American Society of Gene + Cell Therapy

October 28, 2021

The Honorable Janet Woodcock, MD
Commissioner
US Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Comments for Docket No. FDA-2021-N-0891: Reauthorization of the Prescription Drug User Fee Act; Public Meeting; Request for Comments

Dear Commissioner Woodcock:

The American Society of Gene and Cell Therapy (ASGCT) welcomes the opportunity to provide comment on the proposed recommendations for the reauthorization of the Prescription Drug User Fee Act (PDUFA) for fiscal years (FYs) 2023 through 2027 ("commitment letter," or "the letter"). 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 FDA's ongoing willingness to hear from stakeholders about ways to improve and adapt policies to consider the unique attributes of these therapies.

ASGCT supports the commitment letter as drafted and is eager to assist the agency in the PDUFA VII reauthorization and the implementation of the goals in the letter. The Society's detailed comments herein focus on specific provisions of the commitment letter that support a clear and predictable path to market for these transformative therapies and facilitate their development from early basic research to late-stage and post-marketing assessment.

Bolstering 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 in 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.

We are pleased that the commitment letter establishes a goal to hire 228 new FTEs in CBER, nearly 65% of the total new FTEs supported by PDUFA VII. Additionally, we applaud the specific objective of these new staff to *"meet the increasing challenges and demands in this growing field. Increasing staff capacity will overcome existing resource limitations, allowing staff to spend additional time on meetings and submission reviews including those with breakthrough or regenerative medicine advanced therapy designations, expand stakeholder outreach, invest in new policy and guidance, and facilitate development and use of regulatory tools and scientific technologies."* This objective is critical to successfully bringing new gene and cell therapies to patients and will enable the agency to be a partner in realizing the promise of these technologies.

Improving FDA's hiring and retention is a longstanding goal of the PDUFA program. We support the clear hiring goals and follow-up assessment of staff hiring and retention efforts to build upon the lessons learned from the report supported by PDUFA VI. While outside the scope of specific commitments, we encourage CBER to provide more opportunities for CBER staff to learn from, and engage with, scientific organizations such as ASGCT.

Enhancing regulatory predictability by improving engagement and communication

We are pleased by the proposed creation of Type D meetings and clarifying the scope, intent, and timeline for INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs (INTERACT) meetings.

For cell and gene therapy developers, receiving rapid responses to regulatory questions is critical to timely development programs. The establishment of Type D meetings would afford sponsors the opportunity to receive feedback within 50 calendar days regarding "no more than two" issues. This can be especially useful for gene and cell therapy sponsors who have completed a Type B or C meeting and have resulting follow-up questions after internal consideration of the meeting and feedback received. ASGCT welcomes the opportunity to provide additional comment and insight as FDA works to develop more detailed procedures and criteria for these meetings and updates guidance.

INTERACT meetings are especially critical to sponsors developing novel technologies and those without robust prior regulatory experience. While FDA's informal goal has been to respond to INTERACT requests within 21 calendar days and to hold meetings within 90 calendar days, we recognize, from member reports, that FDA has not been able to meet this goal in practice under current staffing levels. Especially during the COVID-19 pandemic, 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. We are pleased that the commitment letter provides the staffing support necessary to include a formal goal of holding INTERACT meetings within 75 calendar days of request. We also support the new scope of INTERACT to focus on truly challenging scientific and regulatory issues in early-stage development and leave specific questions in this stage to the newly created Type D meeting. We believe this combination will allow better utilization of FDA resources and greater clarity for developers.

As stated in our initial comment letter, ASGCT believes that user fee dollars allocated to CBER should be invested in modernizing CBER's digital infrastructure, and we are pleased that the commitment letter specifies investments in modernizing CBER's IT systems and supporting "knowledge management." 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 products on the market and a very robust pipeline of clinical development programs, learnings across programs using similar technologies or vectors, for example, many help the agency and developers address problems earlier in development, course correct, and achieve better outcomes for patients.

Expanding guidance for industry

We support producing guidance for industry documents to help clarify development challenges for gene and cell therapies. When developed and implemented, guidance documents 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 efficiently and effectively use scarce research dollars to answer questions that will contribute to expeditious advancement of the field for patients. Primary investigators from academic institutions initiate early-phase clinical trials in gene and cell therapy as well.

We are pleased that the commitment letter includes so many proposed guidance documents, and specifically note support for the creation of guidance documents on the following:

- Best practices for communication between IND sponsors and FDA.
- Use and submission of patient preference information to support regulatory decision making.
- Evaluation of efficacy in small patient populations using novel trial designs and statistical methods.
- Use of Bayesian methodology in clinical trials of drugs and biologics.
- Leveraging prior knowledge (both proprietary and public) in chemistry, manufacturing, and controls (CMC), nonclinical, and clinical data across therapeutic contexts.
- Updating the *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions* guidance documents to include additional information regarding post-approval requirements (including RWE) and CMC readiness. We respectfully request that this update include additional examples and clarity regarding acceptable parameters for CMC in the post-approval setting to fulfill such requirements.
- Common questions and answers regarding gene and cell therapy development. ASGCT looks forward to participation in the public meeting to inform the development of this guidance, and respectfully requests that the agency consider the following topics:
    - 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 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.
    - 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 looks forward to participating in the RFI to identify additional priority areas for guidance development as proposed in the commitment letter.

Focusing on Chemistry, Manufacturing, and Controls (CMC) Data

Several factors contribute to the frequent compression of manufacturing development timelines for gene and cell therapies. Development of these therapies is often accelerated due to early efficacy in serious diseases with unmet medical need. In

addition, the complexity of these products requires additional manufacturing development, while less prior CMC knowledge exists to leverage in development of these products compared to small molecules and traditional biologics. As a result, CMC development is inevitably continuous throughout the duration of clinical studies.

Given these distinct differences from other products, ASGCT is pleased that the commitment letter focuses on CMC data and the outsized role it plays in the development and review of cell and gene therapies. We strongly support the inclusion of the following goals:

- Establishment by FDA (CDER and CBER) of a "CMC Development and Readiness Pilot" to put a risk-based approach to CMC development into action for products intended to treat serious diseases or conditions that have an unmet medical need. The pilot will offer participants two additional Type B meetings focused on CMC issues and increased communication regarding the appropriate timing (including post-market) of information submission. This pilot includes a public disclosure requirement to help inform the field more broadly, which ASGCT believes is critical to long-term success in aligning CMC and clinical development timelines.
- Developing a strategy document incorporating lessons learned from the pilot and public meetings.
- Conducting a third-party assessment of current CMC practices to determine best practices and areas for improvement.
- Updating the MAPPs to improve communication regarding quality-related information and issuing a new MAPP on "approaches to address CMC challenges for CDER-related products with accelerated development timelines…"

ASGCT appreciates your consideration of these comments and looks forward to continued partnership with the agency. If you have any questions, please contact Betsy Foss-Campbell, Director of Policy and Advocacy, at bfoss@asgct.org.

Sincerely,

David M. Barrett, JD
Chief Executive Officer