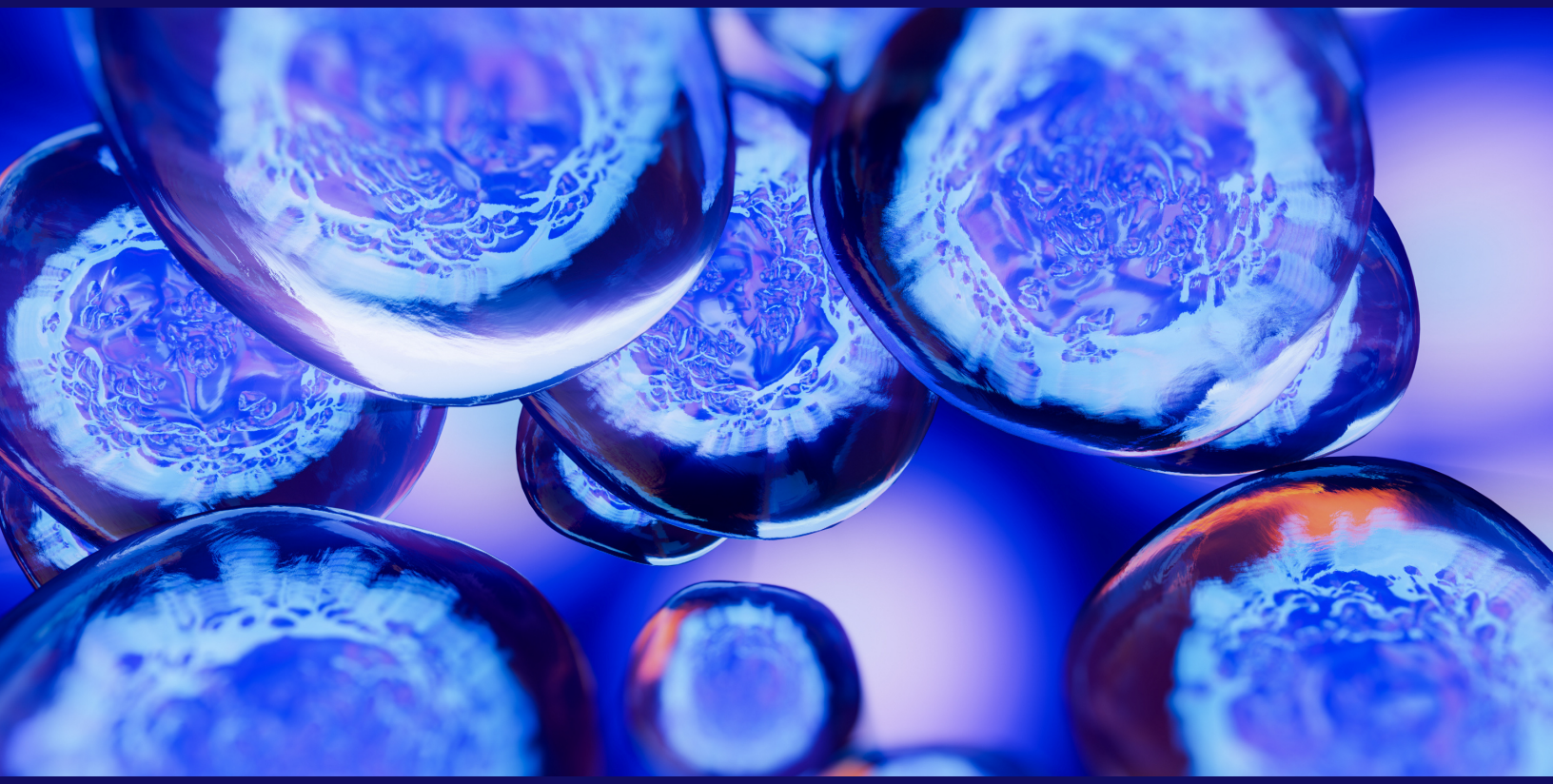
Cell & Gene Therapy Update:

Solving the Challenges Unique to Autologous Therapies



Cell Therapy Manufacturing Requires Information Management Solutions to Assure the Safety & Efficacy of These Promising New Treatments

"The personalized nature of cell therapies means that regulators are requiring organizations to demonstrate end-to-end visibility that ensures chain of custody, identity, and condition. New facilities face pressure to identify, prioritize, and implement the necessary IT systems."

Introduction

The number of cell and gene therapies in clinical trials, and reaching commercialization, are growing rapidly as new platforms and technologies are developing. CAR-T and TCR engineered immunotherapy products are just two current examples of technologies in the news recently because of FDA new product approvals.

Startups and new facilities are being established to manufacture this new generation of bespoke therapies. One of the most exciting aspects of this new approach involves autologous transplantation of cells (in which tissue or blood cells are harvested from an individual patient, expanded, modified, edited, or otherwise conditioned in an aseptic manufacturing environment, prior to the donor receiving their own modified cells via transfusion).

Irrespective of the modification, the manufacture and delivery of these cell therapies share similar attributes of processing distinguishing them from pharmaceutical or biopharmaceutical products.

Uniqueness of Cell & Gene Therapy

Personalized Product – In this process the patient's own cells are returned to them after the manufacturing process. This has several implications:

Figure 1: Typical CAR-T Cell Therapy Process

- A manufactured batch is for one patient. This means there are potentially far more 'product' batches running through an individual manufacturing facility than traditional pharma/biopharma. This equates to more batch record data that needs to be stored and available for future process development analysis, and the potential for more batch-to-batch variability.
- The starting material (the patients' cells) is variable in quality (e.g., number of viable cells in a sample, or responsiveness of cells in the process may vary). This means that it is difficult to implement a truly standardized process across all batches (e.g., times for induction or cell expansion may vary depending on the quality of the starting material).
- It is essential that the resulting product is administered to the same person from whom the cells were taken. The ability to confirm patient and batch match at various points in the processing, while maintaining an absolutely solid chain of custody, are critical.
- Made to Order – The nature of this treatment type precludes the need to inventory key starting material since it begins only after the patients cells have been harvested. This means that production scheduling can be constantly

changing as cell collection times are subject to changes outside the control of processing facilities. Production capacity planning becomes more difficult, making it impossible to build an inventory of finished goods.

Largely Manual Manufacturing Processes – Current manufacturing processes are largely manual, conducted in an aseptic processing environment, with operators transferring the product to containers for different steps in a multi-step process, manually setting and checking equipment setpoints and process parameters, and manually removing samples for QC purposes. This means that a lot of the process data that might be available through supervisory control and data acquisition (SCADA) systems in more mature continuous processes, is manually recorded in the batch record.

Large Number of Input Materials – Due to the complexity of the process and its largely manual multistep nature there are many reagents and disposables used in a single batch. The bill of materials for a single batch may be several hundred items (an order of magnitude more than traditional pharma/biopharma products). All these materials need to be available in manufacturing inventory, suitably quality controlled, and fully lot traceable to the manufactured batch.

Extended Supply Chain – Collection of starting cell material at clinics, and shipment to manufacturing sites, introduces another cold supply chain (in addition to the cold supply chain associated with the final product distribution) requiring validation, as well as the storage locations and handling conditions. The supply chain extends beyond the traditional pharma/biopharma manufacturing and is truly end-to-end, encompassing both the cell collection and product administration points, where storage, handling, and patient identity need to be confirmed. This extended supply chain requires a broader and deeper integration of data across multiple partners (e.g., clinics, couriers, in-house manufacturers, CMOs) than with traditionally formulated therapeutics.

Implications for an Information Management Strategy

Figure 2 maps some of the key information management (IM) capabilities needed to support cell therapy manufacturing and supply to the ANSI ISA-95 standard Levels and Functions model. Many of these capabilities are required (either practically or from a regulatory perspective) to support a commercially launched product. There are, however, few therapies that are currently commercially launched and many organizations are at the clinical trial stage (early phase through pivotal trials). For these startup companies, or independent spin offs of larger established companies, the priorities for standing up these information technology capabilities will need to be established.

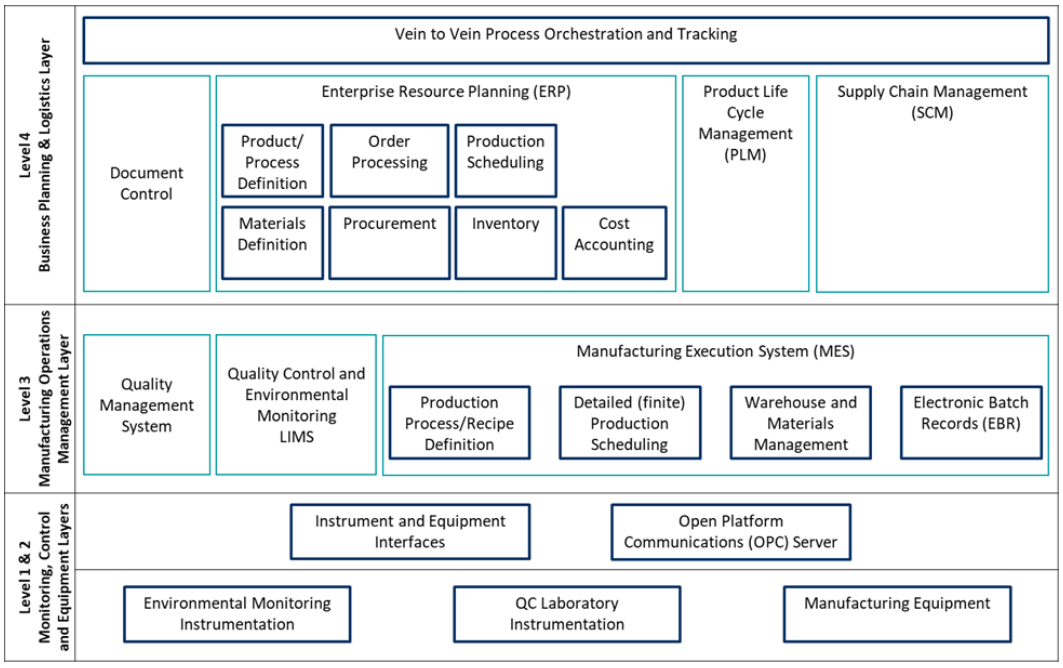


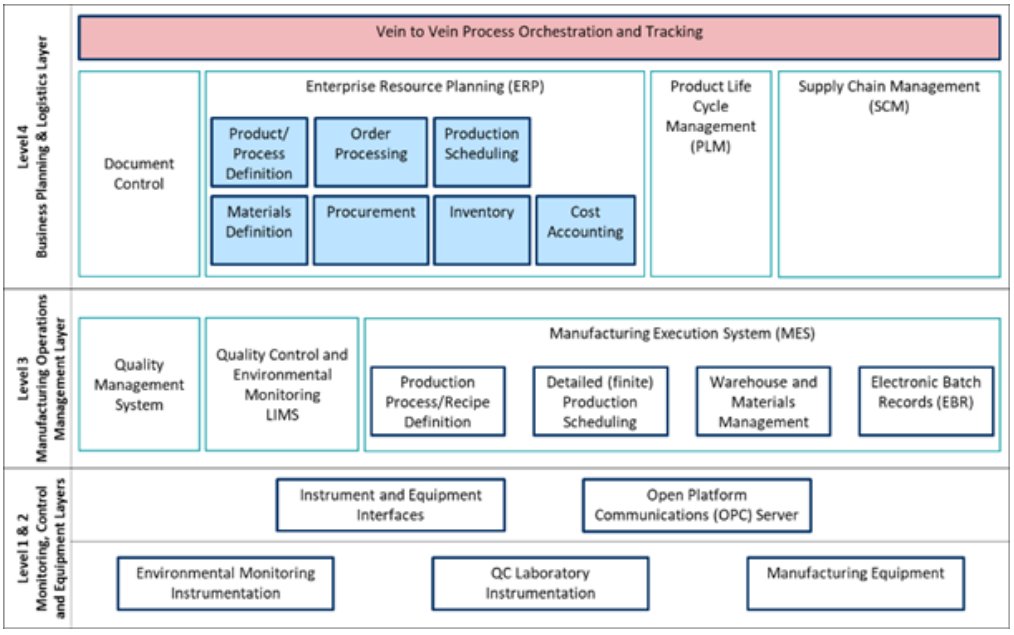
Figure 2: Cell Therapy Manufacturing and Supply IM Capabilities (Mapped to ISA-95 Model)

The following examines key capabilities and considerations for some of the Level 4 and Level 3 systems.

Level 4:

Enterprise Resource Planning

Given the number and criticality of material inputs to the processes it is essential to establish, early on, a clear definition of product lines, the high-level process steps for each line, associated bills of materials (BOMs), material identifiers, definitions, and specifications. The ability to electronically procure materials and manage multi-location material inventory (i.e., receipt, storage, restocking points, distribution, and valuation) is also needed.



Enterprise Resource Planning (ERP) solutions provide such capabilities in addition to being able to process orders, perform cross site production scheduling decisions, manage product lot number assignments, and coordinate material use. ERP systems provide a common environment to instantiate key master data (such as sites, suppliers, material items, product ids and names, employees, accounts). Solutions may also extend into Level 3 and encompass site warehouse management, kitting and issuance of materials.

Cloud based systems offer a relatively quick route to establish ERP for basic financial and cost accounting needs, but the introduction of production material definition and control functions will require GMP validation. The time and effort needed to establish these capabilities will need to be assessed given the velocity and maturity of operations. As such some organizations may opt initially for a light ERP implementation that focuses on order processing, production scheduling, inventory management, and financials in the short term. The implementation of GMP relevant areas such as lot number assignment and materials and warehouse management can then be implemented as part of the Level 3 systems (MES, or standalone solutions).

There are many commercially available ERP suites that provide the full range of capabilities discussed above. Given that a solution will, eventually, need to include some GMP functions organizations should look for solutions that have a track record of being successfully validated by other pharma/biotech companies.

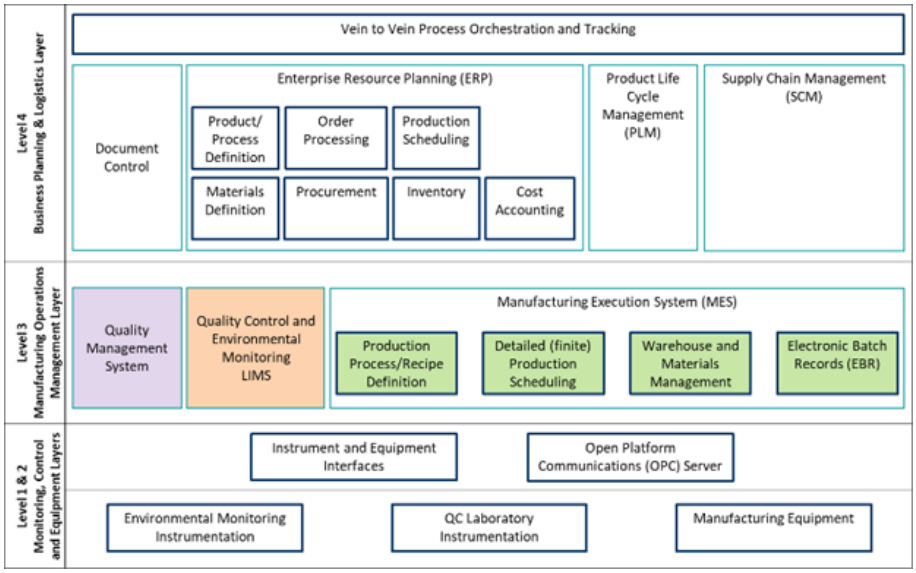
Vein to Vein Process Orchestration and Tracking

The need to unambiguously manage the end to end supply chain from patient cell collection through treatment/infusion means that orchestration and tracking capabilities requires early attention. Initially, this work may be done manually but demonstrated systems capabilities will be required for license application (BLA) and should therefore have already been proven during later phase clinical trials.

Capabilities in this area include:

- The ability to orchestrate and provide user interfaces or backend integrations to connect.
- Support key processes and different actors in the supply chain (i.e. clinical collection sites, couriers, manufacturing sites, and clinical treatment sites). Such systems need to facilitate the confirmation of identity at various points in the chain.
- Track and manage the chain of custody (who has possession of the product at every step) and chain of condition (storage and handling conditions).
- The system must also act as the source of record for traceability of the products from a specific collection event through the final use and disposition of intermediate and final products.
- GMP validation and compliance with personal information data handling regulations are also key considerations when designing or selecting a suitable system.

Characteristics of such systems map well to business process management software suites and some organizations have built custom solutions on top of BPM platforms. Relatively new dedicated commercial solutions do exist in this space and offer the promise of more standardized (and hence lower risk and cost) solutions that include many standard components such as courier integrations, and are cloud instantiated (offering easier access for use by the multiple third parties that need to access such platforms).



Level 3:

Quality Management System

Quality management processes and procedures supported by systems should be established early to ensure a secure, document lifecycle management for SOPs, work instructions and manufacturing documentation.

Processes for manufacturing incidents, non-conformance and deviations, corrective action, audits and preventative action, change control, risk and mitigation, and training and personnel qualification management all fall under the Quality Management System.

Quality Control LIMS

The typical cell therapy manufacturing process includes tens of 'in process' sampling points per batch as well as final product testing, and batch specific and general environmental monitoring and sampling. QC testing of incoming materials also needs to be performed and documented. Initially sample and test result management may be handled manually (on paper) but will rapidly require electronic systems support as the number of patients (and batches) grows. Many mature manufacturing QC LIMS and Environmental Monitoring (EM) commercial solutions exist that can address the needs in this area. However, it should be noted that EM operations and workflows are unique and usually require specific solutions complementary to standard LIMS solutions.

Manufacturing Execution System

Manufacturing shop floor needs have typically been accommodated via paper and manual processes through early clinical. Going forward, systems will be needed to offer more accurate modeling of the manufacturing process for different product lines along with resource (people, equipment, shop floor) requirements and execution times so that finite capacity planning can be performed. The resultant models are used to provide electronic detailed production schedules across product orders.

Warehouse management capabilities will be needed to support site specific receipt, storage, and subsequent kitting and batch record capture of issued materials (if not handled within the ERP solution).

Implementation of electronic batch records (EBR) may also be considered but should be assessed relative to the maturity of the manufacturing process. Some of the key benefits to EBR implementation include the ability to review by exception and the availability of electronic data for process development use. Modern EBR systems are certainly easier to adjust but the manufacturing process must be stable enough to warrant the time and effort that will be expended in development and particularly validation.

There are many commercial MES solutions in the marketplace. Most cover the range of capabilities described above. Many have a specific focus on pharmaceutical manufacturing with consulting resources who are familiar with the pharma domain.

However, as noted at the beginning of this paper, cell therapy processes are somewhat unique, smaller scale, multiple batch and employ limited process automation so some of the solution capabilities may not be directly applicable. The MES space has lacked in investment for a period of time but there appears to be renewed interest in revamping the technologies. Flexibility to deal with changes and user interface usability should be high on the list of evaluation considerations.

Conclusion

Organizations planning, or coping with the demands for rapid growth to pursue—or maximize capabilities of—these new types of therapeutics must devote time and expertise to:

- Consider their unique business processes,
- Identify the information management needs to support those processes and,
- Prioritize implementation of those capabilities aligned with the trajectory of their product development plans in light of finite resources.

Constructed properly, a strategic roadmap for IM capability solution selection and implementation will effectively guide investment and align stakeholder's expectations around the timing of technical capability implementation.

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