American Society of Gene + Cell Therapy

August 2, 2024

The Honorable Diana DeGette
2111 Rayburn House Office Building
Washington, DC 20515

The Honorable Larry Buschon, MD
2313 Rayburn House Office Building
Washington, DC 20515

Dear Representative DeGette and Representative Buschon,

The American Society of Gene and Cell Therapy (ASGCT) welcomes the opportunity to respond to your request for information on the Cures 2.0 Act and what is needed in future legislation to ensure access to innovative therapies. ASGCT is a nonprofit professional membership organization comprising more than 6,300 scientists, physicians, patient advocates, and other professionals. Our members work in a wide range of settings including universities, hospitals, government agencies, foundations, and biotechnology and pharmaceutical companies. Many of our members have spent their careers in this field performing the underlying research that has led to today's robust pipeline of transformative therapies.

A core portion of ASGCT's mission is to advance the discovery and clinical application of cell and gene therapies (CGTs) to alleviate human disease. To that end, ASGCT supports policies that foster the adoption of, and patient access to, new therapies, which thereby encourage continued development of these innovative treatments. We commend your continued efforts to advance medical research, patient access to novel therapies, and the modernization of healthcare delivery systems.

Since the first CAR T-cell therapy approval in 2017, the field has developed an exponential pipeline with over 4,000 therapies in development and over 2,000 active clinical trials.[1] Many gene therapies currently in development address rare genetic disorders, cancers, and target indications with high unmet medical needs. The field has grown rapidly and offers the potential to deliver safe, effective, and transformative therapies to patients who often have no other options.

If you have questions about any of the information provided below or would like additional feedback, please contact Margarita Valdez Martínez, Chief Advocacy Officer, at mvaldez@asgct.org.

[1] American Society of Gene and Cell Therapy, Citeline (July 2024). *Gene, Cell, & RNA Therapy Landscape: Q1 2024 Quarterly Data Report.* https://www.asgct.org/global/documents/asgct-citeline-q2-2024-report.aspx

American Society of Gene + Cell Therapy

Sincerely,

David Barrett, JD
Chief Executive Officer
American Society of Gene and Cell Therapy

Request for Information from Stakeholders on the Enacted Cures 2.0 Act

1. Do the policies included in Cures 2.0 that have advanced through legislation or executive action meet the needs that the original Cures 2.0 bill aimed to address?

ASGCT acknowledges the intent of Cures 2.0 and is pleased that many of the policies included in the bill have been advanced by congress and the executive branch. We support the legislation's original goals of accelerating medical research, increasing patient access to novel therapeutics, and enhancing telehealth services.

Sec. 203. Increasing Diversity in Clinical Trials

ASGCT appreciates the Act's focus on improving diversity in clinical trials. ASGCT supported[2] the spirit of the 2022 FDA guidance[3] encouraging the inclusion of broader demographic groups, such as different ages, genders, races, and ethnicities. This is crucial for understanding how treatments work across various populations. By including diverse populations in clinical research, the field can ensure that the resulting data is more reflective of the real-world patient population, leading to better-informed regulatory decisions and equitable access to new treatments. Moreover, diverse clinical trials help identify potential differences in treatment response and safety among subgroups, which is particularly important for rare diseases where genetic variability can significantly impact therapy outcomes. In this vein, it is also important to ensure allowances for small patient populations where recruitment for rare disease clinical trials may face additional challenges.

In light of the current enrollment challenges in trials for cell and gene therapies for rare diseases, ASGCT believes there will likely be several cases where there is not enough clinical trial data to characterize the safety and efficacy of an investigational product, let alone differences in safety and efficacy for a specific racial or ethnic population. For these cases,

[2] American Society of Gene and Cell Therapy [Regulatory Comments] (2022). *Diversity Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Trials Guidance*. https://www.asgct.org/advocacy/policy-statement-landing/2022/diversity-plans-to-improve-enrollment-of-participa

[3] Food and Drug Administration (2022). *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials: Draft Guidance for Industry.* https://www.fda.gov/media/157635/download

ASGCT suggests flexibility where sponsors can use data from foreign countries to both evaluate the drug and identify any differential effects among racial or ethnic subgroups.

In addition, for products with smaller patient populations, premarket diversity plans should take into account potential post-market studies that can provide more diverse data and a better analysis. This would allow for more timely access to necessary treatments for patients while also providing a better understanding of the effects on different subgroups. In addition to providing sponsors with another opportunity to assess a drug in a specific subgroup who may not have been well represented in pre-market studies, the use of post-market studies to achieve enrollment targets would likely not slow development or marketing approval of a product, which is particularly important for drugs for serious or life-threatening conditions with high unmet need.

ASGCT plans to comment on the recently re-released draft guidance document[4] regarding implementation of diversity action plans before the September deadline.

Sec. 309. Post-Approval Study Requirements for Accelerated Approval

ASGCT believes post-market surveillance is critical to ensure approved products remain safe and efficacious. Robust post-marketing requirements are in place for products approved under the accelerated approval pathway based on an "effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict [such] an effect…".[5] Many gene therapies could be approved based on this pathway, as their mechanism of action is to affect the underlying cause of disease (a genetic mutation resulting in altered protein production) for which the long-term impact on outcomes may not be possible to assess within the duration of a traditional clinical trial.

As more CGTs are approved by FDA that require further post-market assessment, it is critical these assessments are designed to answer the scientific questions at hand, be practical to effectuate in the market, and not impede patient access. Many of the post-marketing studies for products approved under the accelerated pathway have proven to be difficult to complete due to difficulty accruing and retaining patients. Post-marketing studies designed with greater consideration of practical barriers and adoption of RWE will be more likely to accrue and retain patients, giving the Agency and product sponsors more rapid and complete information about the performance of marketed products.

Sec. 501. Advanced Research Projects Agency for Health

The establishment of the Advanced Research Projects Agency for Health (ARPA-H) will drive transformative breakthroughs in the CGT field by addressing critical challenges in the development and manufacturing processes of these therapies. The agency's mandate to

[4] Food and Drug Administration (2024). *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials: Draft Guidance for Industry.* https://www.fda.gov/media/179593/download

[5] Food and Drug Administration (2014). *Expedited Programs for Serious Conditions, Drugs and Biologics: Final Guidance for Industry.* https://www.fda.gov/media/86377/download

support high-risk, high-reward research lends itself to the goals of advancing CGTs which face known challenges with manufacturing bottlenecks. CGTs are uniquely positioned to address unmet medical need in rare disease communities but may not be a good fit for traditional funding models. By funding research to enhance manufacturing capacity and efficiency, ARPA-H can significantly reduce costs and improve access to life-saving treatments. Moreover, ASGCT advocates for a strong collaboration between ARPA-H and the FDA to ensure integration of regulatory requirements throughout product development.

2. What elements might be missing that are essential for further progress?

Medicaid Coverage of Gene and Cell Therapies

One critical area requiring attention is consistent Medicaid coverage for gene therapies. Federal action is necessary to ensure that all state Medicaid programs cover FDA-approved gene therapies for their labeled indications. Currently, states are restricting coverage based on clinical trial criteria or requiring additional information beyond FDA-approved labeling.[6] Compliance can be achieved by improving federal guidance and transparency efforts supporting implementation of statutory requirements and supporting states in integrating new CGTs into Medicaid benefits. ASGCT would welcome the opportunity to work with federal agencies and policymakers on proposed policy solutions[7] to overcome these patient access barriers. Specific recommendations include the following:

Issue additional guidance to states outlining current federal requirements for coverage to label

The Centers for Medicare and Medicaid Services (CMS) should issue additional guidance to states reiterating the expectations of current requirements relating to coverage to label. This guidance could also identify products that recently received FDA approval, ensuring states are aware of potentially impactful products coming to market.

Reiterate current requirements for timely access to covered benefits

Congress can work with CMS to reinforce timely coverage of CGTs and limit the unnecessary and time-consuming demands for additional criteria to be met beyond the FDA-approved labeling. CMS should also consider reforms to prior authorization and precertification policies to minimize the burden on providers and patients and expedite decisions.

[6] Allen, J., Berry, D., Cook, F., Hume, A., Rouce, R., Srirangam, A., Wellman, J., McCombs, C. (2023) *Medicaid coverage practices for approved gene and cell therapies: Existing barriers and proposed policy solutions.* Mol. Ther. *29*(513-521). https://www.cell.com/molecular-therapy-family/methods/fulltext/S2329-0501(23)00077-3

[7] Allen, J., Berry, D., Cook, F., Hume, A., Rouce, R., Srirangam, A., Wellman, J., McCombs, C. (2023) *Medicaid coverage practices for approved gene and cell therapies: Existing barriers and proposed policy solutions [Solutions Summary].* https://www.asgct.org/global/documents/advocacy/policy-solutions-summary.aspx

Establish clearer channels for stakeholders to report noncompliance with federal coverage rules

CMS should establish a clear method for patients, providers, manufacturers, and other members of the public to identify instances in which state policies relating to coverage of CGTs falls short of federal expectations.

Create a public dashboard

CMS should establish a public dashboard tracking coverage policies, denials, complaints, and discrepancies in coverage and reimbursement for each product across states. The information would be useful in quantifying the true scope of any problems or overly restricted coverage.

Consider federal audits

Congress could direct federal investigative agencies to conduct regular reviews of compliance with federal Medicaid coverage rules as new CGTs come to market. This review could be conducted by the Office of the Inspector General, the Government Accountability Office, or other federally supported entities tasked with tracking compliance with federal regulations

Additionally, access to genetic testing remains inconsistent across Medicaid programs. Genetic testing is crucial for early diagnosis and potential gene therapy treatment, and ensuring broad access can help quantify patient numbers, spark investment in rare diseases, and more accurately direct research. Early diagnosis through expanded newborn screening can lead to timely interventions, significantly improving patient outcomes. By identifying treatable genetic disorders early, healthcare providers can initiate gene therapy treatments at a stage when they are most effective, potentially reducing long-term healthcare costs and improving quality of life.

Sec. 304. Increasing Use of Real-World Evidence

ASGCT continues to support[8] the increased use of real-world evidence (RWE) in regulatory decision-making as noted in Cures 2.0, particularly for rare disease indications with small patient populations. Traditional clinical trials often face challenges in enrolling sufficient numbers of participants from diverse backgrounds, which can limit the generalizability of findings. Utilizing alternative data sources like RWE, which includes data from electronic health records, patient registries, and real-world clinical practice, can help create more inclusive and representative clinical trials. This approach can facilitate the collection of valuable efficacy and safety data from broader patient populations, ultimately leading to more robust and applicable regulatory decisions.

[8] American Society of Gene and Cell Therapy [Regulatory Comments] (2023). *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Guidance.* https://www.asgct.org/advocacy/policy-statement-landing/2023/considerations-for-the-design-and-conduct-of-exter

The FDA guidance, *Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products,*[9] does not meaningfully advance the use of external controls and real-world evidence (RWE) in drug development for rare diseases, potentially limiting sponsors' ability to overcome challenges in this area. The guidance focuses on the challenges associated with externally controlled designs and RWE without providing actionable recommendations to sponsors to support successful therapeutic product development. ASGCT does not believe that such a focus fulfills the legislative intent of the provisions of the 21st Century Cures Act that FDA cites as an impetus for issuing this guidance.

Sec. 305. Improving FDA-CMS Communication Regarding Transformative New Therapies

Enhanced coordination between FDA and CMS remains essential to ensuring approved products are being covered and reimbursed in a way that reaches patients. While the original Cures 2.0 draft bill proposed a legislative approach to streamline this communication between FDA and CMS, more formalized and efficient processes are still needed to align regulatory approval and coverage decisions, especially for products using expedited pathways like the Regenerative Medicine Advanced Therapy (RMAT) Designation. Products approved by FDA under the accelerated approval pathway are “full approvals” and should be considered in payment policy decisions. ASGCT believes the policy solutions outlined above are an important step toward streamlining communications.

Sec. 308. Guidance Regarding Development and Submission of Chemistry, Manufacturing, and Controls Information for Expedited Approval

ASGCT also appreciates updates to FDA guidance on CGT manufacturing requested in the original Cures 2.0 Act – such as the *Manufacturing Changes and Comparability for Human CGT Products,*[10,11] *Potency Assurance for CGT Products,*[12,13] *Advanced Manufacturing Technologies Designation Program,*[14,15] and *Platform Technology Designation Program*[16] guidance documents. Unlike conventional drugs, CGT manufacturing often evolves in parallel with clinical

[9] Food and Drug Administration (2023). *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products: Draft Guidance for Industry.* https://www.fda.gov/media/164960/download
[10] Food and Drug Administration (2023). *Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products: Draft Guidance for Industry.* https://www.fda.gov/media/170198/download
[11] American Society of Gene and Cell Therapy [Regulatory Comment] (2023). *Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products: Draft Guidance for Industry.* https://www.asgct.org/advocacy/policy-statement-landing/2023/manufacturing-changes-and-comparability-for-human
[12] Food and Drug Administration (2023). *Potency Assurance for Cellular and Gene Therapy Products: Draft Guidance for Industry.* https://www.fda.gov/media/175132/download
[13] American Society of Gene and Cell Therapy [Regulatory Comment] (2024). *Potency Assurance for Cellular and Gene Therapy Products Guidance.* https://www.asgct.org/publications/news/april-2024/society-response-fda-potency-assurance-for-cellula
[14] Food and Drug Administration (2024). *Advanced Manufacturing Technologies Designation Program: Draft Guidance for Industry.* https://www.fda.gov/media/174651/download
[15] American Society of Gene and Cell Therapy [Regulatory Comment] (2024). *Advanced Manufacturing Technologies Designation Program Guidance.* https://www.asgct.org/advocacy/policy-statement-landing/2024/advanced-manufacturing-technologies-designation-pr
[16] Food and Drug Administration (2024). *Platform Technology Designation Program for Drug Development: Draft Guidance for Industry.* https://www.fda.gov/media/178938/download

development, necessitating changes to improve yield and efficacy based on early clinical findings. ASGCT has highlighted the need for FDA to adopt flexible, phase-appropriate guidelines that consider the unique complexities and developmental stages of CGTs, ensuring that regulatory requirements do not stifle innovation or delay patient access to transformative therapies. Additionally, it is important for FDA to incorporate prior knowledge and standardized approaches to streamline development processes, reduce regulatory burdens, and support the scalability and efficiency of CGT manufacturing and potency assurance strategies. Greater flexibility in FDA guidance can enable sponsors and manufacturers to meet real-world patient demand, bring manufacturing closer to the bedside, and reduce production costs.

3. What additional reforms, support mechanisms, or incentives are needed to enhance or improve the effectiveness of the steps already taken, including any structural reform to agencies, offices, or programs involved?

Congress and CMS should work to advance novel payment arrangements such as value-based payments (VBPs) and outcomes-based arrangements (OBAs) that spread the cost of therapies over time and often tie reimbursement to patient outcomes. To achieve this, policymakers can build on the CMS rule modifying current Best Price reporting requirements,[17] and continuing to work with stakeholders to implement the Centers for Medicare and Medicaid Innovation (CMMI) Cell and Gene Therapy Access Model.[18] Congress could consider policies that would enhance the federal government's role in covering Medicaid costs of these therapies. The federal government, for instance, could increase its share of payments to states (the federal match percentage; FMAP) for new CGTs. Alternatively, the Medicaid and CHIP Payment and Access Commission considered establishing CGT as a separate Medicaid benefit.

To enhance the effectiveness of current initiatives, we recommend establishing a framework for providing ancillary support services for advanced therapeutics, particularly CGTs. Due to their complexity, CGTs are often administered only at specialized centers, requiring patients to travel long distances. This creates financial barriers for patients and families. The Patient Access Act, introduced by Representatives Guthrie and Barragán is a positive first step to addressing these barriers. While there is some precedent for manufacturers to provide travel and lodging support without violating anti-kickback statutes,[19] other critical support areas lack similar allowances.[20]

For instance, CGT patients often undergo myeloablation, which can result in infertility. Currently, sponsors cannot provide fertility preservation support, except in limited circumstances like the CGT Access Model for sickle cell patients. We propose developing a comprehensive method to allow manufacturers to offer these and other ancillary support services, thereby removing

[17] Centers for Medicare and Medicaid Services (2022). *Technical Guidance – Value-Based Purchasing Arrangements for Drug Therapies Using Multiple Best Prices [Medicaid Drug Rebate Program Notice].* https://www.medicaid.gov/prescription-drugs/downloads/mfr-rel-116-vbp.pdf
[18] Center for Medicare and Medicaid Innovation, Centers for Medicare and Medicaid Services (2024). Cell and Gene Therapy (CGT) Access Model Overview Factsheet. https://www.cms.gov/files/document/cgt-model-ovw-fact-sheet.pdf
[19] Department of Health and Human Services, Office of Inspector General (July 2024). *OIG Advisory Opinion No. 20-02 [Favorable].* https://oig.hhs.gov/documents/advisory-opinions/765/AO-20-02.pdf
[20] Department of Health and Human Services, Office of Inspector General (July 2024). *OIG Advisory Opinion No. 24-06 [Unfavorable].* https://oig.hhs.gov/documents/advisory-opinions/9940/AO-24-06.pdf

additional barriers to access for advanced therapies while maintaining appropriate safeguards against abuse.