American Society of Gene + Cell Therapy

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Comments for Docket No. FDA-2023-N-0398 for "Methods and approaches for capturing post-approval safety and efficacy data on cell and gene therapy products, Public Listening Meeting; Request for Comments."

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to submit comments on the public listening meeting "Methods and Approaches for Capturing Post-approval Safety and Efficacy Data on Cell and Gene Therapy Products," held on April 27, 2023. ASGCT is a nonprofit professional membership organization comprised of 6,000 scientists, physicians, and other professionals working in cell and gene therapy (CGT) 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. The mission of ASGCT is to advance knowledge, awareness, and education leading to the discovery and clinical application of genetic and cellular therapies to alleviate human disease.

ASGCT would like to thank the Agency for organizing this public listening session on topics crucial to advancing the CGT field and improving patient outcomes. ASGCT appreciates the opportunity to comment on the key themes explored in the listening session; the significance of alternative study designs; the development and establishment of product- and disease-based registries; real-world data collection; and determining specific safety and efficacy outcomes for which post-approval follow up may be required.

Alternative Study Designs, Including Decentralized Studies

Alternative study designs, including decentralized studies, are crucial in advancing cell and gene therapy research. Embracing these approaches can benefit patients in need by allowing researchers to accelerate the development and adoption of innovative cell and gene therapies. Alternative study designs, such as decentralized trials, can increase patient access and make participation more feasible for a broader population. The tools that are developed for the collection of effectiveness data remotely for clinical trials supporting approval also can serve as a more convenient way to collect important efficacy data post-approval in a patient's home environment.

Traditional clinical trials may face challenges in recruiting a diverse range of participants due to geographical limitations or lack of awareness. Alternative study designs, including decentralized trials, can help overcome these barriers by enabling participation from a broader range of patients, leading to more representative and generalizable results. These same considerations also are relevant in the post-approval setting, especially for patients living in remote areas who may be less likely to travel to tertiary institutions.

Clinical trials for CGT products often require specialized infrastructure and manufacturing and clinical administration facilities, which can further limit patient participation in a traditional trial structure but may be mitigated by decentralized or other innovative trial approaches. Incorporating decentralized study designs can aid researchers in gathering data from patients in their natural environments, which may provide a more accurate assessment of treatment outcomes and long-term safety. This real-world evidence can complement the findings from controlled clinical trial settings, enhancing the overall understanding of the therapy's impact. Innovative study designs can also offer a more patient-centered and efficient way to collect pre- and post-approval safety and efficacy data, ultimately leading to better treatment outcomes.

Development and Establishment of Product-based and/or Disease-based Registries

Registries are large, observational databases that can capture real-world data on the safety and effectiveness of medical products and treatments. These registries contribute to ongoing research efforts to benefit patients and advance medical knowledge of CGTs. By tracking patients' outcomes and adverse events beyond the limited scope of clinical trials, registries enable the collection of comprehensive, long-term safety data. This information is invaluable for evaluating the safety profile of therapies and identifying potential long-term risks or side effects.

ASGCT recognizes that registries provide an essential platform to assess the real-world effectiveness of CGTs, going beyond the controlled environment of clinical trials. By collecting data from a larger patient population, registries offer valuable insights into the therapy's performance, its impact on disease progression, and overall patient outcomes. This real-world evidence complements the findings from clinical trials and plays a vital role in guiding treatment decisions and further research.

In 2022, ASGCT provided comments on Docket No. FDA-2021-D-1146: Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products, in which the Society highlighted that increased utilization of real-world data (RWD) derived from registries has the potential to facilitate the inclusion of more representative patient populations, leading to a more accurate reflection of the risks and benefits of gene and cell therapy products. ASGCT also expressed appreciation for the involvement of the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Office of Clinical Pharmacology (OCP), while encouraging collaborative efforts to be reflected in the guidance documents. ASGCT urged the FDA to actively work towards implementing the final version across different product categories.

Furthermore, ASGCT recognized that CGT trials, especially for rare diseases, often involve small sample sizes due to limited availability of patients. ASGCT encouraged consideration on how registry data can be

effectively utilized to better understand these CGT products within the broader population and clinical care settings. ASGCT acknowledged that registries can introduce biases based on their design. The Society respectfully suggested that future guidance should include FDA's current thinking on how sponsors can manage bias when utilizing data from existing registries, particularly for products under development to address unmet medical needs. Information also needs to be provided to organizations that set up the collection of these data to address bias, missing data points due to missed appointments, inconsistent data collection, etc.

Real-world data collected in clinical settings through digital health technologies, electronic health records, insurance claims databases and other administrative data-based and population-based data sources.

Real-world data can provide insights into patient outcomes and help identify safety concerns that may arise after approval. The information collected from these sources can also aid in making patient care decisions and facilitate the advancement of novel therapies. Therefore, collecting and analyzing real-world data is crucial to advance the CGT Field and improve patient outcomes.

In additional comments on Docket No. FDA-2021-D-1146: Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products last year, ASGCT emphasized the importance of real-world evidence (RWE) for CGTs with durable treatment effects. Particularly, ASGCT highlighted the reliance on paradigm-altering modalities like CAR T-cell therapies on RWE to demonstrate their effectiveness. ASGCT urged the Agency to consider anticipated treatment effects and the inherent differences between CGT and small molecule therapies when implementing the standards outlined in the guidance. Additionally, the Society requested that the final guidance for real-world data (RWD) reference areas where considerations may differ for CGT products or those with durable treatment effects.

Regarding data transparency, ASGCT encouraged the Agency in our previous RWD guidance comments to provide additional clarity regarding the data it already has access to outside individual sponsor applications. Currently, ASGCT member CGT sponsors report obtaining patient-level data through contracts, only to discover that the Agency already possesses such data. Enhancing knowledge about the Agency's data access can streamline resources and foster convergence around FDA-audited and inspected data.

Additionally, when commenting on Docket No. FDA-2022-D-2983: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Guidance, ASGCT expressed gratitude to the Agency for recognizing the need for sponsors and investigators to utilize externally controlled clinical trials to demonstrate the safety and effectiveness of drug products. The Society emphasized the importance of establishing standardized protocols and guidelines in the guidance to ensure the safe and effective conduct of trials, especially for cell and gene therapy developers focused on rare diseases with high morbidity and mortality rates. ASGCT noted that the draft guidance does not significantly advance the use of external controls, including those based on RWE, potentially hindering sponsors' ability to address practical and ethical challenges in developing treatments for rare diseases.

This is particularly relevant for CGT which have the potential to cure or prevent disease progression for patients with the rare genetic diseases.

ASGCT suggested that a new draft of the guidance should align with Congressional directives and initiatives like the "Operation Warp Speed" pilot for rare disease drug development announced by CBER Director Peter Marks, provided clear recommendations on the utilization of external controls, including RWE, to support product development. The revised guidance we proposed should also offer guidance on collecting, analyzing, and submitting control data that best supports regulatory approval when traditional trial designs are unethical or unfeasible. By doing so, the FDA could ensure that externally controlled trials are conducted scientifically, rigorously, and transparently, with considerations for potential biases and limitations, thereby reducing the burden on both sponsors and the Agency through clear recommendations rather than case-by-case interactions. Another focus should be on what is most important to patients as they deal with their disease. Emphasis should be placed on these patient-focused benefits as well as their assessment by patient-reported outcomes (PROs). Traditionally, these PROs have to be validated based upon large amounts of clinical data. However, it should be recognized that such large amounts of data would not be available for small, rare disease patient populations. Dr. Mark's has called for a 'degree of flexibility' in assessing these PROs for rare patient populations.

Determination of specific safety or efficacy outcomes for which collection of post-approval safety or efficacy data may be necessary for cell or gene therapies.

In our comments for Docket No. FDA-2021-D-0398: Human Gene Therapy Products Incorporating Human Genome Editing; Draft Guidance for Industry***,*** we emphasize that the advantages and limitations of components should not be compared or evaluated in relation to other products under development. Each development program and resulting Biologics License Application (BLA) should be assessed within the context of unmet needs, available therapies, the severity of the condition, the intended patient population, and the safety, efficacy, and quality data provided in the BLA. These advantages and limitations should also consider that technologies may evolve during a product development program. AGSCT also suggested that this should not be a regulatory barrier or negatively impact how the FDA reviews a BLA if the safety, efficacy, and quality data meet licensure standards.

Determining specific safety and efficacy outcomes and collecting post-approval data is crucial for the long-term safety evaluation of CGTs and assessing treatment outcomes. These activities help identify rare events, conduct comparative analyses, optimize treatments, and inform regulatory decisions. They are vital for evidence-based healthcare decisions, patient safety, and responsible utilization of cell and gene therapies. While CGTs undergo rigorous testing during clinical trials, long-term safety monitoring is necessary to identify potential adverse events or safety concerns that may arise over time. By determining specific safety outcomes and collecting post-approval safety data, researchers and regulatory agencies can assess the therapy's safety profile in real-world settings and make informed decisions regarding patient safety. For example, to reduce the total number of patients receiving the commercial product required for long-term follow-up data collection, studies should consider leveraging the long-term follow-up data generated from clinical trial patients to meet the post-approval commitment. Consideration of such approaches is able to ensure the ongoing evaluation and

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optimization of cell and gene therapies, thereby promoting the responsible advancement of this innovative field.

Thank you for your consideration of these comments. If you have any questions about the Society's comment, please do not hesitate to contact Margarita Valdez Martínez, Director of Policy and Advocacy, at **mvaldez@asgct.org**.

Sincerely,

David M. Barrett, JD

Chief Executive Officer