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Cell & gene therapy orchestration: supply chain management in real-time

Andreas Göbel & Dr Camila Mendes

With more Cell & Gene Therapies (CGT) entering the market, many pharma companies are currently looking into their supply chains and adapting them for the complexities and requirements that come with these novel therapies. Many startup biotech companies are doing the same thing, but with the advantage of being able to start with a greenfield project. The complex, highly collaborative supply chains of CGT require control and visibility to fulfill the very high requirements for safety, resilience, and speed that come with the underlying drug products. A very high degree of process complexity and the involvement of many different contributors, each with numerous intermediates and handovers, combine to ensure that it is almost impossible to manage more than 50 patients per year with simple tools such as Excel spreadsheets and web portals. There is a 'magic tool' that can provide the necessary support here – one that has been talked about for several years now: the Cell & Gene Therapy Orchestration Platform (Orchestration Platform). Biotech companies may require Orchestration Platform features that support regulatory requirements, such as chain of identity and custody, logistics management, and general collaboration. But as they move with their assets through preclinical, clinical, and eventually, commercial, it becomes clear that each of these different phases come with added requirements for the Orchestration Platform. Step by step, they will require features on different levels (workflow and integration, manufacturing, operations, tactical and strategic), depending on the product lifecycle and organizational state. In this article, we will detail all levels of a complete end-to-end supply chain management approach for personalized therapies. We will also highlight critical features of and key considerations for an Orchestration Platform and describe the phase in the product lifecycle in which each single level begins to generate its full value.

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The more biotech and pharma companies in the emerging high-growth area of CGT want to scale their production and global access to their products, the more they come to realize, they need to put more effort into their supply chain management.

This is to be expected right from the beginning, as the first patients are onboarded into first clinical trials. Whereas traditional pharma products involve supply chain and operational complexity only at the commercial phase, CGT setup and operational challenges continue throughout the clinical stages and into commercialization.

Supply chains in CGT are complex for a variety of reasons, starting with but not limited to complex manufacturing processes, high levels of coordination during the product and patient journey, and new regulatory compliance requirements. The good news is that the answer to the problems stemming from these complex supply chains is a single, consolidated Orchestration Platform.

An Orchestration Platform is usually a computerized application that coordinates all multi-enterprise critical activities across the supply chain and supports improved supply chain management in make-to-order environments by implementing full supply chain protocols (clinical, laboratories, manufacturing, and logistics). The Orchestration Platform executes these protocols through a workflow engine, providing a therapy control tower and data capture with reporting that realizes the chains of identity and custody.

To understand the need for such a platform and related methods, it is essential to look at the history of conventional production planning. "Today most mid-sized and large manufacturing enterprises throughout the world use a planning method and tool called Material Requirements Planning (MRP). This method and tool were conceived in the 1950s with the increasing availability, promise, and power of computers." [1].

DEFINITION OF MRP

"A set of techniques that uses bill of material data, inventory data, and the master production schedule to calculate requirements for materials. It makes recommendations to release replenishment orders for material. Further, because it is time-phased, it makes recommendations to reschedule open orders when due dates and need dates are not in phase. Time-phased MRP begins with the items listed on the MPS and determines (1) the quantity of all components and materials required to fabricate those times and (2) the date that the components and material are required. Time-phase MRP is accomplished by exploding the bill of material, adjusting for inventory quantities on hand or on order, and offsetting the net requirements by the appropriate lead times" [2].

From 2010, around 80% of manufacturing companies implemented an ERP system, simultaneously implementing a compatible MRP module.

Today, the methods and principles of MRP have been improved and adapted to tackle the ever growing "volatility and uncertainty of demand, and the complexity and ambiguity of product portfolios and supply chain networks in which companies now operate (VUCA)" [3].

From that point of view, the supply chains of CGTs are nothing other than a 'very VUCA' environment, and it seems to be logical to further extend existing supply chain management methods to overcome the specific challenges that arise here on top of traditional manufacturing models.

It is very likely that Cell and Gene Therapy Orchestration Platforms and related methods, as a special way of supply chain management, will establish themselves in the same way that MRP did in the past for traditional manufacturing models. We will see personalized therapy vendors implement Orchestration Platforms alongside their ERP, similar to what happened with MRP.

However, Cell and Gene Therapy Orchestration today is vastly non-standardized, in contrast to traditional supply chain management methods.

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The following describes a general scheme explaining the different domains of a Cell & Gene Therapy Orchestration Platform, based on established pharma supply chain management methods but enriched with the specific needs of CGT. From this, a peer-reviewed discussion shall commence to establish standardized terms, principles, and methods related to Cell and Gene Therapy Orchestration.

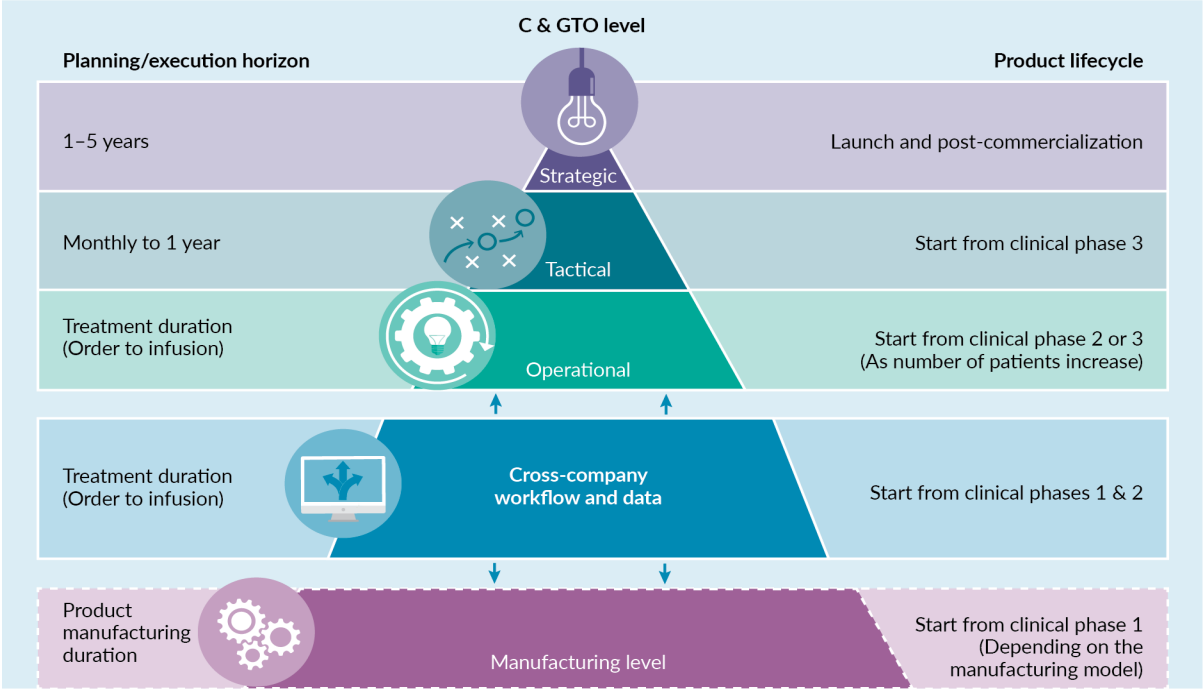
DEFINITION OF CELL & GENE THERAPY ORCHESTRATION

A set of techniques that uses order data, inventory data, supply chain network data, master data and a set of different but dependent service schedules to calculate the optimal supply chain sequence to execute a predefined supply chain protocol for the purpose of a cell and gene therapy in a make-to-order environment. It makes recommendations to release replenishment orders for consumable supply materials. Further, because the supply situation of patients living cells is highly variable and volatile, it makes recommendations to reschedule the therapy partially or completely when supply dates move, manufacturing is delayed, or logistics services cannot be provided. Cell and Gene Therapy Orchestration (C&GTO) begins with the clinical order involving an initial scheduling process determining an infusion date proposal, the possible starting material extraction appointments the number of drug product batches to be produced and materials required to fabricate those, and the dates when the materials are required. C&GTO, by default, fulfills regulatory requirements like chain of identity (COI) and chain of custody (COC) and optionally, additional features like label and document management."

Based on established supply chain management methods such as LEAN supply chain management, the different features of a platform implementing the C&GTO paradigm can be grouped by different levels (Figure 1).

FIGURE 1

Supply chain management planning addresses different types of problems according to the decision horizon.



All those levels from long-term (strategic), medium-term (tactical) and short-term (operational) are part of the holistic C&GTO concept. The C&GTO concept has the cross-company workflow & data level at its core but is also connected to higher supply chain planning levels and to day-to-day activities in the manufacturing level at the bottom. In this picture, we present an overview of the C&GTO levels according to the planning or execution horizon and additionally linked to the product lifecycle phase when each level becomes relevant.

IMPLEMENTING SUPPLY CHAIN PROTOCOLS ON THE CROSS-COMPANY WORKFLOW & DATA LEVEL

No matter the phase of development, companies need to set up supply chain workflows and upstream and downstream integrations with supply chain partners, building a 'supply chain protocol'. At this stage, the entire supply chain protocol from order to infusion – including logistics and manufacturing is defined and configured in a single system for real-time transparency, automation, and visibility of each step in the therapy's journey. It also contains the full data model to be filled during protocol execution from connected data flows or by manual input.

The possibility to freely define different flows and dynamic data models, as well as an engine executing the defined therapy supply chain protocol, are the key elements of this level and form the backbone of every C&GTO.

The established protocol definition, execution, and data consolidation in one system ensures that all actions and notifications are tracked by collecting information from multiple stakeholders and connected systems, and connecting them into one central source of truth, which allows users to act quickly on the actions that are required to drive the therapy for each patient. This is also equally important for reporting and data analysis over the entire process.

BOX 1

Features for CGT orchestration platforms at cross-company workflow level.

At the cross-company workflow level, CGT supply chain orchestration platforms need to offer features like:

- **Therapy Control tower**: The therapy control tower is more than a usual dashboard. It has not only a transparent overview of all scheduled, ongoing, and past therapies with a condensed view on status but also presents a concrete proposal for action. It usually comes with the ability to drill down on every single process step and provides the full capability of acting as a supply chain responsible person.
- **COI COC and COCn**: The COI ensures that a patient gets the treatment specifically produced for them, including tracking for each patient throughout the 'vein to vein' process. This ensures treatment of the patient with the correct cells. COC ensures chronological documentation that records the sequence of custody, control, transfer, and analysis – not just in manufacturing but throughout the logistics and treatment processes. Additional to both – COI & COC – there is also the chain of condition (COCn) that tracks the temperature and other key variables critical to quality and viability of the treatment from the starting material throughout the final drug product.
- **Real-time tracking**: For full transparency and especially as an input for other levels of the orchestration platform, real-time tracking gives just-in-time insights into geographical movements and temperature conditions of transported goods, and into process details like handovers and step state status changes.
- **Configurable workflows**: Fully flexible and configurable workflows are one of two core elements of a non-bespoke C&GTO platform, because nobody knows what tomorrow's therapy supply chain and manufacturing protocols will look like.
- **Dynamic data model**: This is the second core element for building the foundation of a fully flexible orchestration platform. It is particularly crucial because data models of different therapies may differ substantially.
- **Generic and dedicated data integration**: Data integration describes a way to consume data from external interfaces and having data consumed from owned interfaces. It may seem to be a contradiction, but one needs both: on the one hand a generic integration infrastructure to support future systems and devices, which are not yet known. On the other hand, one needs the capabilities to integrate into today's commodity systems, like MES and ERP systems, with easy-to-configure dedicated data integration modules. Also, the orchestration platform itself must be consumable, by both users and machines. For a machine-to-machine communication it needs to expose application programming interfaces (APIs) based on well-established standards, like HTTP REST or more specifically in a clinical environment, FHIR.
- **Data protection**: Compliance with global data protection regulations like GDPR, HIPAA, and French HDS is a must, since every personalized therapy touches patient health records and person-related information.
- **Labelling**: Several steps of supply chain protocol imply the management, printing, and/or tracking of labels, such as ISBT128-compliant blood bag labels, logistics service provider labels, and sample labels.

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KEY CONSIDERATIONS FOR IMPLEMENTING A CROSS- COMPANY WORKFLOW & DATA LEVEL

Flexibility & scalability

A supporting IT system for a company's first CGT can be complex, costly, slow, over-specific, not scalable, incomplete, and unsuitable for having several different therapies in their portfolio or pipeline without careful thought and planning. By adhering to C&GTO principles, the cross-company workflow and data level must be a flexible solution suitable for a range of therapies, and not tightly specific to one therapy. A flexible system architecture supports the implementation of various therapies' protocols. Additionally, systems must be easily scalable for adjusting into new market requirements, and scalable for global clinical and global commercial set-up.

Standards

Common platform cloud solutions and industry standards are essential to enable diverse value chain partners to connect to the integrated vein-to-vein orchestration system. Adoption of common user-interface standards across life science companies, suppliers, and medical centers will simplify operations, reducing the administrative burden and risk of error from using different systems for each cell therapy manufacturer.

To manage COI and COC, orchestration platforms need further integration to systems in the manufacturing & operational levels. Implementing a fully integrated, digital vein to vein platform and supply chain, dramatically increases throughput and unlocks the potential for full automation with the goal of a "self-driving therapy supply chain". This will increase both the speed and accuracy of the manufacturing process while reducing the likelihood of COI and COC errors.

INTEGRATIONS & REMOTE CONTROL ON THE MANUFACTURING LEVEL

In the traditional biomanufacturing business, there is typically an ecosystem of many different manufacturing plants for three processes: drug substance, drug product, and packaging. In CGT, these processes vary enormously in terms of capacity and complexity. In the personalized CGT manufacturing processes, where each batch is unique to an individual patient, the production of such living cell-based products is inherently variable, and the manufacturing process must be able to accommodate this variability. Many of these challenges can be traced back to process challenges like paper-based quality assurance/quality control (QA/QC) and the failure to establish the CMC process for CGT early on. To make sure, this complexity does not affect quality, efficacy, compliance, and accountability in the entire vein-to-vein process, an orchestration platform should support an integration into existing Manufacturing Execution System (MES).

Further, the required flexibility should also support new or even future manufacturing models. For example, in point-of-care manufacturing models, the manufacturing process must be fully covered by the orchestration platform. Here, the manufacturing protocol becomes part of the larger supply chain protocol, being converted into standard operation procedures (SOPs), which effectively 'remote control' on-site operators during their daily work.

KEY CONSIDERATIONS WHEN IMPLEMENTING FEATURES AT THE MANUFACTURING LEVEL

Real-time & remote release

Traditionally, biopharmaceutical manufacturers release involves review of in-process control data, batch records, test records, and off-line release testing of drug substance and

drug product. The current QC sampling and testing process is burdensome, though – it is labor intensive with many potential opportunities for errors in sampling, labeling, transporting, storing, and testing. This can take several weeks after production, causing significant delays in product release.

CGT challenge all QA/QC steps and require a fully digitized and faster product release while maintaining product safety. It is required that in the QC processes, deviations are detected through real-time feedback by sensors and systems, and a more proactive QA rather than reactive investigations to improve process control, leading to quicker product release.

During the real-time manufacturing process, the captured data must meet the needs of QA and QC, whilst allowing sign-off by remote QC specialists. Furthermore, eliminating or minimizing these opportunities for errors will make the overall manufacturing and 'testing' processes easier and more predictable, which translates to a more reliable supply chain.

CROSS-COMPANY SCHEDULING ON THE OPERATIONAL LEVEL

When the number of drug product batches increases in late-stage clinical phases or after commercialization, there are new challenges on a more operational level, namely with the scheduling of those tasks in the supply chain protocol that require an appointment or a certain amount of a limited production capacity. Once a therapy is ordered, its' delivery must be optimized towards the 'time to patient' KPI, within agreed lead times. However, due to patients' poor health condition, the cell collection schedules can change at very short notice, in turn influencing the subsequent schedule and thus requiring a re-scheduling of all subsequent steps.

The flexibility needed for scheduling and re-scheduling can be achieved in a C&GTO platform by tightly integrating the schedules of as many parties as possible with bi-directional data flow. The scheduling needs to cover all upstream (doctor, patient, logistic) and

BOX 2

Features for CGT orchestration platforms at manufacturing level.

At the manufacturing level, C&GTO platforms need to offer features such as:

- **MES integration**: Manufacturing execution systems, MES for short, are used to track and control data points between patient, donor, raw material, and material management. With a MES, biomanufacturers achieve higher maturity levels in their manufacturing, as they enable manufacturing automation (less manual processing steps in processing a batch) and integrate vertically and horizontally into the manufacturing technology ecosystem.
- **Standard operating procedures (SOP) management and execution**: SOP management and execution turns the supply chain and manufacturing protocols of the cross-company workflow level into high-quality SOPs. They can be executed by manufacturing operators and healthcare professionals.
- **Manufacturing devices integration**: New manufacturing models, like point-of-care approaches, require the tight integration of various manufacturing devices into the orchestration platform for automation and documentation purposes. In more traditional manufacturing, this is covered by MES systems.
- **Electronic batch record**: With Electronic Batch Recording (EBR) systems, the patient's material can be correctly identified at any time during the process. EBR systems also record manufacturing locations or used equipment. This caters to CGT regulations which specify that the cells need to be identifiable at any stage of the manufacturing process, to secure CoI. Next to the severe effects of administering the wrong drug (i.e. based on cells from another patient), this also prevents the cost generated by failed batches.
- **Labeling**: Shop-floor systems should be integrated to enforce the traceability and manage the patient data and information to be printed on labels. Digital controls in the manufacturing facility will leverage and extend new industry labeling and tracking standards to ensure chain of custody, chain of identity, and chain of condition (tracking of transport conditions).
- **Document management**: This ensures a secure, documented lifecycle management for SOPs, work instructions and manufacturing documentation.
- **Deviation management:** Deviation management is the process of detecting, evaluating, and correcting deviations from approved instructions or SOPs. C&GTO platforms streamline the entire deviation management process with the traceability required and provides processes as well as documentation to corrective and preventive activities. This allows organizations to deal efficiently with deviations by automating the data collection and complying with regulatory requirements.

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downstream (manufacturing, logistic, infusion) processes. The biggest advantage of the scheduling automation is the amount of time saved by avoiding manual communications through ineffective channels such as phone or email. Additionally, booking errors stemming from manual scheduling or rescheduling become more unlikely with this approach. Ultimately, the scheduling automation can help to scale the number of batches that can be produced due to an optimal usage of resources, notwithstanding dynamic timing variabilities.

KEY CONSIDERATIONS FOR IMPLEMENTING FEATURES AT THE OPERATIONAL LEVEL

Fully automated & advanced scheduling

Scheduling enables therapy-driven production planning and detailed scheduling for make-to-order environments. It should support real-time, cross-company scenario planning, optimization, and order sequencing. An automated decision support can be reached via integrated cognitive planning engines. Decision-makers can obtain insights into the impacts of detailed scheduling on the supply chain in real-time. Automated scheduling should link advanced scheduling capabilities seamlessly into a cross-company workflow level.

SUPPLY CHAIN SIMULATIONS ON THE TACTICAL LEVEL

Tactical supply chain simulations based on the current network master data allow for predictive planning. This predictive planning can involve an integrated view of logistics, supply, and clinical, revealing insights into the best possible supply chain parameterization to produce as many batches as possible depending on the rather unpredictable level of demand. The entire network of stakeholders involved, through upstream and downstream linkages, in the different processes and activities are checked with regards to inventory management, planning processes, logistics availability, etc.

CGT challenges the tactical level design and simulations, as vendors have to deal with scenarios without inventory buffer for the main starting material (human blood or samples from the patient, in the case of autologous or allogeneic CGT) and further supply and demand uncertainties.

The CGT Sales and Operations Plan (S&OP) that describes the intended procedures for production and distribution of the cell therapy product is also a challenge, because it is impossible to have long-term forecasts for the consumption of materials, which would help to establish appropriate levels of inventory at the cell processing facility as well as throughout the organization's complete supply chain.

BOX 3

Features for C&GTO platforms at operational level.

To achieve this, the operational level needs the following features:

- **Cross-company schedule management**: This means accessing every partner's relevant planning system to ensure access to and integration of the available calendars, slot schedules, and service booking systems of the different parties contributing to a therapy's supply chain.
- **Cross-company scheduling**: Operational real-time scheduling upon a therapy order is utilized with the aforementioned calendars, slot schedules, and service booking systems. Depending on the level of maturity of the integration scenario, this cross-company scheduling and rescheduling can be optimized and semi- or fully automated
- **Inventory management**: To avoid frequent rescheduling reactions of the cross-company scheduler due to supply issues with raw materials and production equipment, decentralized inventory management is key to avoid supply shortages, thus optimizing schedules holistically throughout the therapy supply chain.
- **Logistics scheduling**: Logistics scheduling supports transport service ordering processes. This can even be automatically integrated into the end-to-end scheduling of a therapy, depending on the maturity of the logistics service provider's digital infrastructure for service ordering and consumption.

Key elements of tactical level simulations

- High master data quality;
- Proper parameterization of the supply chain protocol with data points from the master data;
- Choice when it comes to service providers and sites.

SUPPLY CHAIN DESIGN OPTIMIZATION ON THE STRATEGIC LEVEL

Supply chain management addresses different types of problems according to the concerned decision horizon. At the strategic level, long-range decisions are concerned with supply chain configuration: onboarded clinics, number and location of suppliers, laboratories, own production facilities, contract manufacturing organizations, logistics service providers and warehouses, etc.

In CGT, the complexity and scalability of the end-to-end supply chain must be considered as the major factor for strategic decisions determining the commercial therapy performance. This leads to selections around a geographical supply chain network configuration with fallbacks and alternative routes.

Key elements of an end-to-end CGT supply chain network

- Clinical network → clinics and apheresis centers;
- Supply network → supplier selection;
- Production network → manufacturing site location and CMO selection;
- Distribution network → distribution structure and logistics service provider selection.

A full supply chain network design should anyhow be part of an orchestration platform master data configuration because details of this configuration are required during the supply chain protocol execution. Optimizing the existing designs based on insights from the tactical level is the foundational essence of commercially successful CGT products.

FLEXIBILITY & MODULARITY

Independent from the aforementioned levels, an orchestration platform should provide the right degree of flexibility, as nobody can predict how tomorrow's asset will look at the various different levels described.

With increased demand for end-to-end supply chain management, it is important to understand the variety in concrete challenges that sets one company's situation apart from the next. Even though all companies want to form an overall supply management ecosystem, the company size and background make all the difference:

New players in CGT – e.g., new-entrant biotechs with a strong scientific background – usually conquer the complexity of supply chain management step by step. This also means that they do not need all levels from the start. They typically master the levels as their business matures (Table 1).

- In their preclinical stage, they need to establish a supply chain protocol design based on the patient and product journey.
- Entering Phase one clinical trials, they meet challenges on the manufacturing level, e.g., selecting between centralized or decentralized models, requiring a manufacturing protocol design.
- Starting with Phase three and commercialization, they face the number of patients increasing and the next set of challenges on the operational level – for example, how to collaborate more efficiently upstream and downstream, how

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TABLE 1

When to implement which level.

	Workflow & integration level	Manufacturing level	Operational level	Tactical level	Strategic level
Asset state	Pre-clinical	Phase 1	Phase 3 – commercialization	Post-commercialization	Post-commercialization
Asset evolvement					
Implementation process	Supply chain protocol design	Manufacturing protocol design	Scheduling optimization	Data mining and evaluation	Supply chain improvements
Orchestration platform implantation activity					

to adhere to compliance rules, etc. These are questions addressed by scheduling automation and optimization.

- Post-commercialization, they want to understand all the operational planning on the tactical level and identify and predict bottlenecks. By using data mining and simulations they can reassess the supply chain distribution network.
- From this stage, they can deduce and implement supply chain improvements at the company's strategic level.

This calls for a modular system of the C&GTO platform to solve supply chain challenges, giving emerging players the freedom to choose only those modules that they need at any given time in their growth process.

There is another, more technical reason for a modular concept: an orchestration platform needs to be flexible in answering to future requirements that are as yet unknown. These might be with new logistics partners that need to be added, new compliance regulations (e.g., for new markets), or even completely different manufacturing models (e.g., point-of-care manufacturing). Here, it is helpful if only one module needs to be changed, tested, and rolled out. Thus, modular solutions are more responsive to future changes in the environment for CGT.

That said, one should not look for a non-bespoke solution (this describes a solution where every feature is statically built-in code, or hardcoded). Instead, the platform should offer a generic core that can be configured accordingly, depending on the supply chain protocol at hand. This has the huge advantage that the cost for maintaining the solution in a fast-paced environment as CGT is lower. The sweet spot is a modular solution with out-of-the-box features that is still highly configurable, as no CGT vendor's processes resemble the next. Optimally, out-of-the-box features are standardized components, that come along pre-qualified, significantly reducing the amount of work to be performed on the obligatory 'validation of computerized systems' project.

CONCLUSION

Know & control your processes

The end-to-end supply chain process for a personalized therapy can be understood as a 'supply chain protocol'. An orchestration platform can guide through the design phase of such a 'supply chain protocol' and even act as the driving engine on top of the defined process after implementation.

Manufacturing execution in CGT is different

The term execution in MES is gaining a different meaning in CGT, where it relates to 'remote-controlling' human operators or, at the most, involves several different devices that still need the operator as a connector. An orchestration platform can act as such an MES, becoming an integral part of a supply chain protocol execution.

CGT scheduling is production planning optimization in real-time

The traditional production planning optimization systems never had a direct connection into the effective execution. CGT require exactly this connection for scheduling automation and according rescheduling with follow-up events as part of the supply chain protocol. An orchestration platform can establish this connection optimally by bringing a scheduling engine as an integral component.

The commercial performance of a CGT product is governed by supply chain optimization

'The manufacturing process of personalized medicines starts with the raw material extraction and ends with the administration of the resulting product.' [4].

In a commercial context, this means that the greatest optimization potential for the performance of a therapy product is buried inside the supply chain network design itself. An orchestration platform, with simulation and supply chain network modeling capabilities can support fulfillment of this potential.

REFERENCES

1. Demand Driven Material Requirements Planning (DDMRP), Version 2, Carol Ptak and Chad Smith, Industrial Press, Inc., ISBN 978-0-8311-3628-4, page 3.
2. APICS (2013), APICS Dictionary, 14th ed. Chicago: APICS.
3. LEAN Supply Chain Planning, Josef Packowski, CRC Press 2014, ISBN 978-1-4822-0533-6, xvii
4. Lisa Fox, Co-Founder at Broken Lance Biotech Consulting, during Cell & Gene Manufacturing Congress Amsterdam, 2018

AFFILIATIONS

Andreas Göbel
Managing Director, Hypertrust

Dr Camila Mendes
Head of Business Development, Hypertrust

hypertrust
AN ELIXUM COMPANY

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