August 2, 2024

Representative Diana DeGette
2111 Rayburn House Office Building
Washington, DC 20515

Representative Dr. Larry Bucshon
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Washington, DC 20515

Via email: cures.rfi@mail.house.gov

Dear Representatives DeGette and Bucshon,

On behalf of the Alliance for Regenerative Medicine (ARM), I thank you for your continued interest in ensuring Americans have access to a dynamic, patient-centered heath care system and advanced treatment options. We offer the below input on behalf of our diverse membership in response to your recent request for information.

ARM is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As the global voice of the cell and gene therapy (CGT) sector, we represent more than 400 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations. ARM is working to build the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and gathering and analyzing data. We engage stakeholders across the private and public sector to enable the development of advanced therapies and to modernize healthcare systems.

As a representative of the CGT industry, we recognize the importance of the 21st Century Cures Act's (CURES) efforts to accelerate medical research, improve patient access to innovative therapies, and enhance healthcare delivery. CGTs carry forth the spirit of this legislation by demonstrating their potential to revolutionize the way we treat diseases, replacing chronic care with durable therapies that treat the root causes. Regenerative medicine's unique therapeutic approaches often blur lines, and a modernized regulatory framework helps clarify clinical pathways, ensuring that these therapies are appropriately evaluated based on their unique characteristics. Accordingly, ARM looks forward to working with you to advance legislation and support data collection and assessment efforts to ensure patients have timely and equitable access to CGTs.

In light of the dynamic evolution within the CGT sector, which we chronicle below, it is crucial that we enhance our research capabilities, streamline regulatory assessments, and improve access frameworks to ensure lifesaving innovative therapies are available for all patients in an appropriate manner. As such, we offer the following commentary in response to your request for stakeholder input on next steps for the 21st Century Cures initiative:

CELL AND GENE THERAPY PIPELINE

Since the Passage of 21st Century Cures, There Has Been a Rapid Pace of Advancement in the Field of Cell and Gene Therapies, Leading to The Development of Novel Treatments for A Growing List of Patients with Unmet Need.

Since CURES was enacted in 2016, 37 of numerous life-changing and often lifesaving CGTs have been approved by the Food and Drug Administration (FDA) for some of the most difficult-to-treat conditions. These include treatments for cerebral adrenoleukodystrophy, beta thalassemia, spinal muscular atrophy, hemophilia A and B, Duchenne muscular dystrophy, sickle cell disease and various forms of aggressive cancers. These one-time administered, durable, potentially curative therapies often bring decades or a lifetime of benefits to the seriously or incurably ill. The consequence of advances in CGT have been likened to the eradication of smallpox.

As an example, for the past decade, treating hematologic malignancies has been and remains one of the main indications targeted by engineered cell therapies. Leading the charge are chimeric antigen receptor T-cell (CAR-T) therapies, which have engineered receptors that target cancer cells. Currently, six CAR-T cell therapies for blood cancers are approved in the United States. However, many more cell therapies for blood cancers, including non-CAR-T approaches, are in the clinical pipeline. In fact, in early 2024, a Tumor-Infiltrating Lymphocytes (TIL) therapy used to treat metastatic melanoma became the first adoptive cell therapy for a solid tumor to be approved. Another approval to treat solid tumors, an engineered T-cell receptor (TCR) therapy to treat advanced synovial sarcoma, a cancer found in soft tissue, could occur later this year. And this is just the beginning, the clinical pipeline for cell therapies demonstrates that treatments for solid tumors maintain a sizeable presence in early-stage trials, showing the potential for more therapies to reach the market in the years ahead.

The CGT pipeline extends beyond oncology care. Gene therapy has shown promise in treating a variety of inherited genetic disorders, such as Duchenne muscular dystrophy and various types of inherited blindness. Many of the new gene therapies are targeting rare, often ultra-rare genetic disorders, which historically had limited treatment options.

The forecast for approvals over the next decade represents an intriguing landscape, with a balanced representation of various CGTs. According to ARMs internal researcher on the sector, there are currently 2,762 engineered cell therapy and genetic medicine developers worldwide sponsoring 1,920 clinical trials across dozens of indications, including rare monogenetic diseases, oncology, cardiovascular, central nervous system, musculoskeletal, metabolic disorders, ophthalmological disorders, and more.[1] The modality of treatments is set expand on the evolution of the sector as well. There are over 225 Phase I clinical trials underway utilizing allogeneic biological sources – so -called "off the shelf" therapies – that will not require the use of the patients' own cells. CGTs made up 10% of all U.S. FDA novel approvals in 2023, up from 7% and 6% in 2022 and 2021, respectively.[2] Looking forward, it will be a potentially unprecedented year for FDA approvals of CGTs, with thirteen more expected in 2024. These include therapies to treat steroid-refractory acute graft versus host disease and metastatic melanoma. Overall,

[1] Alliance for Regenerative Medicine. Sector Snapshot (April 2024). Accessible at: https://alliancerm.org/sector-snapshot-april-2024/
[2] Cell&Gene. 2024's Market Outlook For Cell & Gene Therapies (February 2024). Accessible at: https://www.cellandgene.com/doc/2024-market-outlook-for-cell-gene-therapies-0001

the current pipeline of CGTs is expected to result in an estimated 54-74 new therapies by 2032. There are currently 16 diseases and conditions with an approved gene therapy that we anticipate will grow to over 40 by 2027.

RESEARCH

Through its programs, the National Institutes for Health (NIH) serves as a cornerstone for advancing scientific discovery and innovation in cell and gene therapy, making it a crucial partner for stakeholders to drive progress in this rapidly evolving field.

The 21st Century Cures Act provided the NIH with critical tools and resources to advance biomedical research across the healthcare spectrum, from foundational basic research studies to advanced clinical trials of promising new therapies. More specifically, the Regenerative Medicine Innovation Project was created to support clinical research, in coordination with the FDA, using adult stem cells to further the field of regenerative medicine. Initiatives as such have signified to the scientific, clinical and biopharmaceutical communities that the development of safe and effective regenerative medicines are a priority for policymakers seeking to optimize clinical outcomes. To build on the momentum, ARM notes ongoing efforts by Federal entities to accelerate the development of advanced therapies that address unmet medical needs such as:

Advanced Research Project Agency - Health

Housed as an independent component of NIH, the Advanced Research Project Agency – Health (ARPA-H) has the potential to drive transformative innovation in biomedical research by focusing on high-risk, high-reward projects that often do not receive traditional funding through existing NIH mechanisms. CGTs often face significant technical hurdles, such as issues with delivery systems, scalability, and manufacturing. ARPA-H's support for cutting-edge research can help overcome these barriers by funding projects that address these specific challenges. ARPA-H has the potential to provide support that builds transformative solutions at scale. By facilitating partnerships between academic institutions, industry, and government agencies, ARPA-H helps to create a more collaborative environment. Notably, the Engineering of Immune Cells inside the Body (EMBODY) program exemplifies this approach. Its charge is to revolutionize treatments for life-threatening and chronic conditions by supporting organizations seeking to retrain healthy immune cells and radically alter how immune therapies are developed and delivered. ARPA-H's ability to collaborate with private industry, academic institutions, and other stakeholders is enhanced by its independent status and eliminates time, cost, and access hurdles.. ARM champions the continued support for ARPA-H as an independent entity under the Department of Health and Human Services (HHS) to maintain and expand partnerships that facilitate the translation of research into practical applications and commercially available therapies.

REGULATORY ASSESSMENTS

Federal interagency coordination is pivotal for ensuring that cell and gene therapies are developed, regulated, and made accessible in a way that is safe, efficient, and equitable. By aligning efforts across different agencies, the federal government can address the complexities of these advanced treatments and work towards the unified goal of expanding access to life-changing therapies.

Through CURES and as a result of its implementation, several Federal entities have advanced best practices that address the rapidly evolving needs of the regenerative medicine community.

Standards Coordinating Body

The speed of innovation across the regenerative medicine community has increased through the establishment of the Standards Coordinating Body (SCB) – also established by the Cures Act - which has improved the safety and quality of regenerative medicines, reduced costs to patients, and accelerated regulatory approval of new therapies. ARM has long since served as the "hub of the wheel" amongst key stakeholders. In facilitating the creation of the international Standards Coordinating Body (SCB) for regenerative medicine in collaboration with scientific organizations, accrediting bodies, federal agencies, standard setting organizations, other organizations, ARM has leveraged the legislative framework established in CURES to streamline the landscape of regenerative medicine standards. Since 2017, there have been 190 cell therapy, 119 gene therapy, 169 tissue engineering and 53 supportive standards that have been under review by the SCB.[3] As a result, the emerging regenerative medicine industry, which is highly prone to fragmentation, now has accelerated a cohesive review of several advanced therapies due to a functioning standards system. ARM continues to support the vision of the 21st Century Cures Act by bringing stakeholders from across industry together to have critical discourse about the common practices our community agrees to follow.

Bespoke Gene Therapy Consortium

The Bespoke Gene Therapy Consortium (BGTC) focuses on crafting personalized gene therapies tailored to individual patient requirements, particularly for rare diseases lacking commercial feasibility. ARM is a supporting member of the BGTC. The BGTC goals include conducting 8 clinical trials focused on monogenetic diseases that do not currently have gene therapies in development, due to the lack of a viable commercial pathway. This year the Consortium released a framework for the development and regulatory submission of certain types of gene therapies for rare diseases. The BGTC effort builds on a pilot project led by NIH's National Center for Advancing Translational Sciences (NCATS) known as Platform Vector Gene Therapy (PaVe-GT). This pilot project has successfully helped to introduce greater efficiency to gene therapy trials for rare diseases and offered an opportunity to avoid the standard one-disease-at-a-time approach to therapeutic development that has stymied progress in treating rare conditions. Similarly, by focusing on processes, the BGTC aims to overcome bottlenecks in gene therapy development and ultimately bringing effective treatments to patients with rare genetic diseases more quickly and affordably. While not a direct result of the implementation of the CURES Act, the BGTC embodies the importance of a collaborative interagency framework. To ensure no patients are excluded due to their involuntarily inherited genetic disorders, ARM supports initiatives such as the BGTC that promote development to cutting-edge treatments and research advancements for all.

FDA Rare Disease Innovation Hub

[3] Standards Coordinating Body. The Regenerative Medicines Standards Portal. (July 2024) Accessible at: https://portal.standardscoordinatingbody.org/

More than 90 percent of the estimated 10,000+ rare diseases have no FDA-approved products, and about half of these diseases uniquely affect children. Because a significant number of rare disorders have genetic causes, they are increasingly being addressed by the growing armament of CGTs – including gene therapy and gene editing. The announcement of the Rare Disease Innovation Hub was recently established with a specific focus on products intended for smaller populations or for diseases where the natural history is variable and not fully understood. This initiative marks a pivotal moment in the journey towards better support and treatment for rare disease patients. While this announcement is a key accomplishment, there are additional steps needed to realize its potential. The coordination between the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), which aims to streamline and expedite the development of treatments for rare diseases, signifies the Agency's commitment to ensuring the unique challenges faced by rare disease patients are reflected in innovations within in drug development and regulatory practices. To properly advance the mission of the Hub, the individual selected as the Director of Strategic Coalitions must have a comprehensive understanding of treatments develop specifically for this patient population such as CGTs. As the Committee considers the implementation of this collaborative endeavor, ARM encourages the next iteration of 21st Century Cures to include supportive language that direct critical stakeholders and regulatory bodies to maintain a balanced commitment to the rare disease community.

The Regenerative Medicine Advanced Therapy (RMAT) Designation established by 21st Century Cures is now widely accepted and commonly used by CGT developers. It has made a significant contribution to the field and expedites access to care for many patients.

As you know, the CURES Act established an RMAT expedited approval program. Since its inception 101 products have been granted the RMAT designation and 8 have received FDA approval. ARM conducted a quantitative and qualitative assessment of the effectiveness of the RMAT expedited approval program by interviewing developers who have received RMAT designation.

Through these conversations, ARM gained valuable insight into developer's experiences with the program, including feedback on the application process and, if granted, their experiences working with FDA. ARM also received worthwhile written feedback from the FDA on their experience with the program and interactions with sponsors. The feedback from both product developers and FDA was generally positive, while also revealing some potential immediate- and long-term improvements that ARM seeks to recommend. For example, clarity on requirements for applications and expectations post approval could be improved via industry education (webinar, conferences, highlights document and/or longer summary of the assessment). In addition, improved FDA program management and increased transparency on metrics and communication can improve the program's effectiveness. Collecting and sharing this information could contribute to the quality of pilot and designation programs in the future, bolstering the accountability of Agency and sponsors in doing all they can to make sure safe and effective CGTs reach patients as soon as possible.

Leveraging real world evidence (RWE) in the regulatory review of CGTs enhances the depth and relevance of data used in Agency assessments, supports informed decision-making and optimizes patient outcomes.

In response to the CURES Act, the FDA created a Framework to evaluate the use of RWE in the approval of new indications for a drug already approved or to help support or satisfy a therapy's post-approval study requirements. ARM continues to support Representatives DeGette and Buschon in their legislative approach to benefit patients by encouraging the increasing the use of RWE. Using the 2023 PDUFA VII-mandated annual reporting of data on submissions to CBER, only four clinical protocols included RWE and there were no resulting approvals based on RWE.[4] This suggests that while the FDA published the guidance titled "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" to outline where RWE can be used when accruing data for submission across the various phases of the review process, a standard approach is not applied. To meet the need for increased standardized RWE sources and improved processes for collecting and analyzing such data, a future iteration of CURES could require the FDA to note in their review documents additional details regarding when and how RWE is being utilized.

ACCESS AND COVERAGE

All patients in need should have timely and equitable access to lifesaving CGTs. The federal government plays a critical role in ensuring Medicare and Medicaid beneficiaries can access FDA-approved CGTs.

ARM urges Congress to ensure CMS take into account complex manufacturing processes, impact on innovation, and ensures timely access to treatments when establishing reimbursement policies. Currently, many CGTs are administered in the hospital inpatient setting. ARM has long advocated that the current hospital inpatient reimbursement methodology does not adequately support hospitals for assuming the financial risk of providing lifesaving CGTs.

In Medicare, when Congress instructed CMS to offer additional payment as an incentive for health care institutions to provide a new technology, "add-on payments" have supported patient access to advanced therapies. ARM believes that without further improvements to the NTAP program, CGTs will be out of reach for many Medicare beneficiaries and further, biotechnology companies could be discouraged from developing CGTs for the Medicare population due to insufficient eligibility criteria and reimbursement. Further, settings of care may vary based on treatment modality, payer policy, patient complexity, and other factors. It is anticipated that the provision of CGTs on an outpatient basis may trend upward in the future to improve patient access to care and reduce health system costs and patient out-of-pocket costs. In both inpatient and outpatient settings of care, the provider must also invest considerable amounts in preparing their facilities and staff for unique CGT protocols, and it is imperative that reimbursement is adequate to incentivize uptake of new CGTs and sustain patient access to these innovative treatments.

Medicaid is an important payer for CGTs, including many approved therapies that treat rare genetic diseases in pediatric patients and for other treatments on the horizon that address more prevalent conditions. Given states' budgetary and staff resource constraints and lack of formalized coverage policies in the burgeoning area of CGTs, Medicaid patients encounter unique challenges accessing treatment, and companies launching new CGTs and treatment centers must confront financial risks when bringing CGTs to this population. Medicaid treatment delays for CGTs are common, and in some

[4] Food and Drug Administration. Real-World Evidence Submissions to the Center for Biologics Evaluation and Research (June 2024) Accessible at: https://www.fda.gov/vaccines-blood-biologics/real-world-evidence-submissions-center-biologics-evaluation-and-research

instances, beneficiaries must wait months or even over a year to successfully navigate coverage requirements. ARM published an issue brief in November 2023 detailing this as one of the most common Medicaid barriers to accessing CGTs. Medicaid reimbursement for CGTs should also be established at levels that ensure providers are adequately compensated for providing these innovative therapies, which may require Medicaid agencies to make additional payments outside of traditional inpatient bundled payment. Congress should consider legislation to provide enhanced funding for these separate payments for CGTs though an increased federal Medical Assistance Percentage (FMAP) or other means.

Overall, CGTs are unique and highly complex, as are the patients they are intended to treat, and there is no one-size-fits-all financing approach that adequately addresses the diverse needs of patients and healthcare systems. Thus, there are a variety of financing structures that are common within this sector. Notably, appropriately structured outcomes-based agreements (OBAs) could address payer uncertainty regarding real-world efficacy that supports the durability and value of these cutting-edge therapies. These agreements are designed to support risk-sharing by aligning financial incentives with the real-world performance of the treatment. These arrangements shift some of this risk to the manufacturer by linking payment to the therapy's actual performance in improving patient health. ARM urges Congress to pass the Medicaid Value-based Payments for Patients (MVP) Act to provide regulatory certainty to manufacturers seeking to enter into OBAs and to evaluate the impact of OBAs on patient access, health outcomes, and healthcare expenditures.

When designing benefits that include gene therapy coverage, policymakers should evaluate coverage for related services, like fertility preservation, which can be essential for patients to receive treatment.

Efforts to direct the Congressional Budget Office (CBO) to more accurately reflect the long term, cost-saving potential of preventive healthcare initiatives facilitate the ability for the health system to support providers seeking to offer clinical relief beyond disease state maintenance.

While traditional pharmaceuticals deploy chronic approaches to treat symptoms of disease, CGTs are often administered in a single or a limited number of doses, and offer durable and potentially curative, effects. CGTs can have high upfront costs but reduce health care spending over time by addressing the underlying precipitants of the pathophysiology, reduces the severity of illness, and lowers overall health care utilization. Accordingly, the scale of their benefits cannot be captured in abbreviated treatment intervals, and thus, when evaluating their place in a legislative proposal it is essential to identify their impact over an appropriately extended period of time. Since CGTs generate long term spending reduction but consolidate their anticipated investment upfront, the current CBO scoring methodology fails to properly capture their value. For many of the diseases targeted by approved CGTs, the standard of care is relatively costly. For example, before the advent of gene therapy, a severe hemophilia B patient requires more than $21 million in lifetime care costs. With traditional treatment regimens, lifetime healthcare costs for a severe sickle cell disease patient range from $4 to $6 million.[5] We commend Congresswoman Degette's proposal to require the CBO to determine if the proposed legislation would reduce spending outside of the 10-year budget window through the use of preventive health services and mandates a description and estimate of the spending reductions be included in CBO projections if substantial spending reductions are identified. Legislative reforms as such send a promising signal to

[5] Subica, Andrew M. "CRISPR in Public Health: The Health Equity Implications and Role of Community in Gene-Editing Research and Applications." American journal of public health vol. 113,8, 2023, available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10323846/

patients, researchers and innovators that novel treatments will be examined for the full scope of their benefits used.

We look forward to contributing to the ongoing dialogue surrounding further iterations of the 21st Century Cures Act. Our industry remains committed to collaborating with policymakers, healthcare providers, and patient advocates to shape a healthcare landscape that prioritizes innovation, access, and patient outcomes. Thank you once again for your leadership on these issues.

ARM welcomes the opportunity to meet with you and other members of the Energy and Commerce Committee to discuss our recommendations in greater detail. Please reach out to Monet Stanford at mstanford@alliancerm.org with any questions.

Sincerely,

Erica Cischke, MPH

Vice President, Government Affairs, Alliance for Regenerative Medicine