Making – and Scaling – Advanced Medicines

Industry leaders unpack the manufacturing innovations driving the next generation of advanced medicines in our latest eBook

the Medicine Maker x PHCbi FUJIFILM FUJIFILM Biotechnologies

Manufacturability and the Winners in Advanced Therapies

Are developers still underestimating the engineering sophistication required to scale advanced therapies in the real world? Alan Boyd discusses

Drug development is often described in eras: the age of small molecules, the rise of biologics, and then the emergence of cell and gene therapies. Few experts have worked directly through each transition

Meet Alan Boyd. He has spent over four decades in R&D, watching the industry progress from a time when ACE inhibitors and beta blockers represented the cutting edge to a landscape where the central challenge is no longer discovery alone, but the ability to manufacture living medicines at scale, reliably and cost-effectively.

"When I begin working with a client developing a cell or gene therapy, I tell them right from the start that they will face manufacturing challenges," says Boyd. "It's important to anticipate these issues and ensure the right expertise is in place to address them."

In this interview, Boyd – who is today the founder and CEO at consultancy firm Boyds – explores the challenges facing the sector, from understanding manufacturing to surviving a hostile funding environment.

You've been working in drug development for 40 years. What have been the most exciting developments you've seen in terms of new therapeutics and scientific discoveries?

Over the past 40 years, I have witnessed several distinct eras in medicine. In the late 1960s and 1970s, there was a strong focus on discovering and developing new drugs, particularly those designed to target specific receptors or enzymes. This was the era that gave rise to beta blockers and ACE inhibitors. For instance, the ACE inhibitor lisinopril (marketed as Zestril) was approved in the 1980s for the treatment of cardiovascular conditions. Around that time, when I joined ICI, I worked on developing this third ACE inhibitor that was approved for both heart failure and hypertension.

The 1990s marked the beginning of the next major phase, with the emergence of antibodies and biologics – innovations that went on to revolutionize medicine, especially in fields like rheumatology. By the late 1990s and into the 2000s, this progress expanded to include cell and gene therapies. Also, from the mid-2000s onwards, we saw remarkable growth in immunotherapies.

It is really in the past 20 to 25 years that we have experienced a true revolution in medicine. For the first time, we are moving beyond treating signs and symptoms (as I was originally trained to do) and beginning to achieve actual cures for certain diseases. Gene and cell therapies, in particular, have opened the door to modifying patients' immune systems to fight or even eliminate disease. This

"We are moving beyond treating symptoms and beginning to achieve actual cures."

ability to move from treatment to potential cure represents one of the most exciting developments in modern medicine.

How have the challenges around drug development changed?
In the first half of my career, I worked predominantly with new chemical entities, where manufacturing was relatively straightforward. As Head of Medical Research at Zeneca, my department was often the rate-limiting step in getting a new drug approved. Today, however, with the advent of immunotherapies and cell and gene therapies, the rate-limiting step has shifted. It's now manufacturing.

The key difference is that we are working with biologics that are living organisms rather than stable chemical structures. When I begin working with a client developing a cell or gene therapy, I tell them right from the start that they will face manufacturing challenges. It's important to anticipate these issues and ensure the right expertise is in place to address them.

Another major challenge is cost. Much of the progress in advanced therapies so far has focused on rare diseases, which makes development and production particularly expensive as the volume of sales is limited. The real opportunity now lies in finding ways to reduce the cost of both development and manufacturing, so these transformative therapies can reach more patients.

You previously spoke to us in 2022 – and you predicted that cell and gene therapy companies may have to fight for funding in the near future. How has the investment landscape for gene therapies fared in 2025?
Securing funding was challenging in 2022, and over the past two to three years it has become even more difficult, particularly in the cell and gene therapy space. It's not for lack of effort; many companies simply haven't been able to access the necessary funding. I saw a similar pattern during the 2008 recession. The US continues to lead globally in life sciences investment, but within Europe, the UK remains the frontrunner in attracting the most funding.

What can help make a company stand out from the crowd?
When assessing or conducting due diligence for a company or product, I use what I call the "five Ps":

- **People.** Who is running the company? What is their experience and track record?
- **Patent.** What intellectual property does the company hold related to its product?
- **Product**. Is there solid data being generated? Can it realistically be developed? Is it druggable, scalable, and capable of being manufactured at the necessary scale?
- **Profit.** Is there a clear path to profitability, and does a viable market exist for it?
- **PR.** How well does the company communicate its progress? Are key milestones, such as clinical trial starts or result announcements, clearly shared to help increase visibility and company valuation?

Your consultancy offers expertise in several areas. What type of advice is in high demand??
While the cell and gene therapy market has slowed, we've seen a real resurgence in the development of new chemical entities. It feels as though the focus has shifted back to traditional chemistry, such as small molecules, organic chemistry, and antibody-drug conjugates.

The use of RNA-based medicines also seems to have passed its peak. A few years ago, many companies were moving into RNA or RNA-based therapies, and of course, we saw the success of RNA vaccines. However, that initial excitement has faded, and the spotlight has now returned to other therapeutic modalities.

Link
Read the full article online

Digital Twins in CAR-T Manufacturing

Here's why the Cell and Gene Therapy Catapult is excited about the potential of digital twin technology.

By Marc-Olivier Baradez, Head of Data Sciences, Cell and Gene Therapy Catapult

The ability to engineer a patient's own immune cells outside of their body and reinfuse them to fight cancer is nothing short of a lifesaving revolution. This is what CAR-T cell therapies have delivered to over 30,000 patients since 2017. Complex cell and gene therapies are here to stay. In the next five years, an estimated two million more patients will be eligible for these potentially curative CAR-T treatments alone.

Sadly, the scale required to achieve global demand is not attainable under current manufacturing models. These processes are a blend of people and automation islands requiring specialized skillsets that are intricate, expensive, and time consuming to scale. Every touchpoint in the manufacturing process introduces risks, such as contamination, inconsistency, or outright failure. These issues drive up costs and prolong timelines.

I think we can do something about these challenges. If we are to make CAR-T therapies truly accessible, we must fundamentally rethink how we approach their manufacture. Enter the digital twin.

Imagine a computerized system that feeds from all information

"I envision a future where digital twins optimize protocols through modeling and simulation, enabling faster decision making and reducing the need for extensive manual monitoring."

pertaining to the making of these complex therapies, the composition of the patient's blood, the ingredients of the medium that will expand the therapeutic cells, the process parameters that control the physics, chemistry, biochemistry, and biology of the entire manufacturing process. Such a system, designed to be an accurate in silico replica of the physical process, could break through the bottlenecks of existing approaches.

How? By using a technology platform that incorporates real-time monitoring. We can throw state-of-the-art process analytical technology at the digital twin challenge to capture, in real-time, all those important parameters. For the data that cannot be captured instantaneously, we can deploy streamlined processes to generate at-line and off-line analytics, a hybrid of devices and digital tools that rapidly generates this vast amount of data and transforms them into actionable formats. Like a photograph capturing a scene in an instant, we can capture all that we can during the manufacture of a CAR-T product; a snapshot for multiple products and multiple scenarios of the process, multiple times, quickly.

Why? The digital twin feeds on this data. Its purpose is to use all relevant associations in the dataset, all correlations, all hidden rules, to drive instructions to the manufacturing platform and make it produce the best quality product as quickly and as efficiently as possible. However (and this is where we are with CAR-T manufacture), those associations need to be worked out first. By collaborating with UCL's Stephen Goldrick, the Cell and Gene Therapy Catapult hopes to develop advanced process models for CAR-T manufacturing. These modeling endeavors will help identify what is important to control, and a digital platform to simulate a wealth of scenarios, giving us options to identify which will optimize the manufacturing process.

Smooth sailing from here? Not quite. How do we close the loop? How can the digital twin bring virtual instructions to life in the real world? Dynamic process control requires a seamless blend of cutting-edge integrated technologies. We must track the biological fingerprint of the patient's cells as critical quality attributes. A solid good manufacturing process (GMP) is essential to ensure that all data are adequate and directed to the digital twin in accordance with regulatory standards, using the right channels. This is critical because most CAR-T manufacture issues stem from poor cell quality and characterization, as well as process variability and limited control strategies. Then, the process must unfold under the guidance of the digital twin, with commands and instructions flowing smoothly through communication pipelines that link the twin to all the machines. Luckily, there exist a few standard communication protocols and data formats that enable this, but few technologies have yet been connected at scale – especially in a GMP setting – and even fewer involve cutting-edge sensors and a digital brain running the entire operation.

Developing a digital twin for CAR-T manufacturing is a marathon, not a sprint. I envision a future where digital twins optimize protocols through modeling and simulation, enabling faster decision making and reducing the need for extensive manual monitoring. The automation of manufacturing and analytical technologies, combined with the insights offered by digital twins, will allow the production of CAR-T therapies at a lower cost and greater scale. Patients will benefit from quicker access to more affordable therapies.

A thriving industry delivering life-changing therapies to the world through powerful collaboration, sharing knowledge, and making breakthroughs. Right now, the CGT Catapult is expanding these capabilities through partnerships, innovative deployment of next-generation equipment and facilities, and access to unrivalled ATMP datasets. The goal is to inspire stakeholders from all fields to push technologies forward, establish industry standards, and drive collaborative efforts with the aim of digitalizing the sector. Greater patient access to these lifesaving therapies cannot be achieved at scale without digitalization, and digital twins are central to making that vision a reality.

Link
Online Article

Advancing AAV Manufacturing Quality

Overcoming the limitations of the triple plasmid transient transfection method for AAV manufacturing.

By Efrain Guzman, VP of Innovation and Business Development, NewBiologix

Gene therapy is defined as the use of genetic material to treat or prevent diseases. The genetic material, DNA or RNA, contains instructions on how the functions of the cells should be modified. As this genetic material needs to be delivered inside the cells, viruses are often used as the vehicle for this purpose. The most commonly used is the adeno-associated virus (AAV).

Discovered in 1965, AAV was first used for gene therapy applications in the 1980s. In the 1990s, advances in recombinant DNA technology resulted in the establishment of the method that is still used today for the manufacture of AAV products: the so-called "triple plasmid transfection system." Although some small modifications have been made, the reality is that the system for producing AAV has not changed for almost 30 years. In my view, this represents an arrested development in the field.

The triple plasmid transient transfection method has been found to be difficult to adapt to large production volumes, impacting the homogeneity of the production batches, as well as the cost of goods to produce gene therapy medicines. Furthermore, in AAV production using the triple plasmid transfection system, large amounts of plasmid DNA are introduced into the virus-producing cells, normally the HEK293 cell line. The plasmids contain the genetic information to produce the virus, and the information needed to treat the disease, as well as any DNA not relevant for AAV production such as bacterial genes. Thus, pieces of plasmid DNA, as well as DNA from the HEK-293 cell genome, can be incorporated into AAV particles during the manufacturing process, possibly impacting the quality of the gene therapy drug product.

Thus, the challenge is to manufacture AAV gene therapy products of the highest possible quality by monitoring, adapting, improving, and controlling manufacturing processes so we can reduce the number of failed production batches because of the low quality of the products.

By focusing on DNA encapsidation, one of the fundamental issues in AAV manufacturing – ensuring that the viral vectors contain the correct full-length therapeutic DNA while minimizing the presence of truncated, partial, or empty capsids – can now be addressed. Advances in DNA sequencing technologies have enabled manufacturers to establish a series of quality-controlled processes to carefully assess how much undesired plasmid or cellular DNA is present in the AAV drug product. This data can be used to adapt, modify, or improve the manufacturing process to obtain the lowest possible amounts of contaminating DNA. Analytics of this kind are fundamental for the production of efficient and safer gene therapy treatments for human use.

Going one step further to include analyses of the integrity of the AAV-encapsidated therapeutic transgene is the innovation required to drive the industry forward.

Third-generation sequencing and bioinformatic solutions applied to AAV-based gene therapy products are a powerful tool for characterizing the integrity of AAV genomes, identifying variants, mutations, and contaminants – and thereby confirming AAV purity, which is crucial for the development and quality control of AAV-based gene therapies.

These solutions can and will result in the production of AAV gene therapy products of the highest quality possible, with the most chance of therapeutic success for patients.

Link
Online Article

Building a Resilient CGT Workforce

With competition for skilled employees in cell and gene therapy manufacturing high, companies need to ensure they are investing in training and mentorship.

By Daniel Palmacci, Executive Committee Member and Head of Specialized Modalities, Lonza

Life-changing treatments with unmatched efficacy are being held off by manufacturing in a tight bottleneck. Not only are manufacturing processes for cell and gene therapies (CGT) slow, complex, and hard to scale, but the manual nature also demands a highly skilled workforce. Hiring, training, and maintaining this critical mass and pool of talent might be the biggest challenge at hand for drug developers as well as CDMOs. With the CGT field in its infancy, the teams with the experience to develop a product from pre-clinical to cGMP manufacturing are few.

Skilled workers are needed at every level, from cell biologists, molecular biologists, immunologists, organic and analytical chemists, and biochemical and biomedical engineers, to manufacturing technicians, and more. With CGT job postings growing 400 percent in just four years, and specialized skills in cell therapy expected to increase by 75 percent by 2026, the industry faces an urgent need for skilled professionals to meet this demand. Developing this talent isn't optional – it's an industry imperative.

Keeping a finger on the pulse and walking in the shoes of the personnel developing cell and gene therapies is essential. To this end, I regularly gown up and enter the clean room to remind myself of the meticulous procedures.

The wide range of processes, including open operations, where the cells or genetic material are manipulated outside of a fully enclosed system and exposed to the surrounding environment, makes CGT manufacturing a demanding profession. For instance, the manual skill required for open operations to perform cell separation, purification, and transduction while observing the protocols of a high-cleanliness setting or Grade B environment is immense.

Though parts of the CGT process are automated, tailoring therapies to individual patient needs requires knowledge and practice of many delicate procedures. For example, stringent aseptic protocols, as well as freezing and thawing protocols, must all be completed within strict clinical schedules. CGT personnel must be able to seamlessly navigate both automated and hands-on manual processes. However, this hands-on approach can also be highly rewarding in that it fosters a profound connection to the patient, making a career in CGT manufacturing a deeply meaningful and purpose-driven profession.

Investing in robust training, mentorship, and professional development is important for all companies and CDMOs involved in CGT manufacturing. Precision and adherence to strict protocols are non-negotiable. Technicians must not only oversee automated systems, but be prepared to work in open labs using manual procedures prone to contamination. Training in contamination control and aseptic techniques is imperative.

A successful training program should be designed to meet these demands head-on. New technicians should undergo an intensive training regimen to equip them with the knowledge and hands-on experience necessary to achieve excellence. It is also important to emphasize continuous skill development to keep pace with industry advancements and retain a world-class workforce.

Manufacturing personnel will seek opportunities to grow their skill sets, and companies should respect and encourage those desires. Encouraging open dialogue between employees and managers is one way to promote professional development, although that requires a culture where employees feel secure enough to freely express grievances, concerns, and ideas. Providing skilled employees with talent development opportunities through an expat program can be a great incentive for employees, allowing them to learn in multiple locations to deepen their understanding of the product development journey. In Lonza, for example, many team members have moved across regions, from Texas and New Hampshire, to the Netherlands or Singapore.

Link
Read the full article online

Making CAR T Truly Off the Shelf

Could a single infusion transform a patient's own T cells into cancer-fighting machines? Researchers are betting on single-stranded DNA and lipid nanoparticles to make in vivo CAR T a scalable reality.

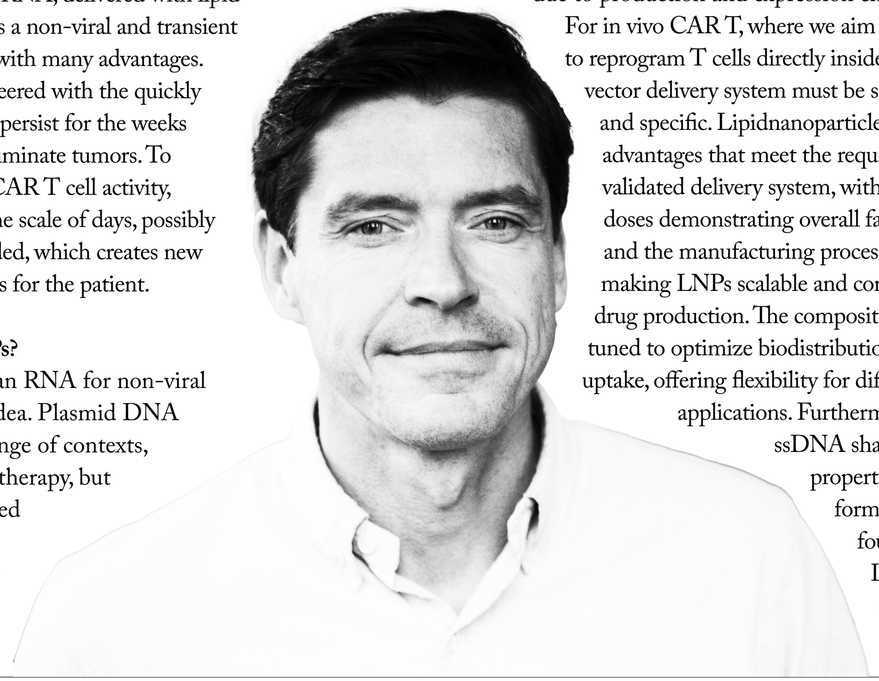
By Hendrik Dietz, CEO, CPTx

To achieve scale in the cell and gene therapy field, we must overcome manufacturing barriers. In traditional ex vivo CAR T manufacturing, T cells are harvested from the patient, engineered with viral vectors, expanded, and reinfused to the patient, who has also had to endure lymphodepletion. This is laborious, expensive, and burdensome for the patient. In contrast, generating CAR T cells directly in the patient with a simple infusion would enable off-the-shelf production of CAR T therapies and drastically improve patient access, while avoiding the straining lymphodepletion procedure.

How do we make this happen? In my view, single-stranded DNA (ssDNA) can make in vivo CAR T therapeutics a commercial reality.

Viral vectors are the current, conventional workhorses for autologous and allogeneic CAR T manufacturing because they can deliver large genetic payloads and integrate into the genome to provide long-term expression. However, genetic integration comes at the cost of insertional mutagenesis risks and has unpredictable long-term effects. Cancer patients, already immunocompromised, thus face a complex mix of additional risks of genotoxicity, inflammation, and immune responses from a viral vector-based in vivo CAR T treatment.

mRNA has also been explored as a potential in vivo approach for CAR T therapeutics. mRNA, delivered with lipid nanoparticles (LNPs), is a non-viral and transient gene vector alternative with many advantages. But CAR T cells engineered with the quickly fading mRNA will not persist for the weeks or months needed to eliminate tumors. To maintain the required CAR T cell activity, frequent redosing, on the scale of days, possibly even hours, will be needed, which creates new risks and health burdens for the patient.



Why ssDNA and LNPs?

Using DNA rather than RNA for non-viral delivery is not a new idea. Plasmid DNA has been tested in a range of contexts, from vaccines to gene therapy, but has faced hurdles related to innate immune activation, particularly in immune cells such as T cells, and inefficient nuclear entry. What distinguishes ssDNA is that it overcomes several of these key barriers.

ssDNA can be used both for transient expression and for permanent genetic CAR integration, allowing to engineer fit-for-purpose therapies. Interest in ssDNA as a non-viral vector has been peripheral traditionally, and it has been frequently written off due to production and expression challenges.

For in vivo CAR T, where we aim to use a simple infusion to reprogram T cells directly inside the body, the genetic vector delivery system must be safe, durable, scalable, and specific. Lipidnanoparticles (LNP) offer several advantages that meet the requirements. It is a clinically validated delivery system, with billions of vaccine doses demonstrating overall favorable safety profile and the manufacturing processes are well established, making LNPs scalable and compatible with large-scale drug production. The composition of LNPs can be tuned to optimize biodistribution, stability, and cellular uptake, offering flexibility for different therapeutic applications. Furthermore, because mRNA and ssDNA share similar biophysical properties, existing mRNA LNP formulations provide a useful foundation for developing LNP systems suitable for ssDNA delivery.

Link
Read the full article online

Manufacturing at scale shouldn’t mean compromising on precision.

We protect science so you can scale advanced therapies with confidence.

Designed to scale with you. From process development to commercial production. Consistent, validated performance across every stage of advanced therapy manufacturing.

PHCbi

The Multifaceted Future of Pharma: The Manufacturing Challenges of Advanced Therapies

As cell and gene therapies become more commonplace, focus has now moved onto manufacturing efficiency and improving access for patients.

The curative potential of cell and gene therapies is well acknowledged, but access and affordability are significant issues. Experts discuss why access is the true measure of success and how more efficient, cost-effective manufacturing processes can help.

We asked: What has/have been the key disruptor(s) driving the industry over the past ten years, and how will this change in the next 10 years?

Here, we include views related to the manufacture of advanced therapies.

The Evolution of Manufacturing – with David Smith, VP of Development, BioCentriq

To enable continued growth, these therapies need to be democratized to the masses, akin with how digitization of DVDs took reign over VHS; only through standardization was there a significant reduction in cost, improved production technology (consumable and hardware), and increased adoption even enabled films in the headrests of cars. The next step was online streaming…

The next generation of cell and gene products are already reducing manufacturing timelines, delivering more potent, smaller doses, reducing vein to vein time – and we are completing it with digitized, automated solutions. With this all-in place, acceleration will continue over the next decade. I hope to see standardization of agile manufacturing platforms across the industry, rapid analytical strategies enabling same day administrations, point of care treatment, and true democratization of cell and gene therapies.

Learning From Biologics – with Jason Bock, CEO, CTMC

The vast role played by the immune system across a spectrum of diseases has been the key disruptor in the biotech industry over the past decade. Biotech has developed therapeutic strategies to either activate or regulate the immune system for different purposes. For cancer treatment, checkpoint inhibitors are used to release the brakes on the immune system, while for autoimmune diseases like rheumatoid arthritis, anti-TNF medications are employed to suppress the immune response.

Precise targeting and long serum half-life of monoclonal antibodies have been utilized as tools to modulate specific pathways of an immune response. As our understanding of the immune system has deepened, the industry has shifted to a more direct path to utilize immune cells as the effectors. The ability to directly engineer an immune response that can persist for years

– or even decades – through living cells has enormous potential. The emerging field of cellular therapy will generate new therapies to treat refractory medical conditions, and could transform how healthcare is administered through the single-dose, curative potential of this modality.

While current progress is promising, autologous cell therapy comes with challenges in chemistry, manufacturing, and control for developers. These therapies are the most complex ever developed as they are derived from each patient's own cells. This uniqueness necessitates a complete reimagining of the traditional supply chain and economics. Since the starting material is the patient's own cells and manufacturing occurs on demand, the relationship between the clinic and manufacturer is intertwined in such a way that the manufacturer functions like a pharmacy for cell therapies. Although the field has seen dramatic clinical efficacy responses, creating a fit-for-purpose supply chain infrastructure that meets demand at a manageable cost remains a significant hurdle.

One approach to overcome these challenges would be the creation of key regional manufacturing hubs around the country aligned with major medical and population centers. An industrial, built-for-purpose regional "cell pharmacy" could develop locally integrated supply chain and logistics to streamline the coordination of cell collection, production, and infusion. These hubs could provide cell therapies from multiple commercial sponsors to benefit from economies of scale and drive a shift from open and manual processes to closed, automated ones. Digital, cloud-based quality systems will be essential to maintain consistency and process control across such a network. Such interconnectedness is a key differentiator from the concept of fully decentralized, localized manufacturing.

We have a golden opportunity to transform healthcare from the continuous management of chronic conditions to a short-interaction, curative model. Cell therapies have demonstrated efficacy in illnesses ranging from terminal cancer to sickle cell disease. By leveraging what we have learned over the last decade in complex biologics manufacturing controls and applying those lessons in this new context, we can revolutionize health treatments. Future generations will likely look back in amazement at how medicine was practiced before the advent of cell therapy.

True Success is Measured by Access – with Carolyn Sasse, Head of Clinical Operations, Data Science and China Development, Astellas Pharma

Over the last ten years, gene therapy has transformed from an emerging technology to an area of immense growth. With hundreds of gene therapy clinical trials underway, many biotech and pharmaceutical companies are dedicated to making this new era of genetic medicines a reality.

True progress and success will be measured by patients' ability to access treatments. Trials must be designed in a way that will support approval and reimbursement. Payors must see the value of a potential one-time gene therapy treatment and be able to approve treatments based on endpoints that are expected to predict the clinical benefit and durable effect. Industry, health authorities, and payors must adapt their strategies to account for what patients and their caregivers value. Only through this collaborative approach can we effectively seize the tremendous opportunity to broadly deliver gene therapy for patients.

Production Efficiency is Crucial – with Hideki Shima, Chief Manufacturing Officer, Astellas Pharma

Cell and gene therapies can play a key role in addressing unmet medical needs, but a step change in manufacturing is needed to enhance affordability and supply to reach patients in need. Over the past few decades, the antibody yield has also increased by hundreds of times. At Astellas, we have observed a similar trend with AAV production. Continuous efforts will enhance productivity with reduced manufacturing costs, enabling these new innovative medicines to truly support patients.

Three elements can help increase production efficiencies. First, we need to increase productivity per unit volume; for example, if we can increase the cell density by ten times in one reactor, the yield will also increase. Second is output per host cell or individual organism per unit time. Through advanced cellular genetic engineering, we can modify cell characteristics and their environmental tolerance to increase productivity. Third, I believe that scale up can be assisted by digital technology. Digital technology will allow us to conduct more simulations with even more precise predictivity. Improvement of monitoring and analytical technologies will also support the pursuit of a robust process in handling cell and gene therapies.

The next ten years will be an exciting journey of exploration and significant advancements in the field.

Overcoming Outdated Processes – with Jason C. Foster, CEO, Ori Biotech

Manufacturing remains a critical barrier to scaling cell and gene therapies, limiting the clinical and commercial impact of this life-saving new class of therapies. As we look ahead to the next decade, a pivotal focus must be placed on scaling impact by ensuring these treatments are approvable, accessible, and affordable.

Autologous cell therapies present challenges that the industry has never faced before – both in manufacturing and supply chains. The industry has applied the best learnings from biologics and other modalities in the first iteration of processes, but repurposing equipment from other modalities has only gotten us so far. We now need a second generation of more bespoke, automated technologies to solve these challenges and really make a step change in patient access. CGT developers are essentially manufacturing companies. To achieve commercial viability, we need to prioritize manufacturability, CMC, and viability as equally as we do safety and efficacy early in the development journey.

The cell and gene industry is at a crossroads. It must transition from its traditional, labor-intensive methods to more modern, efficient systems that automate better biology, accelerate product development, and scale the clinical and commercial impact of this new generation of therapies. To enable widespread patient access, manufacturing platforms must support a seamless transition from R&D to commercial-scale GMP manufacturing. This will allow innovative advanced therapies to reach the market and patients faster by reducing development time, increasing throughput, lowering COGS, and reducing batch failures.

Furthermore, the manufacturing of cell and gene therapies is hampered by outdated, paper-based practices carried over from

"Digitization and automation are key to reducing errors, improving efficiency, and enabling scale."

large-batch pharmaceutical manufacturing. A 1,000-paper batch record is appropriate when it represents thousands of doses, but it's a different story when the same type of record is required for every batch of a personalized autologous cell-based therapy. Practices like these are only one way in which outdated manufacturing practices hinder efficiency and, more importantly, limit the ability to scale cell and gene therapies to meet growing patient needs.

To overcome these challenges, a radical transformation is needed. Moving away from paper-based records to digital systems will introduce much-needed flexibility and real-time data access, facilitating better decision-making and faster responses to process deviations. This shift, when combined with automation, will streamline workflows, reduce human error, enhance overall throughput, and reduce batch failures, making it possible to scale production to meet increasing demand.

Advanced, automated manufacturing technologies can significantly improve efficiency by eliminating batch processing inefficiencies and reducing the need for extensive human intervention. Smart manufacturing systems that incorporate sensors and data analytics will further enhance equipment uptime and provide valuable insights into process performance, ensuring that manufacturing processes are both scalable and adaptable.

Digitization is another component of the puzzle that will enable real-time monitoring and control of the manufacturing process, providing critical insights that can be used to optimize operations. By leveraging data analytics, manufacturers will be able to identify trends and patterns that may not be apparent through manual inspection, allowing for proactive adjustments to improve efficiency and quality. Advanced sensors that monitor critical parameters in real time allow for immediate detection and correction of any deviations from the desired process conditions.

Data collected from these sensors can be analyzed to identify opportunities for further optimization, driving continuous improvement in the manufacturing process. Critically, this empowers scientists to take back control. Current systems constrain their ability to innovate and optimize processes. By providing a platform that allows scientists to design processes according to their needs rather than being dictated by the system, we put control back in their hands.

Addressing these critical bottlenecks and embracing modern manufacturing solutions will enable the industry to scale its impact and ensure the viability of advanced therapies. This holistic approach is crucial for transforming healthcare and meeting the growing demand for innovative treatments. By leveraging the latest technologies and approaches, the industry can overcome the limitations of traditional methods and pave the way for a new era in drug development and manufacturing.

Aiming for First-in-Line – with Brian Burke, Chief Commercial Officer, Tozaro

The near-term value is very much around oncology and rare diseases, with autoimmune disease also now a consideration. The big question is how do we get the economics and safety profile of these therapeutics to a level where they can be deployed routinely as a first line treatment, or even in individuals who are not already presenting with serious symptoms or who are at risk of death?

For example, neurological and cardiac health tend to decline on a gradual basis over several decades until there is an acute presentation of ill health. In some cases, genotypic or other biomarker evidence may have offered pre-disease insight. Over the next 10 plus years, the challenge, therefore, is to be able to prescribe the correct cell or gene therapy at the right stage, potentially even prior to full presentation of the pathology. This requires a different paradigm for designing, personalising and manufacturing treatments to ensure they are safe and can be generated in an affordable manner.

Within cell and gene therapy manufacturing, viral vectors are often a crucial component in providing treatment, however manufacturing remains both opex and capex intensive. As manufacturing becomes more decentralized, new tools are required to increase efficiency of production while reducing the footprint

required to achieve this. Exploration of new technologies, such as synthetic affinity reagents, is helping to solve the challenges in viral vector processing by increasing yield of functional virus per manufacturing run, which consequently increases total capacity whilst reducing manufacturing costs – a key pivot point.

Over the coming years, advancements in how we manufacture cutting-edge therapies will be a main driver in broadening their uptake.

Moving to Automation – with Alex Sargent, Director of Process Development, Cell & Gene Therapy, Charles River Laboratories

With over 4,000 cell and gene therapies currently in development, according to the American Society of Gene and Cell Therapy, this market will continue to grow at an accelerated pace over the next 10 years.

As the number of approved cell and gene therapies continues to expand around the world, it will bring new challenges about how to increase affordability and availability. The focus will shift from feasibility to fulfilment in cell and gene therapies, and we will need to come up with new and better ways to manufacture and deliver these types of drugs. Shifting how we manufacture cell therapies could dramatically improve cost and access. Adopting automation for both the manufacture and testing of cell therapies has the potential to improve this industry. Current methods for manufacturing are often laborious and rudimentary, relying on systems and technologies developed decades ago to produce and grow cells in research laboratories. As the need to grow cells clinically and commercially for therapies has emerged, so too have fully automated systems and new technologies. Shifting more towards automation and technology, when appropriate and applicable, can elevate the way we make cell therapies so that they are affordable, safer, and more attainable for the patients who need them.

I would like to see the cost of cell therapies go down and their availability go up. I believe investing in automation and new technologies to manufacture these therapies can help achieve that. I also believe going from autologous, individualized therapies to allogeneic, universal therapies, where appropriate, can also help significantly drive new and effective cell-based treatments to patients on a global scale. If we continue to work towards these goals, we may see the promise of cell and gene therapy realized in our lifetimes, and diseases that today are a death sentence will become treatable and curable.

Gene Therapy for Common Ailments – with Curran Simpson, CEO, REGENXBIO

Gene therapy has the potential to change the way medicine is delivered for millions, and we are only at the beginning of seeing its impact and unleashing its full potential. Today, more than 30 cell and gene therapies have been approved by the FDA and thousands of patients with rare diseases, such as sickle cell disease and hemophilia, have benefited.

I believe the next wave will be even more transformative – bringing gene therapies from rare disease communities to the masses. Clinical researchers are exploring gene therapies for common ailments such as retinal, cardiovascular, metabolic diseases, and cancer. As we continue to advance this science and identify additional gene delivery mechanisms, significant breakthroughs are on the horizon.

"Each gene therapy requires a highly specialized manufacturing process that is difficult and costly to scale."

But the path forward isn't easy. Each gene therapy product will require a highly specialized manufacturing process, which can be difficult and costly to standardize and scale. Quality manufacturing is crucial to all stages of gene therapy development for both rare and common diseases, and I believe that the sponsors who invest in manufacturing and process development early will be the ones to succeed in this field.

The challenges in bringing these new medicines to patients are significant, but I'm confident we will overcome them. With researchers, physicians, sponsors, payers and patient communities working together, we have the potential to truly unleash the curative potential of gene therapy.

Incorporating AI into Manufacturing – with James J. Cody, Associate Director, Technical Evaluations, Charles River Laboratories

Some of the biggest disruptors to the field over the past ten years have been the market approvals of AAV vector-based gene therapies such as Glybera (by the EMA in 2012) and Luxturna (by the US FDA in 2017). Though gene therapy has been an active area of investigation for several decades now, these approvals set the stage for an increasing number of AAV approvals.

Similarly, oncology-directed therapeutics have also seen an increasing pace of clinical approvals, including the adenoviral vectors Gendicine (first approved in China in 2003) and Adstiladrin, as well as other modalities such as CAR-T therapies. The recent COVID-19 pandemic also prompted the swift commercialization of mRNA-based and adenoviral vector-based genetic vaccines.

It is reasonable to assume that the pace of approvals will continue to accelerate over the next 10 years. In fact, the FDA itself anticipated approving 10-20 cell and gene products per year by 2025, according to a statement released in 2019. In parallel, there is also a trend towards streamlining vector manufacturing to increase efficiency, shorten timelines, and drive down cost both for the vectors themselves and for critical raw materials such as plasmids. A number of technologies are likely to see wider adoption. For example, engineered and novel capsids will improve targeting and potentially reduce off-target effects. Engineered cell lines (both packaging cell lines and stable producer cell lines) may be employed to boost upstream productivity, perhaps through synthetic biology techniques.

I also believe that manufacturing as a whole (both upstream and downstream) will increasingly involve AI and mathematical modeling for in silico process optimization. However, while these techniques may guide the overall strategy and/or help identify key conditions, any type of process optimization will need to be backed by data collected from actual manufacturing runs. To that end, there will also be advances made on the product testing front, with new testing methods developed to shorten turnaround times and reduce required sample volumes, preserving material for clinical and commercial use. To date, many manufacturing challenges have already been addressed by taking a platform approach to both manufacturing and testing. A platform approach enables similar products to be more rapidly advanced through development.

The challenge going forward will be to balance the advantages of having a robust platform with the increasing variety of novel products and new manufacturing technologies. In this regard, having a modular approach (incorporating new technologies into "tried and true" platforms) will be advantageous.

Finally, the regulatory review process will also likely become more streamlined, aided by the ever-accumulating data of platform processes. The recent reorganization of the FDA's Office of Tissues and Advanced Therapies into the Office of Therapeutic Products demonstrates an anticipation of the growing tide of new product applications and a dedication to streamlining the review process.

Link

Read more about the future of pharma online

FUJIFILM

FUJIFILM Biotechnologies

Choose experience over trial and error

Your CDMO shouldn't be learning on your program

Few challenges in gene therapy development are as complex as viral vector production. Each step requires deep technical expertise to navigate the complexities associated with different viral vector types and their production needs.

- Process development
- Analytical development
- Tech transfer
- Scale-up
- GMP production
- Fill/Finish

AAV | Adenovirus | Lentivirus | HSV | MVA

We've done it all.

With over 50 INDs supported and 5+ active pre-commercial programs, FUJIFILM Biotechnologies' teams bring the experience to design scalable processes, reduce manufacturing risk, and keep your gene therapy programs moving forward.

fujifilmbiotechnologies.fujifilm.com/contact

Decentralized CAR-T: From Vision to Viability

What will it take to make decentralized CAR-T manufacturing work in the real world? Three experts discuss in this roundtable.

As cell and gene therapies progress, infrastructure must keep pace. Policymakers are responding, but policy alone won't close the gap between life-saving therapies and the patients who need them.

Centralized CAR T manufacturing has a number of structural problems including long vein-to-vein times, strained collection capacity, and geographical barriers that limit access for many patients. One way the field is beginning to address these issues is by rethinking where and how apheresis happens. Mobile leukapheresis units and regional hubs are emerging as a practical way to bring cell collection closer to patients and donors, with early pilots showing shorter timelines and broader reach.

The Blood and Cells Advocacy Roster (BCAR) brings together expert voices from across the industry to discuss how such models can work in practice. By linking apheresis sites, community hubs, and initial processing capacity under shared quality systems, BCAR experts are exploring whether decentralized starting material supply can be scaled without compromising regulatory standards or manufacturing consistency.

Here we speak with BCAR members Adrienne Mendoza, Chief Operations Officer at BBG Advanced Therapies and Senior Vice President at BioBridge Global; Amy Hines, Vice President of Clinical Apheresis at Vitalant; and Trevor Smith, Senior Manager, Regional Marketing, Terumo BCT to find out more.

How can we address bottlenecks associated with centralized CAR T manufacturing?

Amy Hines: The answer lies in using a network of apheresis collection and cellular therapy processing facilities that operate under a unified quality management system. We help address several well-known bottlenecks in centralized manufacturing, such as collection capacity (inpatient, outpatient), patient access to qualified apheresis collection services, and variability in starting material procurement processes. Initial cell processing and cryopreservation, when applicable, also addresses centralized manufacturing bottlenecks by more predictably delivering cellular starting material to the manufacturer when a manufacturing slot is available.

Adrienne Mendoza: We've all seen the limitations of current CAR T manufacturing models; long wait times, complex logistics, and geographic barriers that make access harder than it should be. BBG is tackling these bottlenecks by focusing upstream, where the journey begins: cell collection, testing, cryopreservation and logistics.

Mobile leukapheresis centers and regional access teams allow us to decouple the first input to CAR T manufacturing, which

"We address bottlenecks by creating access, meeting patients where they are, and building scalable manufacturing capacity without compromising quality or control."

is the process of collecting the patients' cells from the clinical site and bringing them closer to patients and healthy donors. This reduces vein-to-vein time, lowers costs, and expands the pool of clinical delivery sites/medical centers that can participate in advanced therapy delivery. But that's only the first industry transformation. These access points will form the foundation for a distributed GMP manufacturing model. For example, a pharma partner can engage with us for leukapheresis and for the execution of a regional manufacturing protocol – with real-time visibility, quality oversight, and compliant review/release built in. That's how we translate local access into scalable manufacturing capacity, without losing control of quality.

In short, we address bottlenecks by creating access, meeting patients where they are, aligning with sponsors on regulatory-ready solutions, and designing a network that can flex from cell collection all the way through distributed GMP manufacturing, testing, and final product release.

Trevor Smith: While bottlenecks from centralized manufacturing of CAR-T can arise from any number of sources, capacity in collections and manufacturing is often cited as the one of the most significant sources for delay. Robust, automated technologies have a dynamic range high enough to meet the needs of the industry, regardless of modality or indication.

How are you managing quality assurance and regulatory compliance in decentralized or multi-site CAR T manufacturing models?

AH: Our goal is to establish Vitalant as a reliable collaborator in decentralized CAR-T production. Through an integrated network of apheresis and cellular processing centers, we're looking to uphold a harmonized quality framework that aligns with regulatory standards and industry-leading protocols.

AM: Quality and compliance are the backbone of any advanced therapies service organization or biomanufacturing model — without them, you can't have a successful program. Our organization manages this through a unified quality management system that spans every aspect of our service lines: from starting materials, biomanufacturing, and cell therapy testing services. We've built an infrastructure to ensure consistency and compliance, and that allows us to deliver real-time visibility, full traceability, and review-by-exception even in multi-site or distributed environments. It's not just a form factor change of putting paper on digital devices, but instead a true system-level integration that ensures compliance with automation, validation and dynamic content. This reduces bottlenecks and enhances quality and compliance enterprise wide.

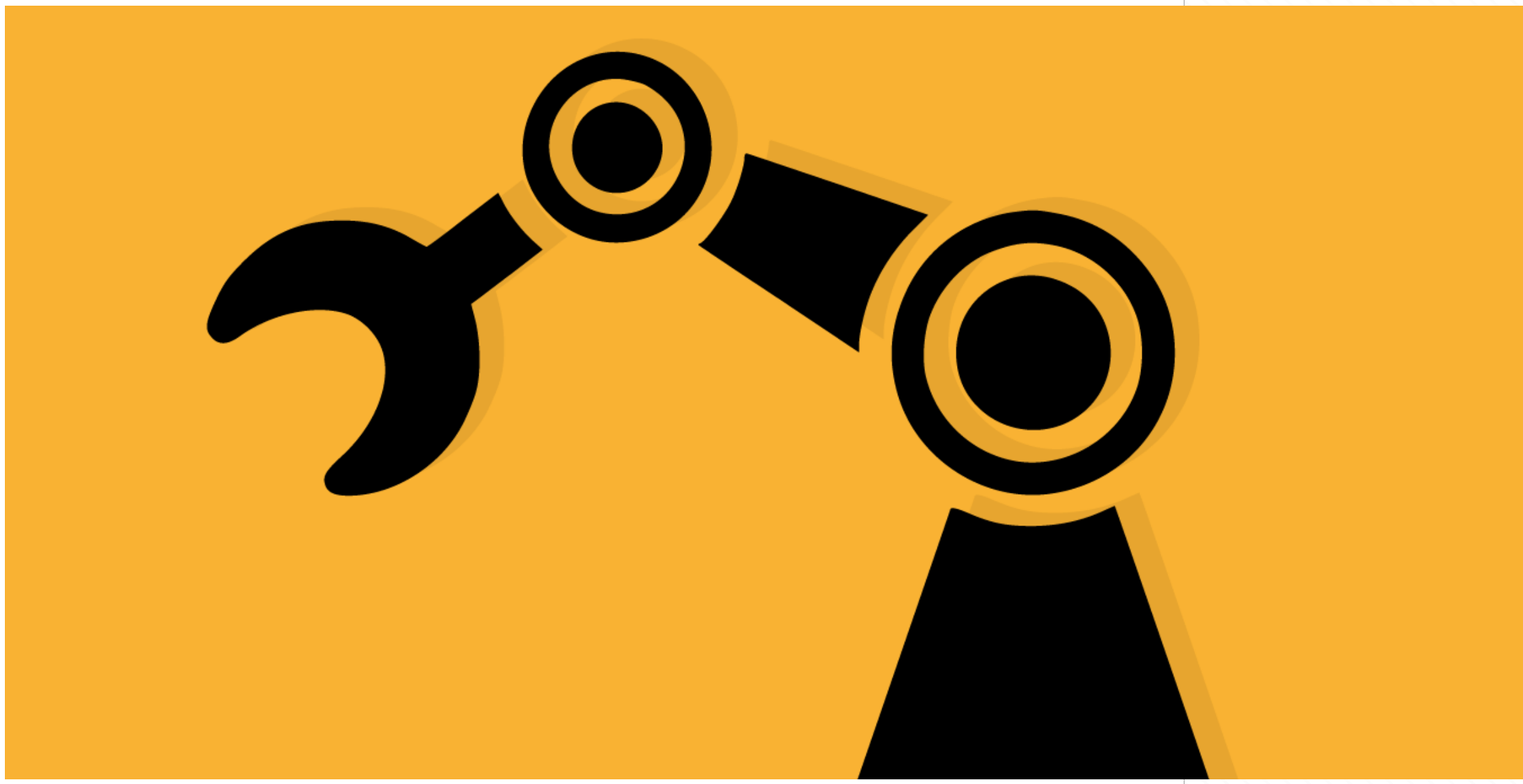
What role can automation play in improving CAR T manufacturing processes?

AM: Automation does show real promise in unlocking efficiencies, lowering costs, and eventually supporting distributed manufacturing models, but the real payoff will occur when we get all the way to fully closed automation, where every consumable is integrated and the process can move outside of heavy, resource-intensive cleanrooms. That's where true scale – at the lowest possible cost, and most accessible to patients and donors – becomes possible.

Link
Read the full article online

Rise of the Robots: Scaling Up Cell Therapies in Small Spaces

Manual processes in cell therapy manufacturing are unsustainable. Bring in the robots.



Multiply Labs, in partnership with Denmark-based robotics developer Universal Robots and the University of California San Francisco (UCSF), has developed a robotic "cluster" that they claim could significantly cut cell therapy manufacturing costs, while boosting output per square foot of cleanroom. We spoke with Multiply Labs CEO, Federico Parietti, to find out more.

How do robotics improve operational savings?
Historically, the biggest bottlenecks in manufacturing cell and gene therapies have been the high cost and low throughput associated with manual processes. These therapies require hundreds of delicate, manual steps carried out by highly trained operators. Even the best technicians can only work so fast, and human hands inevitably introduce variability and contamination. In practice, this means that it is simply not possible to produce enough therapies for all patients who need them. It also means that the cost of the few therapies that do get made are unaffordable for the majority of patients.

"By replicating manual steps with precision and consistency, robotics can scale therapy production while reducing costs and maintaining quality."

By replicating those same steps with precision, consistency, and round-the-clock operation using robotic technologies, we can scale up without sacrificing quality or reproducibility.

Manufacturing space is finite. What design elements enable space optimization?
A key element is recognizing that incubators require way more time to process cells than other instruments. Thus, it is important to have as many incubators as possible, in as dense a configuration as possible. The trick was to engineer the capability of fitting up to 36 independent bioreactors in just one square meter of floor space by stacking incubators. We then added a robotic arm mounted on a z-axis rail, effectively functioning like an elevator to extend its reach to the stacked incubators. This configuration has enabled higher throughput and lower manufacturing costs in the same cleanroom spaces.

How do you ensure robotic process remains compliant?
The FDA and EMA don't want to see new manufacturing processes invented from scratch. They want continuity with processes that are already validated. From a software perspective, we can leverage imitation learning, where robots are trained to perform the same manual steps that a human operator would do. This means that the very data used to train the robots are the motions of the scientists currently performing the FDA/EMA approved manufacturing process steps.

What are the biggest challenges in scaling a robot-powered approach across different manufacturing sites?
The first question people ask is about the ability of robots to truly match manual pharma processes. Scaling advanced therapy manufacturing isn't about making it work once; it's about repeatable operations deployed at thousands of workstations worldwide.

To successfully automate a biomanufacturing process, the robots must be statistically equivalent to corresponding manual processes. Working with academic institutions such as UCSF and Stanford, we were able to compare manual and robotic process steps and show that equivalent results can be achieved.

What's next? What further pharma manufacturing challenges do you expect to be tackled with robotics?
Right now, the obvious applications are in CAR T and other commercial cell therapies, because the demand is urgent and the manual process is unsustainable. The same principles apply to gene therapies, where some conditions affect only a few patients in the world, and even to the manufacturing of RNA therapies and advanced antibodies.
I believe the long-term vision is a robotic infrastructure for advanced therapies. A world where manufacturing is no longer the bottleneck, where the limiting factor is purely the biology of the therapy itself. That's when these treatments can truly become accessible at scale and reach their full potential to help patients in need, wherever they are.

Link
Online Article