White Paper

Are You Ready for Novel Therapies? Building out TechOps Capabilities to Sustain Commercial Delivery: Part 2

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Introduction

The following is the second part of a four-part series describing novel therapy supply chain archetypes, challenges, and potential management approaches.

- Part 1 introduced the four archetypes and their value chains: in vivo gene, ex vivo allogeneic, ex vivo autologous, and in vivo personalized cancer vaccine (PCV) therapies.
- Part 2, below, explains the archetypes' characteristics in more detail and how they differ from established supply chains for biologics.
- Part 3 outlines the supply chain challenges posed by the different archetypes and compares them with those of typical biologics supply chains.
- Part 4 will discuss how organizations can address the challenges facing novel therapy manufacturing and distribution. What considerations are involved in strategic decisions to develop a given novel therapy? How can companies develop required new technical operations capabilities?

Part 2: Deep Dive into Archetype Characteristics—Similarities and Differences

In this chapter, we will identify three characteristics that describe practical supply chain requirements and will use them to understand some of the challenges in managing the four novel therapy supply chain archetypes: in vivo gene; ex vivo autologous; ex vivo allogeneic; and personalized cancer vaccines (PCVs).

These characteristics comprise another descriptive dimension that we can apply across the supply chain archetypes for a deeper understanding of their differences. We will also use these criteria to compare the supply chains of the archetypes with those of established biologic therapies, which share some characteristics with novel therapies.

A Three-Part Characterization of Novel Therapy Supply Chains

Based on our work with cell and gene therapy developers, we have segmented the supply chain requirements of the different novel therapies into three characteristics: manufacturing and development, demand and replenishment, and logistics and providers. These characteristics are defined by their subsegments. (See Exhibit 1.)

Manufacturing and Development. This characteristic focuses on making products available for clinical and commercial use. For novel therapies, key factors include:

- **Ingredients.** The biologic ingredients used in novel therapies are the driving factor behind many of the specialized treatments and controls that make the supply chains so demanding. Where the use of mammalian cells is a mature and established manufacturing process in the sector, processes using human cells must meet higher biosafety and ethical standards and require stringent end-to-end tracking and labeling. Plasmids (genetic structures in a cell that can replicate independently of the chromosomes) have an established track record and comparatively easy decontamination procedures, while viruses have extremely high biosafety risks. All require the use of cold-chain procedures in the supply chain.
- **Labor and Skill Intensity.** In some novel therapy supply chains, manufacturing processes and activities can be mostly automated, with workers used mainly for monitoring automated steps. For others, manufacturing technologies are based on many manual steps, necessitating a highly skilled labor force.

Exhibit 1 - Three Main Characteristics of Novel Therapy Supply Chains

Sources: Expert interviews, BCG experience.

Note: 4PL = fourth-party logistics.

- **Treatment-Related Time Constraints.** For certain novel therapies, such as ex vivo autologous and in vivo PCV therapies, the clock starts running with the collection of patient cells, and the production lead time may be short if the patient's condition changes quickly.

Demand and Replenishment. The organization must have clear visibility into demand stability and how it affects the product life cycle of treatments. This has implications for three critical elements:

- **Demand Pattern over Life Cycle.** For some novel therapies, anticipated demand is comparatively stable over the product life cycle, driven by the need for recurring treatment of existing patients and newly diagnosed patients. In other cases, such as with certain gene therapies that may cure the disease, demand peaks shortly after the launch of the treatment and decreases rapidly as the patient population is cured. Demand thereafter comes from newly diagnosed patients.

- **Opportunity to Build Up Inventory.** For products that don't depend on personalized batches, inventories of intermediate or finished goods can be built up and economies of scale realized. For treatments that use patient cells as inputs, such as CAR T cell therapies and PCVs, inventories are not possible.

- **Batch Size and Degree of Personalization.** As with inventory, the degree of personalization determines the batch size. Bespoke treatments based on a patient's own cells are produced one dose at a time; non-personalized therapies can be produced for an entire patient population.

Logistics and Providers. Novel therapies require a specialized delivery ecosystem to enable timely and secure delivery of therapies to patients. Depending on the therapy, special factors may include:

- **Cold Chain and Tracking.** Most novel therapies involve the use of biologic materials and require cryopreservation (–196^0 C to –80^0 C) at some point. For some treatments, patient cells and finished goods must be cryopreserved for transportation and storage from apheresis (collection of blood plasma) to patient reinfusion. Stringent end-to-end tracking and labeling is required throughout the process for all therapies that involve human cells.

- **Provider Connectedness and Collaboration.** Some novel therapies involve close collaboration between providers and treatment centers, including protocols for apheresis, monitoring, preparation, and reinfusion that are critical for treatment success.

Characteristics as a Window to a Deeper View of the Novel Therapy Archetypes

Below we examine each of the four supply chain archetypes using these supply chain characteristics to understand how they compare with each other and with biologics supply chains.

Biologics. Biologics are therapies that involve the use of mammalian cells in the creation of the drug. Products in this category have been available on the market for several years, and the processes are comparatively mature. Because of the similar involvement of biologic materials in the manufacturing process, as well as their successful track record and familiarity in the industry, they are a relevant point of comparison for novel therapies.

- **Manufacturing and Development.** Biologics are made with mammalian cells, but not human donor cells or viruses. Manufacturing is mostly automated, with employees responsible for running the automated processes. Because human cells are not used, manufacturing is not time critical.
- **Demand and Replenishment.** Demand for rare-disease biologics typically peaks strongly after launch, followed by steady growth as new patients are diagnosed. Batches are not personalized, and companies can build up inventories of intermediate and finished products.
- **Logistics and Providers.** Biologics must be cryopreserved in the supply chain, but do not have other specialized requirements. Apheresis and patient preparation are not required, and coordination with treatment centers is not necessary.

See Exhibit 2 for a summary of biologics supply chain characteristics.

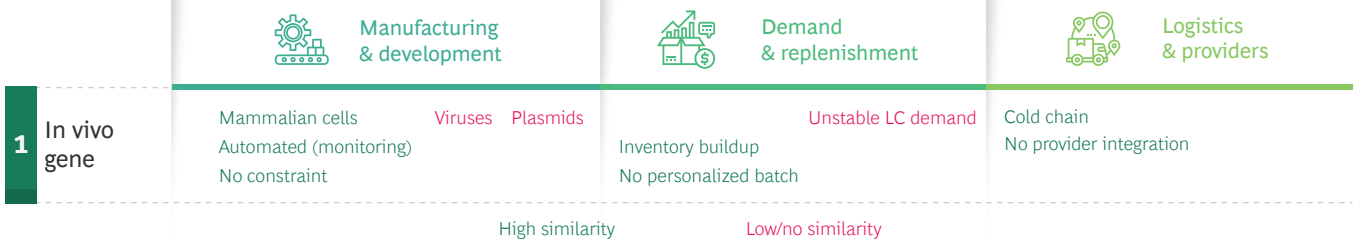
In Vivo Gene Therapies. In vivo gene therapies involve replacement of a defective or missing gene in a specific cell type so the cell can perform its normal role. These treatments rely on a linear supply chain in which plasmid-based therapies are made to stock and manufactured at the pharmaceutical company. Exhibit 3 compares the characteristics of in vivo gene therapies with those of biologics supply chains.

Exhibit 2 - Biologics Supply Chain Characteristics

Sources: Expert interviews; BCG analysis.

Note: LC = life cycle.

Exhibit 3 - Comparing In Vivo Gene and Biologics Supply Chains



Sources: Expert interviews; BCG analysis.

Note: LC = life cycle.

- **Manufacturing and Development.** Like biologics, in vivo gene therapies are created from live biologic material, although, whereas biologics are made solely from mammalian cells, in vivo gene therapies employ mammalian cells, viruses, or plasmids, depending on the therapy. Time criticality is not an issue as neither therapy relies on patient cells as an input. Manufacturing can be largely automated for both.

- **Demand and Replenishment.** Demand for in vivo gene therapies is relatively similar to demand for autologous gene therapy, with strong initial peak sales that diminish quickly. And, as neither in vivo gene therapies nor biologics rely on patient cells as raw materials, batches are created to treat the entire patient population. Manufacturers can thus build up inventory and achieve economic scale.

- **Logistics and Providers.** Both biologics and in vivo gene finished goods must be cryopreserved for transportation and storage. As apheresis is not required, no further integration with providers is required for treatment success. One area of dissimilarity with biologics is that whereas biologics do not require patient preparation in parallel to the manufacturing process, preparation may be required for certain in vivo gene therapies, depending on the particular therapy protocol.

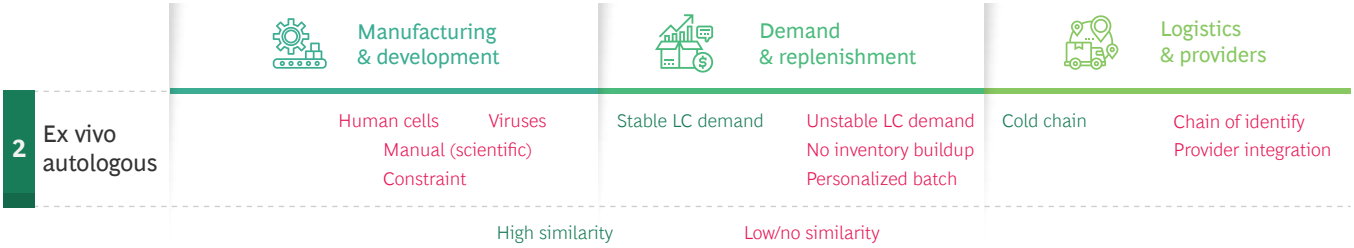
Ex Vivo Autologous. Ex vivo autologous therapies include certain gene and cell therapies and may be applied to a wide variety of ailments. The supply chain is circular, requiring cells or tissues to be taken from the patient; shipped to the manufacturing site where they are genetically engineered, tested, and approved; and then shipped back to the treatment site on a time-critical schedule for reinfusion into the patient. For a comparison of ex vivo autologous and biologics supply chains, see Exhibit 4.

- **Manufacturing and Development.** Ex vivo autologous therapies rely on patient cells as raw materials and on viral transduction methods; hence, human cells and viruses are critical inputs in manufacturing. Manufacturing begins with the collection of patient cells, and because the patient's condition can evolve quickly, the process is time critical. Manufacturing includes manual steps and therefore requires a highly skilled labor force.

- **Demand and Replenishment.** Demand for autologous therapy can be stable or unstable, depending on the volume of new cases, after initial launch. Autologous cell therapy demand is relatively stable over the life cycle, due to high numbers of newly diagnosed cancer patients and future anticipated line extensions. Autologous gene therapy demand, like in vivo gene therapies, peaks strongly after launch and diminishes quickly after the initial patient population is treated. Given that patient cells are crucial raw material, manufacturers cannot build up inventory. Each batch is personalized to a specific patient, and the batch size is "one."

- **Logistics and Providers.** Because an individual patient's cells are collected for manufacturing, a clear chain of identity must be maintained from collection through reinfusion into the patient. Close collaboration with providers for apheresis, monitoring, preparation, and reinfusion is required. Both patient cells and finished goods must be cryopreserved for transportation and storage.

Exhibit 4 - Comparing Ex Vivo Autologous and Biologics Supply Chains



Sources: Expert interviews; BCG analysis.

Note: LC = life cycle.

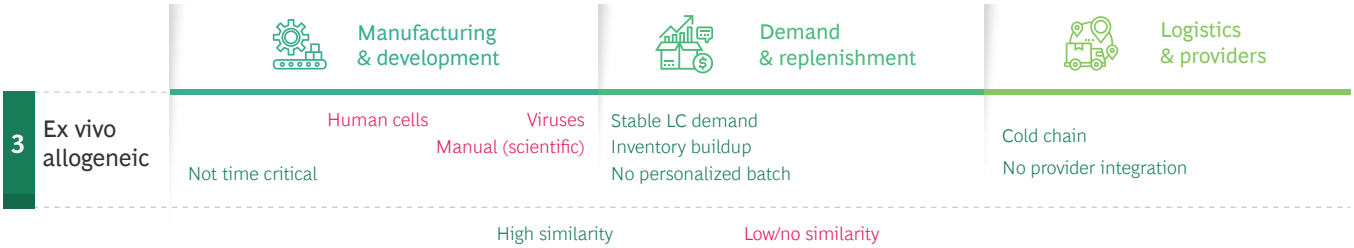
Ex Vivo Allogeneic. Ex vivo allogeneic therapy follows a linear supply chain in which cells or tissues are taken from a healthy donor; shipped to the manufacturing site where they are genetically engineered, tested, and approved; and finally shipped to the treatment site for infusion into the patient. Exhibit 5 illustrates the difference between ex vivo allogeneic and biologics supply chains.

- **Manufacturing and Development.** Ex vivo allogeneic treatments are different from biologics because they use human donor cells as key inputs in the manufacturing process. Whereas biologics rely on automated manufacturing, allogeneic processes require manual steps and a highly skilled labor force. However, neither type of therapy depends on patient cell inputs, and therefore the processes are not time critical.
- **Demand and Replenishment.** Both allogeneic therapies and biologics are characterized by stable demand, with sales peaking after launch followed by steady growth due to newly diagnosed patients. With allogeneic therapies, inventory can be built up as soon as a human donor can be identified, and products are typically manufactured in batches of around 100 doses.
- **Logistics and Providers.** Both ex vivo allogeneic and biologics finished goods need to be cryopreserved for transportation and storage. As apheresis is not required, patient preparation does not need to be synced with manufacturing, but defined protocols for infusion must be followed for allogeneic therapies and integration with donor banks may be needed for the efficient supply of donor cells.

In Vivo PCV Therapies

In vivo PCV therapies are bespoke, single-patient treatments designed to provoke anti-tumor immunity in the patient, and their supply chains are thus very different from biologics supply chains. (See Exhibit 6.) In vivo PCVs rely on a circular supply chain in which tumor and healthy tissue samples are taken from the patient and sequenced. PCVs are manufactured against the neoantigens (tumor-specific proteins), quality tested, and shipped to the treatment site for injection into the patient.

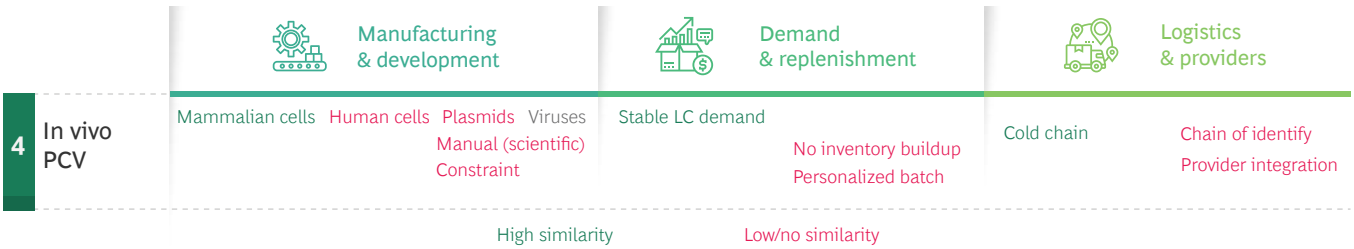
Exhibit 5 - Comparing Ex Vivo Allogeneic and Biologics Supply Chains



Sources: Expert interviews; BCG analysis.

Note: LC = life cycle.

Exhibit 6 - Comparing In Vivo PCV and Biologics Supply Chains



Sources: Expert interviews; BCG analysis.

Note: LC = life cycle; grayed-out items are not applicable.

Manufacturing and Development. Manufacturing of PCVs involves mammalian cells and plasmids; however, unlike biologics, human cells are used to analyze cancer DNA and to identify neoantigen targets. The manufacturing process is kicked off with analysis of patient cancer cells, and because the patient's condition can evolve quickly, the manufacturing process is time critical. Current manufacturing technologies involve a number of manual steps and require a highly skilled labor force.

Demand and Replenishment. Since in vivo PCV therapies are personalized according to the patient's cancer cell expressions, inventories for intermediates and finished goods cannot be built up in large scale as with biologics. However, the demand profile for PCVs is similar to biologics as it is expected to be relatively stable over the life cycle, driven by newly identified cancer patients in approved indications.

Logistics and Providers. Patient preparation may be required, depending on the therapy protocol, but since apheresis is not involved, integration with providers is not necessary. Patient samples and finished treatments must be cryopreserved for transportation and storage.

Key Takeaways: A Summary of the Comparison and the Relationship to Production and Delivery Challenges for Manufacturers

When we combine Exhibits 3 to 6 into one complete picture, we get a clearer view of which archetype supply chains are more similar to or different from the biologics supply chain. (See Exhibit 7.) In particular, we can see that where the in vivo gene and allogeneic archetypes are largely similar to biologics, the PCV and autologous archetypes are at the other end of the spectrum. For companies considering bringing a given type of novel therapy to commercialization, the comparison provides insights into the range of difference in manufacturing and supply chain requirements between novel therapies and the more familiar biologics model.

Exhibit 7 - Comparing Four Novel Therapy Archetypes with Biologics Supply Chains

Sources: Expert interviews; BCG analysis.

Note: LC = life cycle; grayed-out items are not applicable.

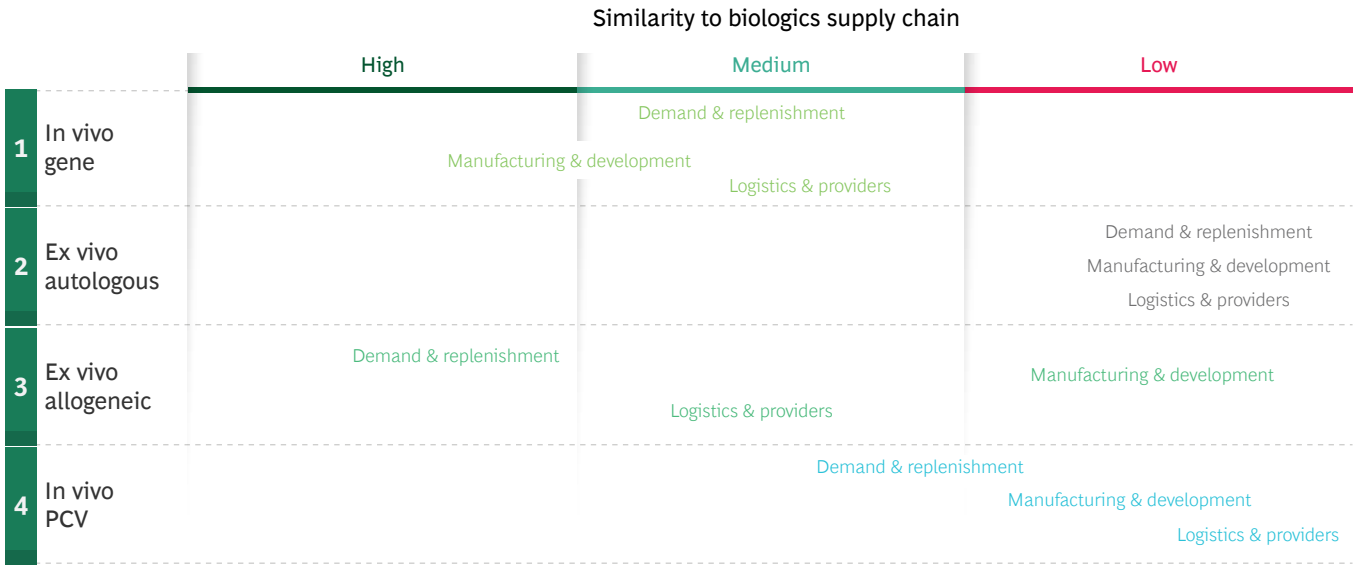
To recap the archetypes in order of similarity:

- The in vivo gene therapy archetype is generally similar to biologics in all three supply chain characteristics, except that both plasmids and viruses are used as inputs, whereas only mammalian cells are used for biologic production, and the in vivo gene therapy demand life cycle is characterized as unstable, compared with biologics. As a consequence, in vivo gene therapies have a comparatively lower barrier to entry for companies experienced with biologic development and commercialization.
- The ex vivo allogeneic supply chain archetype has a mixed profile when compared with that of biologics. They are similar to each other in the criteria that make up the demand and replenishment and logistics and providers characteristics, but quite dissimilar in the manufacturing and development characteristics, due to allogeneics' use of viruses and human cells as well as the requirement for high-skilled manual labor.
- The ex vivo autologous supply chain archetype's characteristics differ from those of biologics in almost every respect. Therefore, organizations attempting to produce and commercialize therapies in this area face the greatest number of challenges for building their supply chains.
- The in vivo PCV supply chain is different from biologics in all three areas, due to the use of human cells; manual production steps; personalized, single-dose production; and requirements for chain-of-identity and close coordination with therapy providers.

Exhibit 8 shows the comparison in yet another view, by placing the characteristics for each archetype along a continuum of high, medium, and low similarity to biologics. Again, the clustering of autologous and in vivo PCV in the far-right, "Low" similarity column reflects how different they are and, consequently, the many unique challenges facing manufacturers that plan to invest in development of these therapies.

In Part 3, we will focus on the specific challenges of novel therapy supply chains that come with the differences from well-understood supply chains (i.e., biologics) as basis for strategic plans.

Exhibit 8 - Supply Chain Archetypes Differ Across All Characteristics



Sources: Expert interviews; BCG analysis.

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