LEVERAGING DIGITALIZATION TO RESOLVE CELL AND GENE THERAPY MANUFACTURING CHALLENGES

Honeywell

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EXECUTIVE SUMMARY

The efficacy of the first cell therapy, Kymriah, which was approved by the U.S. Food and Drug Administration (FDA) in 2017[1], was the catalyst that triggered the cell and gene therapy boom. Manufacturers that were producing conventional products were incentivized to shift to precision medicine, but it has become evident that traditional processes and protocols cannot keep pace as demand continues to grow.

To meet the escalating need for precision medicines, the manufacturing process must be streamlined to enable rapid, reliable production, and digitalization is the key to accomplishing this goal.

1. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/kymriah

THE CURRENT LANDSCAPE

1

Cell and Gene therapy (CGT) manufacturing differs significantly from traditional small and large molecule manufacturing processes, and despite advancements in recent years, CGT manufacturers continue to face significant, unique challenges[2].

Cell therapy involves administering living cells to patients to restore, replace, or augment biological functions impaired by disease or injury. Gene therapy involves replacing a defective or missing gene with a functional copy to restore normal cellular function. CGTs introduce inherent complexity and variability that is not present in traditional manufacturing.

CAR-T (Chimeric Antigen Receptor T-cell therapy) is a form of immunotherapy that involves genetically modifying a patient's own T cells to recognize and attack cancer cells. Once cells are extracted, they undergo leukapheresis, a process that removes white blood cells from the sample, which then is subjected to elutriation to separate components based on size, shape, and density. The next step, magnetic cell separation, isolates specific cell populations for subsequent treatment—employing either transfection or transduction—during which material is introduced into the cells to produce genetically modified CAR T cells.

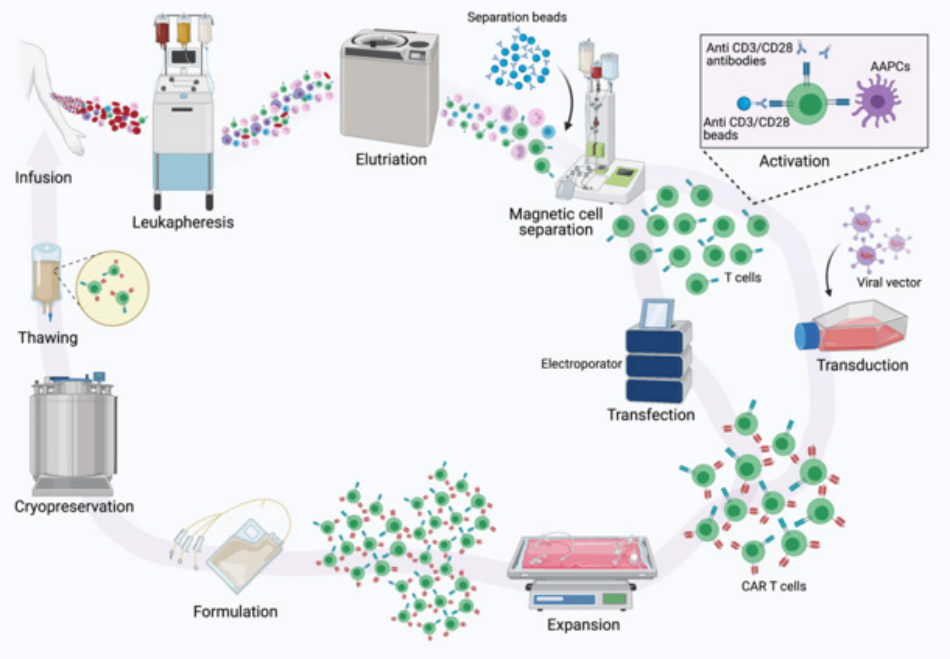

Figure 1: Cell Therapy Manufacturing Workflow[3]

2. Manufacturing Cell and Gene Therapies: Challenges in Clinical Translation - PMC (nih.gov)
3. https://pharmaceuticalmanufacturer.media/pharmaceuticalindustry insights/understanding the continuous process/ Scalable Manufacturing of CAR T Cells for Cancer Immunotherapy)

Next is the expansion process, in which the desired cells are multiplied to produce an appropriate therapeutic dose for the patient. This larger sample undergoes formulation to ensure the final product is safe, effective, and ready to be administered. It is then subjected to cryopreservation to preserve the viability and functionality of cells and establish a cell bank. When it is time for an infusion, the CAR T cells are thawed and reintroduced to the patient (Figure 1).

This complex manufacturing process necessitates sophisticated techniques and quality control measures that ensure product consistency and efficacy. Additionally, chain of custody and chain of identity are critical because they preserve sample identity during the manufacturing processes. Every batch must be strictly tracked from vein to vein so that each patient donor is properly identified from cell extraction, through cell modification, to the point at which the cells are reintroduced[4].

Unlike small molecule manufacturing, CGT involves many operators, including manufacturing scientists and other experts who ensure the stability of the samples as they move through the complex, multi-step manufacturing process. The differences between small molecule manufacturing and CGT manufacturing are significant, and the challenges are different at well. At every stage, failure to meet those challenges can jeopardize the precise processing of small, instable, time-sensitive batches (Figure 2).

	SMALL MOLECULE MANUFACTURING	CELL & GENE THERAPY MANUFACTURING
Patient specificity	• Batches are not patient-specific – Large batch sizes	• Each batch is specific for a particular patient – small batch sizes
Manufacturing time	• Varies, highly controlled and manageable	• Time sensitive; 2-3 weeks with minimal room for errors • Patients in critical condition
Raw material	• Chemically stable and low variability quality-wise	• Highly instable and time-sensitive • Cells collected from patients could be highly variable
Stake-holders	• Relatively fewer leading to reduced complexity	• Increasingly more stakeholders involved – CROs, CDMOs, universities
Equipment	• Large capacity equipment (Scale-up)	• Small bench-top equipment (Scale-out)
Operators' intervention	• Relatively limited	• Manual intervention is frequently required throughout the process
Batch value	• Relatively lower value based on per patient and batch volume	• High value batch

Figure 2: Different Modalities, Different Challenges

4. Cell and Gene Therapies & Their GMP Requirements | Pharmaceutical Engineering (ispe.org)

UNDERSTANDING THE CHALLENGES

2

CGT manufacturers face unique challenges that require innovative solutions to help ensure positive patient outcomes and reduce operational costs in a sustainable way. These include:

Time criticality—The manufacturing window for CGT products often is very short, particularly for autologous cell therapy, which requires cells collected from patient to be genetically modified and readministered into the same patient within 3-4 weeks, commonly known as "vein-to-vein" time. The short development cycles allow very little time for rectifying manufacturing errors, should they occur, which underscores the criticality of establishing and following an error-proof manufacturing process.

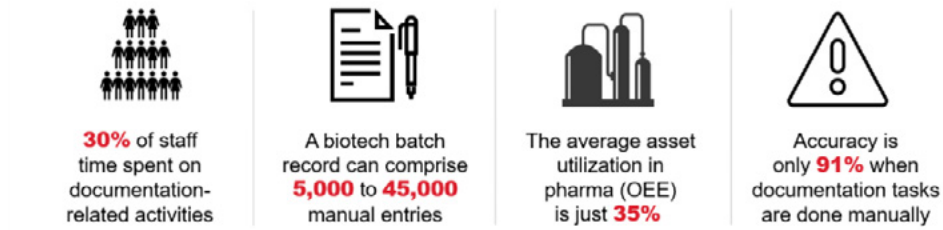

Figure 3: Operational Realities: Industry Primed for Digital Transformation[5]

End-to-end traceability

Maintaining chain of custody and chain of identity is vital within the CGT workflow, particularly when patient-specific batches are produced. Data must be accurately recorded at every stage to make it possible to trace a batch through the entire manufacturing process, and the information must be stored such that it is easily accessible for analysis and decision making (e.g., comparing data across batches). This is extremely difficult with paper records, and even in ideal conditions, is a tedious and time-consuming endeavor.

5. Source: McKinsey, Operations can launch the next blockbuster in pharma, Feb. 16, 2021)

Manual process steps

Despite the adoption of automated closed systems by CGT manufacturers, a significant portion of CGT manufacturing consists of manual processes that require physical intervention by manufacturing technicians and medical personnel. Using a paper-based documentation system opens the door to potentially fatal transcription errors occurring . More than 50% of life sciences plants rely on paper, but statistics show that manual recording is only 91% accurate. In a process that requires 5,000 to 45,000 entries, a 91% accuracy rate could result in 450 to 4,050 errors, which is woefully inadequate for CGT—Imagine mismatching a CAR-T product to an incorrect patient due to a documentation error during cell collection at the hospital![6]

Distributed manufacturing chain

Multiple stakeholders (therapeutic companies, CDMOs, specialized couriers, medical centers) are involved in the manufacturing process at different points. Reliable communication and total manufacturing visibility among stakeholders is vital to delivering within the treatment window and ensure patient safety, but this is a feat that few CGT manufacturers can achieve employing current, outdated, paper-based systems.

Regulatory demands

The regulatory requirements for CGT products are understandably stringent due to the high potency of these drug products and the potentially fatal consequences if processes are not followed precisely and reliably. Because CGT companies find it difficult to standardize and consistently implement GMP practices, designed to ensure product safety and effectiveness, across multiple sites managed by different stakeholders, they often attract heightened scrutiny from regulatory bodies. This could adversely impact their clinical trial outcomes.

Limited Manufacturing Capacity

Demand is outstripping supply for CGT manufacturing, which is driving the need for increased production and intensifying the pressure to reduce batch cycle time and free up manufacturing capacity. Long vein-to-vein times can mean fewer patients reached or even worse, more patients missing the window for treatment. Reducing manufacturing time by even three days (15% to 20% of the total time required) would considerably increase batch throughput and allow more patients to receive treatment.

Low employee productivity

A significant portion of the total manufacturing time is taken up by employees engaging in activities that add minimal value to the overall process—manual documentation and batch record review, rectifying process and documentation errors, waiting for test results, waiting for approval from other stakeholders, etc. CGT companies are struggling to improve productivity without compromising patient safety, against the backdrop of a paper-heavy manufacturing process.

Manufacturers that want to scale up must do so safely, following a manufacturing process that:

- Guarantees compliance to a recipe or Master Batch Record (MBR) and provides proof of compliance
- Ensures all manufacturing data are recorded and secured such that the information cannot be altered or deleted
- Captures and archives manufacturing data for auditing, tracking, and continuous improvement.

6 MANUFACTURING CONCERNS USING TRADITIONAL PROCESSES FOR CGT

1. Suboptimal Electronic and Physical Control of Material
2. Inadequate Batch Production Recording
3. Insufficient Workflow Procedures
4. Lack of Batch Release Controls
5. Data Integrity Failures
6. Ineffective Quality Event Management

6. McKinsey, Operations can launch the next blockbuster in pharma, Feb. 16, 2021

DIGITALIZATION AND THE VALUE OF A MANUFACTURING EXECUTION SYSTEM

3

The industry is changing as the pace of innovation accelerates, and digitalization is the key to connecting disparate processes, expediting batch throughput, and improving tracking and reporting.

Digitalization also is connecting stakeholders within the manufacturing chain, including Contract Development and Manufacturing Organizations (CDMOs) university-based manufacturers, giving therapeutic companies visibility into processes and better control over outsourced events.

As digitalization becomes more pervasive, it is transforming the manufacturing process, improving inventory management, ensuring data integrity, minimizing errors, enabling real-time corrective action and rapid batch release, and harnessing data that can be used to improve manufacturing processes.

Manufacturing Execution Systems (MESs) are leveraging digitalized solutions across manufacturing processes to achieve these goals (Figure 4).

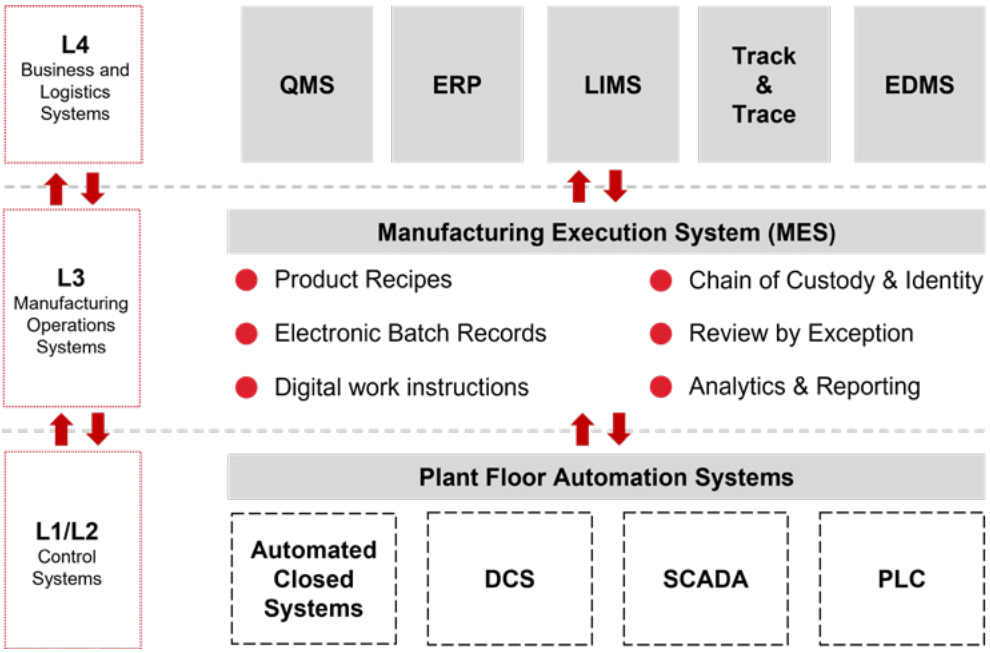

Figure 4: Digitalization Map for Cell & Gene Therapy Manufacturing

One of the biggest transformations on the plant floor has been the automation of closed systems. Automation not only enables consistency, it expedites production. Although discrete closed-system automation is a step in the right direction, it cannot deliver system-wide improvements. The true value of automation can only be realized if individual automated systems can be connected.

An MES makes this possible by bringing discrete functions under the control of a single system to take automation to the next level (Figure 4). Employing an MES also expedites the process of getting automation up and running for a new product line to deliver products to patients faster.

Cell therapy manufacturing needs	AUTOMATED CLOSED SYSTEMS	MANUFACTURING EXECUTION SYSTEMS
Real-time batch monitoring (multiple batches)	++	++++
Ability to reduce manufacturing errors	++	++++
Tracking of Chain of Identity and Chain of Custody	+	+++
Reducing reliance on process technicians	++	+++
Process data analytics	++	++++
Batch recording & Documentation	+/++	++++
Batch Review & Release	+	++++
MES are highly adaptable; customized to each unique workflow		

Figure 5: Automated Closed Systems Vs. Manufacturing Execution Systems (MES)

AN MES TRANSFORMS CGT MANUFACTURING

- Improving data integrity
- Minimizing errors
- Enabling faster corrective action
- Empowering real-time process improvements
- Expediting batch release
- Ensuring compliance

The MES provides an overview of the entire manufacturing workflow for each batch to allow greater control over the manufacturing process, enabling real-time status reports to be generated for batches and materials to prevent errors and shorten changeover time. The MES is the only system that communicates with batch manufacturing, lab information management systems, quality management systems and business systems to coordinate all manufacturing activities. By gathering and storing data from individual processes, the MES gives owners insight into how manufacturing orders are progressing and enables better quality management and improved recordkeeping (Figure 6).

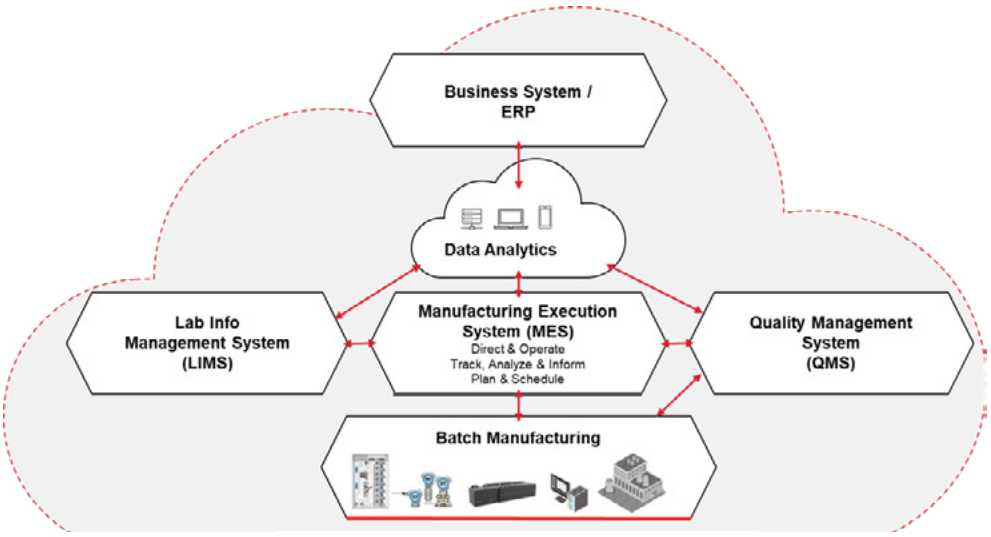

Figure 6: Integrated Pharmaceutical Manufacturing

LEVERAGING A MODULAR OPERATIONS PLATFORM

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The Honeywell Manufacturing Excellence Platform (MXP) simplifies the process of effecting the digital transformation of CGT manufacturing to improve efficiency, quality, and compliance (Figure 7). It combines real-time production visualization, manufacturing execution system (MES), and batch historian capabilities to optimize production efficiency, quality, compliance, and batch release.

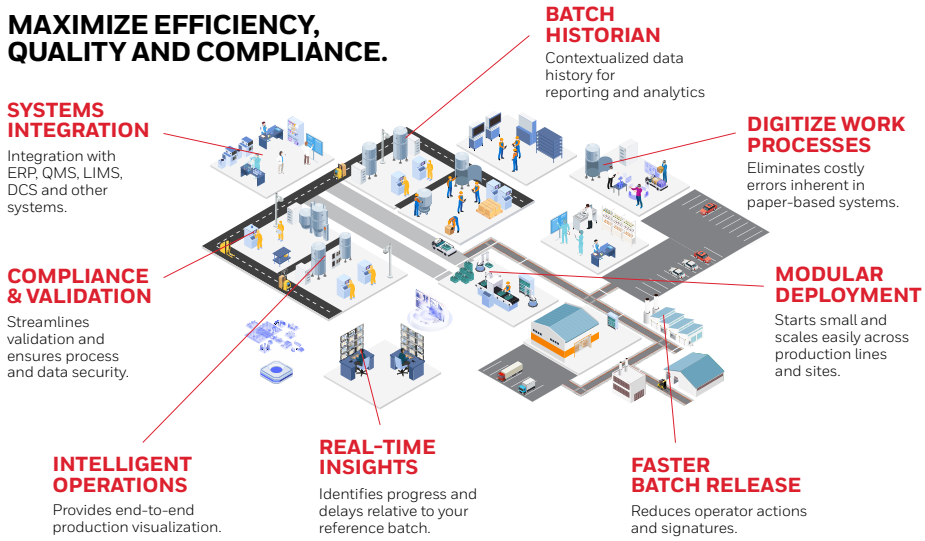

Figure 7: Next Generation Manufacturing Excellence Platform

One of the advantages of MXP for cell and gene therapy manufacturers who don't have a well-developed warehouse management system is inventory management, which is particularly important when dealing with the raw materials for CGT (eg. plasmid and organic components) that are highly unstable and have a short shelf life. Because of the cost of inventory management systems, some manufacturers track raw materials manually, but paper records are not entirely accurate, so there is always a danger of a batch being inappropriately processed. The platform is designed with automated traceability that tracks chain of custody and chain of identity, and guides the operator at each point of the manufacturing process, and doublechecks that what is being done with the raw material is correct for the individual patient by matching patient details with the process for each sample.

The platform uses standardized protocols to ensure alignment at every stage of the process and employs bar coding for checking materials in and out of each process to eliminate confusion.

Automating the calculations required for sample processing removes the possibility of a computation error, and the requirement for electronic signatures to authorize material movement from one process to the next ensures each sample is approved by appropriate personnel throughout the manufacturing process.

With MXP, operators have clear insight not only into what is happening with the batch at a given time, but also what will happen to it next.

The platform connects multiple devices, sensors and equipment from different vendors to allow real-time monitoring of critical parameters (e.g., pH, temperature, agitation rate) across equipment, and integration with a quality management system (QMS) captures and logs quality events and exceptions.

The platform also improves batch release. Using a manual process, batch review takes up to 40 to 50 hours (30% of the total cycle time), which extends the manufacturing process. Manufacturing Excellence Platform (MXP) uses "review by exception" to reduce batch review time to as few as approximately four hours.

When all the manufacturing steps have been completed, MXP generates an electronic batch record (EBR) that includes all data/records collected during manufacturing, including digital signatures. The EBR is fully compliant with cGMP and 21CFR Part 11 requirements and can be generated as a report on demand to demonstrate compliance.

Because the platform is designed to integrate with other Honeywell and third-party systems, including ERP, QMS, LIMS and DCS, it has the capacity to accommodate additional capabilities as a plant progresses along the path to digital maturity.

MXP BENEFITS AT A GLANCE

- Designed as a unified, scalable, modular platform
- Enables rapid corrective action
- Optimizes quality
- Enhances data integrity
- Improves documentation
- Ensures audit readiness

TAKING THE NEXT STEP

Digitalization is the enabler for CGT manufacturing expansion, and MXP is the expedient that makes it possible to provide real-time visibility into operations, shorten batch cycle time, enhance quality assurance, simplify recordkeeping to demonstrate compliance with FDA guidelines, improve inventory control and consistent on-time product delivery.

The need for CGT manufacturing is growing, and as capacity expands, Honeywell is providing the innovation, safety, and efficiency to meet tomorrow's need, ensuring technologies and tools are available to safeguard operations, reduce risks, and control costs.

To learn more, visit hwll.co/MXP or contact a representative.

For more information

Learn more about Honeywell's Manufacturing Excellence Platform, visit hwll.co/MXP or contact your Honeywell Account Manager, Distributor or System Integrator.

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