American Society of Gene + Cell Therapy

January 20, 2023

The White House
ATTN: OSTP
1600 Pennsylvania Ave NW
Washington, DC 20500

RE: Comments for Docket No. 2022-27600, "Request for Information; National Biotechnology and Biomanufacturing Initiative."

Dear Sir or Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on this important request for information. ASGCT is a nonprofit professional membership organization comprised of more than 5,800 scientists, physicians, clinicians, and other professionals working in gene and cell therapy in settings such as universities, hospitals, and biotechnology companies.

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. 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 Society appreciates the willingness of the Office of Science and Technology Policy (OSTP) to hear from stakeholders about ways to improve biotechnology and biomanufacturing policies to advance innovative health solutions.

General Comments

ASGCT supports OSTP's efforts to gather information on biotechnology and biomanufacturing to achieve medical breakthroughs, improve health outcomes, and reduce the overall burden of disease. These efforts are in alignment with ASGCT's strategic vision to be a catalyst for bringing together scientists, physicians, patient advocates, and other stakeholders to transform the practice of medicine by incorporating the use of genetic and cellular therapies to control and cure human disease.

The concept of gene therapy was introduced in the late 1970s after the development of recombinant DNA technology. After the development of basic science and technology for gene transfer into patient's cells, the first gene therapy trial on humans was performed in 1990 by researchers at the National

Institutes of Health. A four-year-old girl was treated for adenosine deaminase deficiency (ADA), a rare genetic disease in which children are born with severe immunodeficiency and are prone to repeated serious infections. Cell and gene therapy products are often developed to treat rare diseases, many of which have small patient populations and disproportionately affect minority populations.

Presently, approved for clinical use globally there are: 24 gene therapies (including genetically modified cell therapies); 21 RNAs; and 60 non-genetically modified cell therapies. The development pipeline for these therapies is robust, with 3,726 therapies in development ranging from preclinical through pre-registration trials. Of those, 2,053 are gene therapies (including genetically modified cell therapies such as CAR T cell therapies) accounting for 55% of therapies, 827 are non-genetically modified cell therapies, accounting for 22% of therapies, and the remaining 23% of the pipeline is RNA therapies. The promise of these therapies to transform the lives of patients, and their families, is enormous and the Society looks forward to working with OSTP to advance the goals of the Biotechnology and Biomanufacturing Initiative (NBBI).

In addition to these general comments, ASGCT provides the below specific comments for OSTP's consideration. ASGCT highlights the timing of this RFI and notes that its issuance parallels similar legislative efforts in Congress. ASGCT recommends OSTP consider recently passed legislation when preparing recommendations to ensure they are aligned with any new statutory provisions.

Specific Comments

Harnessing Biotechnology and Biomanufacturing R&D to Further Societal Goals

1. ASGCT suggests improvements to how the Food and Drug Administration (FDA) handles "platform technologies," which are a critical component to realizing the full potential of gene and cell-based therapies. Platform technologies have the potential to streamline gene and cell therapy development by allowing a single technology, such as a nucleic acid sequence or a vector, to be utilized across multiple products. Without an increased ability to engage with the FDA to assess product platforms and rely on data previously generated for earlier drugs on the same platform, the likelihood of translation from bench to bedside is drastically reduced.

   ASGCT supports reforms outlined in Title II of Division FF of the Consolidated Appropriations Act of 2023. Specifically, Section 2503 which creates a platform technology designation program. This section defines a "platform technology," outlines how additional assistance from FDA in product development (like Breakthrough Designation) should be given to these products, and allows for streamlined manufacturing changes among drugs built on the same platform.

   Under this new provision of law, once a product using a designated platform is approved, follow-on products will now be explicitly permitted to reference data from the previous application, and manufacturing changes to the platform can be done in a single supplemental application for all drugs on such platform. As outlined in Title III of Division

FF of the Consolidated Appropriations Act of 2023 (referred to as the Food and Drug Omnibus Reform Act or "FDORA"), FDA is required to issue a guidance document on implementing the designation within a year.

We believe that this new pathway is a critical component of harnessing biotechnology to alleviate human disease, consistent with the President's Executive Order on Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy. ASGCT encourages OSTP to work with the FDA on the implementation of this new provision of law, including the draft guidance document required to be issued by the end of 2023, to ensure that it meets the needs of the expanding bioeconomy.

2. ASGCT strongly supports funding for the development of medical breakthroughs through the National Institutes of Health and ARPA-H. The Society believes that ARPA-H could be especially helpful for advancing gene and cell therapies. We appreciate that the Biden Administration noted new manufacturing processes to create patient-specific T-cells to destroy malignant cells as an example of a potentially transformative project that ARPA-H could drive.[1] Improvements in manufacturing of gene and cell therapies could result in both greater manufacturing capacity, and increased efficiencies.

   The Society recommends that, while not mandated by Congress, ARPA-H collaborate with the FDA throughout product and innovation development to be sure its programs are generating the data needed to meet regulatory requirements or to alert the agency of potential new authorities it might need. In addition, we encourage swift implementation of statutory changes to the Food Drug and Cosmetic Act that were contained in the Consolidated Appropriations Act of 2023 that will enable the type of breakthrough research ARPA-H is charged with funding to become treatments for patients. As referenced throughout the RFI, this should include improvements to how FDA handles platform technologies and advanced manufacturing technologies.

Building a Vibrant Domestic Biomanufacturing Ecosystem

6. ASGCT supports reforms outlined in FDORA. Specifically, Section 3213 creates an advanced manufacturing technologies designation program that establishes a new product-agnostic review pathway that allows a technology to be assessed and "designated" for a specific context of use before it is included as part of a drug application, de-risking the adoption of these technologies.

   This codifies a recommendation from the 2021 National Academies of Medicine which suggested that FDA implement a pathway to review novel advanced manufacturing

[1] Lander E & Collins F. (2021). *Advanced Research Project Agency for Health (ARPA-H): Concept Paper [draft].* https://www.whitehouse.gov/wp-content/uploads/2021/06/ARPA-H-Concept-Paper.pdf

technologies separately from individual products.[2] Allowing for the use of novel, or established, technologies to be used in a unique way to produce drugs could help greatly expand manufacturing capacities and lower costs. Efficiency and capacity improvements are needed in gene and cell therapy manufacturing technologies as more products receive FDA approval to meet real-world patient demand. This pathway could help those advances become a reality.

Like the platform therapies provision in Section 2503, we believe that this new pathway is a critical component of harnessing biotechnology consistent with the President's Executive Order on Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy. While there are many innovative biological manufacturing approaches in development in the US, they will never reach widespread adoption unless this de-risking mechanism is deployed successfully. ASGCT encourages OSTP to work with the FDA on the implementation of this new provision of law, including participation in the public meeting and draft guidance composition due this year, to ensure that it meets the needs of the expanding bioeconomy.

In addition, ASGCT believes it is imperative that FDA fully embrace the Chemistry and Manufacturing Controls (CMC) Readiness Pilot which was included as part of the Prescription Drug User Fee Program (PDUFA VII) commitment letter. The CMC pilot is intended to help both FDA and product sponsors communicate about expectations earlier in development, as CMC disagreements and hurdles are common and have delayed the development and approval of many gene therapies. The President's Council of Advisors on Science and Technology (PCAST) report to the President on Biomanufacturing to Advance the Bioeconomy pursuant to the same Executive Order focuses on the regulatory uncertainty for certain bioproducts that fall under multiple jurisdictions (or the cracks in between). The report states, "the regulatory approval pathway is clearer for medicines than for other bioproducts. For example, if a new bioproduct is intended to be a drug for human use, it falls under FDA's regulatory authority and is assessed for its safety and efficacy." While this is true in comparison to food or pesticide products, the regulatory uncertainty regarding the CMC standards for gene and cell therapies is still great, even under the sole jurisdiction of the FDA's drug authorities. ASGCT encourages OSTP to incorporate the need for CMC certainty from FDA as a part of the Administration's broader biomanufacturing goals.

International Engagement

16. The use of real-world evidence (RWE) is especially important to measure durable treatment effects for gene and cell therapies that may go through expedited pathways at FDA such as marketed breakthrough, fast track, and accelerated approval. ASGCT

[2] National Academies of Sciences, Engineering, and Medicine. (2021*). Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations*. Washington, DC: The National Academies Press. https://doi.org/10.17226/26009

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supports the Advancing Real-World Evidence (RWE) Pilot Program as outlined in PDUFA VII.

The Society also supports changes in Section 3629 of FDORA which instruct the FDA to update existing RWE-related guidance documents or generate new draft guidance based on the Advancing RWE Pilot Program. ASGCT encourages FDA's updated guidance to provide for the use of RWE to support the post-market assessment of therapies that have received regenerative medicine advanced therapy (RMAT) designation. While products with RMAT designation are currently the only products that are statutorily eligible to use real-world evidence to fulfill post-marketing obligations required by the accelerated approval expedited pathway, developers are still in need of clarity regarding the Agency's expectations. The current RMAT guidance mentions that FDA's Center for Biologics Evaluation and Review (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. To that end, we suggest FDA also update the existing RMAT guidance; additional examples and clarity regarding acceptable parameters in the post-approval setting would be beneficial.

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

Sincerely,

David Barrett, J.D.

Chief Executive Officer