



AZZUR GROUP

Whitepaper

MANUFACTURING A CURE

FOR THE WORLD'S MOST DEVASTATING DISEASES

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Introduction

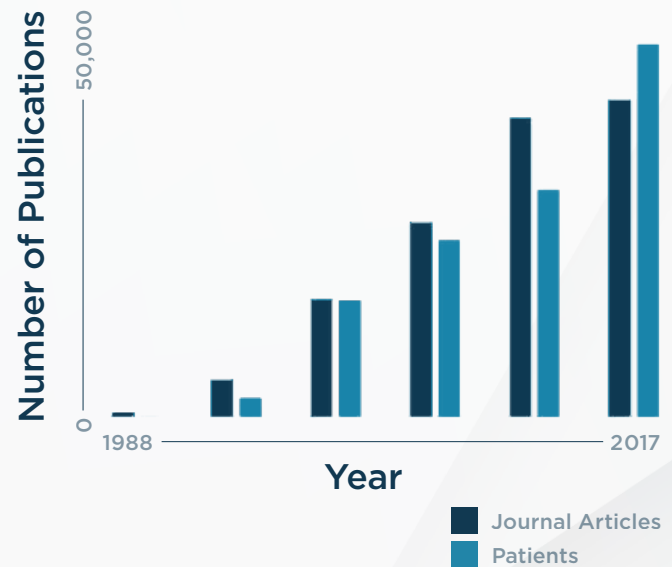
In 2019, the U.S. Food and Drug Administration (FDA) forecasted that by the year 2025, between 10 and 20 cell and gene therapy (CGT) solutions would be approved per year in the United States.¹

That is 17 - 35% of the total number of therapies approved by the FDA in 2018.² An estimated 2,000 human gene therapy clinical trials have been reported worldwide. The focus on CGT is further evident when considering the increased investment on research and patents over the past few decades.

CGT is even more critical now, as we are faced with unprecedented diseases like COVID-19 for which there is no existing cure. While the breakthrough process of using a patient's own cells to manufacture a completely personalized defense mechanism against disease is a novel concept in medicine, the overarching immunotherapeutic approach—teaching the body to fight for itself—has been harnessed since the late 1700s with the advent of the vaccine.³

However, instead of using dead or weakened pathogens to boost an immune response to external threats such as bacteria or viruses, cell therapy in the context of the CAR-T platform utilizes receptors which target antigens expressed exclusively by certain diseases. This allows for a targeted immune response to some of the world's most prolific disease states—the most notable of which today is cancer.

Apart from using cells that are both modified or unaltered to provide a therapeutic benefit, gene therapy introduces genetic material such as DNA or RNA to repair or replace one's own defective/non-functional gene. Introducing this genetic material into the body resolves the genetic disparities or malformations that lead to disease susceptibility, or the disease itself.



¹ Commissioner, Office of the. Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on New Policies to Advance Development of Safe and Effective Cell and Gene Therapies. 15 Jan. 2019, www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics.

² Mullard, Asher. "2018 FDA Drug Approvals." Nature News, Nature Publishing Group, 15 Jan. 2019, www.nature.com/articles/d41573-019-00014-x.

³ History of Smallpox." Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, 30 Aug. 2016, www.cdc.gov/smallpox/history/history.html.

The Process

Cell and Gene Therapy (CGT), also known as Advanced Therapy Medicinal Products (ATMPs) in Europe, is an overarching term used to classify the modification of DNA, cells, or tissues, in order to provide a therapeutic benefit to the patient.

In the case of personalized or autologous platforms, the patient's own cells and/or tissues, or genetic material, are used to manufacture a therapy designed specifically for his or her own body to ward off disease, or repair their biological machinery.

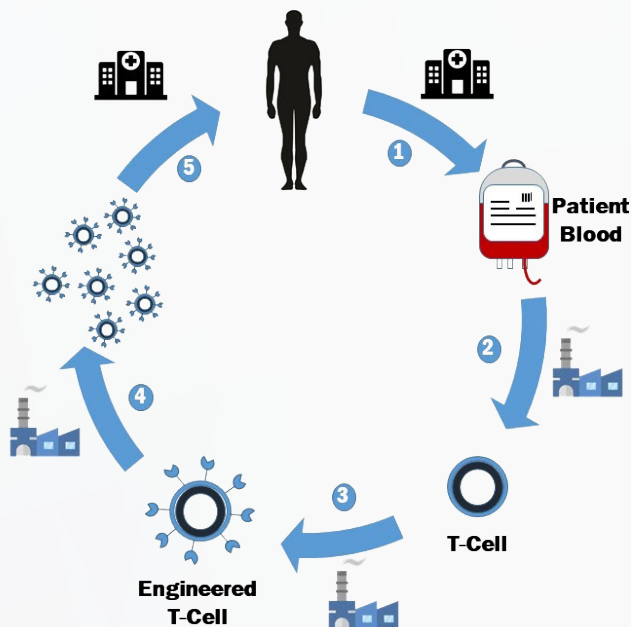
With CAR-T therapy, for example, scientists are not necessarily creating new pharmaceutical agents. Instead, very specific processes try to “teach” immune cells to hunt for, identify, and attack damaged and infected cells in order to improve patient outcomes.

As opposed to traditional pharmaceutical and biologic treatments, the manufacturing and administration of such a personalized and targeted cell and gene therapy is a cyclical process, and subject to a number of challenges.



The Cycle

While the manufacturing and administration cycle is simple on the surface, it is the culmination of decades of research, development, and trials. The process still faces a number of ongoing manufacturing challenges unseen in traditional pharma/biotech.



APHERESIS / LEUKAPHERESIS

Trained clinicians remove blood or other tissue from the affected patient. These cells are the starting material for cell manufacturing.

TRANSPORT TO MANUFACTURING SITE*

Using specific storage and controlled environments for cold storage, the patient's cells are transported from the clinic to the manufacturing facility, which can be by plane for longer distances.

RECEIPT AND ACTIVATION

Cells are received by the manufacturing site for activation and continue the Chain of Custody / Chain of Identity for the material. The patient's own cells are engineered to target the specific disease type.

- A number of novel and proprietary approaches to activation exist.
- At its most basic level, the patient's cells are loaded with appropriate antigens for the preferential disease; these cells then proliferate. As a result, the patient's T-cells are triggered and the immune system initiates a response to fight the damaged cells.

TRANSPORT TO HOSPITAL/CLINIC FOR ADMINISTRATION*

The activated cells are transported back to the clinic where they are received by trained clinicians following appropriate Chain of Custody / Chain of Identity.

ADMINISTRATION

The activated cells are administered to the patient for therapeutic use, where the activated cells will identify and attack diseased cells in vivo.

*The ultimate goal of personalized cell and gene therapies is for manufacturing and activation to take place at the clinic. Therefore, the transportation element may be largely eliminated from this cycle in future advancements. However, with early adoption of such therapies, there are very limited numbers of certified administrators. Until wider adoption is seen with decentralized activity, transportation will be a necessary element of these therapies.

Going to Market

There are a myriad of challenges for Cell and Gene Therapy innovators, both in bringing treatment to market, as well as administering treatment to patients.

Infrastructure is a major hurdle in bringing new cell and gene therapies to market. Today, developers range from small, venture-funded start-ups to some of the world's most known players in life sciences. However, unlike classic pharmaceuticals engineering and manufacturing, the cyclical and personalized nature of the therapy requires multi-phase manufacturing, patient-specific lots, personalized quality control, and accountability for a number of external factors.

The big players, such as Gilead (Yescarta) or Novartis (Kymriah), are fortunate to have existing facilities at their disposal; however, the capital expense and specialized equipment necessary to bring a novel CGT to market can be significant hurdles. Smaller start-ups face different challenges, with limited budgets and a primary focus on the science, they lack any existing infrastructure suitable for manufacture.

Early-stage developers and innovators in the space turn to third party manufacturers — Contract Development and Manufacturing Organizations (CDMOs) — who provide cGMP-ready space on a contract basis where the CDMO develops batches while upholding quality standards. An advantage to the CDMO model is that they can provide in-house expertise, reducing timelines and accelerating the path to market. However, it is important to also consider common drawbacks. These include the potential to lose control of the process, as leasing the operations to a contract organization often comes with reduced oversight of the developer's specialized intellectual property.

Additionally, the risk for human error in CGT development is immense, especially compared to pharma/biotech. The process requires specialized staff with experience in unique technologies and methods. Selection of a partner must therefore be given careful consideration, and one that should include a Quality Agreement to help mitigate those risks.

Another option for third-party development has emerged in the last two years. On-demand cleanrooms. This new solution rivals the CDMO model by offering cGMP operations space, but with uncompromised access and control for the developers. In other words, the developer leases the manufacturing and storage space, as well as equipment, and their staff oversees the entire manufacturing process, reducing risk and protecting intellectual property.

No matter the size of the developer — start-up or established enterprise — bringing a novel CGT to market poses challenges. Careful consideration and risk-benefit analysis is paramount to maintaining quality product throughout the delivery cycle.

FDA Guidance

Today, FDA guidelines within the CGT space are just that: guidelines for quality control and patient safety.

Manufacturers are left to interpret guidance and implement in a way that mitigates risks while improving patients' lives. This means a careful amalgamation of standard cGMP practices (quality assurance, equipment and process validation, documents, data integrity, etc.) and adequate training and aseptic and laboratory validation for off-site, clinic-based operations. While it is not an opportunity to avoid rules and regulations, it is a unique necessity of this new therapeutic platform treating patients with severe illness where time is of the essence.

This poses a divergence from stringent expectations known within the pharmaceutical space.

As such, developers indeed benefit from working alongside certified cGMP consultants experienced in comprehensive, risk-averse, and appropriate quality control methods and documentation. These experts are able to develop innovative and creative solutions for manufacturing. Taking a science and risk-based approach, these consultants can provide flexibility without compromise. And, with a proven track record in the GMP space, such organizations come armed with procedures, templates, auditing experience, and documentation expertise that will help developers mitigate risk and avoid common pitfalls both prior to and after bringing the product to market.

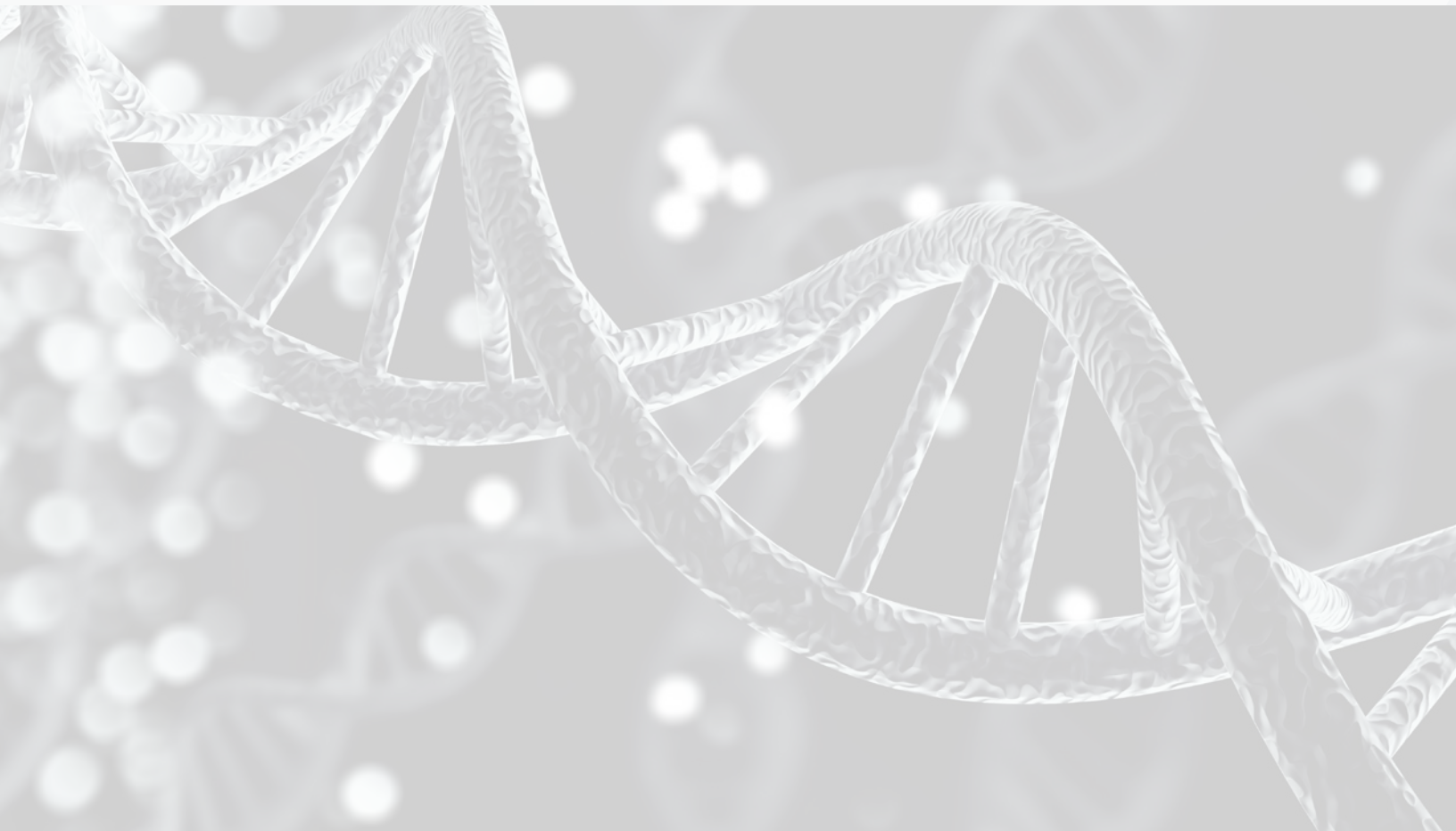


Time to Treatment



Patients undergoing cell and gene therapy or tissue-activated therapy often are at a late stage of relatively high-risk disease, such as cancer.

Patients and their care teams have turned to immunotherapy as an option after the recommended first- and second-line treatment options have failed. As such, the cycle time and time to treatment could mean the difference between life and death. Until manufacturing and activation are streamlined and standardized cGMP practices are in place across all major treatment sites, the risk of delay with transportation will remain an issue.



Training

The aforementioned specialized skill sets required of the CGT developer's staff, as well as those administering the treatment, is key to the success of these therapies.

In addition, unlike other FDA-regulated spaces with large centralized facilities, the ultimate goal for personalized CGT is decentralized at-clinic manufacturing in order to reduce the time to treatment and decrease the patient burden.

To date, the burden continues to be on the manufacturer to train personnel at approved sites in the proper manufacturing, handling, and administrative techniques required for safe and efficacious treatment. This includes formal programs which authorize clinics to administer their therapies. While internal powerhouses in the pharma/biotech and CGT space may be armed with internal training departments that can be deployed across the globe, smaller start-ups lack the resources to train, test, and maintain their projected growth rate.

Both classroom-style or electronic-based kinesthetic learning are necessary for staff to understand the mechanism of action for CGT, as well as how to appropriately activate patient tissue, administer the treatment, and monitor the patient. A number of programs exist today capable of deploying comprehensive training, including third-party organizations with both templated programs and the ability to create customized modules specifically for the developers' needs.

Some consultative trainers will work with start-ups as well as established manufacturers to create customized curricula, branded distribution methods, and robust on-site kinesthetic training. The benefit to working with such an organization is that it allows manufacturers to scale and deploy training in keeping with their growth trajectory. Additionally, it allows their limited staff to focus on innovation and execution, rather than training.



Conclusion



At the rate that innovation is coming to the CGT space, this is undoubtedly an exciting time for the industry to extend its reach to patients.

As the technologies become more advanced and transform, regulations are going to evolve and adapt in order to address the biggest risks to the patient. Regardless of size, CGT developers have many challenges to tackle in order to get their product to market. As interest continues to grow over the next 5 years, competition will drive changes which will only expedite timelines further. Nonetheless, there are numerous resources available to support these organizations, including CDMOs or Cleanrooms on Demand (COD), as well as highly skilled consultants to navigate the ever changing regulatory landscape.



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Javier Cardenas, Ph.D. is a Senior Consultant for Azzur Group, a healthcare and life sciences consulting firm. In this role for the past five years, Dr. Cardenas has facilitated projects improving compliance of cell & gene therapies, sterile injectables, medical devices, and biologics at client manufacturing facilities throughout the Southern California region. Based on a science and risk-based approach, efforts have included CQV (Commissioning, Qualification, and Validation), Quality Risk Management, MS&T (Manufacturing Science & Technology) / Technology Transfer, and Project Management. Having received his M.S. / Ph.D. degrees in Chemical & Biochemical Engineering with a focus in Molecular Biotechnology from the University of California – Irvine, his continued passion is in driving technical advancements and knowledge in the Cell & Gene Therapy space.