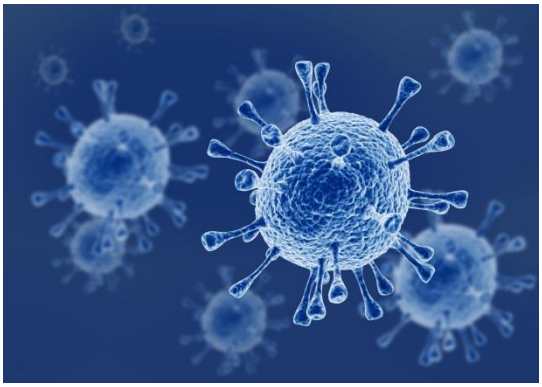
How to Speed Up Cell and Gene Therapy Treatments for Patients, Reduce the Number of Manual Operations and Eliminate Operator Errors

Abstract: This white paper addresses the unique production problems of cell and gene therapy and explains how a manufacturing execution system (MES) can address them. It provides guidance on how to select an MES and a case study of two CAR-T therapy companies scaling up with and without an MES. It is intended for people working in the supply chain, manufacturing operations, quality control or IT departments of cell and gene therapy companies close to obtaining therapy approval or scaling up to commercial manufacturing.

Introduction: Personalized medicine is fast becoming a reality for many conditions. Even in patients with the same disease, generic medicines will commonly help some patients, have minimal effect on some and potentially adverse effects on others. Based on our improved understanding of genetics, the immune system and stem cells, new personalized cell and gene therapy treatments are being manufactured for individual patients. A unique difference is that traditional pharmaceutical manufacturing is 'make to stock' but cell and gene therapy manufacturing is 'make to order' – each 'order' is different and patient specific. In addition for each patient the manufacturing starts with uniquely different material.

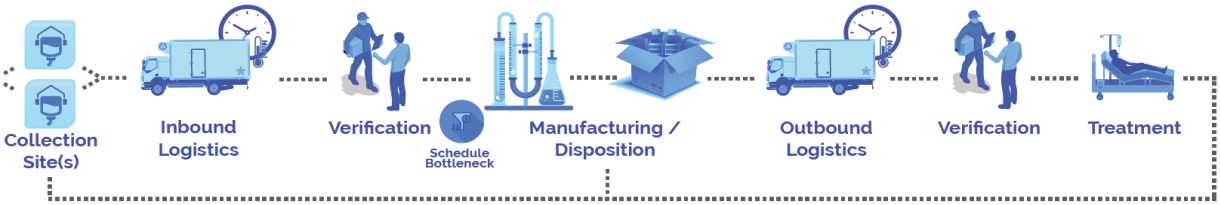


T cells gives our immune systems the capacity to protect against the vast array of bacteria, viruses and fungi that we encounter. As the role of T cells in controlling cancers was recognized, they have begun to be exploited therapeutically. These therapies initiate a bioengineered immune system attack on a patient's cancer cells using modified versions of the patient's own cells.

But how do you manufacture such a therapy? To deliver cell and gene therapy treatments at scale bio-pharmaceutical companies are moving away from complex paper based documentation, integrating many different electronic systems, and automating previously manual verification processes between collection, logistics, manufacturing and treatment centers.

The following ‘Example CAR-T Manufacturing Process’ diagram gives an overview of the typical manufacturing process for these types of therapies.
The process starts with ‘**cell collection**’ usually at a medical treatment facility. In an autologous therapy, a patient’s own cells are harvested, in vitro modified, and then re-infused into the same patient. In an allogeneic therapy the process is similar but different in that the cells are harvested from one or more donors rather than the patient themselves.

In either therapy the cell collection is sent to a manufacturing facility where it is consolidated. Tests are run to analyze the samples and determine the necessary manufacturing process to follow as well as the final dosing quantity. This step highlights another unique problem – the dependencies and branches of the manufacturing process for each patient may be different. Moving on to ‘**cell isolation**,’ the specific T cells for that patient are isolated. This step highlights another problem – how to control for differing patient health samples. In ‘**cell modification**’ genetic material is inserted to modify the cell’s behavior - in this case, it's the expression of a receptor on the T cell. This insertion is done with a viral vector in a process called transduction. The viral vector has the modified DNA sequence needed to express a certain behavior or reaction on the cell. After the cells are modified and within a specific specification, the next manufacturing step is ‘**cell expansion**’ to expand the number of these cells that have the modification of the genetic material. This usually takes a couple of days during which the cells are inside a bioreactor containment vessel and are monitored and grown. The monitoring of the induced T-cells is critical to ensure that the cells are growing and expressing within specification. Once an acceptable range is achieved, in ‘**cell harvesting**’ cells are removed, cleaned, and filtered down. They then go through ‘**quality assurance and testing**’ to make sure that the dosing, specifications and all the safety requirements are met. Finally the product is **packaged, transported**, and returned to the ‘**treatment**’ facility for that patient.



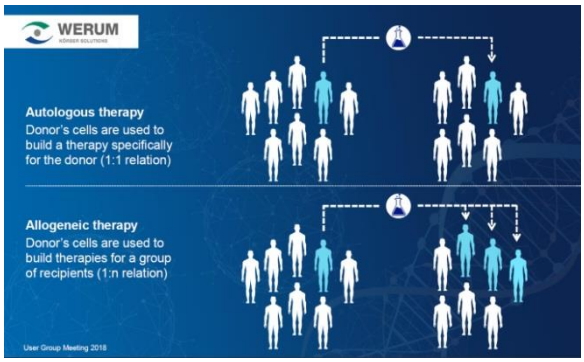
From the patient’s point of view time is of the essence. If a sample is out of specification, there may not be opportunity to manufacture another. It is essential to meet time constraints and to achieve right first time, every time, for every patient. Ensuring the right patient gets the right treatment includes tracking and ensuring chain of identity (COI) for each patient throughout the ‘needle to needle’ process. Similarly tracking chain of custody (COC) ensures chronological documentation or paper trail that records the sequence of custody, control, transfer and analysis, not just in manufacturing but throughout the logistics and treatment processes. There is no room for error.

In August 2017, the FDA approved Novartis Kymriah CTL019 as the first gene therapy to treat pediatric and young adults with B-cell acute lymphoblastic leukemia. To date (End of 2018) the FDA has approved 13 cell therapies, four of them are CAR-T therapies. Many more are in process -- attendees to the 2018 CAR-TCR Conference identified the clinical stages shown in the graphic on the right.

Definitions:

Gene Therapy – is the transfer of genetic material (DNA or RNA) into the cells of a patient's body to treat the cause or symptoms of a specific disease. The transferred genetic material changes how a single protein or group of proteins is produced by the cell. Gene therapy is used to reduce levels of a disease-causing version of the protein, increase production of disease-fighting proteins, or to produce new/modified proteins.

Cell Therapy – is the transfer of intact, live cells into a patient to help lessen or cure a disease. The cells may originate from the patient (**autologous cells**) or a donor (**allogeneic cells**). The cells used in cell therapy are classified by their potential to transform into different cell types. Pluripotent cells transform into any cell type in the body, and multipotent cells transform into other cell types, but their repertoire is more limited than that of pluripotent cells. Differentiated or primary cells are of a fixed type. The type of cells administered depends on the treatment.



CAR-T – Chimeric Antigen Receptor (CAR) T cell therapy. This is a way of modifying the patient's own immune cells (T cells) to express a receptor on their surface that recognizes structures (antigens) on the surface of malignant cells. Once the receptor binds to a tumor antigen the T cell is stimulated to attack the malignant cells.

TCR – T Cell Receptor therapy. Unlike CAR-T cells that recognize proteins expressed on the surface, T Cell Receptors (TCRs) can recognize tumor-specific proteins on the inside of cells. When tumor-specific proteins are broken into fragments, they show up on the cell surface with another protein called major histocompatibility complex, or MHC. TCRs are engineered to recognize a tumor-specific protein fragment/MHC combination.

CRISPR – stands for Clustered Regularly Interspaced Short Palindromic Repeats. CRISPR is a family of DNA sequences found within the genomes of prokaryotic organisms such as bacteria and archaea. They are segments of DNA containing short repetitions of base sequences, involved in the defense mechanisms of these organisms to viruses. A genetic engineering tool can use a CRISPR sequence of DNA and its associated protein to edit the base pairs of a gene.

MES – stands for Manufacturing Execution System, a software/IT solution that provides the link between the equipment/automation level and the enterprise management (ERP system). It electronically executes and documents all process steps ensuring an error-free and guided production and right-first-time manufacturing.

Useful FDA documents on Cell and Gene Therapy:

- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
- Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue Based Products: Minimal Manipulation and Homologous Use
- Deviation Reporting for Human Cells, Tissues, and Cellular and Tissue-Based Products Regulated Solely Under Section 361 of the Public Health Service Act and 21 CFR Part 1271

Seven Unique Problems that MES Can Address for Cell and Gene Therapy Companies:

The introduction above outlined a few of the unique problems of cell and gene therapy manufacturing but here's a fuller, though not exhaustive, list along with MES based solutions.

Problem	Solution
1. **Manufacturing in cell and gene therapy is 'make to order' rather than 'make to stock'**. Each treatment is patient specific and for each patient the manufacturing starts with very different and variable material - especially in an autologous process where every sample is received from a different patient. Patients will have different health levels, different white blood cell counts, different blood types, different genetic backgrounds, and different medical histories. All these differences could affect the way they react to the treatment.	MES as an IT system is designed and proven to enable and control any volume of unique cell and gene therapy treatments. MES helps increase process standardization, for example, to accommodate variability in patient health samples, optimize processes, track critical process parameters (CPPs) and critical quality attributes (CQAs) with real time feedback. MES supports manufacturers being very flexible and optimized in their operations and how they choose different routes for production along with stage by stage testing and tracking.
2. **Speeding up treatment for patients** - getting the correct treatment to the patient in as fast a timeframe as possible.	MES enables manufacturing automation in cell and gene therapy by reducing manufacturing time and risk in most stages. For example, the case study below shows batch review typically takes 30 hours with paper processes, but only four hours with an MES. 38% of 2018 CAR-TCR Summit Survey participants cited '**manufacturing automation**' as the most needed advancement (see graphic).
3. **Right first time, every time** - each treatment must be manufactured right first time. Manual data entries and calculations can lead to errors that could potentially delay the release of the treatment to the patient. Small deviations or errors within each batch or each execution might be caught and corrected when managing tens or perhaps hundreds of patients but once scaled up to thousands or tens of thousands of patients, small mistakes add up significantly.	MES helps ensure right first time manufacturing by reducing human error. MES will catch mistakes upfront during each step rather than at the end. This constant checking and confirmation is the best way to prevent having to ask patients for another batch**.** MES enables automation and automation enables scaling up sustainably with controlled risk factors while also lowering costs and increasing efficiency.
4. **Scalability** - once a therapy is proven, it's time to help more patients. That means scaling up manufacturing without drowning in paper. With paper-based tracking every patient's therapy requires hundreds to thousands of pages that need to be manually reviewed. This takes a lot of time and introduces risk.	MES enables scalability by capturing many manual entries in the batch record (often reducing the number of manual entries by up to 80%), checking and verifying values as they are entered, and replacing manual calculations with automated ones. This prevents errors which may not be caught in time, or are caught too late in the process.
5. **Chain of Identity (COI) and chain of custody (COC) –** ensuring the right patient gets the right treatment includes tracking and ensuring COI for each patient throughout the 'needle to needle' process. Similarly COC ensures chronological documentation or paper	MES helps ensure COI and COC during manufacturing. MES uses material tracking technology such as barcodes and RFID to ensure that the correct materials/ apheresis bags are used in the correct treatments.

trail that records the sequence of custody, control, transfer and analysis, not just in manufacturing but throughout the logistics and treatment processes.	MES also ensures patient kits and lot genealogy are tracked and fully traceable.
6. **Compliance** with all established internal company standards, FDA requirements, any customer treatment facility requirements and architectural IT standards.	MES helps to establish and maintain robust processes, oversight, and governance to ensure that all aspects of manufacturing are in compliance. MES helps ensure data integrity. MES is 21 CFR part 11 compliant. Everything in an MES is audit trailed and recorded without the option to modify data. MES enforces compliance through its EBR engine by mandating a sequence of steps and controlling execution through rights managed access control
7. Manufacturing Intelligence and analytics – in the paper-based process it is difficult to capture data, monitor and analyze what's happening let alone gain new insights.	MES captures all data electronically, presents it in dashboards, and analyzes it for process feedback, insights and improvements. This is especially important in cell therapies where the processes are still changing and evolving. The more data is available the more valuable the system becomes over time.

Twelve Questions to Ask Before Choosing an MES for Cell and Gene Therapy:

How do you address these problems with an MES? Make a list of potential MES suppliers and ask them the following questions:

1. Does the MES supplier fully understand the cell and gene therapy manufacturing process, and speak the language of the industry?

2. Is the MES supplier very experienced in supplying, configuring and supporting cell and gene therapy manufacturing teams? Is their track record supported by cell and gene-therapy customer references?

3. Does the MES supplier offer specific consulting specialists supporting cell and gene-therapy implementations?

4. Does the MES come 'out-of-the-box' ready for cell and gene-therapy workflows and does it address your company's unique needs?

5. Does the MES provide material flow and inventory tracking enabling COI and COC?

6. Does the MES provide Warehouse Management functionality or ability to tie into the warehouse and supply chain?

7. Does the MES have standard adapters for integration?

8. Does the MES enable review by exception?

9. Does the MES offer dashboard overviews of CPPs / CQAs?

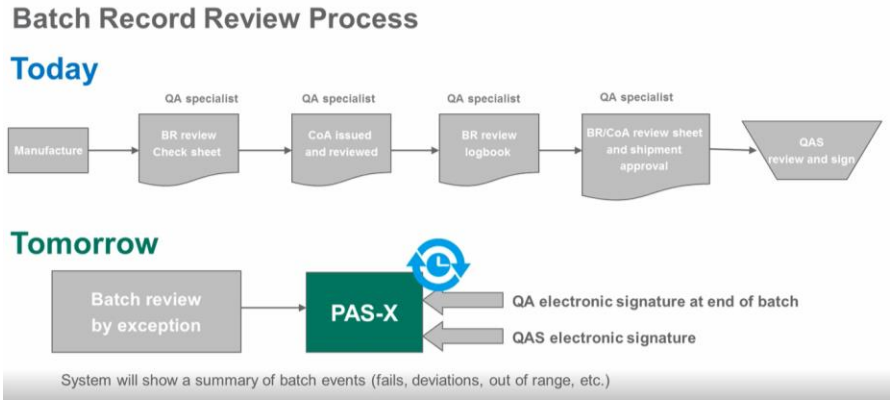
10. Is the MES available ‘on premise’ or ‘in the cloud’? How easily can you switch if you ever want to?

11. What is the MES supplier’s project implementation record?

12. How many people work for the MES supplier company? How many are dedicated to the MES product?

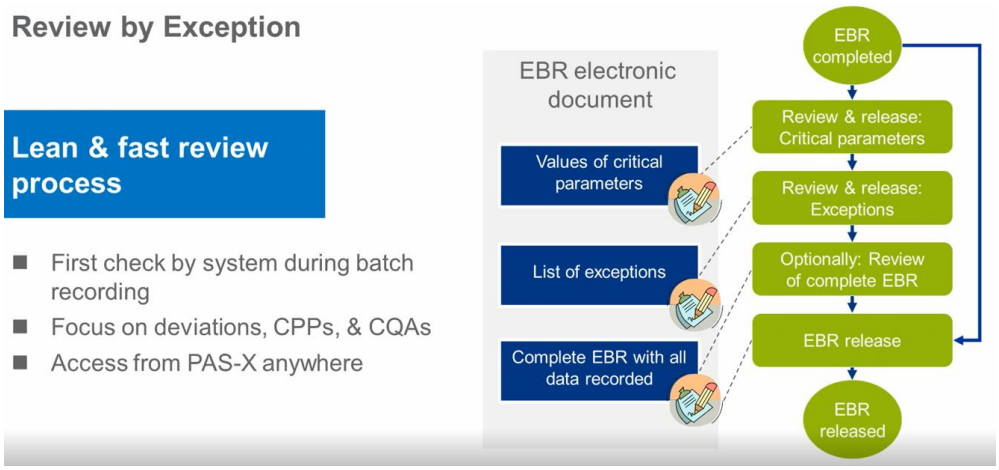
Case Study: Speeding Up Cell and Gene Therapy Treatments for Patients

This case study illustrates how MES addresses the ‘problems’ outlined in the table above. It focuses on speeding up product release – specifically the ‘batch record review process.’ In this anonymized study of two different cell therapy companies, Company A and Company B use autologous CAR-T technology to deliver treatments. They are currently manufacturing on a clinical scale and are looking to scale up fairly soon. Company A decided to continue using paper based processes during scale up. Company B decided to speed up and improve their production control by implementing a MES, specifically PAS-X.



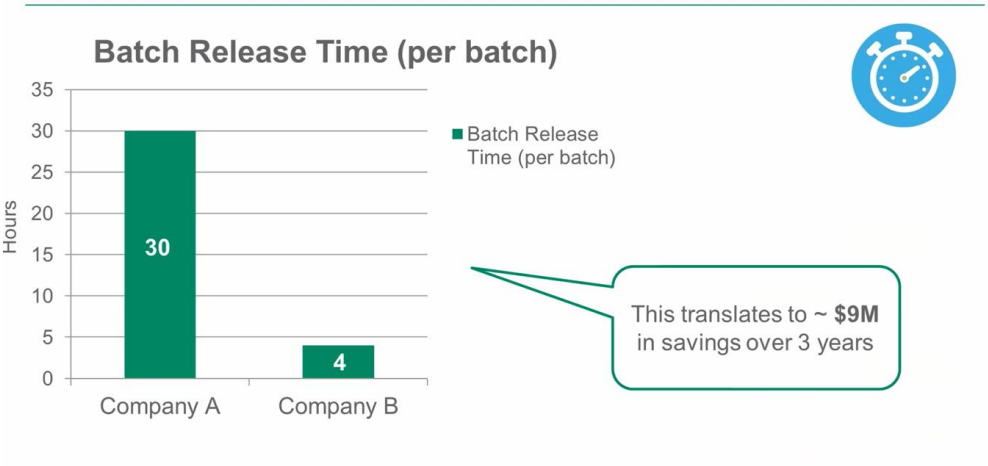
At the top, ‘Today’ is what the batch record process looks like in Company A, the manufacturing process is followed by a review of the batch record and issuance and review of the CoA (Certificate of Analysis). All the logs associated with the batch execution (equipment logs, material logs, any other auxiliary logs) need to be reviewed. Then the batch record, CoA and relevant logs can be reviewed in one collection and finally signed off. This is usually done in sequence, each step is dependent on the previous one and all are heavily dependent on paper. The process is very manual because it's historically been done on paper. QA personnel on the shop floor or in their offices have huge stacks of paper for every batch. Going through each process means reading each paper log, following up with all individuals who were part of the batch and following up on any deviations. The work associated with reviewing each batch is quite high and time intensive.

At the bottom, ‘Tomorrow’ is what the process looks like in Company B with a PAS-X MES implementation. Everything you see at the top would be consolidated within the MES which becomes the system of record for batch execution. All the manufacturing information will already be available, including all equipment logs, all the material usage, all the people who executed, all the reports needed, and any deviations that occurred on the shop floor. The significant advantage here is that it's an electronic system and it's available in real time to be reviewed immediately, so QA personnel don't have to wait until the end of execution to consolidate all documents or even begin the review.



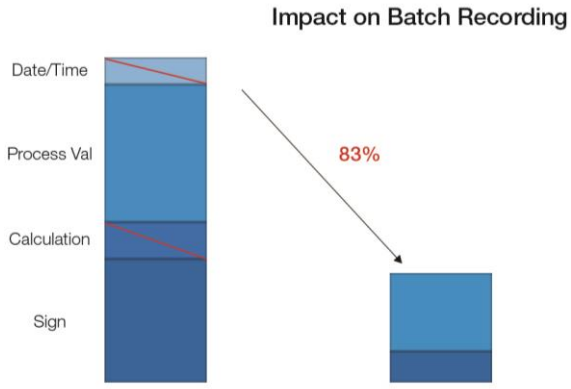
PAS-X provides a portal for the QA personnel to directly look into the electronic batch while it's being executed and address any deviations in real time. By the time manufacturing is finished, QA may already have reviewed and addressed most of the issues for that batch. Everything is audited within the system and reports can be pulled and printed automatically. PAS-X also enables review by exception functionality - which is the ability to review only the exception and critical parameters within manufacturing. The idea is that if the process and system are validated, the MES can be the first quality check. This has powerful implications down the line in speeding up time to treatment.

PAS-X MES can enforce all the value requirements, the number of significant digits, the value format and date entry. Whatever is needed can be parameterized including who can enter particular data and when they can enter it. Essentially there is the opportunity but no longer the need to look at every step, especially if it's automatically captured or not relevant to batch viability. PAS-X can guide the reviewers to where exceptions occurred and focus only on their critical process parameters (CPPs) and critical quality attributes (CQAs). Access can be from anywhere within the plant or even from personnel’s homes. If something breaks down in manufacturing and you need to call a supervisor or QA personnel, perhaps late at night, they can log in through a portal from home rather than go to the site unless that's necessary. It is always possible to review everything that's been done.



Let's look at some results. Initially for both companies, batch release time was around 30 hours per batch and Company B was able to reduce this time to 4 hours per batch. This has huge ramifications for scaling up activities. For Company B, in theory, this translated to around $9,000,000 in savings over three years with their current scale of projection of around 5,000 batches a year.

Another impact from implementing PAS-X as the EBR or system of record was the huge reduction in processing time of the actual treatment. The chart below shows one of Company B's processes without and then with PAS-X MES. This is just one of their manufacturing processes. You can also see that using PAS-X eliminates some manual work, date/time entries and calculations by automatically capturing, calculating, and auditing all this information. Operators no longer need to execute manual activities such as retrieving data from an equipment or IT system.



The number of process values was also dramatically reduced as many of them were repeats or spot checks since it was a manual process and some were values retrieved from equipment and other systems. These are now automatically collected by PAS-X through interfaces with those systems or equipment. The number of signatures was significantly reduced too as PAS-X performed spot checks and was configured for signatures only at critical steps - the CPPs or

CQAs. Of course, if you want to sign off on everything just as previously, that too can be configured.

Finally here are a few qualitative benefits gained by Company B leading to faster treatment of the patient:

- Increasing the right first time ratio – you can see the reduction in operator workload. The removal of the manual calculations and data activities translates to a decrease in potential for human error and deviations in the process. This helps increase right first time and also increase efficiency.
- Removed paper from the shop floor.
- Compliant within architectural IT standards.
- Use electronic chain of identity and chain of custody throughout manufacturing.

Conclusions:

1. **Consider using an MES if you are an established company or a start-up operating small-scale cell or gene therapy manufacturing:**
   - **At late stage clinical trial**
   - **Early stage clinical manufacturing**
   - **Scaling up for large scale manufacturing**

2. **Use the suggested questions to help evaluate MES suppliers.**