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PATIENT DATA CARE

# Supply Chain Orchestration in Advanced & Personalized Therapies

## Decision support based on cell & gene therapy best practices

White Paper

# Introduction

Personalized cell & gene therapies (CGT) have quickly transformed the pharmaceutical market since the approval of the cell therapies KYMRIAH (Novartis Pharmaceutical Corporation) on August 30, 2017, and YESCARTA (Kite Pharma, Incorporated) on October 18, 2017. Both treatments offer the opportunity of potentially curative therapies for different types of leukemia, with KYMRIAH indicated for B-CELL-ALL and DLBCL, and YESCARTA for DLBLCL and PMBCL. Since then, further cell & gene therapies have been approved by the FDA while the number of clinical trials in the segment of cell & gene therapies increases year by year.

Those therapies require drastically changed supply chain processes, especially when they are made available to patients at scale. This paper supports supply chain executives at pharmaceutical companies in understanding the complexities and requirements of personalized cell & gene supply chains. It outlines necessary steps for a comprehensive supply chain orchestration in order to keep complexity and cost under control. And it serves as a thought base and inspiration for paving the way from (pre)clinical trials to the successful commercialization of such therapies.

## CONTENTS

# Why are cell & gene therapy supply chains different?

**Cell & gene therapies show specific characteristics that result in new and additional requirements for process execution and supporting IT systems compared to more traditional therapies:**

## SENSITIVE HANDLING

Unlike traditional therapies and off-the-shelf drugs, manufacturing and supply processes for cell & gene therapies require sensitive handling not only for transportation, storage, temperature, and manual processes but also regarding patient data and identity.

## CHAIN OF IDENTITY

The Chain of Identity (CoI) is a very important topic for therapies with a very high degree of personalization, like autologous cell therapies. Here we are at a level of 1:1 donor/recipient. The material is based on living cells of the patient, which are extracted, modified, expanded, and infused back into the original patient. Therefore, it is essential to maintain and safeguard the CoI throughout the entire supply chain process.

## MANY STAKEHOLDERS

Therapy processes strongly depend on the close involvement and collaboration of an extensive number of stakeholders (see picture 1) in multiple steps. This increases complexity and the need for harmonized orchestration of all corresponding supply chain activities across all stakeholders. Simultaneously, the process flow and execution must remain transparent at all levels.


**Picture 1:** Additional stakeholders needed for cell & gene therapy orchestration pre/post treat-ment

## VISIBILITY AND TRACEABILITY THROUGHOUT ORCHESTRATION

All steps in manufacturing and distribution with their multiple touchpoints need to be orchestrated across all stakeholders in accordance with the treatment schedule. In this process, full visibility and traceability always need to be adhered to and made available to different groups and roles.

## GXP GUIDELINES

Living cells, raw materials for further production and intermediate products are subject to a high degree of qualitative and quantitative variability that directly impact the therapy efficacy. Therefore, all manufacturing and distribution steps need to adhere to strict quality and safety requirements according to GxP guidelines.

## CHAIN OF CUSTODY

Mishandling carries the risk that the therapy can become derailed. Therefore, the Chain of Custody (CoC) is the most important documentation element. Standardized labeling of the patient donor sample collection, subsequent QA/QC samples, and the final pharmaceutical product, as well as a consistent transport track and trace approach are mandatory measures in the field of cell & gene therapies.

## MAKE-TO-ORDER AND SMALL LOT SIZES

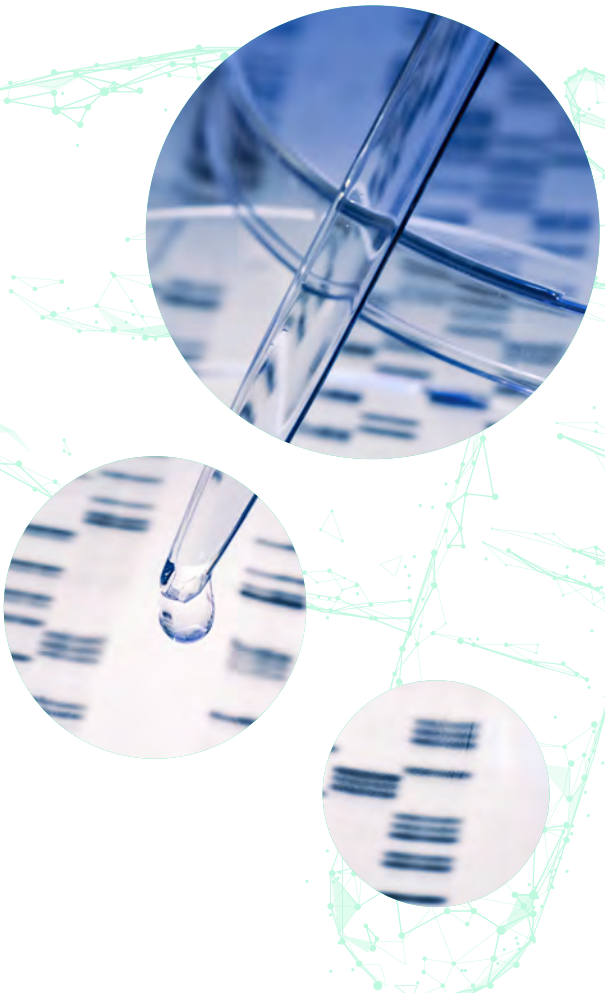
In contrast to one-fits-many treatments, cell & gene therapies start at the patient or a donor and end with the patient. In many cases, the production of the drug is triggered by a physician's order, in comparison to traditional production scenarios that are based on a demand forecast. From a supply chain perspective, this is a make-to-order environment with small lot sizes, which is substantially different compared to the traditional make-to-stock production models in pharma. The established processes for production, supply chain, and logistics of pharmaceutical products were not designed and built to support these changed basic conditions.

## SCALING

The production of cell & gene therapy drugs cannot be scaled as easily as traditional small molecule medicines. The latter are usually scaled by automated processes, centralized manufacturing, and rely on a long shelf life (or a shelf life formulated to maximize storage). In contrast, cell & gene therapies require many manual process steps and input from skilled production operators in dedicated production sites. The high degree of human labor makes production process automation almost impossible. However, an adequate scale-up can still be achieved by automating the remaining supply chain components and information flows.

# Cost factors in cell & gene therapies

**Most cell & gene therapies are based on complex manufacturing and distribution steps that are highly individualized per treatment. This partially explains the price of cell & gene therapies ranging from USD 375.000 to USD 850.000 (as approved in the US in 2017).**



A **recent study*** investigated the manufacturing cost of high-priced cell & gene therapies and potential areas for cost reductions. They found that the estimated cost of goods sold (COGS) for the approved cell therapies are in line with the general bio-pharmaceutical range of 15 to 25 percent of the list price. Interestingly, more than 70 percent of the COGS are manufacturing costs, with almost half the amount attributed to personnel for QC / QA and supply chain management.

Supply chain costs mainly result from necessary efforts to achieve cross-company process orchestration. In the clinical trials we have seen so far, orchestration often is a manual process driven by paperwork and forms, usually conducted by a dedicated case manager.

Technology-supported processes have the potential to relieve case managers from error-prone manual work. They can facilitate highly automated planning and orchestration across all parties. The prerequisite: digitalization, standardization, and collaboration.

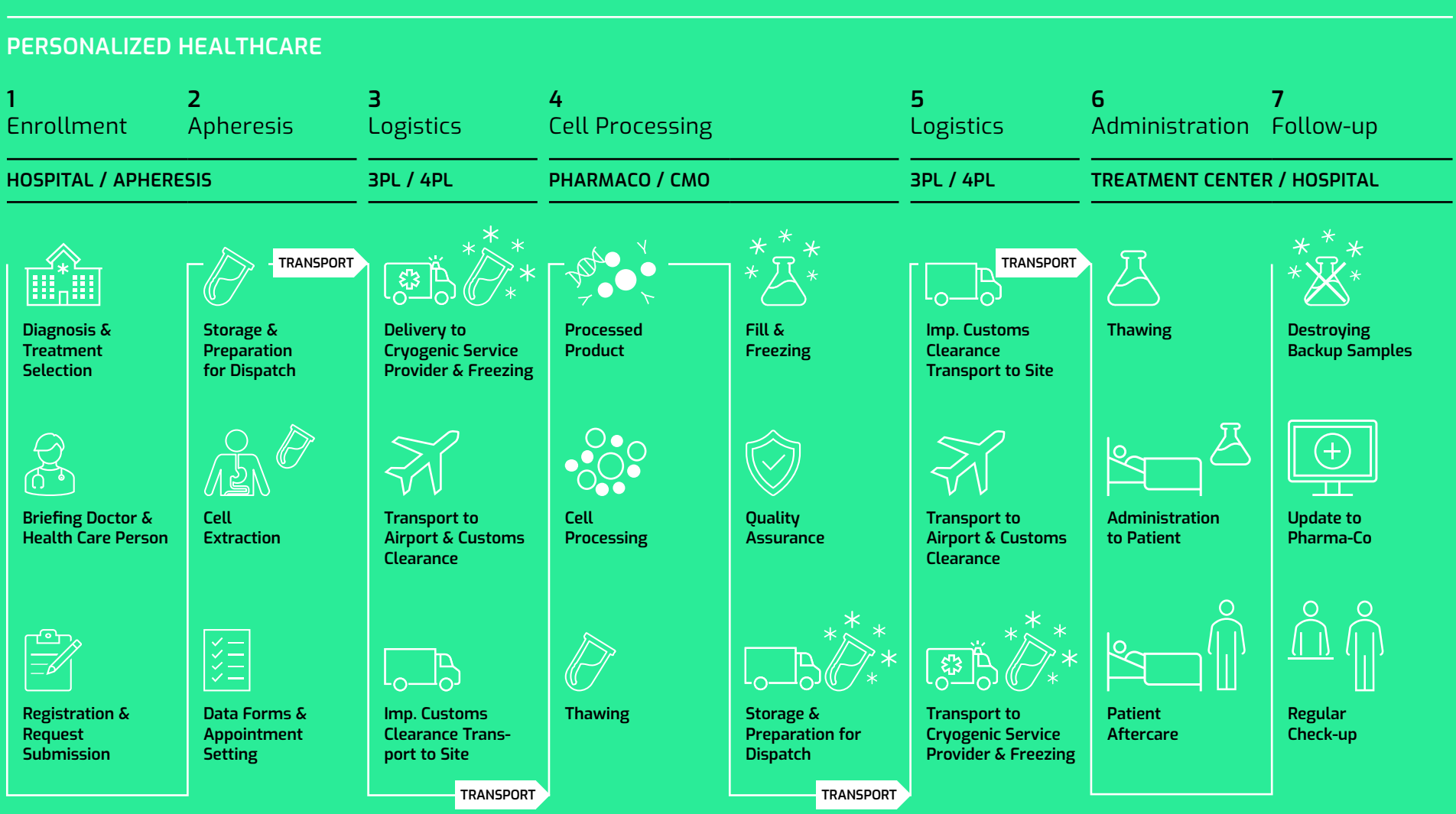
With increasingly more CGT entering commercialization soon, a frictionless and automated supply chain process is required across all steps from manufacturing to the delivery of personalized therapies.

In the following chapter, we will explore how to orchestrate these new processes.

* "The long road to affordability" by Katy Spink and Andrew Steinsapir, Dark Horse Consulting Group
https://www.researchgate.net/publication/330623902_The_long_road_to_affordability_a_cost_of_goods_analysis_for_an_autologous_CAR-T_process

# Orchestrating cell & gene therapies

**The following chapter will show the complexity of the process and the different stakeholders involved based on the example of a CAR-T therapy process. The process of executing a cell & gene therapy starts in a hospital. Based on blood tests or tissue samples, a physician decides on the specific therapy (from a given vendor) and starts registration and eligibility checks. A unique identifier is created early on that clearly and unequivocally marks the patient's case throughout all tests and analyses that are conducted with the individual patient's blood or cell material.**




**Picture 2:** The process of a personalized therapy based on the example of autologous cell therapies

## EXTRACTING THE MATERIAL

When eligibility checks for the cell & gene therapy are completed successfully, the physician orders the cell & gene therapy. At this point a case manager is involved to drive the orchestration process with external partners: an apheresis center for the cell extraction and a logistics service provider (LSP) for the transport. The handover from hospital or apheresis center to the LSP, as well as all handovers in the process to follow, need to be organized and documented to ensure CoC and CoI.

## TRANSPORT TO PRODUCTION

The LSP transports the fresh or frozen material to the pharmaceutical production site, where the drug is produced. From the logistics side, the transports will include additional complexities like cryogenic transport. In many cases, there also is a need for transport of cell material across borders, which means customs processes with and for material that is usually classified as a biohazard. Here the logistics service provider needs timely information to prepare for transport and customs.

## ORCHESTRATION AROUND DELIVERY

Fresh products in cell & gene therapies have a short shelf life. They need to be delivered to the hospital and administered to the patient without delay.

Parallel to this, the hospital will have to have scheduled prior health checks for the patient, and timed additional treatments that need to be finished before the drug can be administered. The procedure itself also needs to be scheduled. To administer the treatment as soon as it arrives at the hospital, the physician and other parties in the hospital need prior information on the expected delivery date as soon as possible, as well as timely information in case of delays, e.g., at customs.

## INTERLACING PROCESSES

**Even in a best case scenario, we see a process including several parties with their individual processes that, as a whole, makes orchestration in cell & gene therapies complex:**

_ The hospital with different functions: the physician, the laboratory, a case manager, etc.
_ In the US, third-party providers like an apheresis center, with different functions as well
_ At least one LSP for cold transport of the frozen goods between parties
_ Pharmaceutical production site

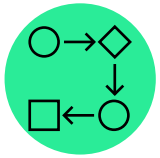
External workflows like customs procedures also have to be taken into account.

# CGOP: Common ground for cooperation among partners

**The complexities outlined above show that successful cell & gene therapies rely on a tightly orchestrated collaboration between independent organizations that have a shared interest in a treatment process and the associated data.**

A digitalized solution in form of a Cell & Gene Orchestration Platform (CGOP) can relieve case managers of having to manually track and orchestrate all the necessary steps in an audit-proof paper trail.

**The implementation of a CGOP is an industry-proven way to harmonize and optimize the supply chains of personalized medicines. CGOPs provide the required level of cross-organizational orchestration, automation, and optimization which, at scale, cannot be achieved manually:**



Cross-company collaboration and workflow integration instead of single and isolated process owners

Quality assurance and compliance with regulations through consistent documentation, even though compiled by different parties

Transparency about production capacities and their impact on treatment timelines for physicians and treatment centers

Automation and system integration capabilities to ensure scale up and scale out during the commercialization phase

Compliance with existing data privacy and security regulations securing highly sensitive patient data

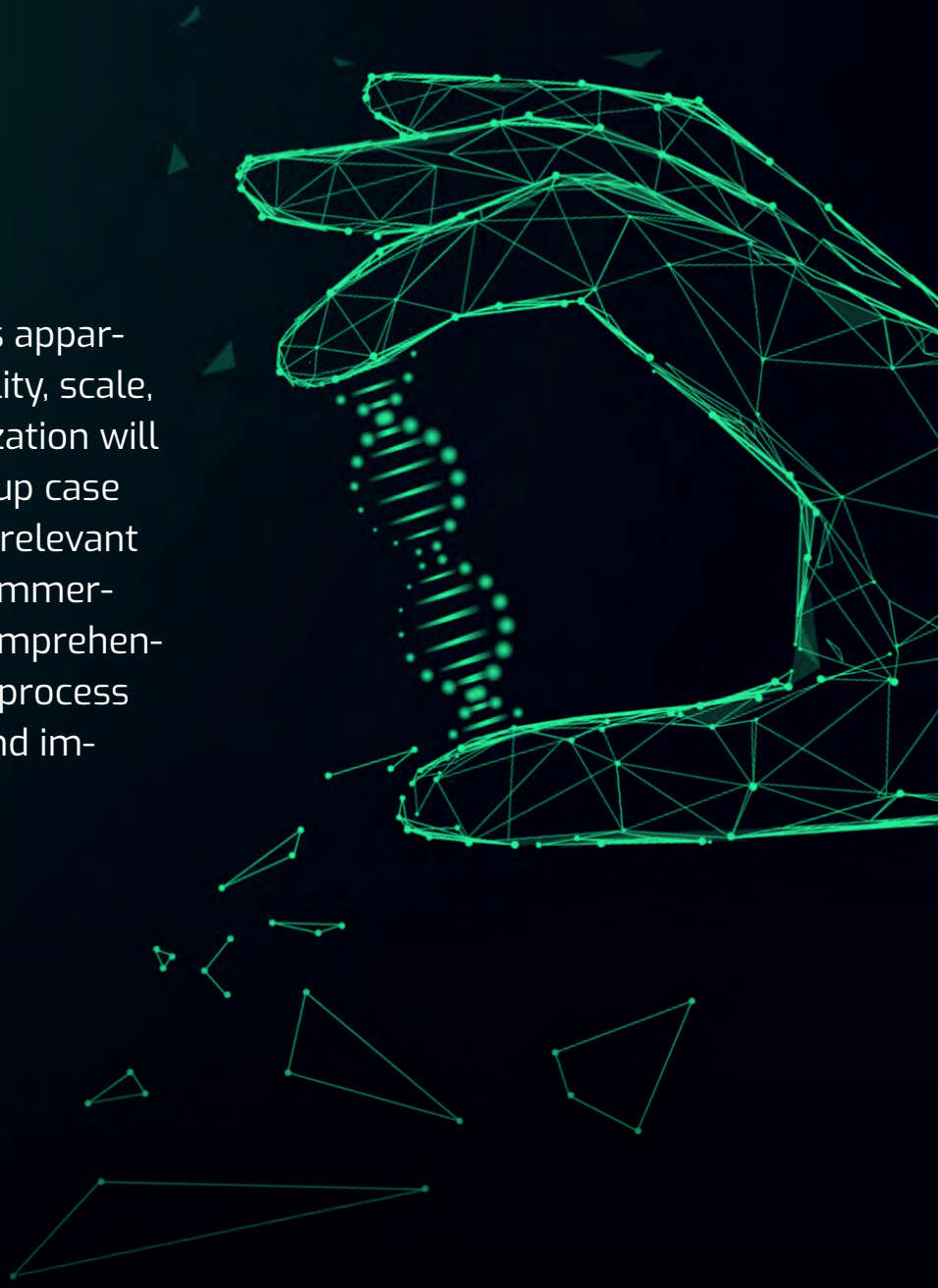
Digitalization can help cater to all those needs that arise when producing for small batch sizes with personalization requirements in contrast to mass market manufacturing. A technology-based CGOP then works as the common ground between partners, supporting and relieving the case manager. So far, the industry lacks standardization for personalized therapy data formats. A CGOP can therefore help to build a bridge between information silos and different systems involved. Lastly, a CGOP ensures a closed information loop (as opposed to existing systems and processes that are controlled by one party).

## The earlier a fully digital solution is implemented, the higher the probability to succeed with cell & gene therapies at scale without compromising process quality.

The case manager can focus on the human aspects of the role and efficiently handle more cases, deal with exceptions, and review for system improvements. Here lies potential to reduce the above-mentioned personnel cost for supply chain management significantly, while simultaneously working more efficiently and decreasing the probability of mistakes in cell and gene therapies.

# Conclusion

With about 1400 cell therapies in development* in 2021, it is apparent that a manual process for orchestration will hinder quality, scale, and effectiveness. Digitalization, automation, and standardization will help achieve more efficient processes, lower cost, and free up case manager capacity for patient-oriented tasks. Connecting all relevant stakeholders will help cross the threshold to scaling and commercializing personalized cell & gene therapies. This ensures comprehensive coordination and automation of information as well as process flows, which results in a frictionless therapy supply chain and improved outcomes for patients.



* Source: "Cell Therapy Development" by Robert Levine, Cancer Research Institute
https://www.cancerresearch.org/en-us/blog/june-2021/io-cell-therapy-development-in-2020-pandemic

# About us

Hypertrust Patient Data Care enables pharmaceutical and biotech companies to set up, orchestrate, operate, and scale a frictionless supply chain. We ensure highest data security based on latest technology, decentralization, and pharmaceutical standards. Hypertrust Patient Data Care enables pharmaceutical and biotech companies to set up, orchestrate, operate, and scale a frictionless supply chain. We ensure highest data security based on latest technology, decentralization, and pharmaceutical standards.

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**PLEASE CONTACT**

**Lars Berneburg**
Head of Sales

Hypertrust Patient Data Care
Gabrielenstraße 9
80636 München, Germany

mobile +49 172 1842675
l.berneburg@hypertrust-patient.com
www.hypertrust-patient.com