Rockwell Automation

Transforming cell & gene therapy manufacturing

Digitalization and automation promise a better way to streamline the transfer of cell and gene therapies from drug discovery – to commercial production.

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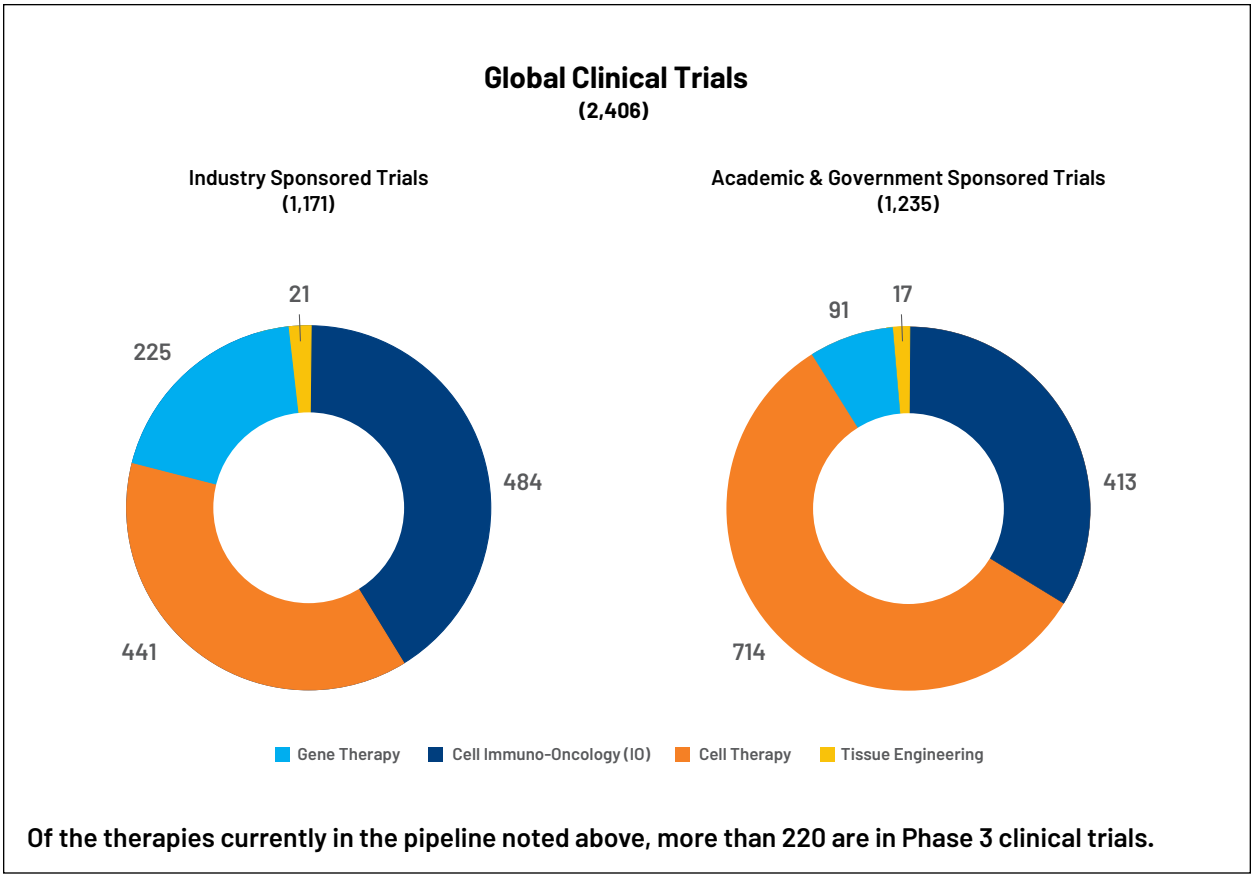
Tremendous advances offer new hope

Since the 1990s, cell and gene therapies (CGT) have offered new hope for patients suffering from rare and difficult to treat diseases. Treatments rely on either patient cells that are harvested, modified and returned (autologous therapies) or suitable donor cells (allogeneic therapies).

Therapies based on the transfer of cellular material, such as bone marrow transplants and T-cell and stem cell treatments, have become effective tools to combat cancer and other diseases – and to regenerate and repair tissue.

Likewise, gene therapies – the modification or replacement of a missing or malfunctioning gene – promise to change the trajectory of inherited conditions like cystic fibrosis and Huntington's disease.

Today, cell and gene therapy is one of the fastest growing markets in the biopharma industry, with an expected compound annual growth rate (CAGR) of 33.6% through 2026.[1] Currently, more than 2,000 CGT trials are underway globally.[2]



Of the therapies currently in the pipeline noted above, more than 220 are in Phase 3 clinical trials.

Data source: Alliance for Regenerative Medicine[2]

But despite tremendous advances and unprecedented growth, biopharma companies typically struggle to transfer and appropriately scale new therapies from the drug discovery phase – to clinical and commercial production.

Common challenges slow speed-to-market

While the manufacturing modalities for autologous and allogeneic therapies differ, both encounter scale-up challenges that can be traced to a similar discovery and development process. Specifically, three common issues can lead to challenges impacting clinical studies and beyond.

1. **Manual data analysis & workflow systems**
   Like all biologic process development, CGT discovery begins in the laboratory environment with scientists taking the lead. To expedite experimentation, work on the bench is small scale – often limited to a unit of one.

   What matters to the scientist is the process – and how efficaciously and efficiently the therapy delivers the desired results. Of course, patient safety is also a critical concern. Many research bodies rely primarily on manual and paper-based systems for data analysis and workflow during the discovery phase.

   How to scale that therapy for clinical trials and into commercial manufacturing using digital technologies and modern control systems is not the purview of a typical bench scientist. As a result, digitalization and automated production processes are often afterthoughts at best.

2. **Complex supply chain planning and logistics**
   Cell and gene therapies introduce new challenges to supply chain planning and logistics that emerge as early as clinical trials. To support limited biologic lifespans, "cold chain" storage and shipping must be used that include the monitoring of time in refrigeration (TIR) and time out of refrigeration (TOR) across the value chain. Also, strict chain of identity, custody and condition regulatory mandates must be met, which require a paper or secure electronic audit trail.

   Logistics have become even more complex in recent years as more pharmaceutical and contract research organizations (CRO) – and contract development and manufacturing organizations (CDMO) – have introduced virtual and home-based clinical trials, requiring temperature-controlled cell retrieval and shipment to coordinate with home care visits.[3]

   Allogeneic cell and gene therapies can be "made to stock," like traditional biologics – and therefore, share similar logistic challenges. But in "batch of one" autologous therapies, supply chain planning and logistics become even more complex since the patient's own genetic material must be collected, modified and returned for patient infusion and treatment[4].

> "Today, patients must wait an average of six to eight weeks for treatments, and 90% of therapies may not be delivered as originally planned. Imagine what will happen when the thousands of CGT patients today evolve into hundreds of thousands by decade's end." – EY[5]

3. **Custom-designed technology transfer processes**
   A therapy's critical quality attributes (CQAs) are identified through painstaking experimentation in the laboratory – as are the recipes and critical process parameters (CPPs) required to replicate results consistently regardless of batch size. But transferring technology from the research lab to a pilot or commercial production environment is challenging. While on the surface, common commercial production techniques for active pharmaceutical ingredients (APIs) are feasible for allogeneic therapies, scale-up is more complex.[6]

   Why? The input material for small molecule APIs is purely chemically derived and can be scaled linearly using various modeling methodologies. The starting material for cell and gene therapies is human-derived and cannot be scaled linearly due to attributes such as cell viability, which can change at various scales. The non-linear nature of the process means the therapy must be tested and modified to consistently ensure efficacy and safety at various volumes.

   Today, technology transfer (or tech transfer) often relies on time-intensive multivariate analysis using paper-based and manually sourced data and custom-designed processes. For companies that have a significant number of therapies in the pipeline – some the result of recent mergers or acquisitions – the lack of reusable, structured digital content and a standard approach slows the transition to commercial scale.

Digitalization and automation change the equation

Digitalization and automation can improve cell and gene therapy processes and tech transfer. But while digitalization is becoming a priority for many cell and gene therapy companies, few have fully embraced the approach.[7] The reasons why the industry lags behind others in digital maturity can be traced to many factors – ranging from risk aversion to reliance on specialized processing equipment that is not capable of connecting to a digital environment.[8]

Given a history of regulatory and technological challenges, how can CGT companies best position themselves for successful commercial scale-up? The answer is prioritizing digitalization early in the process.

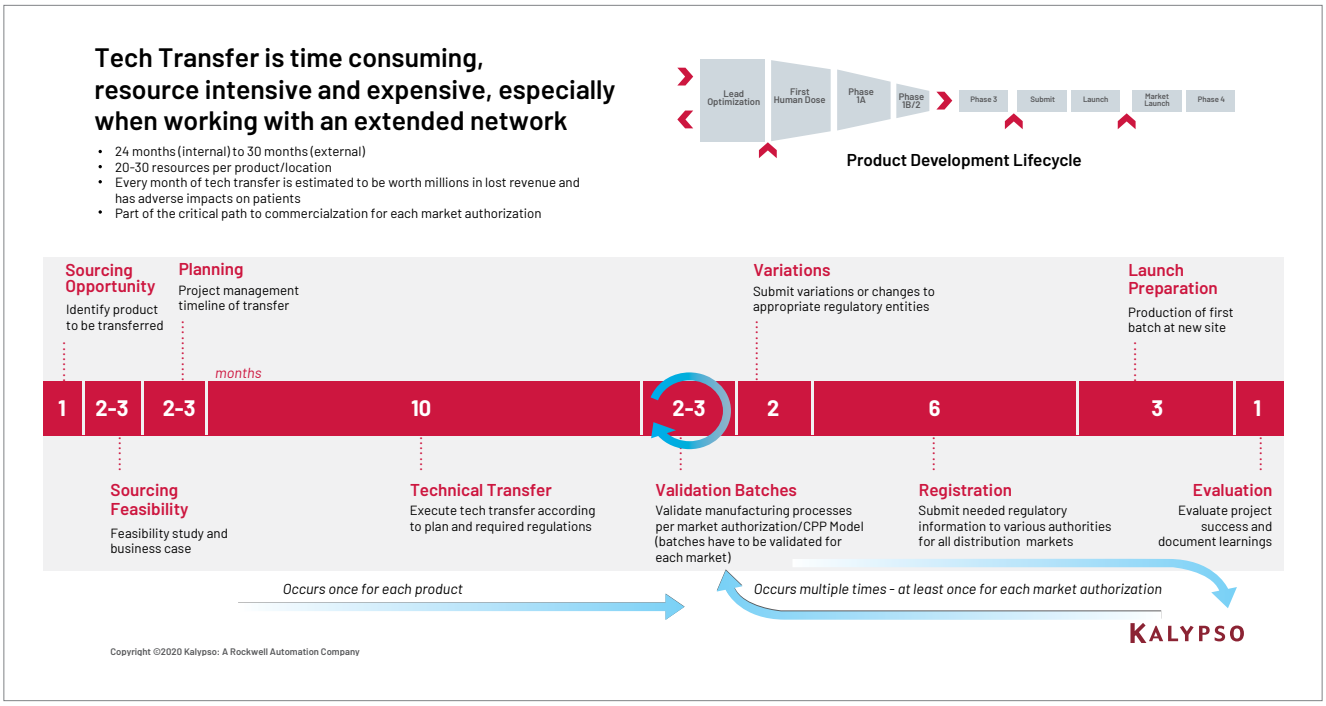
Enabling digital technology transfer

Ultimately, the goal of tech transfer is a digital recipe that seamlessly scales and maintains critical quality attributes from laboratory volumes to those required for clinical trials and commercialization.

But in today's world, tech transfer is rarely seamless – and recurs many times as processes move from research and pilot environments to internal and external clinical and commercial manufacturing facilities. Each tech transfer event – for example, moving from one internal manufacturing site to another or to an external site or CDMO – slows time to market.

To streamline that process, producers must establish a continuous digital thread – or continuous process and data flow – from discovery through manufacturing. But unfortunately, the data assets required to establish that digital thread are often siloed, not harvested and poorly leveraged.

How can producers better enable digital transformation during tech transfer? They must establish reusable digital product/process data and mechanisms for data change management, data governance and data exchange across the digital value chain. And that means developing a structured data model in digital knowledge management systems, such as product lifecycle management (PLM) software that aligns with appropriate International Society of Automation (ISA) standards and can be easily consumed by downstream manufacturing and process control systems.



The critical role of MES in CGT scale-up & commercialization

To satisfy stringent regulatory requirements, exhaustive paper documentation became the status quo across the CGT industry.

But as more therapies are exiting the development pipeline and moving toward commercialization, more companies are looking for ways to streamline their operations – while maintaining good manufacturing practice (GMP) compliance. When producers make digitalization a priority during tech transfer, they can more quickly take advantage of automation systems to achieve these goals.

In fact, the optimal automation solution can provide significant operational flexibility and greatly reduce the effort on the receiving end of tech transfer. For allogeneic therapies, a manufacturing execution system (MES) can consume the digital data generated during tech transfer – and ease production management and compliance.

MES software integrates production systems and enterprise resource planning (ERP) systems, and allows producers to create a digital electronic batch record (EBR) that tracks patient cell samples, raw materials and equipment – and documents the process.

Just as important, an MES automates and enforces adherence to established standard operating procedures (SOPs), thereby controlling both the recipe and the workflow. This is a tremendous benefit in the early state of an evolving industry like CGT and especially with autologous therapies where processes can be highly manual and require skilled operators.

A word about standards

The Standards Coordinating Body for Gene, Cell, and Regenerative Medicines and Cell-Based Drug Discovery (SCB) is taking the lead in the development of standards to help accelerate innovation and reduce the costs of commercialization and scale-up.[10,11]

The SCB is focused on complementing other standards development organizations (SDOs), including the International Society of Automation (ISA). Specifically, the ISA-88, Batch Production standard is referenced in their Regenerative Medicine Standards Landscape[12] report.

Cell and gene therapy organizations can reduce integration challenges and costly project delays by specifying and implementing ISA standards as early in the process as feasible. In addition to ISA-88, relevant standards include: ISA-95, Enterprise-Control System Integration; ISA-99, Industrial Automation & Control System Security; ISA-101, Human-Machine Interfaces; and ISA-18.2, Management of Alarm Systems for the Process Industry.[13]

An MES can also identify an abnormality at any point in the process – and enable producers to resolve issues quickly in two ways:

- **The system enables review by exception.** An EBR eliminates the time-intensive line-by-line confirmation of manual data entries and batch quarantine. Instead, quality reviewers can focus on critical process exceptions – occasions triggered by alarms within the system.
- **The system manages chain of identity, custody and condition through lot genealogy and traceability.** When a deviation does occur, the MES quickly identifies all batches, lots and raw materials that were impacted, significantly reducing root cause analysis investigation time.

Simply put, investing early in an MES solution can be one of the most cost-effective ways to streamline compliance and speed time to market for both allogeneic and autologous therapies.

Process control system considerations

Disposable, single-use technology (SUT) is ubiquitous in cell and gene therapy research and is rapidly becoming the technology of choice not only for preclinical or clinical trials – but for commercial scale[9]. To improve production flexibility, cell and gene therapy organizations must find ways to integrate multiple SUT processes and equipment ranging from bioreactors upstream to chromatography skids downstream.

Not every CGT company has the same integration strategy for SUT applications. Some are evolving to site-wide orchestration by a traditional distributed control system (DCS) – the same solutions used for large API systems. What those DCS solutions don't provide is the production flexibility required for smaller-volume processes and plug-and-produce equipment.

Other companies choose systems that give more autonomy to individual machine control platforms. This "islands of automation" approach reduces a biopharma company's ability to achieve a comprehensive process control strategy – or glean any insights through analytics that can improve quality and production throughput.

A better way: A modern DCS

A modern DCS allows producers to incorporate SUT equipment in a scalable, flexible system that runs on industrial Ethernet, uses open communication protocols and complies with best practices – including international cybersecurity standards.

Some DCS suppliers recommend an integration approach based on a single control platform – which means equipment and instrumentation may be initially delivered without control systems and before factory acceptance testing (FAT). A uniform control system is applied during the integration process. But "dumb" equipment delivered without control systems before the FAT can cause significant coordination and validation challenges in the end.

Conversely, a modern DCS based on EtherNet/IP™ can communicate directly with a wide range of controllers. This means smart process skids can be delivered with their native control systems intact, thereby expediting the FAT and validation.

Through the modern DCS, integrated skids can share common infrastructure resources, such as user accounts and security settings, without losing application independence. This allows companies to take advantage of the application expertise of multiple skid vendors. It also enables a consistent operator experience and centralized batch reporting, critical factors that support tech transfer.

Essential enablers: Network infrastructure & equipment

Network infrastructure design and equipment selection are also important components of an efficient digital production environment.

A manufacturing reference architecture (MRA) featuring a Converged Plantwide Ethernet (CPwE) design, provides users with the basis to successfully deploy the latest digital technologies. Optimized for both operation technology (OT) and information technology (IT), these industry-focused architectures enable information sharing between business systems and manufacturing control systems.

Equally important, a well-designed CPwE infrastructure provides the foundation for a good cybersecurity model built on segmentation and defense-in-depth strategies.

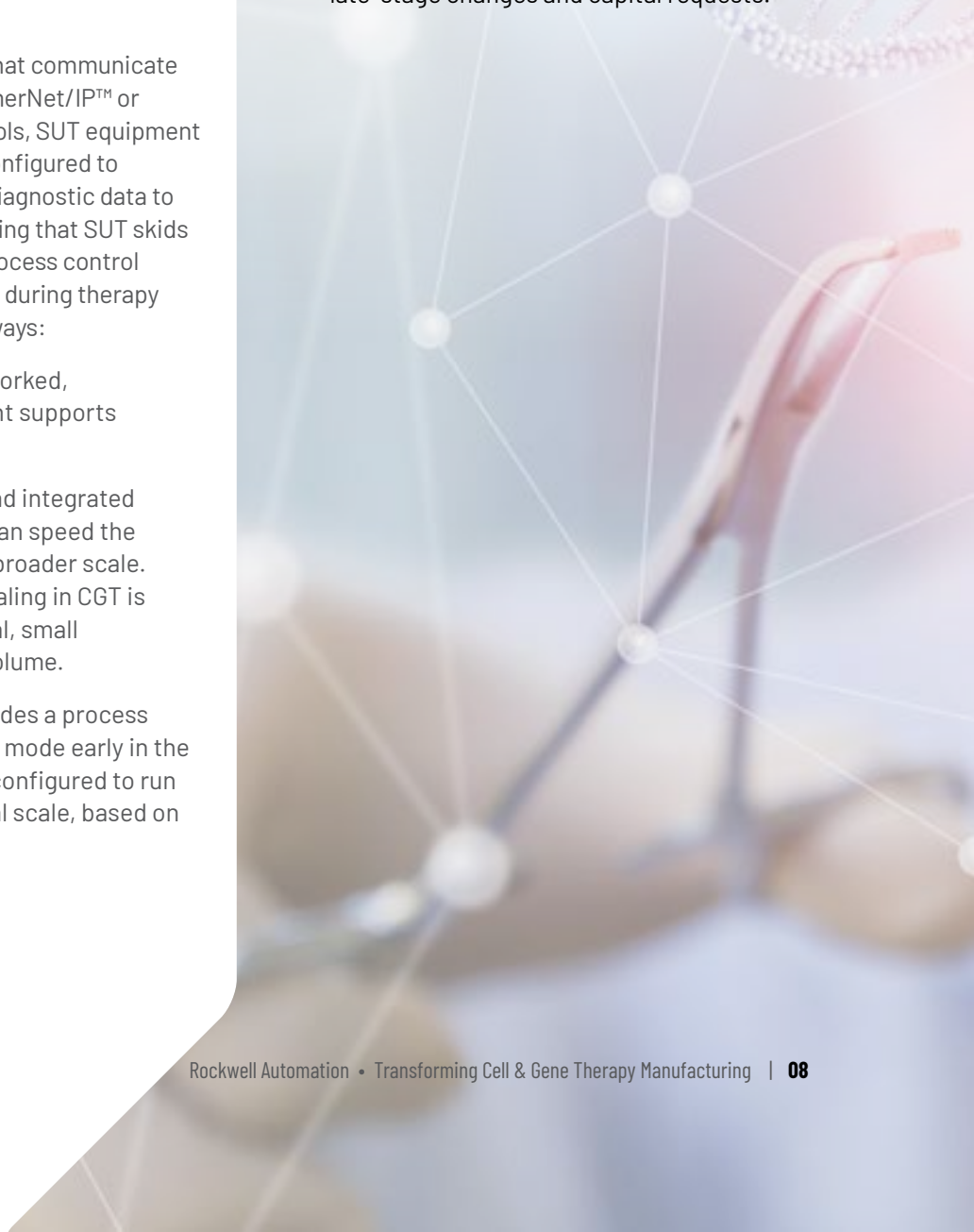
Specifying equipment and devices that communicate over industrial protocols, such as EtherNet/IP™ or OPC® UA, is critical. On these protocols, SUT equipment and instrumentation can be easily configured to communicate with and deliver rich diagnostic data to the process control system. Confirming that SUT skids are network-ready – and include a process control platform – pays significant dividends during therapy development and scale-up in three ways:

- First, the modular nature of networked, plug-and-produce SUT equipment supports agile process design.
- Second, digital data collection and integrated multivariate data analysis tools can speed the reproducibility of the therapy at broader scale. Keep in mind, the objective of scaling in CGT is increasing the volume of identical, small batches – not increasing batch volume.
- Finally, SUT equipment that includes a process control system can run in manual mode early in the scale-up process. And easily be configured to run repeatable recipes at commercial scale, based on the manual outcomes.

The benefits of digital twin technology

Producers can lay the groundwork for easier scale-up with digital twin technology. Built using emulation/simulation software, digital twins are dynamic digital models that can be used to solve technology challenges in the virtual world early in the equipment development cycle. In fact, digital twins can be built as soon as equipment designs are complete.

Going a step further, digital twins can also facilitate virtual commissioning. In other words, a digital twin can be connected to the real operational logic of its control system for testing before the equipment is built, thereby avoiding late-stage changes and capital requests.



Take the next step

No doubt, improving speed to market will likely remain one of the most compelling challenges the CGT market will face for years to come. Prioritizing digitalization – and laying the foundation for manufacturing success early in the process – is critical in this dynamic and rapidly evolving field.

Learn how Rockwell Automation – and its digital business unit, Kalypso – can transform cell and gene therapy discovery, tech transfer, production and commercialization with a digital thread and industry leading automation platforms. **Visit us online**.

Notes

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