American Society of Gene + Cell Therapy

November 16, 2023

Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Comments for Docket No. FDA-2023-N-3742, "Scientific Challenges and Opportunities to Advance the Development of Individualized Cellular and Gene Therapies; Request for Information"

Dear Sir/Madam,

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on the request for information document *Scientific Challenges and Opportunities to Advance the Development of Individualized Cellular and Gene Therapies*. ASGCT is a nonprofit professional membership organization comprised of 6,200 scientists, physicians, and other professionals working in cell and gene therapy (CGT) in settings such as universities, hospitals, government agencies, foundations, 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 appreciates the opportunity to comment on regulatory strategies to support manufacturing changes and comparability for human CGT therapies.

ASGCT appreciates FDA's attention to these topics, as individualized CGTs have become a frequent topic for developers. The themes derived from the RFI and our subsequent recommendations highlight the challenges and opportunities within the CGT landscape. We believe that through collaborative efforts, we can navigate these challenges and continue innovative development of individualized CGTs while ensuring patient safety and product quality.

Below are our responses for each requested section:

A. Manufacturing

Leveraging Prior Experience and Collaborative Opportunities: Manufacturers have the capacity to leverage their expertise to establish subsequent product development and Investigational New Drug (IND) applications. This practice holds the promise of heightening manufacturing consistency while concurrently shortening development timelines.

ASGCT would support the Agency in the establishment of collaborative platforms designed for the purpose of sharing data and facilitating the exchange of process knowledge. These platforms would serve as conduits for seamless knowledge transfer while still maintaining strict confidentiality. The collective effort between industry and regulatory bodies should align to promote the widespread application of validated processes and best practices. The aim is to enhance manufacturing consistency while effectively addressing the challenges linked to small batch sizes and the unique characteristics of individualized CGTs.

In the context of small batch sizes, the number of vials required for release and stability testing is an issue for the field. Sampling and archiving can be challenging for sponsors. For example, when it comes to CAR-T therapies, a substantial percentage of the final samples are reserved for archiving purposes. It's imperative to define the duration for which these samples should be archived. We therefore propose that the Agency offer clear guidance on the sampling and archiving of CGT products. Guidance should be developed to address the retention period for these samples, ensuring they remain available for potential future reference and/or analysis. With regard to AAVs, we see an opportunity to leverage and de-identify existing data on adverse events and follow-up requirements to better inform Agency recommendations.

In the context of stability and fill volume, we encourage the utilization of match-to-match volume as opposed to relying solely on vial surface area. This approach offers a more comprehensive and representative understanding of the product's stability and suitability for release. It also provides an opportunity for collaboration among sponsors with similar CGT products. Collaborative efforts can result in the pooling of valuable data and promote standardized practices. We suggest that data generated from such collaborative efforts extend beyond just stability and fill volume. It should also document critical process and manufacturing know-how. Importantly, the data can be linked to clinical outcomes, providing a holistic view of the product's performance. For example, when considering cell viability, there have been instances where known therapies were approved based on compassionate exemption, and the patients responded positively. This raises questions about the relevance of specific Critical Quality Attributes (CQA) or Quality Control (QC) assays if they are not directly correlated with clinical outcomes.

ASGCT acknowledges that while FDA's current guidance is relevant for many development programs, individualized therapies may exhibit unique patterns based on clinical experience. Hence, we suggest an approach that allows for flexibility in criteria and specifications based on clinical data. The Society recommends that sponsors be permitted to revise their product specifications as new data emerges, enabling the continuous improvement of CGT products and ensuring that they align with clinical needs.

Enhancing Efficiency, Cross-Referencing, and Flexibility in Manufacturing:
The cross-referencing of master files in the context of CGT manufacturing can lead to increased efficiency and knowledge sharing. To streamline this process, the Society suggests clearly defining what aspects can be cross-referenced across the field, not only within the same manufacturer but also for wider application. Additionally, for aspects of stability testing that have become well-characterized in the field, we propose reducing the need for repetition in each product's development.

For ultra-rare diseases, we suggest exploring flexibility around the requirements for three process performance qualification (PPQ) runs. The Agency could consider alternatives such as using the three runs for commercialization, acknowledging the unique challenges posed by ultra-rare disease therapies.

Facilitating information sharing is also possible through third-party analytical testing sites, which can build standardized assays. These assays may need confirmation for each individual product but offer a framework for analytical plans that can be widely shared. This approach may also encourage analytical contract research organizations (CROs) to create master files for different assay platforms. We recommend defining which aspects of testing can be cross-platform and which should be tailored to the specific product. For instance, identity and potency would be specific, while aspects like durability and robustness might be shared.

We would also like to acknowledge the importance of the Advanced Manufacturing Technologies Designation Program (AMTDP). The program has the potential to be a critical driver of standardization and efficiencies through the incorporation of platform technologies. ASGCT sees particular value in AMTDP's emphasis on timely, interactive, collaborative, and cross-disciplinary FDA reviews for designated products involving senior managers and experienced staff. ASGCT members report that other major drivers of their participation would include that AMT-designated drugs will be expedited by FDA and that the holder of a designated AMT can reference or rely upon data and information about the AMT for use in manufacturing other drugs in the same context of use for which the designation was granted. ASGCT looks forward to seeing more details about AMTDP as it is developed.

Risk-Benefit Profile:
The development and approval of individualized CGTs have a unique risk-benefit profile due to the nature of diseases they aim to treat, prompting a reevaluation of existing regulatory guidelines. These personalized therapies differ from conventional approaches, presenting unique challenges related to both potency and purity.

The variation in risk associated with personalized treatments necessitates a comprehensive review of existing regulatory frameworks. The potency of individualized CGTs plays a pivotal role in defining a potency threshold specific to personalized therapies. For that reason, the Society suggests guidelines specific to individualized CGTs, taking into account their unique risk-benefit considerations.

Process Validation:
Process validation is a component in the manufacturing of CGTs. The Society underscores the significance of attaining consistency in manufacturing processes, particularly in scenarios where each batch is tailored to an individual patient. The challenge of accommodating the diversity of mutations found in monogenic diseases necessitates careful attention. To further advance the field, the Society recommends active collaboration between the FDA and stakeholders. This collaborative effort should focus on standardizing approaches for process validation that are tailored to the individualized characteristics of CGTs. The establishment of comprehensive guidelines and standards to ensure process consistency is imperative in driving progress within the CGT sector.

Method Validation:
Method validation, particularly in cases where revalidation for different patients is not required, constitutes a vital aspect of CGT development. We would like to underscore the importance of flexibility in adapting validation methods to the specific context of CGTs. There are instances in which method revalidation for every patient may not be necessary, emphasizing the need for adaptable validation approaches, especially in expedited or small-scale CGT trials.

The Society strongly recommends that FDA develop guidelines for method validation tailored to the unique attributes of individualized CGTs. The implementation of customized validation criteria for diverse CGT products can significantly streamline the development process without compromising patient safety. This approach ensures that validation practices remain robust while accommodating the distinct characteristics of individualized therapies.

B. Nonclinical Development

Leveraging Nonclinical Studies for Related Products:
Regarding the extent to which nonclinical studies can be leveraged to support related or similar technologies, clarity on regulatory expectations in this context is needed. For example, when a product employs the same manufacturing platform with only the transgene being modified, there is a potential opportunity to leverage safety studies, typically conducted in a non-disease state model. However, it remains uncertain if a risk-based approach may be used to argue that prior safety data is relevant to the related product. Clarity is needed on whether existing genotoxicity data from one product can be leveraged for a second product that uses the same nuclease/gRNA for editing, but utilizes a unique donor sequence.

The Society asks for clear guidance on how much FDA is willing to accept this risk-based approach and whether specific elements of a nonclinical safety package are more likely to be acceptable for data leverage from similar products. The acceptance will also depend on how the different transgene affects the product's activity. Nevertheless, there is a significant opportunity, especially when dealing with safety studies conducted in non-diseased or naïve model systems. The Society would also like clarity on the acceptance of alternative model systems, such as organoids. The Society requests guidance on what the Agency expects as an alternative when no directly relevant animal model is available.

Nonclinical Approaches for Unique Disease/Condition:
When discussing nonclinical development approaches, the Society seeks clarity on the feasibility of building a nonclinical package with safety assessments conducted in non-disease state, naïve model systems when no relevant animal models exist or when available models cannot replicate the disease or condition. Furthermore, we aim to understand to what extent these can be combined with *in vitro* model systems. In situations where relevant animal models are lacking, leveraging safety testing through non-disease state models and *in vitro* modeling should be considered. Overall, the Society suggests that clarity on regulatory expectations for alternative testing methods is crucial.

Preclinical Studies for Dosing Strategy:

The issue of higher expectations or burdens in preclinical studies to understand and justify dosing strategies for clinical use is particularly relevant, given the trend toward accelerated and smaller clinical development plans. Leveraging data from related or similar technologies is a challenge that hinges on the definition of similarity. The Society asks the Agency to provide insights into what is considered related or similar technologies and how to assess their degree of similarity. The challenge lies in comparing technologies where manufacturing processes may not be public information. Therefore, understanding what the Agency deems as similar is a complex process. Establishing different categories is feasible, but the actual comparison can be intricate due to limited visibility into manufacturing processes.

Flexibility in Proof-of-Concept Studies:
Flexibility from the Agency, is needed in cases where a clear, established proof of concept or a pre-established animal model is unavailable. Understanding the extent of flexibility allowed on the nonclinical side to support subsequent submissions is important to the field.

Approaches to Standardization:
There remains a vital aspect of computational approaches that requires attention. We believe there should be more clarity provided on what the Agency accepts and expects when sponsors employ different computational methods. Currently, there is a lack of standardization in field despite the general framework outlined in the Agency's guidance on Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial. The guidance encompasses a combination of methods for analysis. However, translating this framework into practical and well-accepted analytical methods remains challenging. Standardization is crucial not only in terms of analytical methods but also in the execution of the analysis. The Society asks for guidance regarding the interpretation of true off-targets, the ideal number of replicates for target validation, and the integration of high-resolution sequencing methods with orthogonal genome-wide techniques.

C. Clinical Development

Clinical Data:
Interpreting clinical data in the context of rare diseases and individualized treatments presents unique challenges and opportunities. There is a pressing need for clarification regarding the interpretation of clinical data in conditions where the natural history of the disease is lacking or exhibits significant heterogeneity, which is often the case for rare diseases. The key concern is how much can be leveraged from natural history studies when the disease progression is not well understood. Clarity is needed on whether the Agency will accept such data as a control in studies, especially given the recent emphasis on randomized control trials (RCTs) due to disease heterogeneity. It's crucial for programs to understand when natural history data may be appropriate and when RCTs are required, particularly for rare diseases.

Safety and Efficacy:
The Society would like to highlight flexibility in interpreting safety and efficacy data when dealing with small patient populations. In such cases, making statistically significant conclusions can be challenging. Determining the extent of flexibility FDA is willing to allow is crucial. Furthermore, when dealing with a limited patient pool, the development and linkage of potency assays to patient outcomes becomes significantly more challenging. The original expectations for qualified

and validated assays prior to registration data and process performance qualification (PPQ) can be complicated. This is an opportunity to explore whether different expectations can apply, focusing on confirming manufacturing consistency from lot to lot, rather than having potency assays directly tied to patient outcomes for smaller, accelerated clinical development plans.

Addressing the challenges and opportunities in interpreting clinical data for rare diseases and individualized CGTs requires clear guidance, flexible approaches, and collaborative efforts to enhance safety and efficacy assessments.

D. Additional Questions To Consider

In addressing the unique scientific challenges related to ultra-rare individualized CGTs, one concept to consider is that "the process is the product." In cases where the manufacturing process remains the same but specific components differ, the Agency might explore the possibility of exercising flexibility. This flexibility could entail reducing the amount of data needed when altering individualized medicines' components. For example, if only the guide RNA is changed, and there's a comprehensive understanding of the underlying process, it might not be necessary to compile an entirely new package to support these modifications. This approach could streamline the development process, making it more feasible to accommodate individualized ultra-rare CGTs.

To address challenges associated with developing individualized ultra-rare products for patients, the Agency could explore alternative pathways that capture promising treatments without the need for full-scale commercialization. This approach would enable the development of treatments that may not be financially viable for traditional commercialization but still hold significant promise for the individuals who desperately need them. The goal is to create a regulatory framework that encourages and supports the development and availability of these treatments.

The Society appreciates the Agency's efforts to understand the challenges and opportunites for the successful developement of cellular and gene therapies. As stated throughout our comments, there are many opportunites for the Agency to provide additional guidance to the field. We would welcome the opportunity to collaborate with you on future workshops, science tools and discussion papers.

Thank you again for your consideration of these comments. If you have any questions about the Society's comments, 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