

# Manufacturing Cures: Infrastructure Challenges Facing Cell And Gene Therapy Developers



As more regenerative medicine products approach clinical testing and commercialization, stakeholders in the field are increasingly pressed to address substantial challenges, including pricing and reimbursement, GMP manufacturing, clinical availability, and patient accessibility to these life changing therapies.

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Over the past decade, advanced therapies have transitioned from academic dream to a clinical reality. With the recent approval of AveXis/Novartis AG's Zolgensma, a gene therapy for spinal muscular atrophy (SMA) Type 1, and the international approvals of Novartis' Kymriah, Kite Pharmaceuticals/Gilead Sciences Inc.'s Yescarta, and Spark Therapeutics Inc.'s Luxturna, it is clear that increasing numbers of patients will benefit from regenerative medicine therapies in the coming years.

Though this field has the potential to dramatically transform the health care landscape and treat patients who have in the past had limited or no treatment options, the shifting treatment paradigm also presents development and marketing hurdles which are different from traditional therapies. To ensure broad patient access to these transformative therapies in a timely manner, sector stakeholders must now convene to identify and address these challenges.

### Logistical Considerations For Cell And Gene Therapies

In contrast to the current generation of medical products in wide use, products based on a biological material require special logistical considerations, both in development and delivery. Products that rely on biological starting material have shorter shelf lives, greater temperature sensitivities, and increased complexity and cost related to purity and identity testing.

In addition, the supply chain for managing these new products is incredibly complex. As the demand for cell and gene therapies increases, therapeutic developers must

contend with limitations in the supply of starting and ancillary materials involved in the production of these therapies.

In the case of gene therapies, viral vectors – which make up the delivery method of 80% of gene delivery-based therapeutics currently in clinical development – are expensive and time-consuming to produce and characterize. For certain cell therapies, the production of appropriate cell lines for the development of therapies can be limited by the quality and quantity of the starting material. In many cases, researchers can only obtain a small number of cells which then require weeks of labor to cultivate and expand to a sufficient number for development of the therapeutic product to begin.

Though large pharmaceutical companies continue to show increased interest in cell and gene therapies, whether through in-house development, in-licensing, or partnering deals, many current therapeutic developers are startups with limited resources. Often, these developers rely on a single source supplier to provide critical equipment and materials, which introduces additional risk and potential bottlenecks in the development process.

The supply chain for autologous cell therapies is further complicated. These therapies rely on the patient's own cells, which are collected during an initial appointment at a clinical facility. They are then purified, genetically or chemically modified, and expanded in order to produce the desired therapeutic effect before they are re-administered to the patient. This process typically takes weeks, relies on seamless transfer and management of materials between clinical sites and manufacturers, and delivery timelines are easily disrupted by patient-specific issues, resulting in delayed or lost opportunities for treatment.

In addition to potentially increasing the time it takes to administer these therapies to patients, the personalized nature of these autologous therapies also means that developers are unable to take advantage of the economies of scale that are created when manufacturers of traditional pharmaceuticals produce large quantities of a product. The quality of the final product is strongly related to the biology of the individual patient's cells. Lot failures can commonly occur due to quality issues

such as a failure of the cells to expand, or poor response to *ex vivo* modifications.

Post-approval, cell and gene therapy manufacturers often run into another hurdle: supply and capacity planning. Demand for a specific product may be difficult to determine. This is particularly true for therapies for orphan indications, where the number of infants born or patients diagnosed with a disease, as well as the overall patient population, can be extremely variable. Additionally, it can be difficult to predict uptake post-approval, particularly when pricing is contentious. This can result in an acute disconnect between available resources for therapeutic development and patient need, with both parties suffering the ill effects.

Finally, differences in Chemistry, Manufacturing and Controls (CMC) requirements from country to country and duplicative processes for testing, reporting, and clinical submissions can place an undue burden on developers. The cost of manufacturing products for clinical trials and commercialization post-approval is particularly challenging and risky for small companies, which is exacerbated by international uncertainty. Ensuring that there is sufficient international convergence on regulatory and clinical requirements will allow patients to access safe and effective products without unnecessary costs and delays.

### Increased Urgency In Addressing Manufacturing Challenges

The time for innovation and creative solutions to address manufacturing challenges for cell and gene therapies is now. Over the next decade, there will be a considerable increase in the number of patients who require and qualify to receive these transformative, increasing the urgency for implementation of novel methodologies. According to data maintained by ARM, of the 1,060 ongoing clinical trials in regenerative medicine worldwide, there are 80 cell and gene therapy trials in Phase III, suggesting that the number of approved products on the market will soon increase significantly, and with that, patient demand. The US FDA said in a January 2019 statement that by 2025, they expect to be approving 20-25 regenerative medicine products annually. The EU is also preparing for the coming

## THE RISE OF REGENERATIVE MEDICINE

Regenerative medicines, including cell and gene therapies, augment, repair, replace or regenerate organs, tissues, cells and genes within the body. These therapies have the potential to provide a profound and durable response – often with just a single administration – for patients with a diverse array of serious diseases and disorders. Unlike traditional drugs, these therapies focus on treating the underlying cause of diseases and disorders, rather than focusing on chronic care.

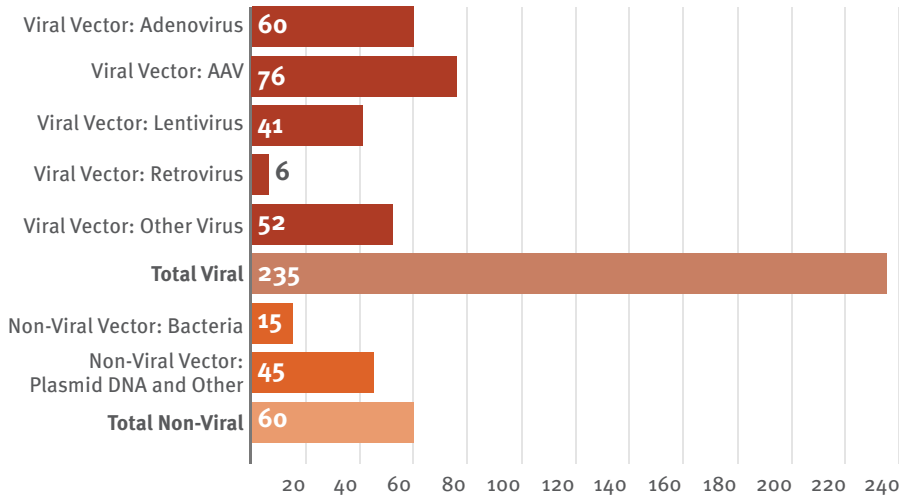
This field is undergoing explosive growth. As of the first quarter of 2019, the Alliance for Regenerative Medicine is tracking 917 regenerative medicine therapeutic developers worldwide including companies active in gene therapy, cell therapy and tissue engineering. 2018 was a watershed year for regenerative medicine financings, with \$13.3bn raised worldwide, and this investment energy continues in 2019. The sector already raised \$2.2bn in Q1, with \$2.1bn raised by gene therapy developers and \$823m raised by cell therapy developers.\* In addition, the global clinical pipeline is robust, with 1,060 clinical trials currently ongoing across a variety of indications utilizing regenerative medicine technologies.

*\*Total amount represents sector-wide figures; some companies utilize technology from more than one technology group. As a result, the total financings amount does not equal the sum of the raises of the individual technology groups. Figures do not include M&A transaction totals.*

wave; at ARM's April 2019 Meeting on the Mediterranean in Barcelona, European Medicines Agency director general Guido Rasi announced EMA expects to approve 10+ products annually in the near future.

Approved products are not the only drivers of demand for cell and gene therapies. The clinical trial pipeline is

**Exhibit 1  
Viral And Non-Viral Vectors In Gene Transfer Clinical Trials**



SOURCE: Alliance For Regenerative Medicine

increasing as well. The FDA is preparing to receive 200+ INDs each year for clinical trials in regenerative medicine. Targeted enrollment in current ongoing clinical trials worldwide is nearing 60,000. By 2030, the MIT NEWDIGS consortium predicts that more than 500,000 people will have been treated with cell and gene therapies in the United States alone.

This increase in demand is partially driven by a shift in focus from monogenetic orphan indications to “mass market” indications with larger patient populations, such as cardiovascular conditions or central nervous system disorders. The first gene therapy for critical limb ischemia, AnGes’s Collatagene, has already received approval in Japan and is currently in clinical trials in the U.S. A number of other indications with large patient populations and correspondingly considerable impact on health care systems are also experiencing increased clinical interest. Currently, there are 13 ongoing cell and gene therapy clinical trials in critical limb ischemia; 13 in diabetes and related complications; 11 in myocardial infarction; nine in stroke; eight in Parkinson’s disease; and five in Alzheimer’s.

In addition to the increase in available products and the size of patient populations, cell and gene therapy developers are also striving for shorter development timelines, driven by the availability of expedited approval pathways, including RMAT, Breakthrough, and Fast Track des-

ignations in the US; PRIME designation in the EU; and SAKIGAKE designation in Japan. These designations help to ensure that patients are able to access innovative therapeutics as efficiently as possible, but shorter timelines mean that developers must begin to plan their large-scale manufacturing strategy early on in the development process – sometimes before they even begin to dose patients – or risk collapse post approval.

As these therapies have begun to come to market, investors have taken an increased interest in how companies plan on handling large-scale manufacturing. On a panel on the investment outlook at ARM’s March 2019 Cell & Gene Investor Day, Aquilo Capital Management Principal Patrick Rivers commented that the issue and challenge of “manufacturing becomes questions one, two, and three” when making investment decisions. Sector stakeholders will need to work to provide innovative solutions to manufacturing hurdles in order to maintain investor interest and foster the furthered growth of the sector.

**What Are The Solutions?**

Many therapeutic developers in the cell and gene therapy space have turned to professional manufacturing organizations, both CMOs and CDMOs, to help develop and manage their manufacturing programs. Startups and small therapeutic developers, who may not have the resour-

es to manage manufacturing in-house, may particularly benefit from outsourcing strategies. Larger CMOs and CDMOs are often able to take advantage of economies of scale, where smaller developers cannot, and their specialized knowledge and equipment can help to streamline and standardize the manufacturing process.

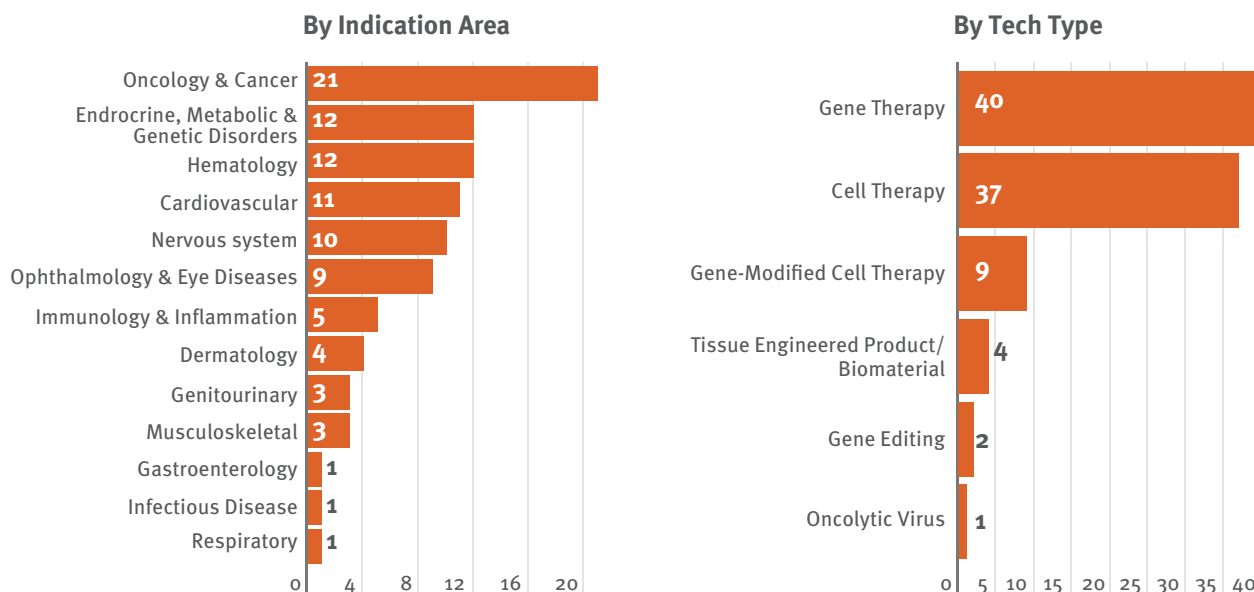
However, outsourcing can have drawbacks. The developer may have less oversight over the manufacturing process, and disruptions at the CMO or CDMO can create bottlenecks for the developer – particularly if they rely on a single CMO or CDMO to fulfill their needs. In addition, the majority of current generation regenerative medicine products are highly specialized, requiring bespoke components and specifically trained staff. The traditional CMO model struggles to accommodate such unique and non-standard technology approaches, which can result in delayed tech transfer and negatively impact the developer and their patient population.

Because of this, many therapeutic developers are planning to handle their manufacturing in-house, or with a combination of in-house and outsourced services. While this approach may be more difficult for startups and can introduce new complications for developers to achieve the time and cost savings provided by large-scale manufacturing set-ups, it does provide additional oversight and quality control.

The increased interest in in-house manufacturing options has recently led to a balloon of M&A activity, with CMOs and CDMOs becoming attractive acquisition targets. In the past year, Novartis acquired CellforCure, a French CDMO, to expand their manufacturing capabilities in the production of their CAR-T therapy Kymriah; Hitachi acquired apceth to increase their manufacturing capabilities in Europe; Thermo Fisher paid \$1.7bn to acquire CMO Brammer Bio; and Danaher paid \$21.4bn to acquire GE Healthcare. Manufacturing, and pinpointing the associated solutions has become an attractive, if challenging, business.

Additionally, as the science in this field advances, we may see other solutions that address some of the current issues with manufacturing. An increasing number of cell therapies are allogeneic or “off-the-shelf” cell therapies. Because

**Exhibit 2**  
**Expedited Approval Pathway Designations By Indication Area And By Technology Type**



SOURCE: Alliance For Regenerative Medicine

these therapies are not personalized like autologous cell therapies and do not require the starting material to come from the patient being treated, the manufacturing and distribution process reaps the benefits from economies of scale, and the therapy is able to be administered to the patient much more quickly. In gene therapy, increased interest in next-generation non-viral delivery methods – including nanoparticles, nanospheres, transposons, electroporation, excitation, and others – may partially alleviate the need for viral vectors, which are expensive and time-consuming to produce.

With this said, it should not be solely the responsibility of companies to alleviate manufacturing hurdles. Regulatory agencies across the globe are contributing to the work to address challenges in manufacturing. The US FDA released several draft guidances relating to CMC and manufacturing in March 2018 (finalized in March 2019) and December 2018, which have increased clarity for developers.

Also, both the FDA and EMA have expressed interest in increasing regulatory convergence, which would streamline the process of expanding access to therapies in additional countries. This common interest in novel regulatory methodologies has fostered deeper communication between industry and the agency around needs and

expectations, with organizations like ARM playing a key role in facilitating productive, precompetitive dialogue.

Nonprofit organizations have partnered with regulatory agencies to provide guidance on overcoming manufacturing hurdles as the field grows. The Standards Coordinating Body, an independent nonprofit 501(c)(3) organization that spun out of an initiative of the Alliance for Regenerative Medicine’s Science & Technology Committee, is working to promote the coordination of standards activities, including those involving manufacturing, across the regenerative medicine community to accelerate standards advancement. ARM is currently developing the “A-Gene” and “A-Cell” projects, intended to create a case study-based reference guide on the best practices for the development of gene therapies and cell therapies, respectively. An expert industry team, including 47 contributors from 31 member companies, will address key topics in the development and manufacturing of cell and gene therapies, including comparability, critical quality attributes, the product life cycle, the development and use of standards, regulatory implications, and others. The A-Gene team anticipates publishing their results by the first quarter of 2020; the A-Cell project is expected to publish in late 2020.

**The Future of Manufacturing For Cell And Gene Therapies**

While we have seen considerable improvements to the manufacturing process in recent years, there are still hurdles to overcome. As the regenerative medicine sector continues to grow, and cell and gene therapies are made available to an increasing number of patients, the field will experience an increased need for innovative solutions to manufacturing and infrastructure challenges. It is likely that a combination of efforts – strategic business investments, novel manufacturing models, advances in the science cell and gene therapy, the work of regulatory bodies to promote clarity and convergence in CMC requirements, and cross-sector coordination focused on the improvement of manufacturing processes – will result in significant improvements in the manufacturing environment for cell and gene therapies in coming years.

Cell and gene therapies have the potential to drastically transform our health care systems and improve the lives of hundreds of thousands of patients across the globe in the relatively near future. Stakeholders must now come together to surmount the challenges of manufacturing cell and gene therapies in order to improve access to and fully recognize the promise of regenerative medicine. ❁

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