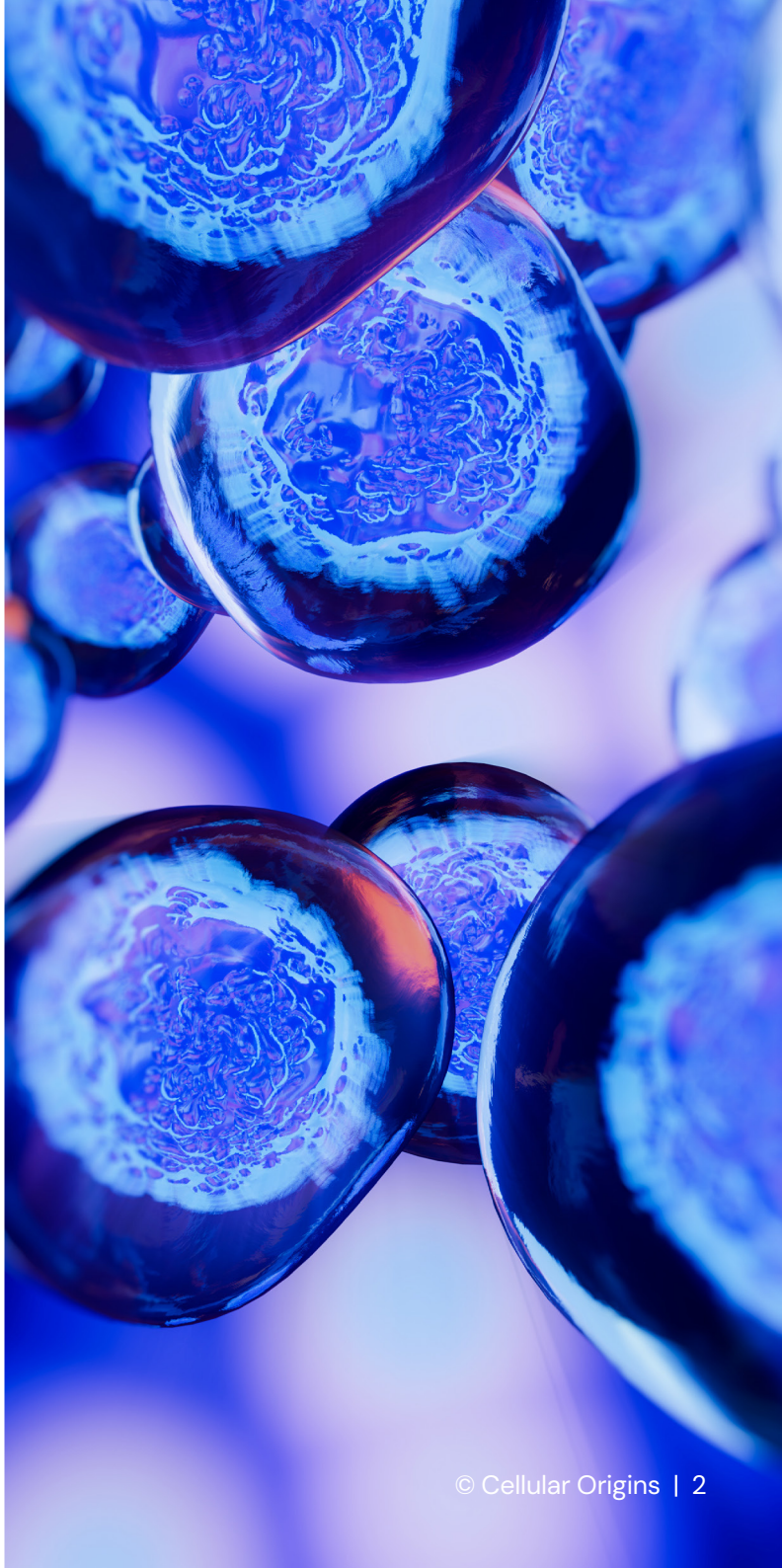
cellularorigins

Industrialising cell and gene therapy manufacturing

Cell-based therapies are advancing rapidly, with the potential to transform treatment across several diverse disease areas with significant unmet needs.

The industry is expected to grow rapidly, with estimated treatment eligible patients increasing to over 100,000 patients per year in the US alone by 2030 from a current baseline is 40,000, driven by an ever-increasing number of clinical trials and approved products entering the market.[1] Therapies like CAR-T have already demonstrated remarkable clinical success,[2] yet only a small fraction of eligible patients currently has access to these life-saving treatments.

While the proof of concept is well-established, the industry now faces a pivotal challenge: scaling manufacturing to broaden access, reduce costs and unlock the applicability of therapies across a wider range of diseases. Achieving this will be essential to meet the needs of a growing patient population and make cell therapies commercially viable on a global scale.



The challenge of scaling manufacturing is less rooted in biology than it is in the current reliance on manual techniques, or at least the manual operation of semi-automated devices and transfer between them and the manual collection of process data. These labour-intensive processes have served well in early-stage research and clinical trials but are prohibitively costly for wide-scale manufacturing. Advanced robotics and digital technologies are required to move the industry forward and achieve the scalability needed to make cell therapies available for more patients.

Cellular Origins is working with an ecosystem of industry partners – including the Cell and Gene Therapy Catapult and technology providers such as Cytiva, Fresenius Kabi USA and Thermo Fisher Scientific – to understand the challenges of scaling cell therapy manufacturing and highlight opportunities to overcome these hurdles with cutting-edge automation solutions. This eBook delves into the role of advanced technologies in transforming the production process, the importance of strategic partnerships, the complex regulatory landscape solution providers need to navigate, and the next steps to making widescale industrialisation of cell therapies a reality.

> *The more patients we treat, the more investment the industry will receive for future innovations. But until this industry becomes truly profitable and self-sufficient, we really need to overcome the challenge of scaling out.*
>
> **George White**
>
> Senior Director of Business Development,
> Cell Therapy, Cytiva

The challenge of scaling cell therapy manufacturing

Cell therapies are inherently complex, using living cells obtained from individual patients (autologous therapies) or donors (allogenic therapies).

This reliance on naturally-derived starting materials, combined with the intricacies of preventing cross contamination while maintaining cell viability, sterility and function, makes scaling these therapies significantly more challenging than conventional medicines, and is further complicated by the need to achieve very short manufacturing timelines from vein to vein. As a result, the industry is now grappling with how to cost effectively produce these treatments at a scale sufficient to meet the growing global demand.

The reliance on manual labour is a major obstacle impeding the scalability of cell therapy manufacturing. Production depends on labour-intensive tasks carried out by highly qualified personnel, with labour alone accounting for up to 50% of total cost of goods for a cell therapy.[3]

This cost is a major barrier to generating a viable and sustainable industry. It also means that large numbers of trained personnel would be needed, with estimates of over 100% increase in the coming years. Manual interventions also always carry with them a risk of contamination. Cell therapy manufacturing therefore needs to be performed in high-classification clean rooms that demand significant resources to maintain, including energy-intensive air filtration systems.

Limiting the number of manual tasks may help to reduce the risk of contamination, increase standardisation and reproducibility, and enable processes to be transferred to lower classification facilities, significantly expediting scale out while reducing costs.

The systems used for cell therapy manufacturing are placed in large, expensive clean rooms, which are only required because of the risk of contamination from the people in that environment. We spend a lot of energy pushing filtered air into these clean rooms, which is a concern for sustainability.

The industry is now looking at how we can change the working environment to bring down the costs, while making processes more predictable and efficient with universal control systems. This way we can produce materials that we know are consistent and efficacious.

Stephen Ward

Chief Technology Officer
Cell and Gene Therapy Catapult

Another major hurdle is the high manufacturing failure rate of approximately 25%,[4] which not only leads to significant financial losses, but also deprives patients – some of whom may not get another chance – of crucial, life-saving treatments.

These failures partly stem from inconsistencies in process control and product quality, potentially caused by human errors or operator-derived variability that add to the inherent variability of the starting materials.

This is compounded by the fact that clean rooms are often isolated and poorly integrated across different sites, leading to a lack of standardisation in procedures and practices. The introduction of automation for cell therapy manufacturing will help to reduce the reliance on manual labour going forward.

If cells do not function in the patient the way we need them to, therapy isn't going to be a success, and this ultimately comes down to the quality of the cells. We therefore need to be able to duplicate the results that we see in clinical trials using industrialised, automated systems. Contamination is also a risk, as the end product cannot be sterilised.

The potential for contamination – from not only microbial sources, but also particulates and chemicals – is a concern for safety and effectiveness, so must be eliminated every step of the way. Excitingly, there are now technologies – such as data monitoring and automation – that are allowing us to address these historical risks or challenges of scaling up.

Mary Kay Bates

Senior Global Applications Scientist,
Thermo Fisher Scientific

The role of robotics and advanced technologies in industrialisation of cell therapy manufacturing

The integration of robotics and automation into cell therapy manufacturing will streamline operations, reducing overheads and labour costs while enhancing scalability and sustainability.

By minimising human error and the risk of contamination, automation could also improve production success rates. Moreover, transitioning to physical and digital automation allows processes to become less dependent on highly skilled personnel, enabling a shift from traditional clean rooms to less restrictive environments.

This transition would free up laboratory personnel to focus on more impactful tasks and research, enabling future innovation, as well as dramatically cutting operational expenses.

Introducing automation and digitisation can help to deskill and de-risk these processes, potentially enabling them to move from class B clean rooms to class C 'ballroom' clean rooms or even beyond that in the future.

This will also help to increase productivity and the robustness of the processes, reducing the number of catastrophic batch failures, which impact patients and lead to a loss of revenue. Costs and labour are the areas that we need to reduce to make cell therapy manufacturing more viable.

George White

Senior Director of Business Development,
Cell Therapy, Cytiva

What does industrialisation look like?

Automation has already been a significant driver of success in many industries. In the bioprocessing sector, this has largely taken the form of isolated standalone systems though rarely involves automatically moving samples between different workstations. These small-scale automation solutions certainly have their place in many settings, but they are unlikely to enable the industrialisation of cell therapy manufacturing alone.

Large-scale industrialisation will instead require complete automation of manufacturing processes. Several vendors provide semi-automated, closed systems suitable for cell therapy manufacturing, either all-in-one or more modular devices servicing single unit operations.

However, confining processes to a single system would require therapy developers to either develop their manufacturing process to fit the requirements of that specific instrument, or change process technologies at a late stage of therapy development.

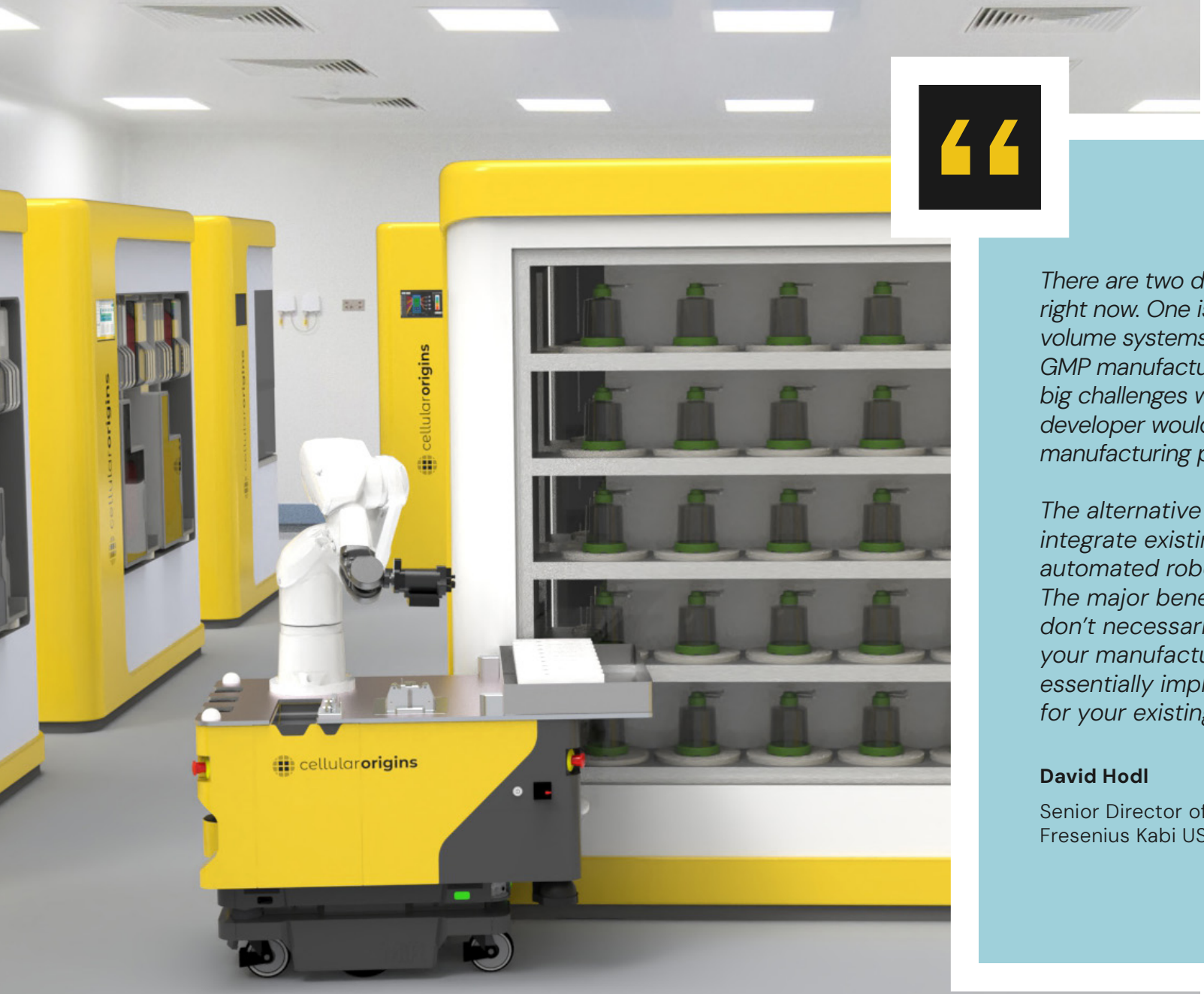
This risks stifling innovation, as fitting to a dictated workflow on a single device negates the possibility of process optimisation to benefit product efficacy and of expanding lengthier unit operation densities over quicker ones to increase production output in a defined manufacturing space. Late-stage changes to manufacturing technologies would also create concerns for regulators, by potentially interfering with the biology and cell-contacting materials of the approved process.

Modular devices inherently offer more process flexibility, but their use at scale necessitates numerous human interactions between unit operations – as well as for the transfer, set-up and operation of these systems – with all the disadvantages previously described.

Independent or technology-agnostic robotic systems could provide an alternative solution that brings together existing technologies from various suppliers and industries into a single automation platform. The adaptable nature of robotics can also cope with changing demand and workflow variations between different types of cell products, such as autologous and allogeneic cell therapies.

These systems are not necessarily radical new inventions; they've substantially helped to grow other industries, and it is with the experience gained in these settings that they can now be applied to cell therapy manufacturing.

However, careful application of automation is essential, especially for late stage or approved products, to ensure that no significant modifications to established processes are required when scaling to commercial manufacturing, so that processes and materials remain unchanged.



There are two different pathways to scale right now. One is larger, all-in-one, higher volume systems that are essentially GMP manufacturing in a box, but the big challenges with those is a therapy developer would need to change their manufacturing process to fit that system.

The alternative approach is to integrate existing unit operations with automated robotic infrastructures. The major benefit of this is that you don't necessarily have to modify your manufacturing process; you're essentially implementing robotic help for your existing manufacturing process.

David Hodl

Senior Director of Business Development,
Fresenius Kabi USA

It's important that these robotic instruments are closed systems to prevent any chances of contamination, preserving the safety and efficacy of therapies. Robots that ensure everything is sterilised are key differentiators.

Mary Kay Bates

Senior Global Applications Scientist,
Thermo Fisher Scientific

Robotic systems allow instruments to be knitted together, so that best-in-class cell processing platforms – as well as innovations being developed now or in the future – can be physically and digitally integrated.

This further encourages innovation and improves the consistency of materials. We can also reduce the amount of time that people need to spend performing routine, repetitive work, so that they can be deployed for more meaningful tasks.

Stephen Ward

Chief Technology Officer
Cell and Gene Therapy Catapult

In addition to automation, digitisation will be a critical step in scaling out cell therapy manufacturing. We are already seeing a transition to electronic batch records instead of paper, and continuing to integrate digital infrastructures will further reduce reliance on manual labour.

This will not only help to ensure full and accurate records, but will also enable harmonisation of data handling and control of equipment from different manufacturers as part of a single platform. Full automation will generate never seen before levels of process data that can ultimately be used to provide feedback and adjust robots in real time, enabling immediate optimisation.

Processing this data will be a huge task, and artificial intelligence (AI) and machine learning (ML) will no doubt play a crucial role in the industrialisation of this industry.

A crucial piece of scaling cell therapy manufacturing will be building and integrating the digital infrastructures to support scaled-up manufacturing processes.

David Hodl

Senior Director of Business Development,
Fresenius Kabi USA

How partnerships accelerate industrialisation and reduce cost of goods

Collaboration across the cell therapy ecosystem is essential to drive industrialisation. Every stakeholder – therapy developers, equipment manufacturers, supply chain partners, and healthcare providers – has a role to play in creating a seamless workflow.

By working together, the industry can address scaling challenges more effectively, ensuring supply chain readiness and preparing health systems for broader deployment. Standardising batch records and digitising workflows, for instance, can enable faster data analysis and improve consistency across operations.

Supply chain partners need to be engaged from the start, allowing them to plan ahead and adapt systems to meet growing demand. Similarly, technology developers can design solutions that manufacturers find scalable and efficient, reducing both the existing risks of failure and the compounding risks associated with scaling manufacturing.

Everyone has a part to play in making cell therapy manufacturing more accessible. The more we can share experiences and knowledge, the faster the whole sector will move on. We're essentially trying to create a bigger sector that everyone can benefit from, which is more cost- and time-effective than companies trying to do it all themselves.

The UK has made great progress with its Advanced Therapy Treatment Centres (ATTC), joining all the leading hospitals active in cell therapy to work in a more standardised way. This is helping to get the NHS ready for deploying clinical trials and, eventually, efficient commercial roll out.

Stephen Ward

Chief Technology Officer
Cell and Gene Therapy Catapult

Partnerships also enable quicker testing and validation of innovative technologies. By deploying systems in real-world environments, stakeholders can identify issues early, learn from the data generated, and improve processes iteratively. This approach not only shapes more reliable systems, but also builds trust through independent validation and shared experiences.

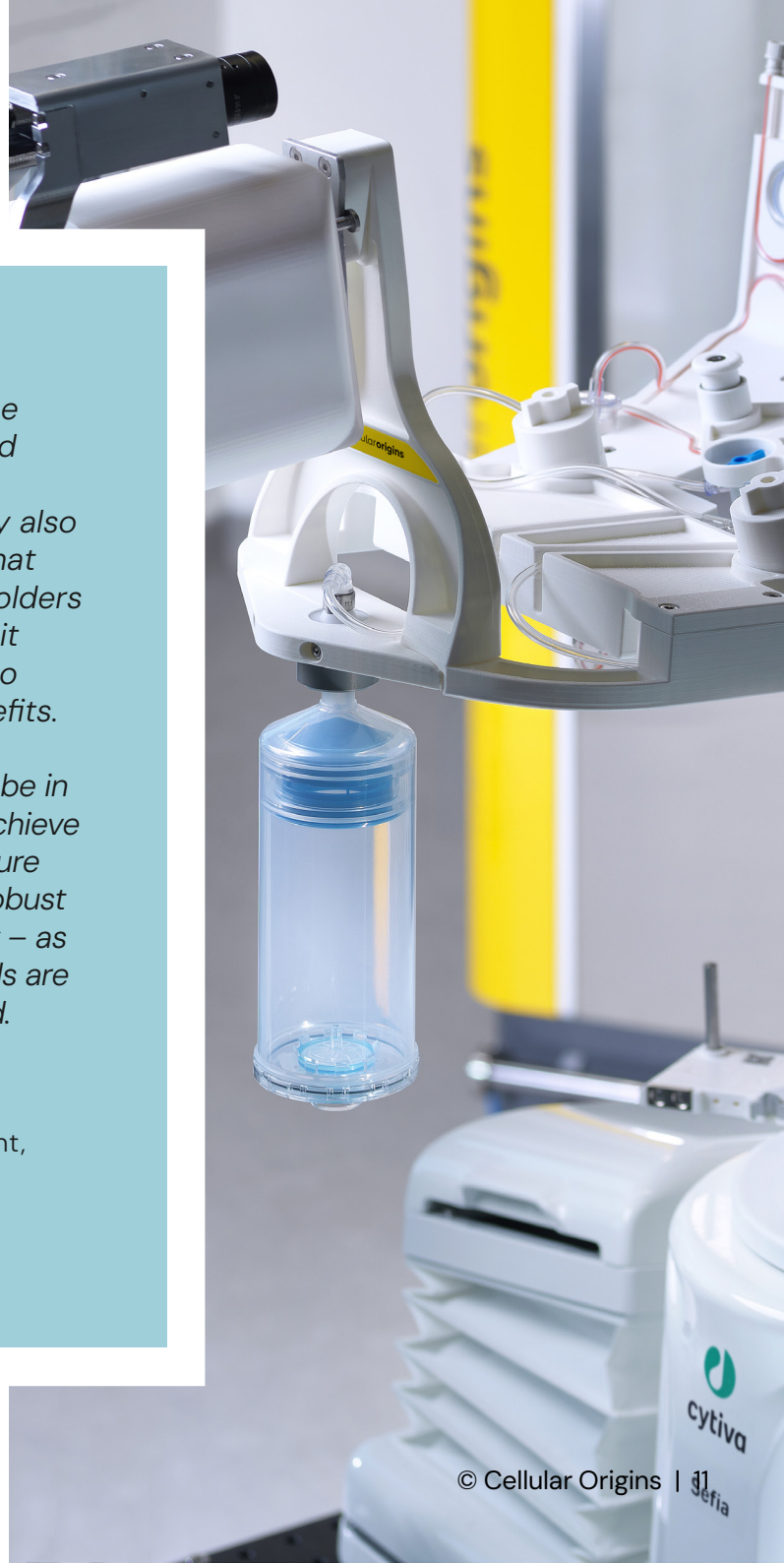
Importantly, true partnerships require alignment across all participants; clear communication, robust service models and shared accountability are crucial for success and de-risking the industry. When these elements come together, the entire sector benefits, creating a stronger, more cohesive foundation for scaling cell therapies efficiently and on a global level.

Collaboration is important because third party validation of automated systems is more credible from independent sources. The industry also needs an integrator; a company that can bring together various stakeholders and join innovations. You can't go it alone in this industry if you want to provide products with actual benefits.

The companies behind you have to be in agreement on how we're going to achieve success. This is critical for making sure vendors deliver products that are robust and efficient – with a secure supply – as we all understand what the demands are and when they need to be delivered.

George White

Senior Director of Business Development, Cell Therapy, Cytiva



How to de-risk industrialised manufacturing

The combination of collaboration, strategic introduction of automation, and early-stage integration of scalable solutions will all help to de-risk scaling of cell therapies. No single organisation can bear the full burden of industrialising the sector.

Collaborative models bringing together expertise from biopharma companies and technology providers enable shared risk and pooled resources. They can streamline innovation and help to navigate complexities such as process standardisation, regulatory alignment and scalability challenges.

Robotic and AI-driven technologies offer significant opportunities to de-risk manufacturing processes. Unlike traditional static or rail-mounted laboratory automation systems, modern robotic platforms – such as autonomous mobile robots with six-axis arms – provide the necessary flexibility to integrate existing workflows across a whole facility.

These systems, coupled with innovative tubing handling and connecting end effectors, can maintain the same sterile fluid pathways with the same consumables and cell-contacting materials used in small-scale clinical manufacturing. This preserves the biology and ensures minimal disruption to the way cells are washed, purified, activated, transduced and grown, as well as preserving their end formulation.

This makes automation suitable for therapies nearing market readiness – or even post-approval – and reduces the need to make excessive changes that could mean lengthy and costly comparability studies.

Additionally, AI tools – like robotic route planning and scheduling – can further optimise processes, use of available manufacturing space, process times and outputs, while reducing variability.

Technology providers and therapy manufacturers that build automation and industrialisation into their manufacturing strategies early can significantly reduce risks later in the development pipeline.

Early planning not only avoids costly retrofits and regulatory risk, but also enables process optimisation from the outset, making the scaling of production – when it is needed – lower risk, faster, cheaper and more efficient.

The ease with which you can modify consumables, software and hardware should be a consideration.

Robotic automation is typically going to be less disruptive to your manufacturing process than having to potentially change your entire unit operation to fit an all-in-one platform.

The risk of impacting the biological process is therefore lower when implementing an automated robotic platform.

David Hodl

Senior Director of Business Development, Fresenius Kabi USA

Regulatory alignment and quality standards

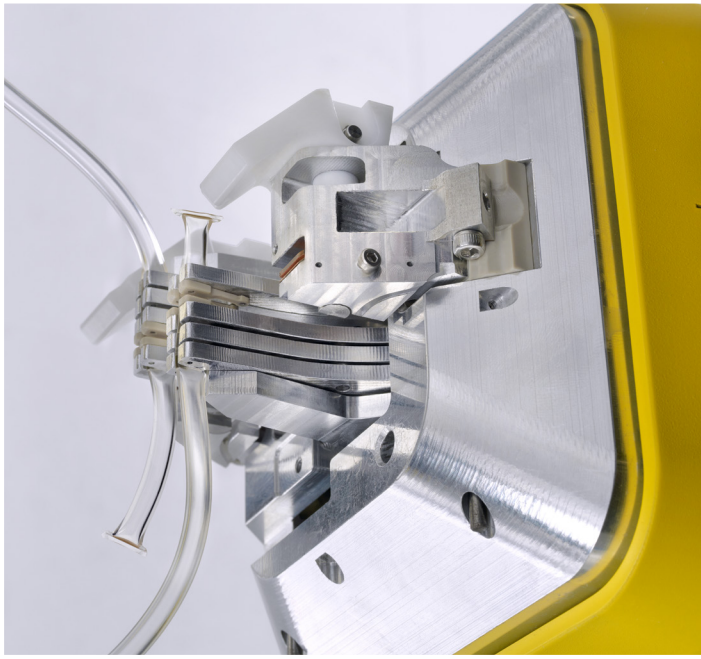
Scaling cell therapy manufacturing hinges on establishing robust regulatory standards for everything from hardware use to consumable connections to digital infrastructure. These standards are crucial to enable easier integration, connectivity and automation, all of which are key elements in achieving scalable manufacturing solutions.

Unfortunately, this has proven to be a significant challenge, and the industry has struggled to create universally accepted frameworks for a number of years. Introducing technology into cell manufacturing processes must be approached with care to maintain product quality, characteristics and integrity, which is obviously a significant priority for regulators.

Regulatory bodies expect any changes to processes to be supported by robust risk assessments and varying degrees of comparability studies – from process data packages to full repetition of clinical trials – to ensure that new methods deliver equivalent outcomes without altering the biology of the product. To ease this process, automation should not change existing processes, but instead incorporate proven, validated tools and existing manufacturing workflows with minimal changes.

Robotic systems that do not introduce any new cell-contacting materials or physical processes, and do not interfere with the underlying biology, can help to minimise the need for additional clinical studies, streamlining the path to scalability.

> *A critical milestone is the development of a base set of standards that are accepted across the industry, allowing easier integration and scaling of manufacturing processes to reduce the cost of goods and minimise labour requirements. These are milestones that we've made some advancements to achieve, but there is still room for improvement.*
>
> **David Hodl**
>
> Senior Director of Business Development, Fresenius Kabi USA



Regulatory authorities have demonstrated strong support for standardisation efforts and manufacturing innovation, recognising that, without significant technological advancements, the industry cannot meet the growing demand for cell therapies.

Regulators understand the critical role technology will play in providing patients with life-saving treatments, while removing labour-intensive processes that are prone to variability and inefficiency.

Importantly, regulatory authorities have shown an encouraging willingness to collaborate with technology providers, engaging in active discussions to understand the nuances of scaling both autologous and allogeneic therapies.

Establishing baseline standards will provide a foundation for further innovation. As these standards become more widely implemented, they promise to level the playing field and accelerate progress across the industry.

It is still a competitive landscape for therapy and tool providers, but there is an understanding that we need a baseline set of standards that all of us have access to. A good example is USB, which is readily accessible to pretty much anybody, but also allows further innovation and benefits everyone. Innovations like this will move the whole industry forward.

David Hodl

Senior Director of Business Development,
Fresenius Kabi USA

Conferences are important opportunities for therapy and tool providers to come together and explain to the regulatory bodies and associated organisations what is important to us, as one voice. Global harmonisation of regulations will really allow us to accelerate therapies to clinic, so that manufacturers don't need to meet different regulations in Asia Pacific and Europe, for example.

Mary Kay Bates

Senior Global Applications Scientist,
Thermo Fisher Scientific

The path to industrialisation

The cell therapy manufacturing industry is at a pivotal crossroads, where it needs to make the step-change to industrialisation.

With advancements in automation, robotics and data integration, we now have the tools to revolutionise production, making therapies more scalable and accessible.

Mobile robots, for instance, have matured to a point where they can operate safely and efficiently alongside humans, and the exciting challenge ahead lies in further improving the technology for this new application, as well as proving its impact at scale.

A critical objective is demonstrating that labour-intensive processes can be automated without compromising biological performance.

Once this is achieved, the path to scaling manufacturing becomes clearer, with the potential to significantly reduce facility sizes and operational costs while increasing dose production by orders of magnitude.

Fully automated facilities capable of producing tens of thousands of commercial doses annually – with a fraction of the footprint and workforce of current set-ups – should be within reach in the next two to three years, increasing to hundreds of thousands of doses within five years.

It must be noted, however, that analytics and quality control challenges remain a crucial part of scaling efforts and need serious consideration.

Current QC cycles – using low throughput technologies to analyse and release batches – must evolve to match the pace of industrialised production, or solving one bottleneck will only lead to another.

This requires further digitisation, more integrated processes, a reduction in the number of unnecessary tests, and the development of robust data standards to streamline testing and regulatory compliance. Industry-wide collaboration through consortia will also be essential to build a consensus on these standards and encourage broader acceptance and adoption.

This, combined with robotics and full automation, will transform cell therapy manufacturing into a scalable and efficient industry.

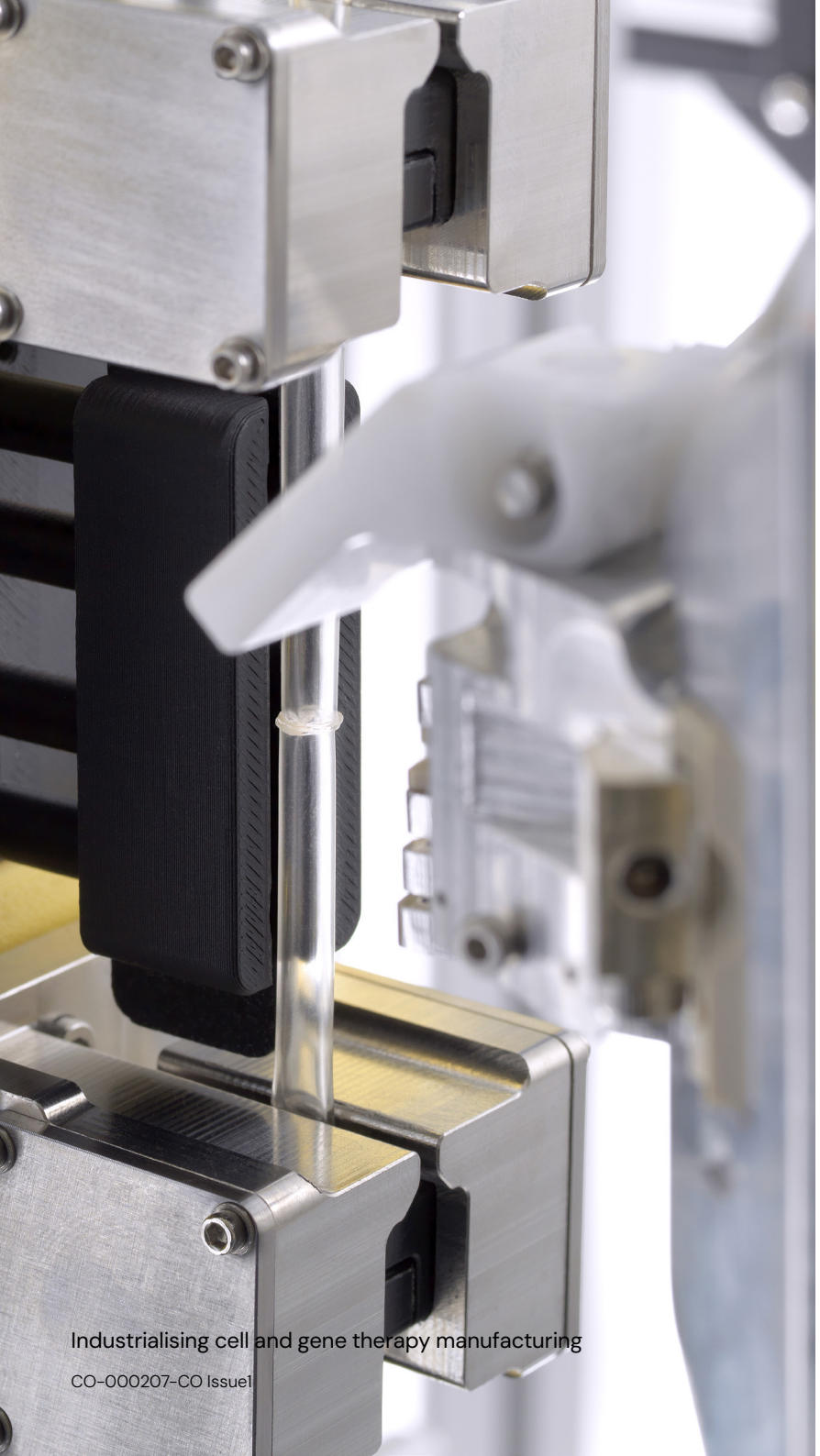
Cellular Origins' ecosystem, Constellation, enables our customers to use the tools and technologies they're familiar with, and without changing process, or without changing the consumable, go to scale.

We know that's important because once you're through clinical trial, you don't want to change biology, you don't want to add in any risk, and you want to move as quickly as possible to commercial scale.

We're now in an exciting time where we're going to be deploying solutions to customers. To be able to give hope to the patients that currently can't get access to these therapies is what really motivates the next few years of our journey.

Edwin Stone

Chief Executive Officer,
Cellular Origins



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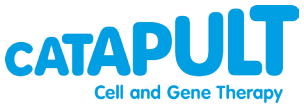
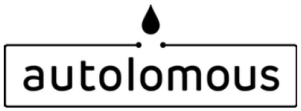
Together in cell therapy automation and enabling wider patient access





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