American Society of Gene + Cell Therapy

December 30, 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 comment on H.R. 6000, the Cures 2.0 Act. ASGCT is a nonprofit professional membership organization comprised of more than 4,800 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 and accessibility to patients of 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. The comments below focus on the specific text in the introduced bill; however, we urge you to also consider the broader concepts included in our initial discussion draft comments (dated 7/16/21).

We have noted suggested "action items" in our comments below in italic text.

Sec. 203. Increasing Diversity in Clinical Trials

ASGCT strongly supports the following provisions to improve diversity in clinical trials:

- An update from FDA on efforts to improve diversity in clinical trials.
- A GAO study on barriers to clinical trial participation.
- 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 their 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.[5,6]

The society notes that there are other provisions contained within this legislation which would help address some of the logistical barriers that can prevent trial participation:

- Increasing the utilization of decentralized trials, as is recommended in Section 310, can expand the reach of clinical trials outside of major medical centers. Decentralized trials will necessitate greater use of remote data collection and other technologies, which should be encouraged as appropriate to reduce the burden of travel and time associated with in-person visits.
- Sections 304 and 309 encourage greater use of real-world evidence in post-marketing studies, which can help capture data from a more diverse set of patients.

Thus, while we strongly encourage the activities in Section 203, we believe that removing structural barriers by updating the way data in clinical data are captured also is a critical component to achieving greater diversity among study participants.

ASGCT would gladly share with HHS insights gained from the Society's creation of patient education materials to inform a public awareness campaign on clinical trials. ASGCT's patient education modules include clinical trials for gene therapies that disproportionately affect minorities, such as sickle cell disease.[7] Similarly, ASGCT would be pleased to recommend a representative to a task force for making www.clinicaltrials.gov more user-friendly, as 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.[8]

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[1] Borghaei H, Paz-Ares L, Horn L, et al. (2015). Nivolumab versus Docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med.*;373:1627-1639. doi:10.1056/NEJMoa1507643.
[2] Motzer RJ, Escudier B, McDermott DF, et al. (2015). Nivolumab versus Everolimus in advanced renal-cell carcinoma. *N Engl J Med.*;373:1803-1813. doi:10.1056/NEJMoa1510665.
[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.
[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.
[5] Borghaei H, Paz-Ares L, Horn L, et al. (2015). Nivolumab versus Docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med.*;373:1627-1639. doi:10.1056/NEJMoa1507643.
[6] Motzer RJ, Escudier B, McDermott DF, et al. (2015). Nivolumab versus Everolimus in advanced renal-cell carcinoma. *N Engl J Med.*;373:1803-1813. doi:10.1056/NEJMoa1510665.
[7] American Society of Gene and Cell Therapy. (2021). *Patient Education*. https://patienteducation.asgct.org/
[8] American Society of Gene and Cell Therapy. (2021). *Clinical Trials*. http://www.asgct.org/clinicaltrials

Sec. 303. FDA Cell and Gene Therapy

We appreciate your concern about the regulatory barriers to the development of gene and cell therapy. However, we should not wait for an additional study to move forward as much of the information requested by the proposed report is known.

The challenges FDA faces reviewing these products are known and documented, including regulations not keeping pace with the latest manufacturing science, and difficulty hiring and retaining staff. The long-standing silos between CMS and FDA also slow adoption of products once they have regulatory approval. *We are pleased to see that other provisions in this legislation (including Sections 305 and 308) aim to address these known hurdles and would encourage you to consider how these provisions can go further as the bill moves through the legislative process.*

We also know that FDA needs additional resources to support the development of these products, and we are pleased that the PDUFA VII performance goals[9] include significant investments in CBER. With regard to the current state of the pipeline, ASGCT has created a clinical trials finder specifically for gene and cell therapies. Below we provide a summary of the trials represented in that finder in the U.S. to help illuminate the current state of cell and gene therapy regulation by FDA, organized in line with the proposed report requirements in Sec. 303(4).[10]

The quantity and nature of the submissions filed with the Food and Drug Administration (FDA) at the time of this letter are:[11]

- Total trials by category: 1,732
  - Gene therapy trials: 570
  - Cell therapy trials: 1,237
  - RNA therapy trials: 61
- Trials by development phase
  - Phase I: 698
  - Phase I/II: 387
  - Phase II: 456
  - Phase II/III: 14
  - Phase III: 95
  - Phase IV: 2
  - Not specified: 80

Sec. 304. Increasing Use of Real-World Evidence

ASGCT appreciates the sponsors' interest in and attention to the use of real-world evidence (RWE) to increase our understanding of marketed breakthrough, fast track, and accelerated approval products. The use of RWE is especially important for gene and

[9] Food and Drug Administration. (2021). *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027.* https://www.fda.gov/media/151712/download

[10] Note that for trials listed below, categories are not necessarily discrete, and a single investigation may be represented under more than one category.

[11] American Society of Gene and Cell Therapy. (2021). *Clinical Trials*. http://www.asgct.org/clinicaltrials

cell therapies with durable treatment effects that may go through these expedited pathways.

However, we would encourage the sponsors to consider adding language that would charge FDA to improve guidance for the use of RWE to support the post-market assessment of therapies that have received regenerative medicine advanced therapy (RMAT) designation. While products with RMAT designation are the only products that are statutorily eligible to use real-world evidence to fulfill post-marketing obligations required by the accelerated approval expedited pathway, developers are still in need of clarity regarding the agency's expectations. 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.

To that end, we suggest that the guidance proposed in Section 304(a) be expanded to include RMAT, or that the section include new language charging the FDA to update the existing RMAT guidance; additional examples and clarity regarding acceptable parameters in the post-approval setting would be beneficial.

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

We appreciate the sponsors' inclusion of language that aims to address 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 drug 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. Accelerating Timeline for Breakthrough and RMAT Designations

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 that 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, and Controls 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. This is also consistent with the updates required by PDUFA VII performance goals.[12]

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.[13]

ASGCT suggests the following changes –

- *Add to the contents of the guidance that FDA shall address when in the development program sponsors should engage with the Agency regarding CMC data and how communications should continue through approval, including during what meeting type (INTERACT, new Part D meetings, etc.) to ensure clear benchmarks.*

[12] Food and Drug Administration. (2021). *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027.* https://www.fda.gov/media/151712/download

[13] American Society of Gene and Cell Therapy. (2021). *Recommendations on CMC Expectations for Gene and Cell Therapy Products*. https://asgct.org/global/documents/advocacy/2021-fda-liaison-meeting/final-cmc-issues-for-liaison-meeting.aspx

- *Additional statutory language amending the Food Drug and Cosmetic Act that clarifying that the flexibilities granted by expedited programs apply to both clinical data and manufacturing data. We are happy to provide legislative language upon request.*

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…"[14] 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, which could also be captured by adding more granular language to Section 304.*
- *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 patients—many of them children—with rare genetic disorders. Early diagnosis is critical for patient access to care and treatment, such as gene therapy, which may halt

[14] 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

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 sequencing. According to Medicaid.gov, over 38 million children were enrolled in Medicaid or the Children's Health Insurance Program (CHIP) as of January 2021, representing just under half of total enrollment in Medicaid.[15] 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.

ASGCT supports the language included in 407 which would help facilitate access to whole genomic sequencing (WGS), whole exome sequencing (WES), and gene panels for all beneficiaries with Medicaid. 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.[16]

Sec. 501. Advanced Research Projects Agency for Health

ASGCT strongly supports additional funding for the development of medical breakthroughs, such as those related to gene and cell therapies, through the creation of the Advanced Research Project Agency for Health (ARPA-H).

We believe that the ARPA-H concept could be especially helpful for advancing gene and cell therapies, as was noted by the Biden Administration in their reference to manufacturing processes to create patient-specific T-cells to destroy malignant cells as an example of a potential transformative project that ARPA-H could drive.[17] 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 also appreciate the references by the Administration and in your text to new platform technologies.

We suggest that the sponsors consider including in Section 501 –

- *A strong mandate that ARPA-H collaborate with the FDA throughout product development; and*
- *Statutory changes to the Food Drug and Cosmetic Act that will enable the type of breakthrough research ARPA-H is charged with funding to become treatments*

[15] Centers for Medicare and Medicaid Services. *January 2021 Medicaid and CHIP Enrollment.* Accessed July 10, 2021. https://www.medicaid.gov/medicaid/program-information/medicaid-and-chip-enrollment-data/report-highlights/index.html.

[16] Manickam K, McClain M R, Demmer L A, 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.*;23:2029-2037. https://www.nature.com/articles/s41436-021-01242-6

[17] Lander E and Collins F. (2021). *Advanced Research Project Agency for Health (ARPA-H): Concept Paper*. https://www.whitehouse.gov/wp-content/uploads/2021/06/ARPA-H-Concept-Paper.pdf

for patients.

- *Per our comments above, this includes new regulatory schemes for manufacturing standards that have not kept pace with new innovations in gene therapy.*
- *We also suggest improvements to how FDA handles platform technologies, which are a critical component of the ARPA-H mission. Without more ability to rely on previous data or engage with the FDA in a product-agnostic way to assess product and manufacturing platforms, the likelihood of translation from bench to bedside is drastically reduced.*

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 disrupted by COVID-19.

This funding is critical to restart interrupted research, fund crucial clinical trials, and support 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 due to the pandemic. ASGCT continues to support this crucial element of the nation's recovery.

Thank you for your consideration of these comments. Please contact Christina Mayer, Senior Manager of Government Affairs, at cmayer@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