to meet our stated objectives and to discuss any limitations to our work. Consistent with our quality assurance framework, we provided the relevant agencies and experts with a draft of our report and solicited their feedback, which we incorporated as appropriate. We believe that the information and data obtained, and the analysis conducted, provide a reasonable basis for any findings and conclusions in this product.

## Appendix II: Expert Participation

We convened a 3-day meeting of 18 experts with assistance from the National Academies of Sciences, Engineering, and Medicine to inform our work on regenerative medicine technologies; the meeting was held virtually on April 13, 19, and 22, 2022. The experts who participated in this meeting are listed below. Some of these experts gave us additional assistance throughout our work, including eight experts who provided additional assistance during our study by sending material for review or participating in interviews and the experts who reviewed our draft report for accuracy and provided technical comments.

**Guillermo Ameer**

Northwestern University

**Anthony Axtala**

Wake Forest Institute for Regenerative  
Medicine

**Glenn Cohen**

Harvard Law School

**Kurt Gunter**

Athenex

**Kelvin Lee**

University of Delaware; National Institute for  
Innovation in Manufacturing  
Biopharmaceuticals

**Tim Miller**

Forge Biologics

**Richard McFarland**

Advanced Regenerative Manufacturing  
Institute; Standards Coordinating Body for  
Gene, Cell, and Regenerative Medicines and  
Cell-Based Drug Discovery

**Maria Millan**

California Institute for Regenerative Medicine

**Mahendra Rao**

PanCELLa

**Liz Richardson**

Pew Charitable Trusts

**David Ridley**

Duke University

**Derek Robertson**

The Maryland Sickle Cell Disease Association

**Krishnendu Roy**

Georgia Tech Cell Manufacturing  
Technologies

**Kris Saha**

University of Wisconsin-Madison

**Kevin Schulman**

Stanford University

**Sohel Talib**

California Institute for Regenerative Medicine

**Kathy Tsokas**

Janssen Inc. Canada

**James Yoo**

Wake Forest Institute for Regenerative  
Medicine

## Appendix III: GAO Contact and Staff Acknowledgments

### GAO contact

**Karen L. Howard, PhD**, Acting Chief Scientist and Director, Science, Technology Assessment, and Analytics (STAA), at (202) 512-6888 or [HowardK@gao.gov](mailto:HowardK@gao.gov)

### Staff acknowledgments

In addition to the contact named above, the following STAA staff made key contributions to this report:

**Sarah Harvey, MS**, Assistant Director

**Cindy Korir-Morrison, PhD**, Analyst-in-Charge and Senior Biological Scientist

**Kristin Hook, PhD**, Biological Scientist

**Eric D. Lee, PhD**, Senior Biological Scientist

### These staff also contributed to this work:

Nora Adkins, Senior Attorney

Virginia Chanley, PhD, Senior Design Methodologist

Jehan Chase, Senior Attorney

Ailene Edwards, Intern

Kaitlin Farquharson, Senior Attorney

John Karikari, PhD, Assistant Director, Economist

Flora Ngo, Intern

Emily Quick-Cole, Intern

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Ben Shouse, MS, Communications Analyst

Walter Vance, PhD, Assistant Director

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