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Dear Chairman Pallone, Ranking Member McMorris-Rodgers, Chairwoman Murray, and Ranking Member Burr,

Federico Mingozzi, Ph.D.
Spark Therapeutics

Maria-Grazia Roncarolo, M.D.
Stanford University

Rayne Rouce, M.D.
Baylor College of Medicine

Matthew Wilson, M.D., Ph.D.
Vanderbilt University

The American Society of Gene and Cell Therapy (ASGCT) writes to express our strong support for the reauthorization of the Prescription Drug User Fee Act (PDUFA) for fiscal years (FYs) 2023 through 2027 by September 30. ASGCT is a nonprofit professional membership organization comprised of more than 4,800 scientists, physicians, clinicians, 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.

Editor-In-Chief

Roland Herzog, Ph.D.
Indiana University

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 PDUFA

CEO

David M. Barrett, J.D.

VII performance goals letter (“commitment letter”, “the letter”) includes many provisions that will improve and adapt policies to take into account the unique attributes of these therapies.

ASGCT supports the commitment letter as shared with Congress and is eager to assist your Committee’s work toward PDUFA VII reauthorization. Below we detail the specific provisions of the commitment letter that support a clear and predictable path to market for these transformative products, in order to demonstrate how a timely reauthorization of PDUFA will help to facilitate genetic and cellular therapy development from early basic research to late stage and post-marketing assessment.

Bolsters 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.

The commitment letter establishes a goal to hire 228 new FTEs in CBER, nearly 65% of the total new FTEs supported by PDUFA VII. The specific objective of these new staff is 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 added staff attention is critical to successfully bring new gene and cell therapies to patients and will enable the agency to be a partner in realizing the promise of these technologies.

Enhancing Regulatory Predictability by Improving Engagement and Communication

The 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 are both critical steps for cell and gene therapy developers.

Receiving rapid responses to regulatory questions is essential to timely development programs. The establishment of Type D meetings would afford sponsors the opportunity to receive feedback within 50 calendar days to “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.

INTERACT meetings are especially important to sponsor 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 know from our members that this has not been the case in practice. Especially during the COVID-19 pandemic, INTERACT meetings have been denied or

cancelled, and in many cases where meetings have been substituted with written responses, the responses are inadequate to answer the questions posed. The commitment letter imposes a formal goal of holding INTERACT meetings within 75 calendar days of request. We also believe that the new scope of INTERACT to focus on truly challenging scientific and regulatory issues in early-stage development, and leaving specific questions in this stage to the newly created Type D meeting, will allow better utilization of FDA resources and greater clarity for developers.

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, can help the Agency and developers address problems earlier in development, course correct, and achieve better outcomes for patients.

Expanding Guidance for Industry

Guidance for industry documents help clarify development challenges for gene and cell therapies. When developed and implemented, guidances can be extremely helpful for in clarifying regulatory pathways and decreasing uncertainty. While intended for an industry audience, ASGCT's academic researchers embarking on basic, translational, and early-phase clinical trials research projects also benefit from understanding FDA views, 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.

The commitment letter includes many proposed guidance documents, but we specifically note the impact to the cell and gene therapy research community of:

- 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), non-clinical, 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.
- Common questions and answers regarding gene and cell therapy development.

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

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, manufacturing process improvements may occur at any time in product development, and in many gene and cell therapy development programs final CMC processes are set during late stages after demonstration of early clinical benefit and optimizing manufacturing processes.

Given these distinct differences, the commitment letter takes steps to recognize the outsized role CMC data play in the development and review of cell and gene therapies through the following goals:

- Updating FDA's Manuals of Policies and Procedures (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..."
- Conducting a 3rd party assessment of current CMC practices to determine best practices and areas for improvement.
- Establishment 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.

ASGCT appreciates your consideration of these comments and work towards a timely reauthorization. If you have any questions or if ASGCT can be a resource to you as you consider how the PDUFA VII agreement will impact the cell and gene therapy community, please contact Christina Mayer, Senior Manager of Government Affairs, at cmayer@asgct.org.

Sincerely,



David Barrett
Chief Executive Officer