American Society of Gene + Cell Therapy

July 16, 2021

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

The Honorable Fred Upton
2183 Rayburn House Office Building
Washington, DC 20515

Dear Congresswoman DeGette and Congressman Upton:

The American Society of Gene and Cell Therapy (ASGCT) welcomes the opportunity to provide comments on the 21st Century Cures 2.0 Discussion Draft. ASGCT is a nonprofit professional membership organization comprised of more than 4,600 scientists, physicians, and other professionals working in gene and cell therapy in settings such as universities, hospitals, and biotechnology 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 the Society's mission is to advance the discovery and clinical application of genetic and cellular therapies to alleviate human disease. Therefore, the development of and patient accessibility to such therapies is of paramount importance to ASGCT's membership.

We appreciate your leadership on these issues and willingness to hear from stakeholders about ways to improve and adapt policies, especially considering the unique attributes of these therapies. Our comments focus both on specific text in the draft, as well as on broader concepts essential to patient access to gene and cell therapies.

Sec. 203. Increasing Diversity in Clinical Trials

ASGCT strongly supports the following provisions and requirements in the discussion draft to improve diversity in clinical trials:

- An update from the FDA on efforts to improve diversity in clinical trials.
- A GAO study on barriers to clinical trial participation.
- The conduct of an HHS public awareness campaign to increase awareness and understanding of clinical trials, particularly in minority communities.
- The establishment of a task force for making www.clinicaltrials.gov more user friendly, including for patients.

The Society believes it is critical to increase minority participation in clinical trials, which

is disproportionately low compared to representation in the population.[1,2] Studies show minority groups are willing to participate in clinical trials but are less likely to be invited to participate.[3,4] The disparity in trial participation also stems from lack of access to medical treatment due to logistical barriers (such as lack of transportation and financial burden, interference with work/family responsibilities, and out-of-pocket expenses) and being less likely to be offered trial information.[1,2]

To inform a such a public awareness campaign on clinical trials, ASGCT would gladly share with HHS insights that the Society gained from creating patient education content on clinical trials for gene therapies and on gene therapy for rare diseases that disproportionately affect minorities, such as sickle cell disease.[5] Similarly, ASGCT would be pleased to recommend a representative to a task force for making www.clinicaltrials.gov more user-friendly, since the Society has produced a clinical trials finder for gene and cell therapies that curates daily the relevant information from www.clinicaltrials.gov, based on Society criteria.[6]

Sec. 303. FDA Cell and Gene Therapy

We appreciate your concern about the regulatory barriers to the development of gene and cell therapy. Some of the barriers are documented and addressed by other provisions, such as regulations not keeping pace with the latest manufacturing science and a lack of communication between FDA and CMS, while others stem from longer-term hurdles at the agency, such as difficulty hiring and retaining staff and collaboration with outside scientists.

There are currently over 1,000 active and recruiting gene and cell therapy clinical trials in the United States. By 2030, more than 60 U.S. approvals of cell and gene therapy products are projected, with more than 500,000 patients anticipated to be treated with gene therapies.[7] As mentioned above, ASGCT has created a clinical trials finder specifically for gene and cell therapies which helps illuminate the current state of development in the US.[8] Given your interest in this topic as evidenced by the proposed study requirements, we hope the following information about the quantity and nature of

[1] Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med.* 2015;373:1627-1639. doi:10.1056/NEJMoa1507643. https://pubmed.ncbi.nlm.nih.gov/26412456/
[2] Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373:1803-1813. doi:10.1056/NEJMoa1510665. https://pubmed.ncbi.nlm.nih.gov/26406148/
[3] Linden, HM, Reisch LM, Hart A Jr, et al. (2007). Attitudes toward participation in breast cancer randomized clinical trials in the African American community: A focus group study. *Cancer Nurs, 30*(40):261-269. doi:10.1097/01.NCC.0000281732.02738.31. https://pubmed.ncbi.nlm.nih.gov/17666974/
[4] Comis RL, Miller JD, Aldige CR, Krebs L, Stoval E. (2003). Public attitudes toward participation in cancer clinical trials. *J Clin Oncol, 21*(5):830-835. doi:10.1200/JCO.2003.02.105. https://pubmed.ncbi.nlm.nih.gov/12610181/
[5] American Society of Gene and Cell Therapy. (2021) *Patient Education.* https://patienteducation.asgct.org/
[6] American Society of Gene and Cell Therapy. (2021). *Clinical Trials*. http://www.asgct.org/clinicaltrials
[7] Massachusetts Institute of Technology NEWDIGS FoCUS Project. (2020). *Updated Projection of US Durable Cell and Gene Therapies Product-Indication Approvals Based on December 2019 Development Pipeline.* https://newdigs.mit.edu/sites/default/files/NEWDIGS-Research-Brief-2020F207v51-PipelineAnalysis.pdf
[8] American Society of Gene and Cell Therapy. (2021). *Clinical Trials*. Accessed July 12, 2021. http://www.asgct.org/clinicaltrials

gene and cell therapy submissions filed with the Food and Drug Administration (FDA) is useful:

- Total trials: 1,669
  - Gene therapy trials: 565
  - Cell therapy trials: 1,200
  - RNA therapy trials: 57
- The status of such applications in the review process:
  - Phase I: 679
  - Phase I/II: 364
  - Phase II: 468
  - Phase II/III: 12
  - Phase III: 95
  - Phase IV: 3
  - Not specified: 78

Sec. 304. Increasing Use of Real-World Evidence

We appreciate the sponsors' interest in and attention to the use of real-world evidence (RWE) to increase our understanding of marketed products. The use of RWE is especially important for gene and cell therapies with durable treatment effects. To that end, we suggest that the guidance proposed in Section 304(a) be expanded to include therapies that have received regenerative medicine advanced therapy (RMAT) designation. Not only is expanding the use of RWE critical for these products, but products with RMAT designation are by statute eligible to use RWE to fulfill any post-marketing obligations required by the accelerated approval expedited pathway.

The current RMAT guidance mentions that CBER will consider the post-marketing requirements on a case-by-case basis but does not provide any examples of what may be appropriate for the considerations listed, such as magnitude of anticipated benefit and size of target populations. We agree that additional examples and clarity regarding acceptable parameters in the post-approval setting provided in guidance would be beneficial.

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

We appreciate the sponsors' inclusion of language that aims to address the barriers that impede coverage and adequate reimbursement for new therapies that receive Breakthrough Therapy designation, Fast Track designation, and accelerated approval. We recommend expanding this requirement to therapies that receive RMAT designation, because gene and cell therapies that receive RMAT designation face the same coverage challenges as products receiving other expedited designations. Therapies that receive RMAT designation show preliminary clinical evidence that the therapy has the potential to address unmet medical needs for a serious condition. The commencement of FDA communication with CMS upon granting of these designations could facilitate better understanding regarding expectations for both payers and product developers, and therefore more timely data collection and coverage of gene and cell therapies.

We further recommend greater coordination between CMS and FDA regarding the confirmatory evidence needed to fulfill post-marketing obligations and demonstrate effectiveness. These measures would allow for expedited coverage with subsequent collection of evidence through mechanisms that are already in place. The Society encourages consideration of additional ways for CMS and/or Congress to provide a more streamlined, consistent approach to providing immediate and uninterrupted coverage for these potentially lifesaving treatments. While greater systemic reforms are needed, we believe the proposal in the discussion draft to establish an automatic communication requirement between FDA and CMS for products using expedited regulatory pathways is a positive first step.

Sec. 307. IND Application Not Needed to Initiate Accelerated Approval

ASGCT requests correction of the title of this section to read "*IND Application Not Needed to Initiate Expedited Approval*." The use of the term "accelerated approval" in the current wording of the title implies use of the accelerated approval pathway, which allows for approval of a therapy based on a surrogate endpoint. However, this provision focuses on the Breakthrough Therapy and RMAT designations (Food, Drug, and Cosmetic Act Sections 506(a) and 506(g)).

With the above correction, the Society is appreciative of this technical provision to extend eligibility for Breakthrough Therapy and RMAT designations to sponsors without an active IND in place who have collected scientifically valid preliminary clinical evidence from studies in foreign countries and meet all other current statutory criteria. While these situations may be limited, it is critical that sponsors of products to treat rare diseases that may have extremely small patient populations in the US are also able to access expedited programs for which they otherwise may qualify.

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

ASGCT is supportive of Section 308, requiring FDA to update its existing guidance to reflect the unique differences in manufacturing between traditional drug products and gene and cell therapies in order to keep the Agency's regulatory scheme on pace with current science. Unlike traditional drug products, gene and cell therapy product manufacturing often develops in parallel with clinical development, with sponsors making changes to improve yield and efficacy based on early clinical findings. In addition, manufacturing process improvements may occur at any time during product development, and in many gene and cell therapy development programs they are made to scale up manufacturing during late stages after demonstration of early clinical benefit. In this respect, final chemistry, manufacturing, and controls (CMC) data for gene and cell therapy products often come later in the product lifecycle.

However, current CMC requirements were developed with small molecule chemistry in mind. For these products, product homogeneity throughout each step of manufacturing and development is critical based on these products' mechanism of action. We believe that, like clinical data, it is appropriate that the type and extent of CMC data must be risk-

based, commensurate with the stage of development and clinical understanding.

ASGCT supports the language that charges FDA to provide greater clarity regarding the type and extent of CMC data required at each stage of regulatory review, including post-market. The Society additionally suggests that FDA also address when in the development program sponsors should engage with the Agency regarding CMC data and how communications should continue through approval to ensure clear benchmarks.

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…"[9] 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 gene and cell therapies 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 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. To this end, we support the language in Section 309.

With a new generation of products that have transformative potential, we suggest that you consider the following additions:

- A guidance on how to implement post-marketing studies that utilize RWE, maximize patient access, and minimize administrative burdens for providers.
- An annual report on FDA's acceptance of RWE to fulfill post-approval requirements to provide product developers precedent from which to learn.
- A public posting of the cell and gene therapies approved using the accelerated approval pathway.

Sec. 407. Expanding Access to Genetic Testing

Genetic testing and genome sequencing hold tremendous potential for diagnosing

[9] Food and Drug Administration. (2014). *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.* https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf

patients—many of them children—with rare genetic disorders. Early diagnosis is critical for patient access to care and to treatments such as gene therapy, which may halt progression of serious and potentially fatal diseases. In addition, diagnosis facilitates access to ongoing and future clinical trials.

Unfortunately, the Medicaid program does not provide consistent access to DNA sequencing. According to Medicaid.gov, over 38 million children were enrolled in Medicaid or the Children's Health Insurance Program (CHIP) as of January, representing just under half of total enrollment in Medicaid and CHIP.[10] Yet there is no consistent standard of coverage across U.S. states and territories for coverage of DNA sequencing, leaving that population without access to diagnostic tests that could benefit their care.

We are pleased with the inclusion of this section to signal that this is a significant issue, and we encourage you to further develop the legislative text to ensure access to whole genome sequencing (WGS), whole exome sequencing (WES), and gene panels for all beneficiaries with Medicaid and CHIP. These diagnostic tests are not experimental procedures. WGS and WES have demonstrated clinical utility and desirable effects on active and long-term clinical management of patients with congenital anomalies; have a higher diagnostic yield; and may be more cost-effective when ordered early in the diagnostic evaluation compared with standard genetic testing, according to a recently released evidence-based clinical practice guideline.[11]

Additional recommended section: Medicaid Coverage to FDA Label for Gene and Cell Therapies

ASGCT recommends the addition of a section within Title IV to address barriers to Medicaid coverage of all FDA-labeled indications for gene and cell therapies. Known problems exist with states failing to cover therapies to FDA-labeled indications for these beneficiaries, despite a federal requirement to do so. Some state payers have misconceptions that after FDA approval, only patients who meet the criteria for the clinical trial should be covered, rather than all those meeting the criteria in FDA's approved label.

FDA approvals for indications beyond trial data are not uncommon, especially for gene therapies.

- First, gene therapies are frequently for the treatment of rare diseases with high unmet need, which limits clinical trial size and duration. According to CBER Director Peter Marks's remarks at the ASGCT 23rd Annual Meeting in 2020:

[10] Centers for Medicare & Medicaid Services. (2021). *January 2021 Medicaid and CHIP Enrollment Data Highlights*. https://www.medicaid.gov/medicaid/program-information/medicaid-and-chip-enrollment-data/report-highlights/index.html.

[11] Manickam K., McClain MR, Demmer LA, et al. (2021). Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. doi:10.1038/s41436-021-01242-6. https://www.nature.com/articles/s41436-021-01242-6

        - Many gene therapy clinical trials have a population size that is equivalent in size to a Phase I trial in a non-gene therapy trial (10 – 100 patients).
        - Gene therapy trials may have Phase I/II trials of 5 – 20 patients for initial dose-finding and initial efficacy, and a Phase II study serving as a pivotal trial (with 20 – 100 patients), using historical controls, patient run-in periods, or other novel trial designs.
        - For very small patient populations, if there is a good baseline or natural history study of the disease, even 4 – 5 patients can give CBER a good sense that the therapy is changing outcomes.
    - Second, gene therapies often demonstrate efficacy early in development. In the same remarks, Dr. Marks indicated that sometimes gene therapies demonstrate efficacy and can be ready for a marketing application after Phase II trials, as data from Phase I is already promising.
    - Third, gene therapies have the potential for substantial improvement over available therapies, or may become the first and only available therapy, for serious or life-threatening conditions. Of the 7,000 rare diseases that exist, which collectively affect 10 percent of the U.S. population, 95 percent have no current treatment.[12] Expeditious development is therefore imperative to meet this high unmet need for diseases that often have great morbidities and childhood mortality.

To summarize, a gene therapy may demonstrate high efficacy early in clinical trials in a small population of trial participants for a devastating disease that has no other treatment.

To understand FDA labeling of populations approved to receive a therapy, it is important to note that FDA's statutory standard for determining the effectiveness of a drug is a demonstration of "substantial evidence," which is defined in Section 505(d) of the Federal Food Drug and Cosmetic Act as:

> *"…evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."*

This legal definition does not state nor suggest that the clinical investigations must exactly replicate the populations the product is intended to treat, but rather support such efficacy in the labeled indication as concluded by the scientific experts at the Agency.

[12] Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development; Field, M.J., & Boat, T.F., editors. (2010). *Rare Diseases and Orphan Products: Accelerating Research and Development*. Washington (DC): National Academies Press (US). doi:10.17226/12953. www.ncbi.nlm.nih.gov/books/NBK56189.

FDA's guidance on demonstrating substantial evidence of effectiveness[13] provides detailed information about how various populations and trial designs meet this standard.

Despite legal requirements to cover these therapies to the FDA label, Medicaid coverage for gene and cell therapies varies widely state-to-state. For CAR T-cell therapy, only 24 states have publicly available coverage policies. Coverage criteria are often more restrictive than the FDA label indication statements for both tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta).[14] Barriers to access for Medicaid beneficiaries are especially concerning for patients with potentially fatal and/or progressive diseases, for which early administration of a therapy may prevent, but not reverse, morbidities and mortality. State program denial of coverage for a therapy for non-medical reasons is not appropriate. Greater enforcement of the requirement for Medicaid programs to cover gene and cell therapies to the FDA-labeled indications would be a significant step in improving coverage and access to these therapies, especially those that receive Breakthrough Therapy and RMAT designations.

Sec. 501. Advanced Research Projects Agency for Health

Whether through the establishment of an Advanced Research Projects Agency for Health (ARPA-H) or through other mechanisms, ASGCT strongly supports additional funding for the development of medical breakthroughs, such as those related to gene and cell therapies. We appreciate that the Biden Administration noted new manufacturing processes to create patient-specific T-cells to destroy malignant cells as an example of a potentially transformative project that ARPA-H could drive.[15] Improvements in manufacturing of gene and cell therapies could result in both greater manufacturing capacity, which is greatly needed, and in efficiencies in manufacturing processes that could benefit the field. We note, per our comments above, that regulatory schemes over manufacturing standards at FDA must keep pace with any new innovations that come from this effort or others.

Additional needs for significant innovation exist within the gene and cell therapy space. Notable areas that would benefit from more attention and support include the development of a sustainable model to advance equitable and efficient development of gene therapies for underserved populations, including ultrarare diseases, that builds upon the initial model and regulatory framework that the Bespoke Gene Therapy Consortium will develop.[16] We agree with the statement by Dr. Francis Collins and Dr. Eric Lander that "breakthroughs aimed at the most vulnerable groups are not only just

[13] Food and Drug Administration. (2019). *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Guidance for Industry – Draft Guidance.* https://www.fda.gov/media/133660/download
[14] Shupe L & Udeze C. (2019). *An Analysis of Healthcare Plan CAR T Cell Coverage Criteria for Medicaid Beneficiaries.* https://pharmafellows.rutgers.edu/wp-content/uploads/2020/08/2019-an-analysis-of-healthcare-plan-car-t-cell-coverage-criteria-for-medicaid-beneficiaries-1.pdf
[15] Lander E & Collins F. (2021). *Advanced Research Project Agency for Health (ARPA-H): Concept Paper [draft].* https://www.whitehouse.gov/wp-content/uploads/2021/06/ARPA-H-Concept-Paper.pdf
[16] American Society of Gene & Cell Therapy. (2021). *ASGCT Grapples With Development for Ultra-Rare Diseases.* https://asgct.org/research/news/july-2021/asgct-grapples-with-development-for-ultrarare-dise

and necessary, they will likely improve care for all patients."[17]

Another need is for more funding to support translational research to ready potential new gene therapy approaches for clinical research. While there are current National Institutes of Health (NIH) efforts supporting translational research, such as the National Center for Advancing Translational Sciences (NCATS) and the Regenerative Medicines Innovation Project (RMIP), there is a need in some disease areas for more study of large animal models (nonhuman primate, pig, and dog) to replicate human disease phenotypes, which may require investment of more significant resources.

Sec. 502. Research Investment to Spark the Economy

ASGCT supports the provision of $10 billion for use by the NIH to provide funding to independent research institutions, public laboratories, and universities throughout the country to continue their work on federally backed projects.

This funding is critical to restart interrupted research, fund crucial clinical trials, and fund student researchers' return to the lab so they can hone the skills needed to be future leaders in the gene and cell therapy field. The Society has advocated for this supplemental funding ever since it became clear last year that labs and clinical trial sites would experience long-term closures. ASGCT continues to support this crucial element of the nation's recovery from the pandemic.

Thank you for your consideration of these comments. Please contact Betsy Foss-Campbell, Director of Policy and Advocacy, at bfoss@asgct.org with any questions. We look forward to further engaging with you in your legislative development process.

Sincerely,

David Barrett, J.D.
Chief Executive Officer

[17] Collins FS, Schwetz TA, Tabak LA & Lander ES. (2021). ARPA-H: Accelerating biomedical breakthroughs. *Science*, *373*(6551):165-167. Doi:10.1126/science.abj8547. https://science.sciencemag.org/content/373/6551/165/tab-article-info