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# Advancing Regenerative Cellular Therapy

Medical Innovation for Healthier Americans

As one of the most promising areas for the next generation of treatments, cellular therapies seek to restore health rather than merely treat disease.



BIPARTISAN POLICY CENTER

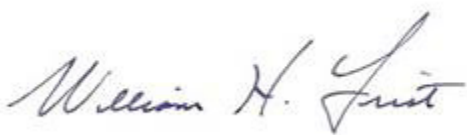
## *Letter from the Co-Chairs*

To keep the United States at the forefront of medical innovation, federal policies should incentivize the development of new technologies that can benefit patients. Earlier this year, the Bipartisan Policy Center released the report, *Advancing Medical Innovation for a Healthier America*, which contains viable policy actions that Congress can take to reduce both the time and cost of developing and delivering safe and effective medical products to patients. Based on in-depth research and interviews with a diverse group of expert stakeholders, these recommendations are designed to accelerate the next generation of cures for diseases such as cancer, Alzheimer's, and Parkinson's disease. One of the recommendations included in the July 2015 report focused on advancing regenerative cellular therapies.

We believe that cellular therapies represent one of the most promising areas for the next generation of groundbreaking treatments. Recent scientific advances in this field, including applications in cardiology, neurology, ophthalmology, and orthopedics, have the potential not just to treat disease, but to cure it. For example, cellular therapy has the potential to halt the progression of degenerative joint disease in the knee or the hip. It can also help to improve a failing heart or a damaged cornea. However, significant regulatory challenges must be overcome for cellular therapy to fulfill its promise.

There are profound differences between inanimate chemicals and living human cells. Yet under existing law, the Food and Drug Administration (FDA) regulates cell-based therapies with a statutory framework using rules—and more frequently non-binding guidance—based on those for chemical drugs, vaccines, and biologics, forcing cellular therapies into an ill-fitting regulatory regime. Moreover, FDA regulatory requirements—where they exist—that are applicable to cell and tissue-based products are often designed for products manufactured and sold on a mass scale. They are either out of date technologically or cannot be readily satisfied when it comes to treatments that are personalized to individual patients and more akin to the practice of medicine. Europe and Japan have outpaced the United States in their policies to grant patients access to safe cellular therapies. The U.S. has a strategic, scientific, and moral imperative to regain its lead in this space without compromising the safety of its citizens or the rigor of its scientific standards. As a critical first step in the process, we need to ensure that our regulatory framework reflects the rapidly emerging scientific knowledge germane to cellular therapeutics.

Thankfully, modernizing the process of discovering, developing, and delivering medical products is a key focus for policymakers this year. We seek to add to and inform those ongoing efforts. We believe that creating a unique regulatory pathway tailored specifically for the safe use of certain regenerative cell therapies is key to advancing 21st century medicine.



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# Introduction

The American population is getting older and increasingly suffering from degenerative, chronic conditions. Between 2010 and 2050, the United States population ages 65 and older is expected to double from about 40 million to 84 million people.<sup>1,2</sup> A significant majority of older Americans suffer from at least one—and often many—chronic conditions, which is expected to drive additional costs and place growing pressure on the health care system.<sup>3</sup> These trends call for new, innovative strategies to keep people healthy.

The primary tools of twentieth century medicine—drugs, medical devices, and surgical interventions—have proved to be remarkably successful in eliminating disease and extending lifespan. But success has been limited with respect to many congenital, age-related, and trauma-induced injuries and diseases involving organ and tissue degeneration. The reigning clinical paradigm emphasizes treatment—palliation and symptom control—rather than curative therapy aimed at resolving the root cause of disease.<sup>4</sup> Furthermore, in most cases, these traditional therapies have a deleterious effect on normal tissues and organs, often resulting in side effects and long-term dysfunction. There is a promising new approach to address degenerative organ and tissue disease and damage: the ability to use human cells as a viable, therapeutic option to rejuvenate, regenerate, or replace diseased organs and tissue.<sup>5,6</sup>

These treatments will not only help patients, they also have the potential to create savings in the health care system by replacing high-cost surgeries and drugs with less expensive, outpatient procedures.<sup>7,8</sup> For example, if diabetes were to be cured through the permanent or semi-permanent replacement of insulin-producing cells, then the lifetime cost and invasiveness of daily insulin injections would be eliminated.

Despite the promise of these new treatments, the existing statutory framework of the Federal Food, Drug, and Cosmetic Act (FDCA) and the Public Health Service Act do not address cell therapy directly. Today's regulations largely prevent a patient from using his or her own cells to treat many medical conditions: a problem that this report seeks to address.

This report offers recommendations to accelerate the availability of safe and effective cellular therapies to Americans in need and improve U.S. competitiveness in the global marketplace. The report builds on initial policy recommendations included in the BPC report, *Advancing Medical Innovation for a Healthier America*, as well as a [technical assistance letter](#) provided to the chairman and ranking member of the Senate Health, Education, Labor, and Pensions (HELP) Committee, both released in July 2015.

## Overview of Cellular Therapy

Regenerative medicine is an emerging field that seeks to restore health rather than merely treat disease. As the National Institutes of Health explains, “Regenerative medicine is the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects.”<sup>9</sup> This field holds the promise of regenerating damaged tissues and organs in the body by stimulating previously damaged tissue and irreparable organs to heal themselves.”<sup>10,11,12,13</sup> Central to the practice of regenerative medicine is cellular therapy, or the use of therapeutic cells to restore healthy organ and tissue function.<sup>14</sup>

Every living tissue in the human body is comprised of cells and they are responsible for carrying out the function and maintenance of every organ in the body. Cells and natural combinations of cells have been used safely and successfully for therapeutic purposes for more than fifty years. Blood transfusions were the first type of cellular therapy and bone marrow transplantation has been a standard of care for patients with aggressive forms of cancer for decades.<sup>15</sup> Organ transplants have become routine in modern medicine and have saved countless lives, while grafts of the skin and cornea for burns or eye injury have been widely employed.<sup>16</sup>

But recent scientific progress using cells derived from either perinatal (umbilical cord and cord blood) or adult (bone marrow, mobilized peripheral blood, and adipose (fat)) tissue has significantly advanced the capacity to use cellular therapies across many other medical specialties, including cardiology, neurology, ophthalmology, orthopedics, organ transplantation, urology, and others.<sup>17,18,19,20</sup>

By providing healthy, functional tissues and organs, regenerative medicine will improve the quality of life for individuals. The National Institutes of Health describes the long-term promise of regenerative medicine as a world where there is no donor organ shortage, where victims of spinal cord injuries can walk, and where weakened hearts are replaced.<sup>21</sup>

## *Different Kinds of Therapeutic Cells*

Cellular therapy is an umbrella term that comprises a number of different cell types. Adult cells, as the name suggests, are found in tissues or organs of adults and children. Embryonic cells are derived from embryos, usually donated for research purposes with informed consent of the donors. The topic of embryonic cells is a controversial one with many scientific, ethical, and political considerations. This report is focused solely on adult therapeutic cells and the potential they hold for regenerative medicine.

There are several key distinctions pertaining to adult therapeutic cells.

- *Autologous vs. Allogeneic Cells:*
  - *Autologous* cells come from the person receiving the treatment.
  - *Allogeneic* cells come from another person.
- *Homologous vs. Non-Homologous Cells:*
  - *Homologous* cells come from the same tissue or organs to which they are being applied.
  - *Non-homologous* cells come from a different tissue or organ than those to which they are being applied.

Autologous cells carry virtually no likelihood of being rejected by or attacking the host. Autologous cells may be the best choice in some conditions, but not others. For example, it is known that older cells may not be as effective as younger cells. Also, if autologous cells are causing the disease process or already harboring the disease susceptibility genes, allogeneic cells may better correct the disease process.

Examples of the use of different types of cellular therapies are provided below.

- An example of *autologous/homologous* cellular therapy would be the application of cells extracted from the left elbow of a patient to the right elbow of that patient to treat lateral epicondylitis (tennis elbow).
- An example of *non-homologous/autologous* cellular therapy would be the extraction of cells from adipose (fat) tissue for injection into the knee to promote cartilage restoration to address injury or age-related degeneration.
- An example of *allogeneic/homologous* therapy is a bone marrow transplant from an unrelated donor to replace the bone marrow and blood of a patient with leukemia who is being treated with high dose chemotherapy.
- An example of *allogeneic/non-homologous* therapy is injection of mesenchymal stem cells or multi-potent stromal cells—both referred to as MSCs, derived from the bone marrow of one patient into another patient’s heart muscle in order to reduce inflammation, help protect the damaged heart tissue, and prevent scars from forming.

## *The Benefits of Cellular Therapies*

For the many diseases and disorders affecting Americans for which there are no effective treatments let alone cures, the application of cellular therapy represents a major frontier for the future—potentially affecting virtually every medical condition, disease, and disorder.<sup>22</sup> The successful application of autologous and allogeneic cellular therapies to address a host of formerly incurable and untreatable diseases offers a potent and practical example of their clinical utility. Moreover, the apparent safety of many allogeneic and autologous cellular therapies provides compelling proof-of-concept evidence of the potential clinical utility of using therapeutic cells more broadly.<sup>23</sup> Many long-term studies have been conducted and are in progress. Preliminary study results suggest that many participants benefit from the application of therapeutic cells. For example:

- Early research suggests impressive contributions of bone marrow derived cellular therapies to bone and cartilage repair and reduction of osteoarthritic and lower back pain.<sup>24</sup>
- Intra-articular injections of MSCs in osteoarthritic patients have demonstrated strong indications of efficacy including significant improvement in cartilage quality in the vast majority of treated cases.<sup>25</sup>
- Patients with severe back pain due to degenerative disc disease have improved dramatically following treatment with MSCs, with 71 percent of optimal efficacy in the improvement of clinical parameters of pain and disability.<sup>26</sup>
- Autologous limbal stem cell expanded cultures are being used to treat moderate to severe cell deficiency caused by physical or chemical burns to the eye in adults.<sup>27</sup>
- The use of cellular therapy has been shown to be effective in controlling graft-versus-host disease (GvHD), to support transplantation medicine.<sup>28,29</sup>
- The use of unrelated donor bone marrow, mobilized peripheral blood, or cord blood cells has increased access to life-saving hematopoietic stem cell transplantation for thousands of patients, especially those of diverse ancestries.<sup>30</sup>

## *Cellular Therapies vs. Drugs*

Cellular therapies represent a significant departure from previous medical breakthroughs. Whereas current efforts to address chronic and age-related diseases rely upon a combination of drugs, biologics, and devices to offer relief from debilitating symptoms, they typically fail to address the root cause of disease.

While a worthy pursuit, symptom mitigation nonetheless represents an imperfect approach to a bigger challenge—the ability to cure rather than merely treat disease symptoms by attacking them at their root cause, which typically entails some combination of organ and/or tissue failure—the very factors that cellular therapies are designed to address.

Complementing biomedical therapies in practice today, cellular therapies aim to restore organ and tissue functions by fostering the management of a patient's inherent ability to regenerate tissue and in some cases (e.g., osteoarthritic conditions), replace missing cells. While drugs address a single target or disease-causing mechanism, cells integrate multiple inputs and act through multiple, coordinated signals in precisely the right amounts and ratios to instruct and/or enable damaged tissues to repair and heal.

## *Safety and Effectiveness*

Pre-clinical and clinical safety testing is being performed to assure safety of the cells themselves, the procedures to administer them to patients, and the manufacturing process employed to render such cells fit for use in the clinic.

A substantial number of clinical trials related to cellular therapy have been conducted and many others are currently underway. As of Nov. 29, 2015, ClinicalTrials.gov included listings for 30,289 studies involving “adult cellular therapy,” with more than 18,000 being conducted in the U.S.<sup>31</sup> Substantial evidence from thousands of completed and ongoing clinical trials offers significant support to the utility of therapeutic cells that have the potential to restore function in a large number of tissues compromised by degenerative or traumatic conditions.<sup>32</sup>

To date, studies and procedures have shown the use of autologous MSCs (adult cells which can differentiate into a variety of cell types, such as bone, cartilage, or fat cells) to be “remarkably safe.”<sup>33</sup> While all of these cells' precise mechanisms of action remain largely unknown, they appear to boost the innate capacity of the affected tissue to heal through pro-regenerative processes.<sup>34</sup>

While a growing number of studies and early practice experience suggest that the risks to both research participants and patients receiving autologous/allogeneic cellular therapies are low, they are not entirely absent, as is the case with any medical procedure. Such potential risks may include in principle: procedural risk, immune response, infection related to surgery if required, and inappropriate cell migration.<sup>35</sup> Therefore any regulatory framework related to cellular therapy—such as the one described below—should seek to maximize safety.

BPC recently conducted a high-level review of 212 peer-reviewed articles published in the past five years and listed in the PubMed database—a resource developed and maintained by the National Center for Biotechnology Information, a division of the U.S. National Library of Medicine at the National Institutes of Health. The specific search term used to identify the articles was “clinical trial study autologous stem cell safety.” Of the 212 articles reviewed, 81 were found to be out-of-scope because the study did not include any safety assessment of autologous cellular therapy or the study only addressed a safety-related issue about drugs and/or

devices. The remaining 131 articles were reviewed to assess safety. Three of the 131 articles described homologous cellular therapies while the vast majority, 128, described cellular therapies that were non-homologous. Of the 131 articles reviewed, 128, or about 98 percent, found the use of autologous cellular therapy described in the study to be safe, whereas only three, or about two percent, of the articles found the use of autologous cellular therapy to have significant safety issues.

A similar analysis was performed using the search term “clinical trial study allogeneic cell safety.” Of the 108 articles reviewed, 76 were found to be out of scope. Of the remaining 32 articles reviewed, 30, or about 94 percent, found the use of allogeneic cellular therapy described in the study to be safe and/or well-tolerated, whereas only two, or about six percent, of the articles found allogeneic cellular therapy to have safety issues.

While lacking the rigor of a formal meta-analysis, these preliminary findings provide compelling evidence that the use of cellular therapies appears to be safe across a wide number of therapeutic domains.

## ***Barriers to Broader Adoption***

One of the most significant barriers to broader adoption of cellular therapies is the existing regulatory regime which includes a statutory framework based on rules—and more frequently non-binding guidance—based on those used for chemical drugs, vaccines, and biologics. Addressing this barrier is the primary focus of this report.

Other barriers to more widespread adoption of cellular therapies include complexity and uncertainty of coverage and reimbursement, the need for greater sharing of data and best practices to support advancements in the field, and the need for additional investments in research.<sup>36,37</sup>

## ***The Need for a New Regulatory Framework for Cellular Therapy***

As recently as two decades ago, few considered the possibility that therapeutic cells might play a prominent role in clinical medicine. Recent breakthroughs in the science of regenerative medicine and cellular therapy are poised to assist in moving beyond relieving symptoms to the promise of rejuvenating, regenerating, and replacing diseased organs and tissue.

## ***How Cellular Therapies are Regulated Today***

Under current U.S. law, cellular therapeutics, including unrelated donor cord blood banks, are regulated by the FDA. However, despite profound differences between drugs and living cells, a new regulatory framework applicable to cellular therapies and tissue transplantation has been only partially developed. Rather than establishing a completely unique regulatory framework, the FDA has moved incrementally into this new area by adapting or modifying a regulatory process developed for chemical drugs, vaccines, and biologics.

While surgical transplantation of a piece of tissue from one part of the body to another—such as coronary artery bypass graft surgery, spinal surgery that uses bone from a patient’s pelvis or rib to fuse vertebrae, or bone marrow transplantation from a related

donor—is recognized as the “practice of medicine” where advance agency approval is not required; the use of isolated cells themselves requires FDA approval in spite of cellular therapy not having a unique fully defined regulatory construct.

Even if cells are transplanted back into the same patient, they are currently regulated as biologics, which are included in the broader statutory definition of drugs, unless they are shown to be unchanged or “minimally manipulated” from the state in which they were originally isolated. The FDA defines minimal manipulation as processing that does not alter the original relevant characteristics of the tissue relating to the tissue’s utility for reconstruction, repair, or replacement, or processing that does not alter the relevant biological characteristics of cells or tissues.<sup>38</sup> As a result, such a paradigm does not address the need to modify or process the cells to make them more effective or the use of a person’s own cells that can evolve to become other types of cells when incorporated into different tissue (e.g., cartilage in the knee or heart muscle) or otherwise help restore function to the site in which they are placed.

Additionally, drug, biologic, and medical device regulatory requirements that were designed primarily for commercial products manufactured and sold on a mass scale cannot be readily satisfied for personalized treatments developed and delivered for individual patients.

The FDA has been engaged in evolving its approach to cellular therapies since 2001, when it created by regulation a three-tiered structure for Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) with the degree of regulatory oversight increasing as product risk potential increases. This regulatory framework is set forth in 21 C.F.R. Part 1271, based upon the agency’s general statutory authority to prevent the spread of communicable disease according to Section 361 of the Public Health Service Act.<sup>39</sup> There exists no comprehensive statutory framework under the Federal Food, Drug, and Cosmetic Act addressing cell therapy. Specifically:

- *First Tier.* The lowest risk category represents the practice of medicine and therefore not generally subject to FDA pre-approval requirements. It includes human organs for transplantation, whole blood and blood-derived products, and extracted human products such as bone marrow.
- *Second Tier.* The mid-level risk category applies to “any human tissue derived from a human body and intended for transplantation into another human . . . that meets the following criteria: minimally manipulated, intended for homologous use, not combined with another agent (with a few exceptions), and either does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function, or if it has such an effect, is intended for autologous use or allogeneic use in close relatives.”<sup>40</sup> Cellular therapies meeting these criteria are known as 361 HCT/Ps and are eligible for regulation solely under Part 1271 (communicable diseases).<sup>41,42</sup> This designation exempts the products from the pre-market FDA approval or clearance process. These products must only meet requirements regarding: (1) registration and listing, (2) donor screening and testing, (3) Current Good Tissue Practices (cGTPs), (4) labeling, (5) adverse-event reporting, and (6) inspection and enforcement.<sup>43</sup>
- *Third Tier.* The third tier comprises what the FDA considers the riskiest HCT/Ps, which are regulated under both Part 1271 and are treated using FDA’s traditional pre-market and post-market approach to regulation of drugs and medical devices under the FDCA and biologics under section 351 of the Public Health Service Act. Tissue and cells are considered 351 HCT/Ps, requiring full pre-approval biologics license applications (BLAs) if they fail to meet the 361 exemptions.<sup>44</sup>



Because 2001 guidance related to registration and listing rules described 361 HCT/Ps as being transferred into “another human,”<sup>45</sup> the FDA excluded autologous cells from falling into the category that would require a full pre-approval BLA. However, in an effort to expand its reach, in 2006, the FDA revised the guidance, changing the phrase from “another human” to “a human,” thereby expanding its BLA requirement to include autologous cells. The portfolio of therapeutic applications of using a patient’s own cells or one from a matched donor is quite broad and in many cases quite analogous to the lowest tier risk category of blood transfusions or transplants.

In 2008, the FDA reprimanded Colorado-based Regenerative Sciences LLC, arguing that its procedures to treat arthritis and orthopedic injury by extracting, culturing, and reinjecting MSCs in the same patient more than minimally manipulated the tissue, thereby requiring substantial clinical evidence and the filing/approval of a full BLA.<sup>46</sup> Although the general focus on safety is critical and laudable, the net effect of this judicial decision and current regulations has confused companies, researchers, and physicians, which in turn, hinders innovation, curtails investment, and ultimately delays the benefits of potential groundbreaking therapies to U.S. patients.

Since 2001, the evolution of the regulatory framework through non-binding guidance documents which lack sufficient public input has been minimal with respect to cell and tissue transplantation and many critics contend that they do not reflect the current science regarding the safety of autologous and allogeneic non-immunogenic therapeutic cells. Moreover, these guidance documents do not recognize the real-world challenges of implementing a program to prepare a traditional BLA costing hundreds of millions of dollars to compile “substantial clinical evidence” demonstrating safety and efficacy before receiving market approval.

The four guidances that directly impact how the FDA regulates human cells and tissue-based products include:

- Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception – October 2014<sup>47</sup>
- Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products – December 2014<sup>48</sup>
- Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations – December 2014<sup>49</sup>
- Homologous Use of Human Cells, Tissue, and Cellular and Tissue-Based Products –October 2015<sup>50</sup>

The first three guidances listed above proved controversial, particularly the recommendations very narrowly defining minimal manipulation. Many stakeholders urged FDA to hold a public meeting for fuller discussion. The latest guidance was issued in October 2015 providing definitions and very narrow examples of exempt homologous use. To address growing public concerns, the FDA announced it would open public comment on all four guidances and hold a public hearing in April 2016.

Taken together, these actions indicate that the FDA recognizes the lack of clarity in the current regulations for cell therapy. However, the FDA is not permitted to change policy through guidance, and the redrafting of non-binding guidances ad hoc without the procedural protections and broad scientific input inherent in legislation or rulemaking holds little promise of resolving the regulatory barriers to cell therapies.

Modernization of the regulatory pathway can occur through the prolonged process of issuing regulations or by Congressional authorization by statute. While issues associated with guidances have spawned vigorous debate among regulators, policy makers, industry,

patient advocates, and other key stakeholders about the best path forward to promote the safe and effective use of therapeutic cells, the fact remains that the U.S. is lagging behind its global competitors in bringing what promises to be one of the most significant advancements of the 21st century—the entrance of regenerative medicine into the clinic and on to the market.

## *Advanced Regulatory Frameworks in Other Parts of the Globe*

From the standpoint of promoting international competitiveness, it is clear that Japan has streamlined its regulatory framework to take the lead in commercializing cell-based therapy by expediting its review and approval process for such therapies. Moreover, the European Union (EU) has granted a special “medical practice” exemption which allows for therapeutic products containing stem cells to be made available to individual patients in European hospitals under the exclusive professional responsibilities of treating physicians. The treatment is usually a custom-made product using the patient’s own cells that are prepared on a non-routine basis adhering to specific quality standards. Within the EU, the hospital or medical practice exemption is only authorized for use by the regulatory authority of the member state where the product is made. In Europe, limbal stem cells (from the corneal limbus) have been registered as a product for eye burns.<sup>51</sup> In Canada and New Zealand MSCs have been approved for pediatric GvHD.<sup>52</sup>

To date, the FDA has been slow to approve non-cord blood-derived cellular therapy for clinical use. The U.S. has a strategic, scientific, and moral imperative to regain its lead in this space. As a critical first step, existing legal and regulatory frameworks must reflect rapidly emerging scientific knowledge germane to therapeutic cells. In particular, any regulatory framework, policy, or practice must be consistent with the mounting body of evidence drawn from thousands of clinical trials demonstrating that the use of autologous and/or allogeneic non-immunogenic cells has proven to be safe in all but a statistically insignificant number of instances.<sup>53</sup>

### **Japan’s New Regulatory Framework<sup>54,55,56</sup>**

On November 25, 2014, the Japanese Government implemented a new system of regulations for regenerative medicine products, separate from medical devices and pharmaceuticals. New Japanese law allows for a seven-year conditional approval of a regenerative medicine product if evidence shows safety is confirmed and “the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit.” This preliminary evidence of efficacy is similar to U.S. accelerated approval requirements. The types of cell products regulated under the new system are not determined by the source of the cells (they may be either autologous or allogeneic), but rather the extent of cell processing or manipulation. Cells that are more than minimally manipulated, for non-homologous use or for gene therapy, are regulated under the new conditional approval program in Japan. During the conditional approval period as well as potential full approval within seven years, “post-marketing safety measures must be taken, including prior informed consent of risk to patients.” In September 2015, Japan approved the first product under these regulations for the treatment of GvHD, a severe complication that can result from bone marrow transplants.

# *A New Regulatory Pathway for Cellular Therapy*

Cellular therapy holds enormous promise for future cures and/or treatments, but more regulatory clarity is required if the field is to reach its full medical potential in the U.S.

## *Policy Goals*

Given the importance of cellular therapies in advancing modern health care and continuing U.S. leadership in innovation, policy goals include:

1. Strengthening the rights of patients to be treated with their own cells or allogeneic cells that do not induce an adverse immune response, while maintaining quality, safety, and efficacy, through:
  - A statutory framework that accelerates patient benefits and increases investment by recognizing the unique and distinct nature of regenerative cell therapies versus traditional drugs; and
  - Creation of a new class of cell therapies where patients are treated with their own cells, or with allogeneic cells that do not induce an adverse immune response that affects their therapeutic activity or safety, so long as the treatment has been shown to be safe and there is at least preliminary rigorously-obtained and well-documented clinical evidence of efficacy.
2. Empowering physicians to treat their patients with the best available, well-documented therapies and develop innovative, yet vigorously monitored, techniques, by:
  - Enabling physicians to deliver care through personalized treatment methods that use therapeutic cells;
  - Improving the ability of physicians to treat patients with safe and effective novel cellular therapies in clinical settings (the safety and requisite efficacy for which has been well-documented), over a specific period of time before full approval is given, and to be reimbursed for that treatment; and
  - Increasing the pace of innovation by lowering the financial barriers to entry in a field in which the significant long-term investments traditionally targeted toward drug development are less available for the nascent business models of precision medicine.
3. Enabling industry to support physicians and patients with safe, proven technologies by:
  - Simplifying and streamlining the rules and classifications for devices used to harvest, manufacture, and administer these therapies, using clearer criteria and a risk-based approach, so long as safety has been confirmed; and
  - Developing clearer, simpler laws for device and reagent manufacturers where needed; improving access to clinically compliant raw materials for scientists and physicians, and harnessing greater innovation from clinical investigators.

As noted previously, other countries with highly sophisticated regulatory systems, including Japan and those in the European Union, have already succeeded in developing a framework to resolve these issues.

As noted previously, initial policy recommendations related to cellular therapies were included in BPC's report, *Advancing Medical Innovation for a Healthier America*, as well as a [technical assistance letter](#) provided to the chairman and ranking Member of the Senate HELP Committee. More detailed recommendations—developed with the guidance of an expert panel—are summarized below.

## Key Principles for Policy Approach

BPC’s proposal to promote the progress of cellular therapy in the U.S. is rooted in a set of core principles—all of which center on the need to promote public health while simultaneously protecting public safety. It is precisely this balance that the FDA seeks to maintain as well, especially when evaluating innovative and potentially paradigm-altering therapies and procedures that may not fit within prevailing regulatory frameworks and pathways, as is the case with many therapeutic cells.

This proposal facilitates the FDA’s capacity to more rigorously and effectively evaluate the safety and efficacy of well-characterized therapeutic cells. It also assures no decrease in safety standards and no elimination of any process currently regulated by the FDA. Furthermore, this proposal does not intend to increase regulation of any procedures for which no advance FDA approval is required today.

## A New Regulatory Pathway

To assure that patients have access to innovative, safe, and effective cellular therapies, the premarket approval process described as the foundation of the BLA must be modified for a unique class of therapeutic cells, including autologous or allogeneic cells that do not induce an adverse immune response that affects their safety or efficacy, that meet the following criteria:

- Are homologous as per FDA definition, and more-than-minimally manipulated, but where processing or fractionation does not alter the biological characteristics of cells or tissues or change their character and function; or
- Are non-homologous as per FDA definition, but are tailored to restore function in the recipient, and are either minimally manipulated or more than minimally manipulated—but where processing or fractionation does not alter the biological characteristics of cells or tissues or change their character and function.

Examples of cells that meet these requirements are summarized below:

Cell Source	Cell Use	Extent of Cell Manipulation	Examples
Autologous or donor allogeneic cells that do not induce an adverse immune response	Homologous	More than minimally manipulated (but same character and function)	<ul style="list-style-type: none"> <li>• Autologous culture expanded adipose (fat) MSCs for subcutaneous injection</li> </ul>
	Non-homologous (but performs or helps restore function)	Minimally manipulated	<ul style="list-style-type: none"> <li>• Autologous adipose stromal vascular fraction to reduce arthritis inflammation in joints</li> </ul>
		More than minimally manipulated (but same character and function)	<ul style="list-style-type: none"> <li>• Autologous lineage—committed or expanded MSC for fistula repair</li> <li>• Autologous or allogeneic bone marrow or cord blood for treatment of acute or sub-acute ischemic heart disease</li> </ul>

This new pathway—under well-defined and limited conditions—creates an alternative to the standard BLA pathway. To this end, BPC recommends a process that would:

- Allow the FDA to grant a time-limited, conditional approval for therapeutic cells based on preliminary though rigorously-obtained and well-controlled clinical evidence of safety and efficacy, without Phase 3 trials;
- Provide patients with limited access to these conditionally-approved therapies with monitoring and reporting requirements to FDA;
- Require the sponsor to submit a BLA—using the accrued data—within three years of receiving conditional approval or negotiate with the FDA an extended conditional period to gather additional data;
- Permit reimbursement during the conditional approval period; and
- Create a simplified and expedited linked approval pathway for devices used in conjunction with cell therapies.

An illustration of this new pathway is highlighted in Level 2 within Figure 1 below.

Bearing in mind the key principles, BPC's aim is to ensure that there is neither deregulation of what currently constitutes practice of medicine (referred to as Level 1 below), nor reduction in current standards for potentially more risky cellular therapies (referred to as Level 3 below). BPC recommends that regulation for such cells remains unchanged, namely:

- *Level 1: Practice of Medicine.* Includes autologous cells (which are cells derived and used in the same person, or cells derived from close relatives), or use of allogeneic cord blood or bone marrow, that are both homologous and minimally manipulated. BPC recommends that such cells continue to be treated as the practice of medicine, exempt from FDA preapproval requirements, but generally subject to Part 1271 regulations (e.g., registration, donor screening, good tissue practices, etc.).
- *Level 3: Standard Pathway.* Includes the following:
  - Autologous, homologous cells that are more than minimally manipulated and do not retain the same character and function; or
  - Autologous, non-homologous cells that do not help restore function and are either minimally manipulated or more than minimally manipulated; or
  - Allogeneic cells that induce an adverse immune response, are either homologous or non-homologous, and are either minimally manipulated or more than minimally manipulated.

BPC recommends that cells described in Level 3 continue to require an investigational new drug (IND) application and a full BLA.

BPC's recommendation for a new pathway for cells defined within Level 2, is designed to facilitate submission of clinical data to FDA and the efficient approval of a discrete subset of demonstrated safe and effective cellular therapies that is not currently possible under existing statutory and regulatory norms. It does so by providing a rigorous and efficient modern pathway that is both cognizant of emerging regulatory science and mindful of the distinct attributes of autologous or allogeneic cells that do not induce an adverse immune response. The pathway preserves the FDA's rigorous oversight of early stage clinical development by requiring prior to conditional approval, the acquisition and analysis of data on safety and effectiveness required to initiate a Phase 3 clinical trial without compromise of its authority to promote and protect the public health.

**FIGURE 1. New Regulatory Framework for Cellular Therapy**

Path	Cell Source	Cell Use	Extent of Cell Manipulation	Disposition	Examples
<b>Level I PRACTICE OF MEDICINE</b> (No change to current law)	Autologous (cells derived and used in same person or in close relatives); use of allogeneic cord blood or bone marrow	Homologous	Minimal manipulation as defined by FDA in 21 CFR 1271.3(f)	Exempt from FDA pre-approval requirements	<ul style="list-style-type: none"> <li>Matched or partially matched—related and unrelated--allogeneic bone marrow, mobilized blood, cord blood transplantation to restore hematopoiesis after high dose therapy to treat blood cancers</li> <li>Donor white blood cells from immune system to treat cancer tumors</li> </ul>
<b>Level 2 NEW PATHWAY</b>	Autologous or donor allogeneic cells that do not induce an adverse immune response	Homologous	More-than-minimally manipulated (but same character and function)**	IND and conditional FDA review; preliminary rigorously-obtained and well-controlled clinical evidence of safety and efficacy, but not Phase 3 trials, reviewed and approved by FDA ; limited patient treatment with routine monitoring/ reporting to FDA; BLA due within 3-years*** ; reimbursement possible during conditional approval period	<ul style="list-style-type: none"> <li>Autologous culture expanded adipose (fat) MSCs for subcutaneous injection</li> </ul>
		Non-homologous (but performs or helps restore function)*	Minimally manipulated		<ul style="list-style-type: none"> <li>Autologous adipose stromal vascular fraction to reduce arthritis inflammation in joints</li> </ul>
			More-than-minimally manipulated (but same character and function)**		<ul style="list-style-type: none"> <li>Autologous lineage-committed or expanded MSC for fistula repair</li> <li>Autologous or allogeneic bone marrow or cord blood cells for treatment of acute stroke, acute ischemic heart attack, and acute perinatal asphyxia</li> <li>Allogeneic or autologous bone marrow, or cord tissue derived MSCs for treatment of acute ischemic heart attack.</li> </ul>

Path	Cell Source	Cell Use	Extent of Cell Manipulation	Disposition	Examples
<b>Level 3 STANDARD PATHWAY</b> (No change to current law)	Autologous	Homologous	More-than-minimally manipulated and does not retain the same character and function	IND and Full BLA	<ul style="list-style-type: none"> <li>Autologous bone marrow MSC manipulated into osteoblasts for bone defects</li> </ul>
	Autologous	Non-homologous (does not help restore function)	Minimally manipulated or more-than-minimally manipulated	IND and Full BLA	<ul style="list-style-type: none"> <li>Autologous bone marrow MSC for ALS, chronic health failure, and acute stroke</li> </ul>
	Allogeneic cells that are immunogenic (induce adverse immune response that may affect safety or efficacy)	Homologous or Non-homologous	Minimally manipulated or more-than-minimally manipulated	IND and Full BLA	<ul style="list-style-type: none"> <li>Allogeneic immunogenic bone marrow, adipose or cord tissue MSC for acute heart attack, and acute stroke</li> </ul>

\* Non-homologous as per FDA definition, but allowing cells to perform or help restore the function in the recipient (to reflect attributes of stem cells to differentiate and coopt biological processes to restore the cells/tissues into which they are placed).

\*\* More-than-minimally manipulated as per FDA definition, but processing or fractionation that does not alter the relevant biological characteristics of cells or tissues, or change their character or function.

\*\*\* FDA may grant extensions to sponsor for BLA filing, within its sole discretion.

This recommendation is the result of an extensive literature review and is informed by expert panel guidance and multiple meetings with key government, industry, and academic stakeholders. It reflects a widely shared consensus that the U.S. cannot continue to maintain its global biomedical leadership absent sufficient regulatory reform concerning cellular therapy. This limited modern pathway to personalized medical use of a well-defined subset of cells recognizes the need for expansion and modification of the regulatory framework brought on by the rapidly expanding 21<sup>st</sup> century science of therapeutic discovery and development.

## *Conclusion*

The extraordinary medical advances of the past century have transformed and improved the lives of billions of men, women, and children. Driving this transformation has been a vibrant biomedical paradigm that continues to deliver increasingly effective and targeted therapies to address much, but certainly not all, that ails us.

Cellular therapy represents a promising new approach that extends beyond the prevailing paradigm of palliation and symptom mitigation to cure rather than merely slow disease progression. The rejuvenation, regeneration, and replacement of diseased organs and tissue aims at attacking the root cause of disease.

There will be obstacles in bringing cellular therapy from the bench to the bedside. But one thing is clear; if the promise of regenerative medicine is to be fully realized, the regulatory approach to cellular therapy must hasten rather than hamper the emergence of this promising new field in a responsible manner. A significant step in this direction would be the adoption of a modern, cellular therapy-specific, relevant, and more rational statutory and regulatory framework for cellular therapy as proposed in this report.



## End Notes

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## *About the Initiative on FDA: Advancing Medical Innovation*

The Bipartisan Policy Center's initiative on FDA: Advancing Medical Innovation is developing viable policy options to advance medical innovation and reduce the time and cost associated with the discovery, development, and delivery of safe and effective drugs and devices for patients in the United States. Former Senate Majority Leader William H. Frist, MD and former U.S. Representative Bart Gordon co-chair this initiative. Janet Marchibroda, BPC's Health Innovation director, serves as the staff director for the effort.

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## *Disclaimer*

The findings and recommendations expressed herein do not necessarily represent the views or opinions of the Bipartisan Policy Center's founders or its board of directors.

# *Notes*



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Founded in 2007 by former Senate Majority Leaders Howard Baker, Tom Daschle, Bob Dole and George Mitchell, the Bipartisan Policy Center (BPC) is a non-profit organization that drives principled solutions through rigorous analysis, reasoned negotiation and respectful dialogue. With projects in multiple issue areas, BPC combines politically balanced policymaking with strong, proactive advocacy and outreach.

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