Alliance *for* Regenerative Medicine

Advanced Manufacturing Strategies to Increase the Reach of Cell and Gene Therapies:

Takeaways from a Scientific Workshop

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INTRODUCTION

As the cell and gene therapy (CGT) field progresses and the number of product approvals continues to grow, there is an increasing demand to incorporate higher-volume production to deliver potentially life-saving therapies to expanding patient populations. From May 16th-17th, 2024, the Alliance for Regenerative Medicine (ARM) held a 1.5-day workshop on Advanced Manufacturing in CGT to cover various strategies for expanding manufacturing capabilities. The workshop brought together CGT therapeutic developers, technology developers, regulatory representatives, and other key stakeholders from across the industry (see the Appendix for a full list of presenters and panelists) to focus **on three primary areas of opportunity: (1) automation & advanced processes/analytics, (2) artificial intelligence/machine learning (AI/ML), and (3) decentralized manufacturing models.**

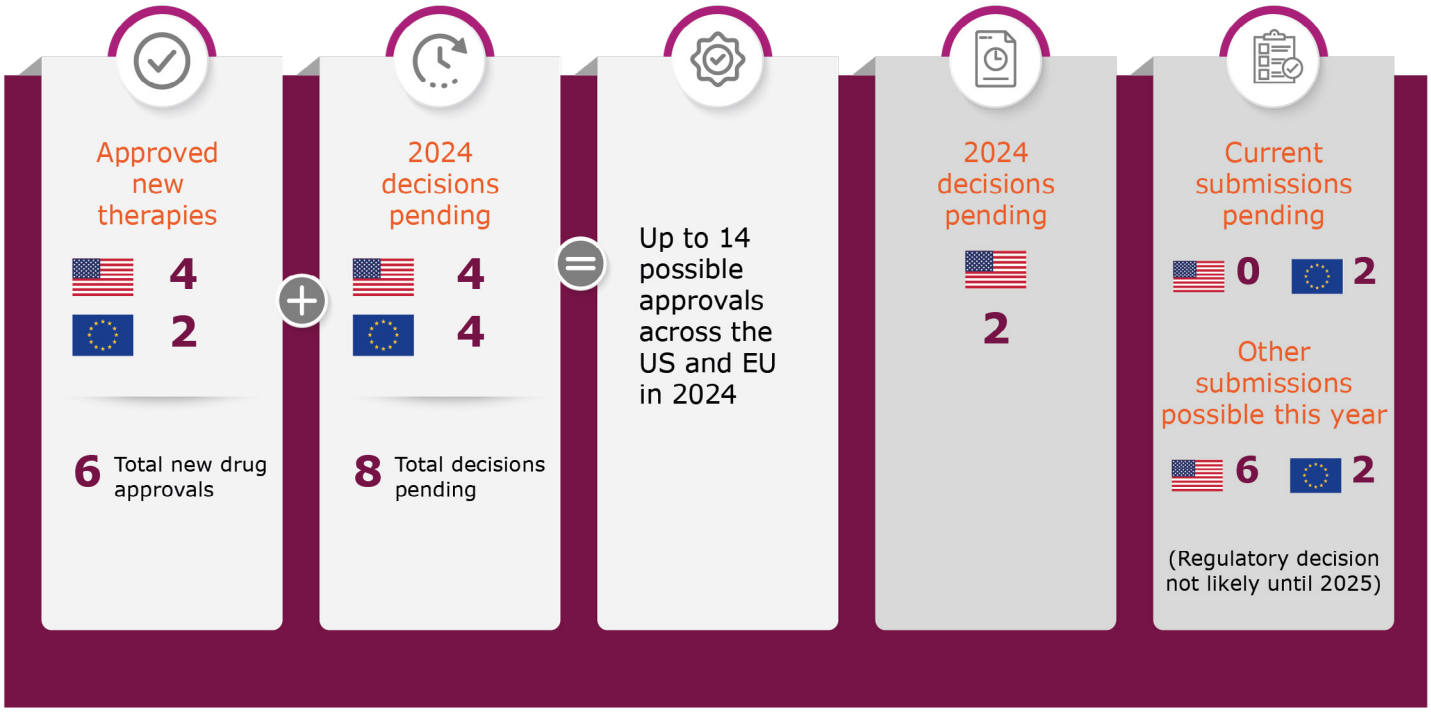
The goals of the workshop were to (1) explore the successes, challenges, and opportunities in developing and implementing advanced manufacturing technologies to meet patient demand, and (2) discuss the interplay between scientific and technological developments, evolving manufacturing models, regulatory considerations, and partnership opportunities in the context of CGT manufacturing. Presenters and panelists from across the industry shared examples of successful partnerships, case studies of specific achievements, and broad perspectives on the role and appropriate incorporation of various technologies and manufacturing models. While most of the principles discussed may be applicable to a broad range of CGTs, many of the case studies focus on CAR T-cell therapy manufacturing given the number of available products in the market. In addition, the workshop was designed to address technical and regulatory components of manufacturing to help facilitate patient access. The issue of payment and reimbursement is beyond the scope of this effort.

For definition of all abbreviations used in this whitepaper, please see the appendix.

Continued growth of the CGT industry

The CGT industry experienced a breakthrough year in 2023, with 7 CGT approvals in the US and 1 approval in the EU. Notable 2023 milestones included the first-ever approval of a CRISPR gene-editing therapy (>10 years after the discovery of CRISPR), 5 FDA-approved gene therapies for rare diseases, and the first approval of a cell therapy to treat Type I diabetes. With an increasing number of IND applications filed over the last 5 to 7 years and a strong global foundation of developers, clinical trials, and overall investment, 2024 is poised to be another standout year for the CGT industry (Box 1), tracking to FDA's 2019 prediction that the Agency will be approving 10 to 20 CGT products a year by 2025.[1] Approvals thus far in 2024 include the first cell therapy licensed for a solid-tumor indication.

Box 1. 2024 regulatory outlook: possible US & EU approvals and submissions[2]



As of October 21, 2024

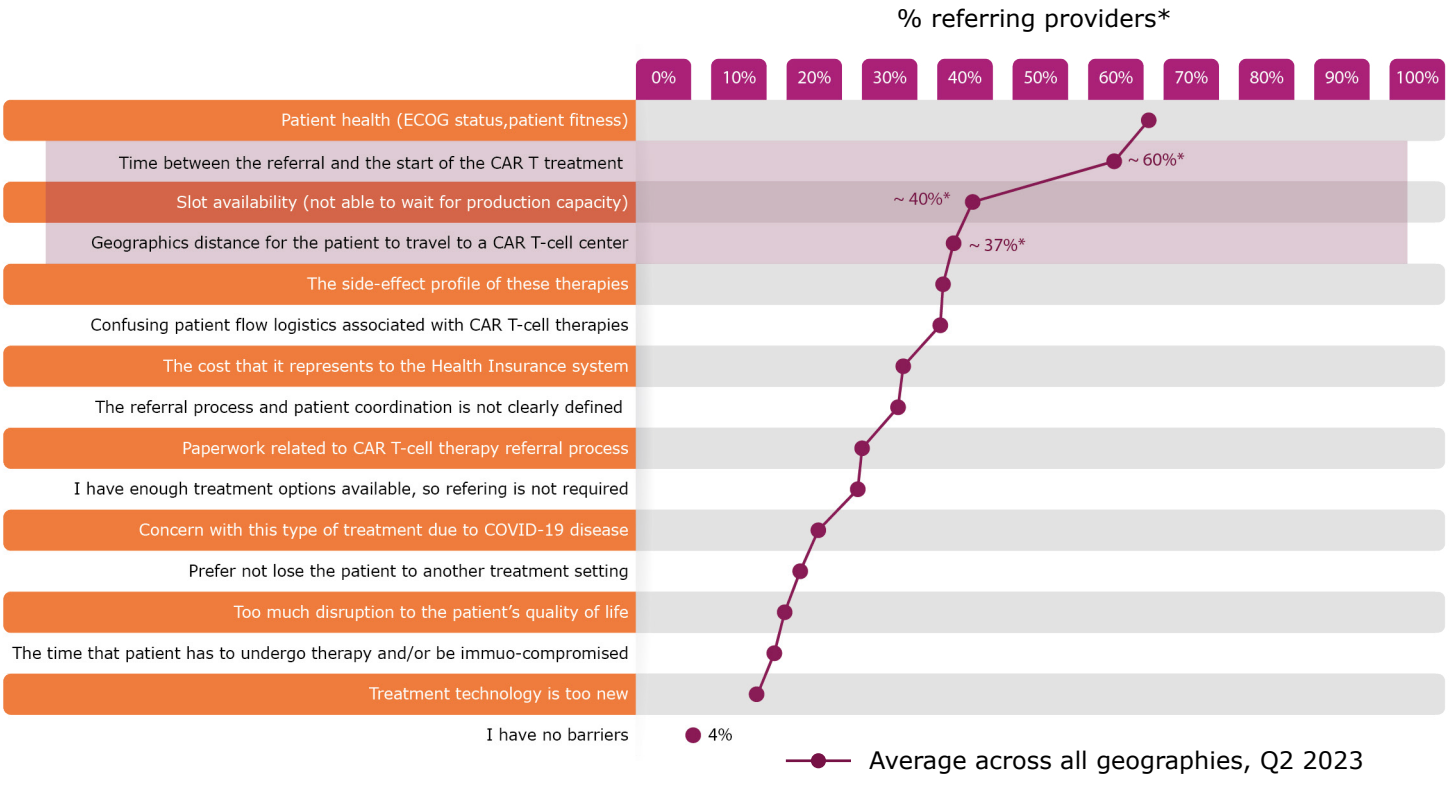
Manufacturing: a key challenge facing the CGT industry

The promise of CGTs is undeniable, and their therapeutic reach is expanding across new indications and into earlier lines of treatment (e.g., Carvykti® as 2nd line treatment of relapsed or refractory multiple myeloma and Yescarta® as 2nd line treatment of large B-cell lymphoma[3,4]), consequently reaching broader patient populations. However, these potentially curative therapies are not without challenges. Perhaps most profoundly, manufacturing capabilities cannot keep up with patient demand, driving up already-high prices and leaving CGTs widely inaccessible to those in need.

"CGT manufacturing incapacity will ensure patient inaccessibility. Even at a cost of $0/dose, current technology cannot produce enough product to meet anticipated demand."
- Industry executive

As a case example of the manufacturing bottleneck, a survey of international providers found that 3 of the top 4 barriers to accessing commercial CAR T-cell therapies can be linked to inefficiencies in manufacturing and/or analytics (Box 2).[5]

Box 2. Patient/provider barriers to accessing commercial CAR T-cell therapies[5]



*Share of referring providers represents those who rated the barrier as "very" or "extremely" important. Includes providers from Brazil, Canada, France, Germany, Italy, Japan, Korea, Spain, and the UK.

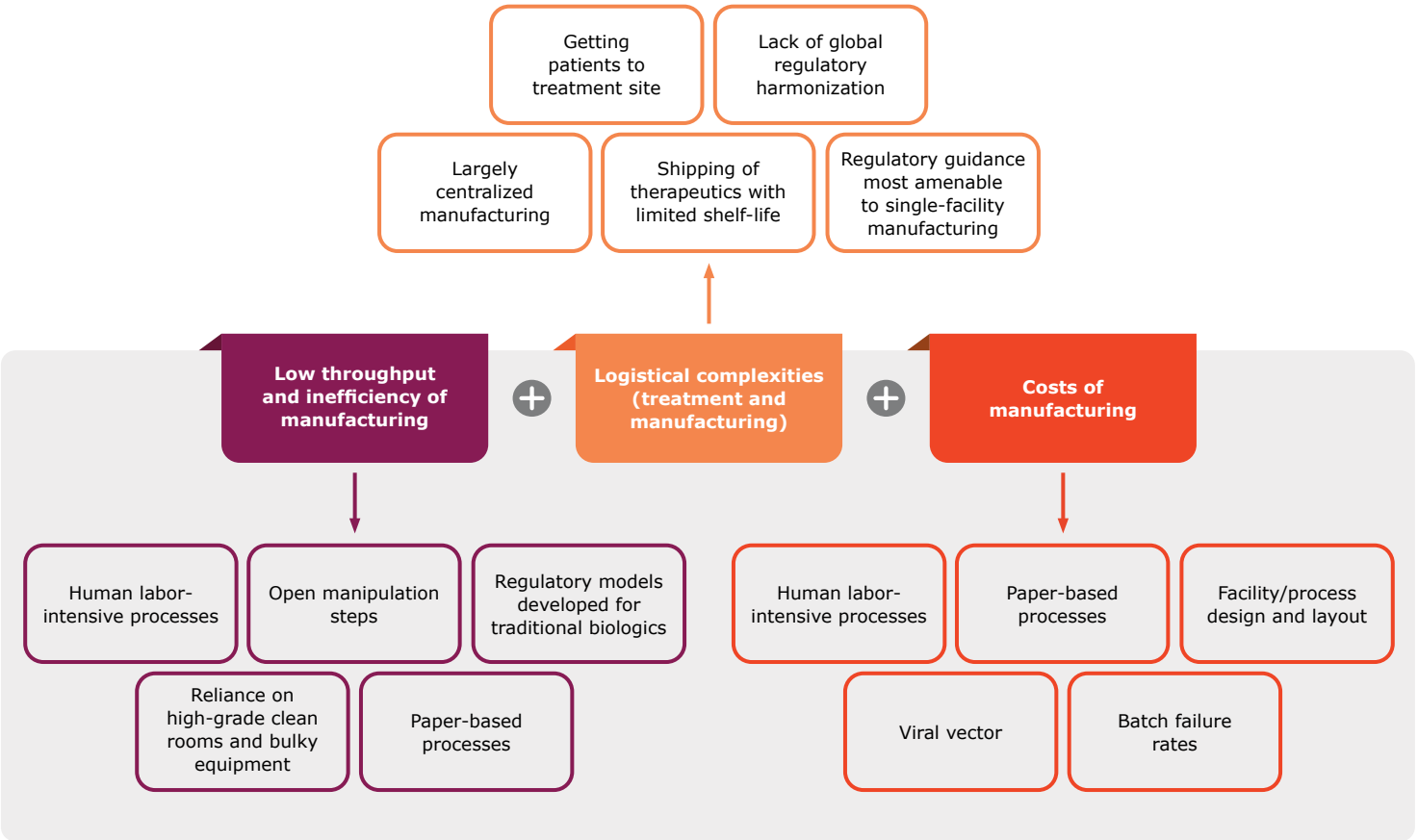
Adapted from: Strengthening pathways for cell and gene therapies: current state and future scenarios. IQVIA Institute for Human Data Science. March 2024.[5]

On the other extreme, drug development and manufacturing for rare and orphan diseases are challenging and cost-prohibitive due to small patient populations, making them often-neglected indications by the pharmaceutical industry. Innovative manufacturing paradigms, such as platform approaches to manufacturing, may be required to ensure feasibility and continued investment in CGTs designed to meet the needs of smaller patient groups.

Meeting the challenge

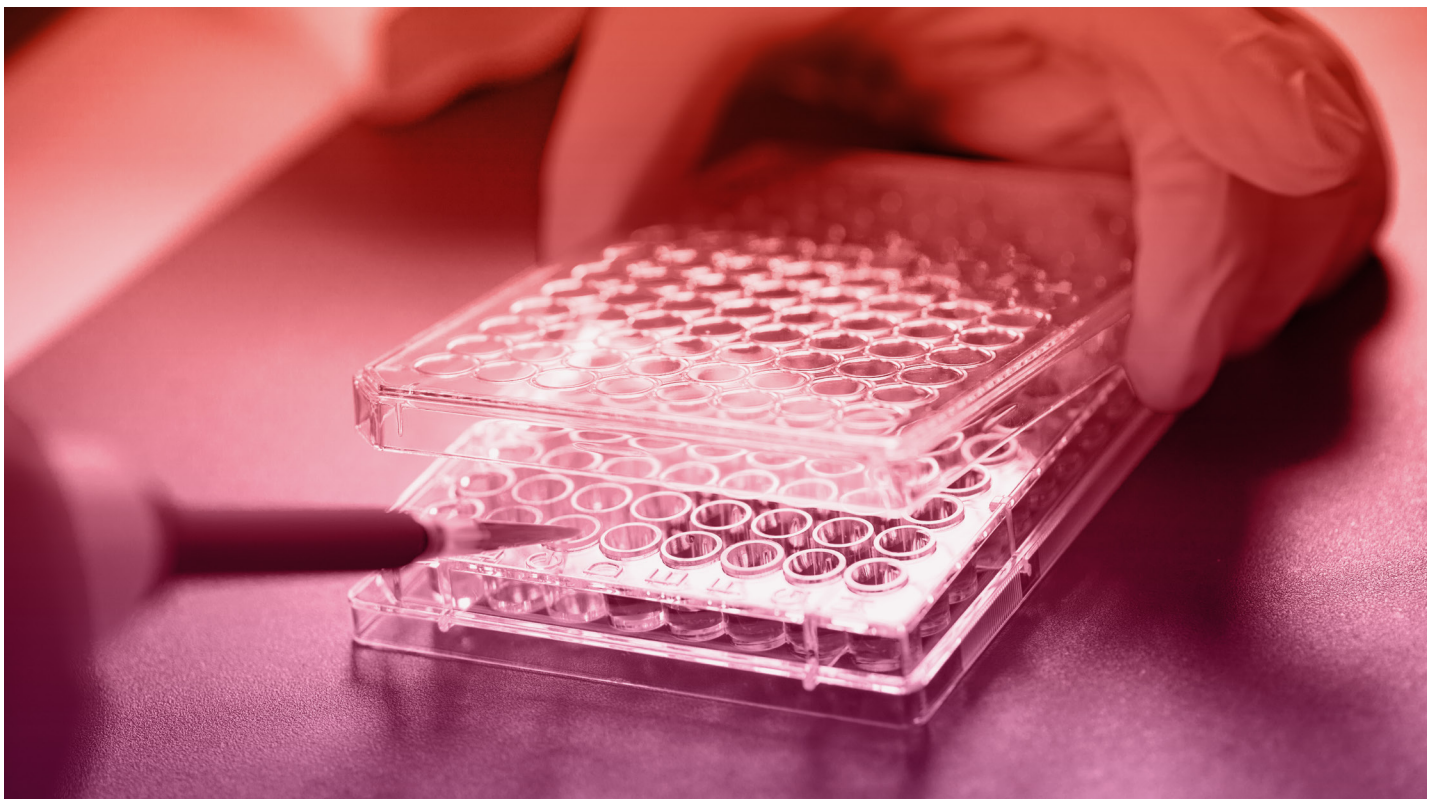
Struggles with the accessibility of CAR T-cell therapies highlight that today's CGTs are too difficult to manufacture, due in part to time-consuming, largely inflexible, human-dependent processes and regulatory constraints. CGT manufacturing also faces significant challenges related to condensed batch sizes and limited overall manufacturing capacity, often yielding small, inconsistent batches that can hinder scalability and reliability. In addition, CGTs are too expensive and too logistically complicated to make widely available and are not commercially viable due to high COGS. Removing the manufacturing bottleneck first relies on a solid understanding of what is driving the current limitations (Box 3).

Box 3. Understanding the drivers of CGT manufacturing constraints



Resolving CGT manufacturing challenges will require creative and consistent effort from all stakeholders. Developers are already starting to incorporate automation, advanced analytics/data digitalization, and decentralized models into their production strategies,[6,7] and alignment between academics, developers, and regulators will be key. To this end, ARM and the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) co-hosted a multi-stakeholder scientific exchange in November 2023, with the goal of identifying reusable elements (i.e., building blocks) of technologies that could be leveraged to improve the time and resource efficiency of CGT development (see the white paper summary from this event[8]). In December 2023, the FDA published a Draft Guidance for Industry on the Advanced Manufacturing Technologies (AMT) Designation Program.[9] The Draft Guidance outlines the proposed regulatory pathway to receiving AMT designation for a manufacturing method (or combination of methods) that incorporates a novel technology or uses an established technology in a novel way that substantially improves the manufacturing process for a drug while providing equivalent (or superior) drug quality.[9] Additionally, in May 2024, the FDA published a Draft Guidance for Industry on the Platform Technology Designation Program for Drug Development, which is intended to result in efficiencies in drug development, manufacturing, and review processes for drug product applications that incorporate designated platform technologies.[10]

This **Advanced Manufacturing in Cell and Gene Therapies Workshop** represents another effort to encourage stakeholder engagement across the CGT industry to address manufacturing hurdles and accomplish the goal of expanding patient access. Each of the technologies and/or strategies of focus (**automation & advanced processes/analytics, AI/ML, and decentralized manufacturing**) can help to address factors that are driving the CGT manufacturing bottleneck.



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