

Regenerative Cell Therapies: Making Safe and Effective Treatments Available to Patients Key Take-Aways from September 19, 2019 Capitol Hill Briefing

Executive Summary of Key Take-aways

During a September 2019 event on Capitol Hill, hosted by the independent, non-profit organization, Alliance for Cell Therapy Now, public and private sector leaders described the promise of regenerative cell therapies and key imperatives for bringing both safe and effective treatments to patients in need. Key take-aways from the event are summarized below:

- Regenerative cell therapies represent the next generation of treatments that are showing great promise for patients in need. Several well-designed clinical trials are being conducted under FDA investigational new drug (IND) protocols.
- At the same time, a handful of clinics have caused patient harm or made questionable claims, taking advantage of vulnerable patients and casting a negative light on this emerging, promising science and industry.
- The 21st Century Cures Act contained several provisions to make safe and effective regenerative cellular therapies available to patients, including extending Food and Drug Administration (FDA) expedited programs to include regenerative therapies and providing funds for research through the National Institutes of Health (NIH). The FDA and NIH are taking several critical steps to advance and support the field.
- A number of actions were highlighted by speakers to help bring safe and effective regenerative cell therapies to patients in need. They include:
 - Gaining consensus on and driving adoption of both standards and best practices to support the development, manufacturing, and delivery of regenerative cell therapies.
 - Developing and launching a national outcomes database or registry of regenerative cell therapies, including the capture of cell characterization data and clinical outcomes using consensus standards, to enable a deeper understanding of the composition and function of cells and the correlation of cell characteristics with clinical outcomes.
 - Significantly expanding workforce development initiatives, including those focused on technical and community colleges, to build capacity and develop a skilled, technical workforce for this growing field.
 - As noted by private sector panelists, increasing funding and capacity within FDA's Center for Biologics Evaluation and Research (CBER) to support increased education, dialogue, and technical assistance for academic and research

institutions, industry innovators, and practitioners, to support their understanding of and compliance with new FDA regulations, as well as continued enforcement efforts against clinics and others that are causing patient harm.

- As noted by private sector panelists, increasing and sustaining NIH funding for regenerative cell therapy research and clinical trials support, to advance the science and the field.

A summary of insights shared during the Congressional briefing is provided below.

Background

The Alliance for Cell Therapy Now, a 501(c)6 organization devoted to advancing the availability of safe and effective cell therapies for patients in need, hosted a briefing in the Senate Hart Office Building on Capitol Hill on September 19, 2019, in collaboration with the Regenerative Medicine Foundation and the Cord Blood Association. Event videos, presentation slides, photos, and speaker bios can be found at <http://allianceforcelltherapynow.org/events/>.

During the event, national leaders representing academic and research institutions, health systems, patients, and the federal government, came together to offer key insights for advancing the development and delivery of safe and effective regenerative cell therapy products to help patients in need. Janet Marchibroda, President of the Alliance for Cell Therapy Now, kicked off the event with a high-level overview of the current state of the field, a summary of key imperatives to advance regenerative cell therapies, and an overview of the event, described below:

- Regenerative cell therapy research and the promise for patients;
- Cell characterization and scalable manufacturing to assure quality control and improve access for patients; and
- A review of federal activities for protecting patients through rigorous science and safety.

A detailed summary of speaker insights in each of these three key areas is provided below.

Regenerative Cell Therapy Research and the Promise for Patients

Regenerative cell therapies represent the next generation of groundbreaking treatments that are showing great promise in cardiology, neurology, oncology, orthopedics, osteoarthritis, and engineering of organs to support patients in need. Several well-designed clinical trials are now being conducted under FDA IND protocols.

Leading researchers shared a summary of research that has been performed or is underway during a panel discussion moderated by Dr. Fred Sanfilippo of Emory University and the Marcus Foundation, the latter of which has provided more than \$100 million in grants to support clinical trials in regenerative cell therapy.

- Dr. Anthony Atala of the Wake Forest Institute for Regenerative Medicine described several studies, including those related to the use of the patient’s own tissue-specific cells for the treatment of shoulder rotator cuff injuries and kidney disease, as well as for the engineering of urethras, blood vessels, and bladders implanted in patients. Dr. Atala also described activities of the Regenerative Medicine Innovation Manufacturing Consortium, a private-public partnership of industry, government, and academia, with the goal of accelerating the production of cell-based therapies for patients by improving and standardizing manufacturing technologies, such as bioreactors, cell media, and bio-inks for 3D printing.
- Dr. Joanne Kurtzberg of Duke University School of Medicine described promising clinical trials underway to assess the use of umbilical cord blood cells and cord tissue-derived mesenchymal stem cells (MSCs) to treat children with hypoxic-ischemic encephalopathy (HIE), cerebral palsy, and autism spectrum disorder, as well as the use of cord blood cells to treat adults with stroke.
- Dr. David Pearce of Sanford Health described clinical trials for cell therapy treatments for patients with osteoarthritis of the wrist, facet joint osteoarthritis, and partial thickness rotator cuff tears. Dr. Pearce also described a multi-center trial of stem cell therapy for osteoarthritis in the knee involving Sanford Health, Emory University, Duke University, and the Andrews Research Education Foundation, which is comparing outcomes of cell therapies, including bone marrow aspirate concentrate, umbilical cord-derived MSCs, and adipose-derived stem cells, against corticosteroid injection.

Panelists described several actions to support the advancement of both safe and effective cell therapies for patients, including the need for additional funding for the NIH for regenerative medicine research and clinical trials support, expanded patient access to therapies deemed to be both safe and effective, increased regulatory support and assistance from the FDA, strategies to improve and reduce the costs of manufacturing, and workforce development initiatives.

Cell Characterization and Scalable Manufacturing

Dr. Krishnendu Roy of the Georgia Institute of Technology (Georgia Tech) described both the challenges and the promising work underway to assist with reproducibly manufacturing living cells at large-scale, with consistent, predictive, and therapeutic quality, at low cost. Dr. Roy highlighted several key challenges associated with this goal, such as the need for greater quality control and assurance, including the identification of critical quality attributes, greater knowledge of the mechanisms of action, development of critical process parameters, and standards and best practices. He also highlighted the importance of a trained workforce, emphasizing the need for a greater number of technical college graduates—who represent the backbone of the manufacturing workforce—as well as undergraduate and graduate degree holders.

Dr. Roy also highlighted several public-private efforts designed to advance cell manufacturing, including the National Science Foundation-funded Engineering Research Center for Cell Manufacturing Technologies (CMA_T), an eight university national consortium between academia, industry, and the government, and the development of a national roadmap, [Achieving Large-Scale, Cost-Effective, Reproducible Manufacturing of High-Quality Cells](#), by the National Cell Manufacturing Consortium with funding from the National Institute of Standards and Technology (NIST) Advanced Manufacturing Technology Consortia (AMTech) program.

Protecting Patients through Rigorous Science and Safety

Several speakers observed that a handful of clinics have caused patient harm or have made questionable claims, taking advantage of vulnerable patients and casting a negative light on this emerging, promising science and industry.

Bernard Siegel of the Regenerative Medicine Foundation offered examples of stem cell clinics direct-to-consumer advertising in southern Florida, and the need for both consumer education and continued efforts by the FDA to address bad actors. Mr. Siegel, private sector panelists, and several meeting participants expressed support for FDA's increased efforts to enforce its regulations and protect patients from unsafe therapies, as well as the need for additional resources to help CBER carry out its public mission.

Mr. Siegel also discussed the need for workforce development initiatives, particularly those housed within technical programs and community colleges, to provide a much-needed, skilled workforce for this growing field. He also called for the capture and sharing of data through a federally-funded outcomes database.

Dr. Amy Patterson of the NIH highlighted her agency's mission, which is to advance the health of all people through biomedical research, as well as NIH principles, including those related to scientific rigor, reproducibility, integrity, and the broad sharing of research data and materials. During her remarks, Dr. Patterson highlighted the NIH's recognition of the promise of regenerative medicine, citing that it is one of the most exciting fields in biomedical research, because it aims to not simply treat symptoms, but to actually replace and restore cells and tissues damaged by injury, disease, or aging.

Like other speakers, Dr. Patterson spoke of the importance of rigorous science and the avoidance of hype, stating that marketing of untested, unapproved products and harms to some individuals using untested products could erode public trust.

Dr. Patterson highlighted a number of scientific barriers related to regenerative medicine which emerged from a multi-sector workshop co-hosted by the NIH and the FDA:

- Need for regulatory support to enable development of robust IND/investigational device exemption (IDE) applications;
- Challenges related to transitioning from laboratory- to clinical-grade manufacturing of cell products;

- Limited understanding of the identity and nature of regenerative medicine cell products used in the clinic; and
- Limited availability of standardized data for analysis across studies, which hampers advancement of the field.

Dr. Patterson emphasized that in-depth cell characterization underpins the research and development pathway toward treatment, and that such characterization should include specifications, critical quality attributes, and deep fingerprinting.

Dr. Patterson also shared NIH's progress in supporting regenerative medicine, including establishment of the Regenerative Medicine Innovation Project, which funds late-stage pre-clinical and IND/IDE-enabling studies, resources to help investigators address critical challenges, and the development of an innovative model to support research. It is important to note that funding for this work—which was authorized by the 21st Century Cures Act—runs out after FY 2020.

Dr. Patterson summarized several key factors that would help realize the promise of regenerative medicine, including:

- Rigorous science and regulatory compliance to advance the field and promote public trust;
- Assisting investigators in developing clinical-grade cell products to optimize the ability to manufacture cells that will produce the intended clinical effects;
- Standardizing and collecting in-depth cell characterization data and individual level participant data to enable deeper understanding of the composition and function of stem cell products and correlation of cell characteristics with clinical outcomes; and
- Use of common vocabularies and a cloud-based platform for sharing, integration, and analysis of product and clinical data to enable analyses across studies.

Dr. Patterson highlighted an NIH-FDA-NIST effort--the Regenerative Medicine Innovation Catalyst—which will help advance progress in these areas. This multi-agency collaboration, to be conducted in consultation with the regenerative medicine community, will establish a network of academic and private sector entities that will conduct the following, serving as pilot for a new model to support and conduct regenerative medicine clinical research:

- Provide manufacturing support and regulatory “coaching”;
- Apply advanced technologies for in-depth cell characterization;
- Develop data standards and common data elements; and
- Promote collection and sharing of standardized cell product and clinical outcomes data.

Dr. Peter Marks, Director of the Center for Biologics Evaluation and Research at the FDA began his remarks by sharing the FDA's commitment to advance the development of safe and effective cellular therapies to help address unmet medical needs, noting that this could be accomplished by:

- Encouraging sponsor interactions with the agency;
- Deployment of all applicable development programs; and
- Appropriate action when needed to protect patients.

Dr. Marks described the two-tier regulatory structure for human cells, tissues, or cellular or tissue-based products (HCT/Ps):

- **Section 361 HCT/Ps**

These HCT/Ps contain or consist of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient (§ 1271.3(d)). Examples include skin, MSCs, and hematopoietic progenitor cells from cord blood. These products are regulated solely under authority of section 361, subject to “Tissue Regulations” (21 CFR Part 1271), and premarket review and approval are not required.

- **Section 351 HCT/Ps**

These HCT/Ps are regulated under the authority of section 361 and section 351 of Public Health Service Act and/or the Federal Food, Drug, & Cosmetic Act. A license is needed to distribute such products in interstate commerce; such products must be safe, pure, potent; and FDA has suspension/revocation power and recall authority.

According to the FDA, to be regulated solely under section 361 of the Public Health Service Act, HCT/Ps must meet the following criteria (21 CFR Part 1271.10(a)):

- Minimally manipulated;
- Intended for homologous use only;
- Not combined with another article (with some 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
 - Has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and is for autologous, 1st or 2nd degree blood relative, or reproductive use.

The FDA has released a suite of regenerative medicine final guidance documents, summarized below, which are designed to clarify existing regulations to make it simpler for sponsors to determine if they need to obtain premarket authorization for their products and to expedite the development and approval of safe and effective innovative regenerative medicine therapies and associated devices.

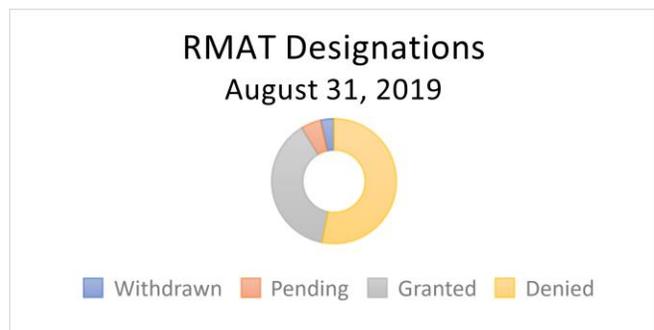
- Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception;
- Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use;
- Evaluation of Devices Used with Regenerative Medicine Advanced Therapies; and

- Expedited Programs for Regenerative Medicine Therapies for Serious Conditions.

To give manufacturers time to determine if they need to submit an IND or marketing application in light of such guidance and, if such an application is needed, to prepare the IND or marketing application, FDA publicized a 36-month period of enforcement discretion which ends on November 20, 2020, for products based on a determination of the risk to public health.

The 21st Century Cures Act contained several provisions to make safe and effective regenerative cellular therapies available to patients, including extending FDA expedited programs to include regenerative therapies. In response to the Act, the FDA created the Regenerative Medicine Advanced Therapy Designation (RMAT). The RMAT designation is applicable to products addressing serious conditions for which preliminary clinical evidence indicates the potential to address unmet medical needs. Designated products are eligible as appropriate for priority review and accelerated approval.

Dr. Marks shared information about the number of RMAT designations granted as of August 31, 2019, stating that of 115 requests, 44 were granted the RMAT designation, 61 were denied, 4 were withdrawn, and 6 are still pending.



Dr. Marks also shared information about two programs designed to provide regulatory assistance.

- The Initial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT) Program, which encourages early FDA interaction with sponsors and replaces the pre-pre-IND meeting process across CBER regarding preclinical, manufacturing and, clinical development plans.
- The Tissue Reference Group Rapid Inquiry Program (TRIP), which helps manufacturers of HCT/Ps obtain a rapid, preliminary, informal, non-binding assessment from FDA regarding how specific HCT/Ps are regulated.

In closing, Dr. Marks reiterated the FDA’s commitment to advance this “tremendously exciting area.” According to Dr. Marks, regenerative cell therapies will only come to benefit people to the extent that “we put rigor into the science to develop such products.”

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The Alliance for Cell Therapy Now also thanks the Regenerative Medicine Foundation and the Cord Blood Association for their collaboration on this event.

About Alliance for Cell Therapy Now

Alliance for Cell Therapy Now is a 501(c)6, independent, non-profit organization devoted to advancing the availability of safe and effective cell therapies for patients in need. ACT Now brings together experts and stakeholders—working in collaboration with other organizations that have a similar mission—to gain consensus on and advocate for sound policies that improve the development, manufacturing, delivery, and improvement of safe and effective regenerative therapies.