American Society of Gene + Cell Therapy

July 7, 2023

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

RE: Comments for Docket No. FDA-2023-N-1259 "Advancing the Utilization and Supporting the Implementation of Innovative Manufacturing Approaches; Public Workshop; Request for Comments".

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to submit comments on the public workshop "Advancing the Utilization and Supporting the Implementation of Innovative Manufacturing Approaches", held on June 8, 2023. ASGCT is a nonprofit professional membership organization comprised of 6,000 scientists, physicians, and other professionals working in cell and gene therapy (CGT) in settings such as universities, hospitals, government agencies, foundations, 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. 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. ASGCT appreciates the opportunity to comment on regulatory strategies to support the utilization of advanced manufacturing technologies for drugs and biological products and the implementation of the new Advanced Manufacturing Technologies (AMT) Designation pathway.

Because of the complexities of CGT products, manufacturing often develops in parallel with clinical development, with sponsors making changes to improve yield and efficacy based on early clinical findings. This development process has led the CGT field to be comprised of products with complicated bespoke manufacturing approaches and little process standardization between products and across the industry. Not only does this strategy slow overall development for the sponsor, but it also takes immense Agency resources to provide feedback on and review completely variable chemistry, manufacturing, and controls (CMC) data for each product. CBER Director Marks has highlighted this issue numerous times and advocated for greater efforts to harmonize manufacturing approaches.

Advanced manufacturing technologies, including platforms, could play a crucial role in streamlining the development process for CGTs where CMC remains the bottleneck in the CGT development. Greater adoption of AMTs would allow

developers to rely on previous data and speed the development of desperately needed therapies for populations who often have few or no treatment options by moving away from complex, bespoke manufacturing processes that inhibit the availability of drug product developers to get all patients high quality, safe, and efficacious drug products. In short, a regulatory process to review AMTs that is clear and predictable to developers would be useful for scalability, consistency, and cost of development, among other benefits. This would increase the likelihood of translation from CGT product development to bedside in order to ensure timely patient access.

CGT manufacturing technologies need improvement to increase efficiency and capacity during the drug development process. This is critical, as more products continue to enter the pipeline and receive FDA licensure, and approval, to meet real-world patient demand. However, the adoption of AMTs has been slow across the industry but especially for biologic products like CGTs. There is a lack of market or regulatory incentive for developing standardized approaches when compared to a bespoke process. In addition, advancing a novel manufacturing technique with a specific product simply adds to the regulatory risk. While a bespoke manufacturing approach with established technologies may be burdensome, complex, and inefficient, it carries less (or is perceived to carry less) regulatory risk than advancing a new approach. The National Academies of Medicine published a report in 2021 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.[1]

We are pleased the Consolidated Appropriations Act 2023 included language to establish a pathway to review manufacturing technologies, including those for gene and cell therapies.[2] This legislation will encourage innovation in the contract manufacturing sector as well as incentivize sponsors to develop and use designated AMTs across portfolios. We recommend that the agency consider the following key pieces of the legislation and intent when developing the draft guidance:

- *Product agnostic:* The AMT designation pathway is distinct from other FDA designations in that it does not require the applicant to be a product sponsor, nor does it require a connection to a specific product. This difference will allow for early innovation and provide sponsors with the assurance that FDA is familiar with a technology before adopting it into a development program that is aligned with the AMTs context of use. This program is a similar construct to FDA's biomarkers program.

- *Early interaction:* One comment at the public meeting suggested a sponsor might seek this designation during the final stages of product development. While this strategy is possible under the construction of the statute, the power of the AMT program for CGTs will be for sponsors to adopt already designated technologies from the beginning of their development programs, whether from their own portfolio or from a contract manufacturer. It will take some time for this process to become a reality, and we would encourage the Agency to allow the submission of

[1] 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

[2] https://www.congress.gov/bill/117th-congress/house-bill/2617

data packages for designations at any time a "person" is able to collect the necessary data.

- *Emphasis on CBER and CGT*: The statute for the pathway includes both drugs and biologics. Presentations at the meeting made clear that through the Emerging Technologies Team (ETT), CDER has become more experienced with AMTs. However, the progress, while positive, has been slow. Since the ETT was established, only one technology has "graduated," and most of the technologies highlighted were versions of continuous manufacturing. The CBER Advanced Technologies Team (CATT) is newer but was established to meet the same goals as the ETT. This new AMT designation pathway gives FDA the opportunity to support the success of CATT and the adoption of AMTs for CGT. We encourage FDA to consider the Agency's goals of greater standardization in CGT manufacturing and the likelihood of improving CMC review efficiency when establishing implementation parameters.

- *Emphasis on "reducing development time"*: The statute provides two examples of how an AMT can "substantially improve the manufacturing process" to be eligible for designation. The first is "reducing development time for a drug using the designated manufacturing method." For CGTs, this prong will be critical, as many technologies in development occur upstream in the development process or are auxiliary processes to create critical components. Having FDA-designated manufacturing technologies in these areas will drive use and innovation.

- *Clarification of the phrase "context of use"*: The statute allows an AMT to be designated for a specific "context of use." Including a description of the Agency's interpretation of the term with examples or previous contexts of use allowed in other programs in the guidance would be particularly helpful in the design of CGT AMTs.

- *Interactive communication:* ASGCT requests that the guidance reflect that the provisions of "interactive communication" involve, at minimum, one "in person"[3] meeting with the requestor for designation of a technology as an AMT.

- *Specific Section for CGT manufacturing processes in the Draft Guidance:* Given the novelty and complexity of CGT manufacturing processes, we would also request specific sections in the draft guidance that would outline the requirements of the AMT Designation Program for CGT manufacturing processes.

- *Clarify interactions with other expedited programs:* Congress specified that the agency should expedite the development and review of applications for products that use a designated AMT, as well as allow for the cross-referencing of data between products that use the same designated AMT. The majority of CGT products currently are being or have been developed for rare diseases. As such, they are already under the scope of other expedited development programs (Fast Track Designation, Regenerative Medicine Advanced Therapy Designation, Priority Review Designation,

[3] Consistent with the definition of in-person meeting in PDUFA VII which can include virtual means

etc.). We request the agency provide clarification regarding how the use of these programs would intersect with the additive value of incorporating a designated AMT.

Thank you for your consideration of these comments. ASGCT looks forward to engaging with the Agency on manufacturing technologies for CGTs, including through the implementation of this new critical pathway. If you have any questions, please contact Margarita Valdez Martínez, Director of Policy and Advocacy, at mvaldez@asgct.org.

Sincerely,

David M. Barrett, J.D.
Chief Executive Officer