American Society of Gene + Cell Therapy

August 23, 2020

The Honorable Stephen M. Hahn, MD
Commissioner
US Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Comments for Docket No. FDA-2010-N-0128: Reauthorization of the Prescription Drug User Fee Act; Public Meeting; Request for Comments

Dear Commissioner Hahn:

The American Society of Gene and Cell Therapy (ASGCT) welcomes the opportunity to provide comment on the Reauthorization of the Prescription Drug User Fee Act Public Meeting held July 23, 2020. ASGCT is a nonprofit professional membership organization comprised of more than 4,400 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.

The Society's comments herein focus on ensuring and publicly communicating a clear and predictable path to market for these transformative products to facilitate development from early basic research to late stage and post-marketing assessment. We appreciate FDA's willingness to hear from stakeholders about ways to improve and adapt policies to consider the unique attributes of these therapies.

Bolster support for the Center for Biologics Evaluation and Research (CBER)

Thanks to diligent scientists across the world, today's pipeline of gene and cell therapies is robust and growing. CBER has over 1,000 active investigational new drug applications supporting clinical research on the transformative therapies of the future. With the rapid expansion of the volume of trials in the gene and cell therapy space, it is critical that CBER is well supported to facilitate the development of these programs.

In 2020, the CBER budget was $419 million (~$150 million in PDUFA fees), while CDER received $1.97 billion (~$797 million in PDUFA fees).[1] Though we appreciate that CDER has historically been, and continues to be, the largest center, resources need to shift to accommodate the shifting focus of therapeutic development before potential bottlenecks may hinder progress. Without an increase in resources, there is a real risk of any level of pressure significantly destabilizing CBER's ability to provide adequate and timely review and development support to developers of gene and cell therapy products.

The pressures that the COVID-19 crisis has placed on CBER has highlighted our concerns. ASGCT members report that many meeting requests for pre-IND, PDUFA meetings, and even engagement during reviews have been significantly delayed. For example, some pre-IND meetings have been delayed by at least 3 months; INTERACT meetings have been denied or cancelled; and in many cases in which meetings have been substituted with written responses, the responses are inadequate to answer the questions posed. Additionally, pre-license inspections have been delayed with potential to impact decision-making on the approvability of these transformative therapies. Responding to the public health emergency with an all-hands-on-deck approach is essential; however, the impact to current development programs demonstrates CBER does not have needed surge capacity for the increasing volume of gene and cell therapies in the pipeline.

We therefore support additional user fee dollars being allocated to CBER, as the current PDUFA funding growth has not kept pace with the current and expected workload increases at the center.

With additional user fee dollars, we believe it is critical for CBER to enhance operational capabilities by significantly increasing CBER review staff. Improvements of FDA's hiring and retention strategy have been a goal of the PDUFA program for many years. While these improvements take place across the FDA to reduce institutional barriers to staffing the Agency at the necessary capacity, we suggest additional efforts to improve the recruitment, training, and retention efforts specifically of CBER staff. We also encourage CBER to increase the number of expert consultants available to support sufficient time in milestone meetings for discussion with sponsors of key scientific issues and the potential acquisition of the patient perspective; and provide more opportunities for CBER staff to learn from and engage with scientific organizations such as ASGCT. Additionally, the Society suggests that FDA develop a collaborative public private partnership with researchers, industry, and other key stakeholders with the specific purpose of addressing crucial issues and barriers in gene and cell therapy development.

Additional dollars to CBER should also be invested in modernizing CBER digital infrastructure. We understand that FDA is involved in ongoing work to modernize the Agency's IT systems and implement "knowledge management." Per ICH Q10 § 1.6.1, knowledge management is a "…systemic approach to acquiring, analysing, storing, and disseminating information related to products, manufacturing process, and components." This type of learning that can draw lessons from clinical development, manufacturing and controls, and post-market experiences, and assist FDA with future product analysis, is critical in the emerging field of gene and cell therapy. With limited gene and cell therapy products on the market and a very robust pipeline of clinical development programs, learnings across programs using similar technologies or vectors, for example, may help the Agency and developers address problems earlier in development, course correct, and achieve better outcomes for patients.

Enhance regulatory predictability by improving engagement

Due to the robust pipeline for gene therapies, ASGCT recommends that FDA pay close attention to the communication processes during CBER review. One recommendation on how to do so follows.

Develop optional CBER-sponsor communication plans early in the development of regenerative medicine advanced therapy- or breakthrough-designated products
Currently, communication plans are used informally within CDER, often for products with breakthrough therapy designation, to identify the most appropriate times for meetings and the type of data to be

[1] https://www.fda.gov/media/135078/download

discussed at each landmark. Given the rapid pace of development of gene and cell therapy, we believe that the option for a communication plan would help set expectations of both CBER and sponsors to reduce unforeseen regulatory hurdles. For example, we suggest that communication plans could be developed to address labeling, post-marketing requirements and commitments, and challenges related to chemistry, manufacturing, and controls (CMC), that open a line of predictable and consistent communication between the review team and sponsors on these most challenging issues.

Expand guidance for industry

We support producing guidance for industry documents to help clarify development challenges for gene and cell therapies. When developed and implemented, guidances can be extremely helpful for both industry and academic members of ASGCT in clarifying regulatory pathways and decreasing uncertainty. While intended for an industry audience, academic researchers embarking on basic and translational research projects also benefit from understanding how FDA views clinical development issues, the types of data FDA requires, and the areas of regulatory uncertainty, to most efficiently and effectively use scarce research dollars to answer questions that will contribute to expeditious advancement of the field for patients. In some instances, primary investigators from academic institutions initiate early-phase clinical trials in gene and cell therapy, as well.

ASGCT recommends that the user fee goals letter includes the development of guidance documents on the following topics:

- *Immunogenicity testing*
  Much progress has occurred in understanding the science of immunogenicity of adeno-associated viral vector (AAV) gene therapy products. However, the utility of such scientific findings in informing product development programs and regulatory requirements remains unclear. FDA guidance would be beneficial to sponsors on the requirements for immunogenicity testing, including data that should be collected and what may be relied upon from previous applications, and recommendations on clinically meaningful metrics.

- *CMC requirements for clinical-stage manufacturing changes for gene and cell therapy products*
  While we appreciate that FDA has released guidance on CMC requirements for IND submission, the Society recommends further Agency guidance on CMC requirements during and after clinical development. Manufacturing process improvements may occur at any time in 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. However, FDA requires that product comparability be demonstrated throughout development to ensure that clinical data can be extrapolated between batches. The extent of comparability must be risk-based, commensurate with the stage of development and clinical understanding.

  The Society recommends Agency guidance on phase-appropriate CMC information that is necessary prior to a Phase III trial, as well as in later stages of development, including comparability criteria, lot release criteria, critical quality attributes (CQA), and critical process parameters for different product classes—retroviral vectors, AAV vectors, CAR T-cell/TCR therapies, and genetically-modified stem cells. Guidance should also include information regarding FDA's views on the design of process validation protocols; the CQAs, potency testing, and analytic assays that are required to support a BLA submission; and the appropriate use of, and requirements for, the BLA supplement process for manufacturing changes.

ASGCT recommends that the user fee goals letter includes updating the following existing guidance documents:

- *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions*[2]. The use of real-world evidence (RWE) is necessary to fulfill post-marketing obligations required by the accelerated approval expedited pathway, for which therapies are eligible that have received the regenerative medicine advanced therapy (RMAT) designation. The 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 suggest that CBER provide additional examples and clarity regarding acceptable parameters in the post-approval setting to fulfill such requirements.

- *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions* and *Expedited Programs for Serious Conditions*[3]. ASGCT recommends that FDA provide greater clarity regarding the manufacturing and CMC data that may be submitted in the post-market setting for certain products. Unlike traditional drug products, gene and cell therapy product manufacturing often develops in parallel with clinical development. Product sponsors can make changes to improve yield and efficacy based on early clinical findings. In this respect, final CMC data often comes later in the product lifecycle. We recommend that FDA take these differences into consideration in post-marketing plans and when considering the appropriateness of rolling review. The guidances should 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.

Promote modern post-market surveillance

Post-market surveillance is critical to ensure that 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…" Many gene and cell therapies could be approved based on this pathway, as their mechanism is likely to produce a durable effect on the underlying causes of disease for which the long-term impact on outcomes may not be possible to assess during 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. 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 products on the market.

With this new generation of products that have transformative potential, we suggest the user fee agreement letter include the following:

- An assessment of FDA's post-marketing study approaches.
- A plan for 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.
- Public tracking of cell and gene therapies approved using the accelerated approval pathway.

[2] https://www.fda.gov/media/120267/download
[3] https://www.fda.gov/media/86377/download

ASGCT appreciates your consideration of these comments. If you have any questions, please contact Betsy Foss-Campbell, Director of Policy and Advocacy, at bfoss@asgct.org.

Sincerely,

David M. Barrett, JD, MS
Chief Executive Officer
American Society of Gene & Cell Therapy