November 12, 2024

Dockets Management Staff (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Comments for Docket No. FDA-2024-N-3945 "The Food and Drug Administration's Draft Strategy Document on Innovative Manufacturing Technologies"

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on FDA's strategy document regarding the implementation of innovative manufacturing technologies. ASGCT is a nonprofit professional membership organization comprised of more than 6,400 scientists, physicians, patient advocates, and other professionals working on cell and gene therapies (CGT) 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. Given this mission, we provide the following comments to ensure that FDA's strategy document supports the effective and efficient adoption of innovative manufacturing technologies.

General Comments

The CGT and RNA therapy landscape is experiencing significant growth and diversification, with more than 4,000 therapies currently in development across various stages. Gene therapies make up nearly half of this pipeline, with 2,042 therapies currently under development, including genetically modified cell therapies such as CAR-Ts.[1] The most commonly targeted

[1] American Society of Gene & Cell Therapy and Citeline. *Gene, Cell, + RNA Therapy Landscape Report: Q3 2024 Quarterly Data Report*. (2024). https://www.asgct.org/publications/landscape-report

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therapeutic areas for gene therapy development are oncology and rare diseases.

There are over 10,000 rare diseases,[2] up to 80% of which can be traced to mutations or changes in a single gene.[3] Gene therapy aims to address the underlying cause of disease, such as gene mutations, by adding new, activating, or silencing genetic material. As a result, breakthroughs in gene therapy are enabling patients with genetic diseases to live and thrive. Investments in rare disease research reflect the field's growing potential to address a wide array of diseases where few or no other treatments are available. As the pipeline expands, the demand for scalable and innovative manufacturing solutions is more critical than ever, requiring streamlined approaches to efficiently bring these transformative therapies to patients.

ASGCT appreciates the intent of FDA's *Draft Strategy Document on Innovative Manufacturing Technologies.* We believe that there are additional opportunities for the Agency to advance regulatory policies and processes in order to encourage the adoption of innovative and platform manufacturing technologies. While ASGCT appreciates FDA meeting the PDUFA VII goals of holding a public workshop and releasing the strategic plan, we encourage the Agency to consider leaning further into its authority to address barriers to the adoption of these technologies. We appreciate Agency leadership's vocal support for the need to standardize manufacturing approaches for gene therapies to reduce development risk and lower the review burden.[4] We believe FDA leadership and stakeholders can work together to ensure advances in CGT manufacturing will help address unmet patient needs.

The National Academies of Medicine (NAM) published a report in 2021 with the stated purpose to "identify emerging technologies—such as product technologies, manufacturing processes, control and testing strategies, and platform technologies—that have the potential to advance pharmaceutical quality and modernize pharmaceutical manufacturing in the next 5–10 years," and that "technical and regulatory challenges [should] be identified and suggestions provided to overcome the regulatory challenges."[5] The final report provided the field with a roadmap for overcoming challenges. ASGCT encourages the Agency to consider the full breadth of suggestions, and to incorporate the NAM's findings and strategies into the strategic plan.

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[2] National Center for Advancing Translational Sciences. (2023). *Our Impact on Rare Diseases*. https://ncats.nih.gov/research/our-impact/our-impact-rare-diseases

[3] Cowe, H., Moorthie, S., Petrou, M., Hamamy, H., Povey, S., et. al. (2018). Rare Single Gene Disorders: Estimating Baseline Prevalence and Outcomes Worldwide. *Journal of Community Genetics, 9*(4), 397-406. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6167259/

[4] Osman, M. (October 24, 2024). Marks Calls For Efficient Manufacturing To Cut Gene Therapy Cost**.** *Inside Health Policy.* https://url.us.m.mimecastprotect.com/s/txDhCyPxAZS91KlHZfpFxQ8d6 Article quote: "'The faster and the more efficiently you bring things through development, the lower cost there (is),' Marks told *IHP*. 'If you don't have to reengineer that whole process every time, but can just change a piece of it, that may make a big difference.'"

[5] 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

Strategy Document Comments

II. Background

A. Reflections on ETP and CATT (Lines 72-97)

The Society supports the goals of CBER's Advanced Technologies Team (CATT) and understands the value the program holds for sponsors and manufacturers. However, the Advanced Manufacturing Technologies (AMT) Designation Program was intended to serve a separate purpose. 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 "longer-than-desired review times" associated with CATT reviews - as noted in the strategy document. The Society notes that references to the CATT process were not included in the authorizing statute. We respectfully request greater clarity on the attributes of technologies that are appropriate for the CATT and AMT programs and request the removal of the tie between the programs' entry criteria as referenced in draft guidance[6] and inferred in the strategy document.

The Society supports FDA's efforts to harmonize regulatory expectations for innovative manufacturing technologies globally. Inconsistent requirements across regions create unnecessary barriers to technology adoption and delay patient access to transformative therapies. By formalizing collaboration with global regulators and expanding engagement with stakeholders, FDA can promote a unified approach that fosters innovation and accelerates global market readiness.

B. Other Considerations and Regulatory Challenges (Lines 114-118)

As noted in the strategy document, manufacturers are hesitant to develop novel manufacturing technologies "due in large part to commercial viability" and "uncertainty regarding the profitability of the research, adoption, and implementation of innovative manufacturing." ASGCT agrees with this assessment and believes the AMT pathway holds promise for overcoming barriers to advanced manufacturing technologies for CGTs.

New innovations in manufacturing have lagged behind other areas in the field. One reason for this delay is the lack of market incentive to develop new, or manufacture

[6] U.S. Food and Drug Administration. (2024). *Advanced Manufacturing Technologies Designation Program; Draft Guidance for Industry.* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/advanced-manufacturing-technologies-designation-program.

approved products, using a novel technology with inherent regulatory risk - whether perceived or real. The Society supported the AMT Designation Program in the Food and Drug Omnibus Reform Act (FDORA) in 2022.[7] ASGCT was pleased that, in alignment with recommendations in the NAM report with and congressional intent, FDA created a pathway to review novel advanced manufacturing technologies separately from individual products. This pathway has the potential to de-risk the use of novel manufacturing technologies in product applications and thereby address market incentives. The creation of a product agnostic pathway is an important step toward the field's adoption of new technologies. If implemented properly, the program could help address the challenges currently facing manufacturers and sponsors of drug products and CGTs.

FDA's position that financial and commercial barriers "lie outside FDA's purview" (lines 43-49) may not fully capture the potential influence FDA policies could have in reducing these barriers. Policies such as data exclusivity periods and priority review vouchers have the potential to address market challenges that hinder the adoption of new technologies. While the AMT Designation Program was designed to address the development and standardization of advanced manufacturing technologies, it also holds promise for easing market barriers and supporting broader adoption.

C. AMT Designation (Lines 134-157)

The AMT pathway holds great promise for the CGT field; a collaborative approach toward the program's implementation is essential to its success. We are concerned that if finalized and implemented as is, the draft guidance could limit the utility of the pathway for BLA holders and therefore for the CGT field as a whole. The Society urges FDA to correct the imbalance of the AMT pathway between CBER and CDER in the final guidance. The Society encourages FDA to revise the strategic plan and embrace this pathway as a way the Agency can address market barriers and barriers to innovation.

In addition, the Society requests additional information on how FDA intends to assess "substantial improvement" of a novel technology, and if "the innovative technology is applicable to commercial products and would be scalable, even if it is still in an early development phase." This information is necessary to understand which novel technologies qualify for the pathway, and to provide certainty to manufacturers who have concerns about investing in research and about market viability.

[7] U.S. Congress. (2023). *Consolidated Appropriations Act (H.R.2617).* https://www.congress.gov/bill/117th-congress/house-bill/2617

As noted by panelists during the public workshop "Advancing the Utilization and Supporting the Implementation of Innovative Manufacturing Approaches,"[8] clarity is needed regarding the "expedited development and review" designation benefits associated with the AMT Designation Program. ASGCT appreciates that FDA aims to provide "timely advice to, and interactive communication with"[9] AMT developers requesting designation. To further meaningful communication, we respectfully request that the final AMT guidance reflects that "interactive communication" involves, at minimum, one "in person" meeting.

III. Action Plan Summary

3. Implement the Advanced Manufacturing Technology Designation Program (Lines 248-257)

The Society submitted comments on the draft guidance[10] and explicitly provided feedback on "the data and information needed to support and obtain a designation." ASGCT requests clarification regarding the use of a "model drug" to understand the proposed AMT's parameters. In the context of CGT development, it is unclear what the Agency views as a model drug, which is also referred to in the draft guidance as a "developmental candidate molecule" and a "representative drug." As CBER products are less likely to be well-characterized, specifying whether models can be representative of a class, rather than only drugs under active development, would help preserve the product-agnostic intent of the pathway.

Furthermore, in alignment with other pathways at the Agency, we request that a publicly available CBER standard operating policy and procedure (SOPP) be developed for the review process of an AMT designation request. The SOPP should include information on the composition of the review committee(s), the role of subject matter experts (SMEs), the selection process for and duties of the designated lead, timelines for data requests, meeting formats, and the level of involvement of senior FDA managers and other Agency staff.

Additional Comments

[8] Duke Margolis Institute for Health Policy. (2023). *Advancing the Utilization and Supporting the Implementation of Innovative Manufacturing Approaches.* https://healthpolicy.duke.edu/events/advancing-utilization-and-supporting-implementation-innovative-manufacturing-approaches

[9] U.S. Food and Drug Administration. (2024). *Advanced Manufacturing Technologies Designation Program; Draft Guidance for Industry*. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/advanced-manufacturing-technologies-designation-program

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

In addition to the above comments, ASGCT would like to highlight select comments that were previously submitted regarding the *Advanced Manufacturing Technologies Designation Program; Draft Guidance for Industry*. We respectfully suggest the following:

- **Lifecyle**
  The concept of "graduating" technologies from the AMT designation warrants reconsideration. Eliminating the designation as technologies become more familiar could disincentivize manufacturers from adopting standardized approaches. A mature regulatory state does not necessarily mean the technology no longer benefits from the AMT Designation Program. We suggest a “Graduated AMT” status, allowing advanced technologies to retain recognition while reflecting the Agency’s growing familiarity. This adjustment would balance resource allocation and drive continued innovation.

- **BLA DMF Rule**
  We would also like to reiterate comments previously submitted in commentary to both the “*Advanced Manufacturing Technologies Designation Program; Draft Guidance for Industry*” and the “*Platform Technology Designation Program for Drug Development; Draft Guidance for Industry*”[11] dockets regarding the final rule *Biologics License Applications and Master Files (89 FR 9743)* (‘BLA DMF rule’).[12] The BLA DMF rule codifies FDA’s policy that BLAs cannot incorporate information about drug substance, drug intermediate or drug product through referencing a drug master file. Both guidance documents implementing novel congressional directives cite this rule as the reason that, notwithstanding if a BLA products utilizes an AMT designated manufacturing method or is based on a designated platform, all information must be submitted with the BLA and cannot cite a DMF. This is contrary to the letter and spirit of these laws.

  FDA has noted that bespoke manufacturing processes in the CGT field lead to long and complex CMC reviews – leading to a high regulatory burden on both the Agency and CGT developers. Eliminating the ability for BLAs to reference DMFs that contain information about a designated AMT, or platform technology, could maintain a high reviewer burden – as the information already reviewed and designated is not clearly delineated. This could disincentivize the adoption of an AMT or platform.

  We urge FDA again to reexamine the BLA DMF rule in the context of CGTs utilizing designated platforms or advanced manufacturing technologies and reform the rule to be a forward-looking policy that facilitates, instead of hinders, the work FDA states it wants to advance.

[11] American Society of Gene & Cell Therapy. (2024). *Society Comments: Platform Technology Designation Program for Drug Development.* https://www.asgct.org/advocacy/policy-statement-landing/2024/platform-technology-designation-program-for-drug-d.
[12] *Biologics License Applications and Master Files, 89 Fed. Reg. 9743*. (February 15, 2024) https://www.govinfo.gov/app/details/FR-2024-02-12/2024-02741

The Society appreciates FDA's commitment to advancing innovative manufacturing technologies and recognizes the importance of establishing pathways that can address the unique needs of the CGT field. Continued focus on regulatory clarity and flexibility will be crucial as the field grows and diversifies, enabling standardized approaches that, in time, reduce the scientific uncertainty and regulatory burden of each new product. To achieve these shared goals, we believe additional strategic adjustments are essential to foster the adoption of advanced manufacturing technologies, streamline regulatory processes, and, most importantly, expand patient access to potentially lifesaving therapies.

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

Sincerely,

David Barrett, J.D.
Chief Executive Officer