American Society of Gene + Cell Therapy

October 4, 2024

The Honorable Brad Wenstrup, DPM
United States House of Representatives
2335 Rayburn House Office Building
Washington, DC 20515

The Honorable Blake Moore
United States House of Representatives
1320 Longworth House Office Building
Washington, DC 20515

The Honorable August Pfluger
United States House of Representatives
1531 Longworth House Office Building
Washington, DC 20515

The Honorable Mark Green, MD
United States House of Representatives
2446 Rayburn House Office Building
Washington, DC 20515

Dear Representatives Wenstrup, Moore, Pfluger, and Green,

The American Society of Gene and Cell Therapy (ASGCT) welcomes the opportunity to respond to your request for information on solutions to secure and enhance domestic medical supply chains. ASGCT is a nonprofit professional membership organization comprising more than 6,300 scientists, physicians, patient advocates, and other professionals. Our members work in a wide range of settings including universities, hospitals, government agencies, foundations, and biotechnology and pharmaceutical companies. Many of our members have spent their careers in this field performing the underlying research that has led to the United States' robust pipeline of transformative therapies

A core portion of ASGCT's mission is to advance the discovery and clinical application of cell and gene therapies (CGTs) to alleviate human disease. To that end, ASGCT supports policies that foster the adoption of, and patient access to, new therapies, which thereby encourage continued development of these innovative treatments. We commend efforts to strengthen medical supply chains, ensure broad patient access to advanced therapies, and boost biomedical research.

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Currently, there are over 4,000 gene, cell, and RNA therapies in development[1] ranging from preclinical through preregistration (meaning a sponsor has requested but not yet received regulatory approval for the product). The pipeline includes over 2,000 gene therapies (including genetically modified cell therapies such as CAR T-cell therapies). Globally, 32 gene therapies have been approved.

While these therapies have great promise to alleviate and cure diseases, there are regulatory and manufacturing challenges. As more products receive Food and Drug Administration (FDA) approval, sponsors must be able to scale up and streamline development and manufacturing processes to meet patients' needs. Our comments below focus on several ongoing FDA initiatives that, if implemented with the correct vision, hold great promise to advance the development and adoption of new technologies in the US. The changes needed to meet this promise are granular but critical to capture the opportunity.

If you have questions about any of the information provided below, please contact Margarita Valdez Martínez, Chief Advocacy Officer, at mvaldez@asgct.org.

Sincerely,

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

Request for Information on Policy Solutions to Secure and Enhance Domestic Medical Supply Chains

6. Insight into the main barriers to domestic production (ex. environmental or FDA regulations, permitting barriers, workforce challenges, etc.) and what policy options Congress has to alleviate them:

How do current U.S. regulations impact your ability to onshore or diversify your supply chain? Are there specific regulatory changes, or flexibilities, that could facilitate these efforts?

ASGCT recognizes the challenges of managing complex global supply chains. We do not have a position at this time on specific policy proposals to manage those challenges. However, the

[1] American Society of Gene and Cell Therapy, Citeline (July 2024). *Gene, Cell, & RNA Therapy Landscape: Q1 2024 Quarterly Data Report.* https://www.asgct.org/global/documents/asgct- citeline-q2-2024-report.aspx

cell and gene therapy (CGT) field faces unique regulatory hurdles compared to traditional small-molecule therapies in the United States. ASGCT members share a core goal of delivering safe, effective, potentially curative therapies to patients who often have no other options. As the field grows, managing production at scale, while maintaining product-specific safety and efficacy, is increasingly critical. However, this need for precise product control often results in complex regulatory and operational requirements that can delay development and limit capacity.

Advances in manufacturing processes have improved production, control, and characterization of CGT products. However, regulatory inconsistencies in the Food and Drug Administration's (FDA's) approach to analytical testing have caused development delays, including clinical holds. While the Society appreciates FDA's ongoing efforts to develop a cohesive strategy to address the complexities associated with evaluating and assuring CGT quality, recent draft guidance documents[2] do not provide sponsors the clarity and direction needed to advance the CGT field and are often inconsistent with the stated goals of agency leadership.

FDA uses the term "potency" to refer to the specific ability or capability of a product to effect a given result. Assays are tests designed to assess various properties - including potency. For CGTs, the link between product characteristics and clinical performance often remains product specific. Potency assays (potency tests) play a key role in informing this link and proving safety and efficacy of therapies.

There are technical and scientific challenges associated with potency test design, execution, and analysis. Compounding these challenges are regulatory inconsistencies in the agency's approach to potency testing. These inconsistencies have caused development delays for therapies which often have high unmet needs. The Society has provided robust feedback to FDA[3] that emphasizes the importance of phase appropriate requirements of potency assay requirements.

8. Current programs that can be utilized to assist in catalyzing new innovative technologies for advanced manufacturing:

The adoption of more standardized platforms across drug development programs will reduce burden for both developers and regulators alike, and reduce uncertainty in new products for patients. Congress provided FDA with critical tools to catalyze the development and adoption of new innovative technologies for advanced manufacturing in the Food and Drug Omnibus Reform Act (FDORA) in 2022. This legislation created both the Advanced Manufacturing Technologies (AMT) Designation Program and the Platform Technology Designation Program. However, notwithstanding the publication of some draft and final guidances as well as positive public commentary from agency leadership, there are several potential benefits of these laws that remain unaddressed by the Agency.

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[2] Food and Drug Administration (2023). *Potency Assurance for Cellular and Gene Therapy Products: Draft Guidance for Industry.* https://www.fda.gov/media/175132/download

[3] American Society of Gene and Cell Therapy (2024). *Potency Assurance for Cellular and Gene Therapy Products Guidance* [Regulatory Comment]. https://www.asgct.org/publications/news/april-2024/society-response-fda-potency-assurance-for-cellula

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FDA Advanced Manufacturing Technologies (AMT) Designation Program

As additional cell and gene therapy products receive FDA licensure, improvements will be critical to meet real-world patient demand, bring manufacturing closer to the bedside, and reduce production costs. New innovations in manufacturing have lagged behind other areas in the field. One reason for this delay is lack of market incentive to develop new CGT products or manufacture approved ones using novel technologies with inherent regulatory risk - whether perceived or real. The National Academies of Medicine published a report in 2021[4] which suggested that FDA implement a pathway to review novel advanced manufacturing technologies separately from individual products to de-risk their use in product applications. ASGCT appreciates[5] that Congress established the Advanced Manufacturing Technologies (AMT) Designation Program in FDORA.[6] If implemented properly, the program could help address the challenges currently facing the manufacturers and sponsors of CGTs.

FDA has continuously noted that bespoke manufacturing processes in the CGT field lead to long and complex Chemistry, Manufacturing, and Controls (CMC) reviews – leading to high regulatory burden on both the agency and CGT developers. ASGCT supports efforts to encourage the development and adoption of more standardized, internationally harmonized manufacturing practices in the industry. While the draft guidance is a useful primer for the AMT pathway, it unduly limits the scope and potential of the program and lacks the level of detail necessary for AMT development including:

Reliance on Legacy Programs
While the Society supports the goals of the CBER Advanced Technologies Team (CATT), the AMT program was intended to serve a separate purpose – that of influencing market behavior. We are concerned that the agency has suggested that, in most cases, CATT interaction should happen prior to AMT, and AMT eligibility should align with CATT eligibility. This limits the ability for technologies to qualify for AMT, both definitionally and logistically given the existing limitations and bottlenecks associated with CATT. FDORA made no mention of the CATT program and FDA should remove the *de facto* links.

"Graduation"
FDA proposes to "graduate" technologies and remove the designation after the agency gains "significant experience". However, this concept runs counter to the underlying law and the goals of the program. CBER leadership often speaks to the need for greater standardization in the manufacturing of CGT products to reduce the burden of review. If an AMT was widely adopted, it would inherently consume fewer agency resources because reviewers would be familiar with the

[4] National Academies of Sciences, Engineering, and Medicine. (2021). *Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations*. https://doi.org/10.17226/26009
[5] Flotte, T., American Society of Gene and Cell Therapy (2024). *House Committee on Energy and Commerce: Legislative Proposals to Support Patients with Rare Disease* [Written Testimony]. https://www.asgct.org/global/documents/advocacy/testimony-of-terence-flotte-md-on-behalf-of-asgct.aspx
[6] United States Congress (2023). *Consolidated Appropriations Act* [H.R.2617]. https://www.congress.gov/bill/117thcongress/house-bill/2617

technologies being used. In this vein, the bottlenecks that are currently caused by bespoke CMC approaches would be alleviated, while simultaneously helping to achieve the goals of the program. Removing the designation meant to serve as a market driver to adopt standardized manufacturing options reduces the potential benefit of the program.

Platform Technology Designation Program

The Platform Technology Designation Program,[7] also created under FDORA, offers a potential pathway for manufacturers to streamline CGT development by adopting standardized platforms for multiple products. Platform technologies, such as viral vectors or nucleic acid sequences, allow manufacturers to leverage existing data across multiple products, reducing the regulatory burden and speeding patient access to transformative therapies. This program would allow those who are granted the designation to receive additional assistance from FDA, similar to what's available for Breakthrough Therapies.[8] We believe this pathway could, if implemented properly, encourage greater adoption of platform approaches in the industry.

Given the great potential of this specific pathway we encourage FDA to embrace the spirit of Congressional intent by addressing several issues in the implementing guidance,[9] including:

Post Approval Changes

Regarding the treatment of post-approval changes to platforms across products, the current requirements for making changes after products are on the market were developed with small molecule chemistry in mind. However, for CGTs, manufacturing process improvements may occur at any time during product development, including post market. For many CGT development programs, process changes are made to scale up manufacturing during late stages after demonstration of early clinical benefit. In this respect, chemistry, manufacturing, and controls (CMC) data for gene and cell therapy products often come throughout the product lifecycle. The spirit of the program is intended to allow a single application for a major CMC change to a designated platform to facilitate, and permit, that change to be effectuated across all products using the platform. We urge that this single application provides a streamlined process and not simply an umbrella of what is essentially multiple individual applications as the draft guidance currently reads. As multiple gene therapies come to market on designated platforms, this program can enable the latest CMC learnings to be

[7] Food and Drug Administration (2024). *Platform Technology Designation Program: Draft Guidance for Industry.* https://www.fda.gov/media/178938/download

[8] Food and Drug Administration (2018). *Breakthrough Therapy Designation*. https://www.fda.gov/patients/fast-trackbreakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy

[9] American Society of Gene and Cell Therapy (2024). *Platform Technology Designation Program Guidance* [Regulatory Comment]. https://www.asgct.org/advocacy/policy-statement-landing/2024/platform-technology-designation-program-for-drug-d

applied across products to ensure timely patient access to these transformative therapies.

Definition of Significant Efficiency
The statute requires that applicants for the designation program submit information to the agency to "justify why the use of the platform technology *has a reasonable likelihood to* bring significant efficiencies to the drug development or manufacturing process and to the review process for the application". However, in the implementing guidance, FDA changes the standard to require applicants justify why a technology WILL bring significant efficiencies. The types of data and information to support a reasonable likelihood standard and a definitive effect are different, and it would be nearly impossible to prove an efficiency in the review process for the first follow on product (when the platform is initially eligible) before the first follow on is approved.

Additionally, FDA defines "significant efficiency" as "…help streamline drug development or manufacturing and review". However, an increased efficiency to a sponsor may not increase efficiencies for the agency, and vice versa. Information on how process improvements to either the sponsor or agency will be measured is a critical piece to implementation that has been overlooked by FDA.

Drug Master Files

In the Society's comments to FDA regarding both the AMT and Platform Designation programs, we reiterated concerns regarding the final rule *Biologics License Applications and Master Files* (89 FR 9743) ('BLA DMF rule').[10] The BLA DMF rule codified FDA's policy that BLAs cannot incorporate information about drug substance, drug intermediate or drug product (DS/DI/DP) through referencing a drug master file. This blanket rule does not address situations such as the Designation programs which are statutorily directed to allow the referencing of data and will limit the success of these endeavors.

In the AMT program draft guidance, FDA states that a BLA "*should not incorporate by reference a designated AMT, including by referencing a DMF that contains a designated AMT*" because "*a BLA holder is expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license*". This is directly contrary to the authorizing statute, which "*allow[s] the holder of an advanced technology designation, or a person authorized by the advanced manufacturing technology designation holder, to reference or rely upon, in an application submitted under Section 505* ***or Section 351 of the Public Health Service Act*** *[emphasis added], including a supplemental application, data and information about the designated advanced manufacturing technology for use in manufacturing drugs in the same context of use for which the designation was granted*." This policy, if finalized, would be against

[10] American Society of Gene and Cell Therapy (2024). *Advanced Manufacturing Technologies Designation Program Guidance* [Regulatory Comment]. https://www.asgct.org/advocacy/policy-statement-landing/2024/advanced-manufacturing-technologies-designation-pr

the direct letter of the law, and against the intent of AMT designation to speed progression of standardized and novel manufacturing methods for CGTs to market

The implementing guidance of the Platform designation also cites the BLA DMF rule as the reason that, for BLAs of products based on a designated platform, all information on the platform must be submitted with the BLA and cannot cite a DMF. Eliminating the ability for BLAs to reference DMFs that contain information about a designated platform technology diminishes the value of the designation and keeps the reviewer burden high – as the information already reviewed and designated is not clearly delineated.

We strongly suggest that that FDA revise the 2019 "Drug Master Files: Draft Guidance for Industry" and the BLA DMF rule to clarify that cross-referencing Master Files is permitted for holders of, or those with a right-of-reference to, an AMT-designated technology or platform technology in BLA applications.

9. What types of public-private partnerships could be most effective in accelerating the onshoring of pharmaceutical manufacturing?

To accelerate the delivery of safe and effective treatments, ASGCT supports policies incentivizing the development of platform technologies and innovative manufacturing approaches. Public-private partnerships fostering these priorities, like the Bespoke Gene Therapy Consortium,[11] are critical for field-wide solutions. ASGCT also encourages regulatory agencies to facilitate the adoption of innovative statistical methods and novel trial designs suitable for small populations. Coordinated efforts between Congress, FDA, industry, and other stakeholders in this space are critical for bringing gene and cell therapies to patients more quickly.[12]

Congressional intent has been clear that reforms are needed to improve domestic manufacturing capabilities. ASGCT looks forward to working with your offices to ensure that the spirit of forward-thinking legislation is realized to foster greater manufacturing technology development and adoption in the US.

[11] National Institutes of Health (2024). *Accelerating Medicines Partnerships (AMP): Overview.* https://www.nih.gov/research-training/accelerating-medicines-partnership-amp
[12] American Society of Gene and Cell Therapy (2024). *Request for Information: Predecisional Draft National Centers for Advancing Translational Science Strategic Plan 2024- 2029* [Legislative Response]. https://www.asgct.org/advocacy/policy-statement-landing/2024/comments-on-predecisional-draft-ncats-strategic-pl