



Distribution and Supply  
Chain Models in the Cell &  
Gene Therapy Landscape

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# Cell and Gene Therapy



# Introduction

## Cell & Gene Therapy, a paradigm shift in the treatment landscape?

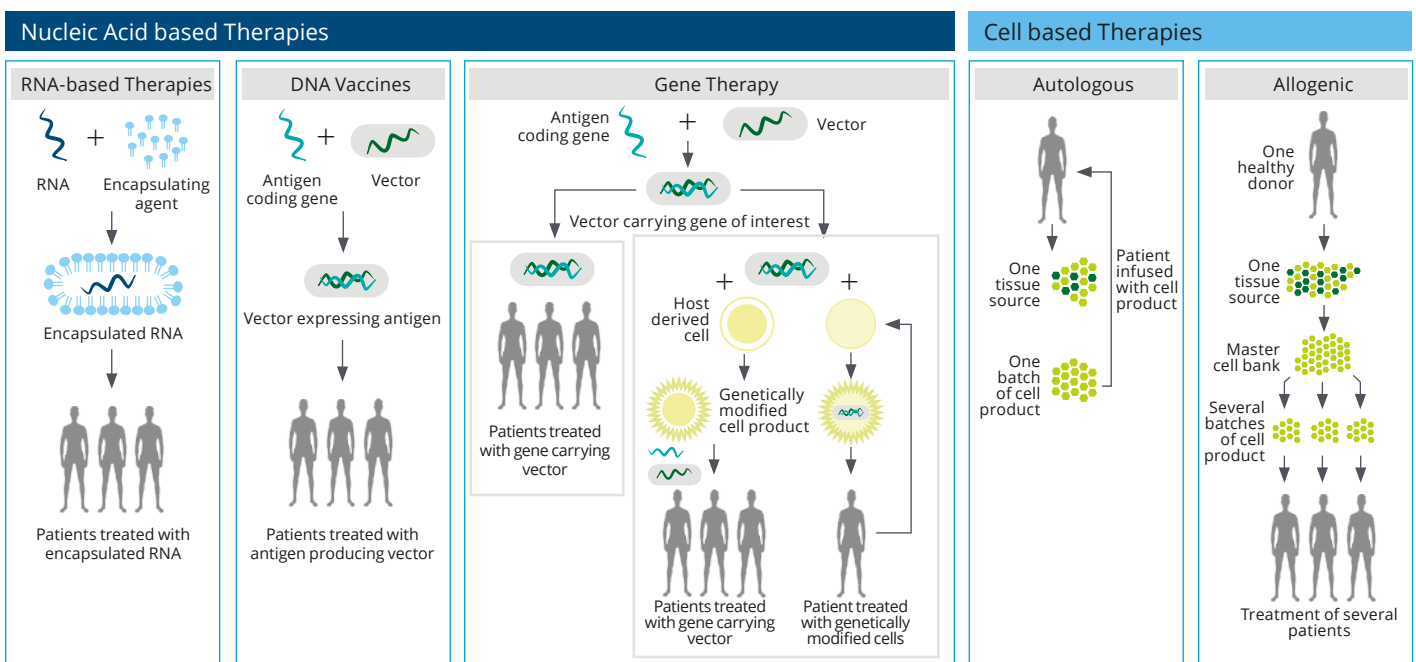
The pillars of modern medicine, if we may call them so, span across RNA-based therapies, which includes encapsulated RNA to neutralize proteins causing undesirable gene expressions; DNA Vaccines which include a vector expressing antigen to stimulate immune responses; Gene therapies which include a vector carrying a gene of interest to replace or restore a protein function (both in vivo and ex vivo); And finally cell therapies including for instance engineered immunotherapy, to introduce healthy cells replacing the diseased or missing ones (both autologous and allogenic) (see Figure 1).

Cell and gene therapies (CGT), including personalized medicines have rapidly transformed the curative treatment landscape. It offers value for patients with few to no other therapy interventions for either maintenance or cure within specific disease areas, many of which include rare and ultra-rare diseases. The personalized nature of these therapies, demand a greater degree of operating model sophistication, pinned to several

functions leading up to a closed loop supply chain and distribution system. The complexity stems from an end-to-end traceability of viable cells to manufacturing to bedside infusion, and to long term follow-up. Further, the reduced scale and volume of patients including a greater degree of transparency of manufacturing process to patients and treatment physicians, and several mandated regulatory requirements.

Biopharma companies are rapidly investing<sup>1</sup> in this complex space, about \$13 billion has been invested globally in advanced therapies such as CGT. In addition, with more than 900 companies globally focused on such advanced therapies, and over 1,000 cell and/or gene therapy clinical trials currently underway, the industry could see numerous approvals – as many as 10 to 20 new therapies per year starting in 2025. Over the last few years, the number of approvals of such therapies in the US and/or EU highlight the robust activity within this space. This number will likely only accelerate with time.<sup>1,2</sup>

**Figure 1. Pillars of modern medicine**



Source: 1. Deloitte, 2020. 2. Alliance for Regenerative Medicine, 2018 annual report, accessed March 17, 2020; Commissioner of Food and Drugs

The complexity and increasing scale presented by CGT necessitates fundamental shifts and innovation needed within operating and distribution models. Moreover, this shift should be made at the beginning of the forefront because of two reasons. First, the therapeutic modalities are rapidly expanding, and the complexity of the clinical targets are becoming more precise than ever. Secondly, the alternative approach to bringing these medicines to patients, with manual interventions and follow-ups, as currently done for some clinical supply chain processes, can breakdown quite quickly at commercial launch.

Further, current pharma operating models<sup>2</sup> have not been tuned to manage the complexity of processes, management systems and capabilities necessary to bring CGT to market. Though, an intricate design and organization of logistics and distribution model, thereby promising patients and Treatment Centers safety, visibility and timely delivery, could be a source of differentiation in the competitive life sciences market.

To do so in a structured way, the CGT journey can be segmented into three flows: patient, product and payment flows. In this paper, we will focus on the product flow and explore the supply chain complexities and required capabilities and outlines three major distribution models in the CGT supply chain.

The subsequent sections aim to answer questions such as:

- What are the primary drivers facilitating the CGT operating model?
- What differentiates CGT from traditional distribution models?
- How will CGT change the way biopharma companies collaborate with logistic partners?
- How do biopharma companies partner with distribution firms\*?
- How are distributors innovating beyond their traditional role?

“There are patients out there that have no other options, whether that’s because its stage four cancer or some genetic disease. I think the beauty of the therapy is that they’re using the body as the therapy.. (...) You’ve got to get your cells back because they’re toxic to everyone else is what it boils down to. What’s going to be important moving forward with this supply chain is traceability and control.”

**Simon Ellison, cell and gene therapy service director at World Courier**

\* For the rest of this paper, a freight supplier is considered as a company which only provides logistics services on behalf of the biopharmaceutical company, while a distributor provides additional services, such as order management or invoicing, or bears financial liability for the product.

Source: 1. McKesson 2. Pharmaceutical Processing World

# 1. Cell and Gene Therapy Landscape



# 1. CGT Landscape

Cell and gene therapies will force disruption in traditional biopharma business models and supply chains

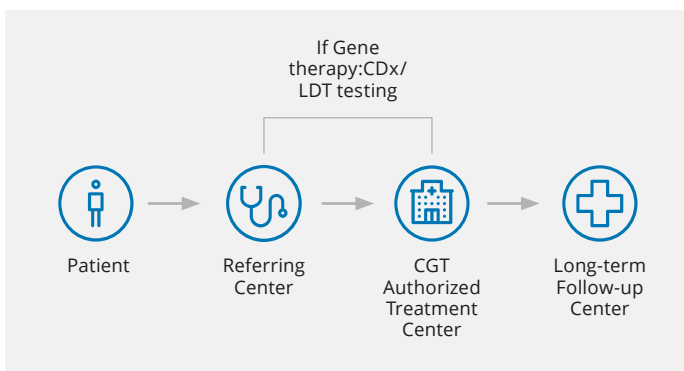
CGT are rapidly transforming the treatment space with the promise of long-term patient maintenance or cure. In order to do so successfully, biopharma companies need to solve for the intricacies involved in their unique supply chain. Unlike the typical value chains of traditional biopharma products, CGT value chains are high-touch, high-visibility, closed loop end-to-end connectivity and require the involvement of stakeholders with highly specialized capabilities.

We visualize the end-to-end CGT journey into three main dimensions to highlight the distinct challenges: **patient flow**, **product/therapy flow** and **payment flow**.

### Patient Flow:

Patients are at the center of CGT, as these therapies are unique and personalized to each patient. Hence, defining the specificities of the end-to-end patient journey is critical for a successful commercial launch. To define the patient flow, biopharma companies must design *how patients will receive CGT and associated care*. What are the unique touchpoints, handovers and stakeholders involved across the patient care pathway?

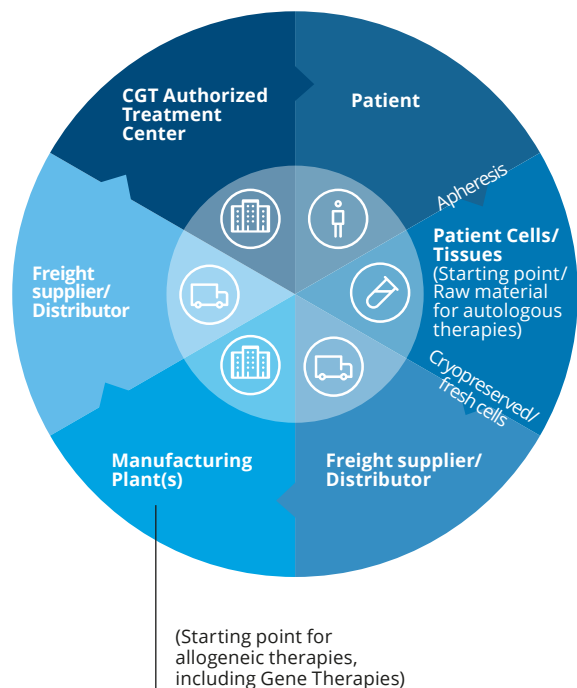
Figure 2. CGT patient flow



### Product/Therapy Flow:

Unlike traditional biopharma products, for which the role of biopharma companies in the product supply chain diminishes after completion of product manufacturing, high value CGT products demand a close involvement of biopharma companies from start of patient cell/tissue collection (for autologous therapies) or just-in-time product manufacturing release (for allogeneic therapies) until therapy infusion. The design of the product flow, which is the focus of this paper, must consider *how CGT products will be delivered from the biopharma company to the end user/administration center including the roles and responsibilities of distribution partners and supporting technology infrastructure*.

Figure 3. Autologous cell therapies product/therapy flow and allogeneic gene therapy product flow



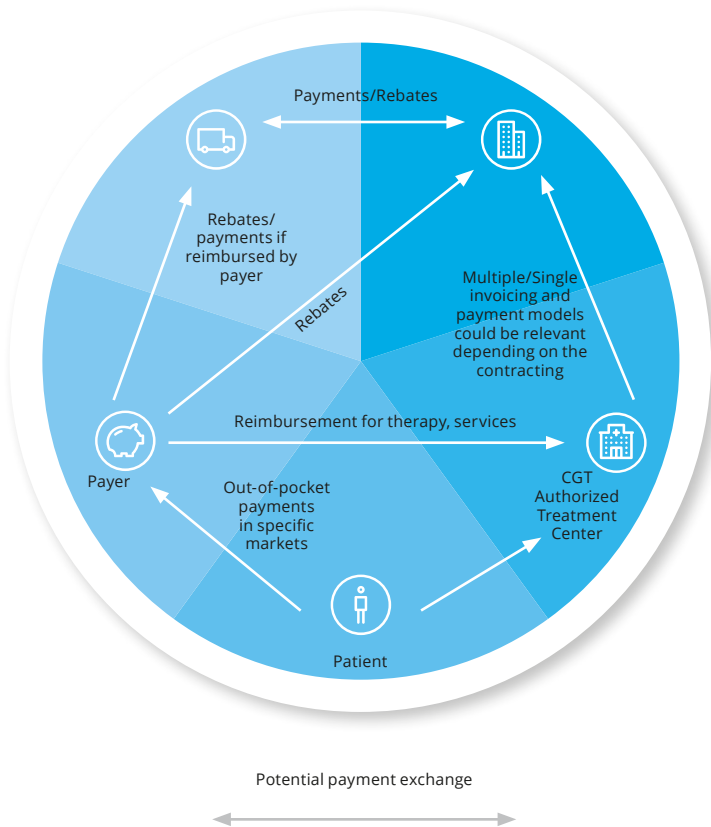
**Payment Flow:**

Given the relatively high price points usually associated with CGT products and the expected relative financial burden and risk of transferring 'high-value' products across borders, including internationally in some cases, from manufacturing hubs to treatment sites, a clearly laid out financial flow is critical for a successful launch.

Before biopharma companies begin planning and executing on innovative pricing models and contracting modalities, a fundamental understanding of payment flows across stakeholders considering stakeholder buy-in across the board (payers, distributors, treatment centers and patients), is critical.

The payment flow defines how biopharma companies and external stakeholders exchange payment for CGT products and care, both in terms of the involved stakeholders as well as the payment modalities. While this paper links typical payment routing to the three distributor models, it does not zoom in on the pricing models and contracting modalities, specificities on reimbursement pathways across markets.

**Figure 4. CGT payment flow**





## 2. Supply Chain Complexities and Required Capabilities

## 2. Supply Chain Complexities and Required Capabilities

Specific supply chain capabilities are required to handle the distinct complexities associated with the high touch and personalized supply chain of CGT products

A view on the treatment modalities spread across in-vivo gene therapy to allogenic therapies compared to autologous and mRNA-based vaccines presents a diverse matrix of product characteristics which drive the complex needs for distribution and the set up of operating models.



**In-Vivo Gene Therapy**



**Allogeneic Cell Therapy**



**Autologous Cell Therapy**

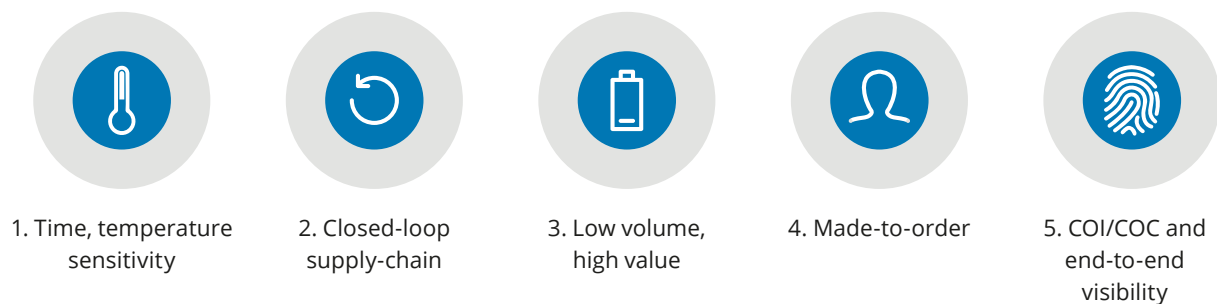


**mRNA Based Vaccine**

Characteristics	Source of raw material	Patient cells not involved in developing the final therapy.	Healthy donor's cells are modified to create the final therapy	Patient cells are modified to create the final therapy. Tissue extraction is based on manufacturing schedule	Patient cells used to customize the final therapy
	Level of personalization	Drug product is manufactured for multiple patients	Drug product is manufactured for multiple patient	Drug product is manufactured for individual patient	Drug product is manufactured for individual patient
	Manufacturing strategy	JIT. Make to Pack vectors production (viral, plasmid) for direct administration (in-vivo)	Make to Order or Make to Pack (Master cell bank)	Make to order (no cell banking)	Make to order
	Final drug product formulation	Cells are targeted in-vivo	Final product has live cells	Final product has live cells	No live cells in final product (only mRNA liposome)
	Cold Chain requirements	Shipped on dry ice (-60 to -78°C)	Shipped at low temperatures (2°C to 8°C) or cryopreservation (-60 to -196°C)	Shipped at extremely low temperatures through LN vapor storage (-150 to -196°C)	Stored at very low temperatures (-70°C)
	Mechanism of actionw	Specific genes are targeted for addition or deletion through a viral vector	Donor's cells are extracted and engineered to recognize cancer cells and destroy them	T-cells are extracted and engineered to recognize cancer cells and destroy them	Neo-antigens that are expressed by cancer cells are identified and the immune system activated

This complexity is driven by five main components, requiring biopharma companies to develop distinct capabilities to meet these requirements.

**Figure 5. Five main CGT complexities**



The risks involved in maintaining and monitoring these complex supply chains can be mitigated with customized solutions built with GxP at its core. Further, several of these solutions are also certified by independent certification bodies to offer quality/regulatory compliance and end-to-end and full-visibility across the value chain to stakeholders.



#### **Complexity 1: Time, temperature sensitivity**

In the case of autologous therapies, patient's blood is apheresed and collected in a certified laboratory environment. The apheresed white blood cells have a short half-life, often only a few hours, before the quality could begin to deteriorate. To ensure apheresed cells maintain viability, specific temperature requirements (ultra-cold ice or liquid nitrogen storage) must be fulfilled. The same applies for manufactured CGT products (both allogenic and autologous), which need to be stored and handled with precision and care (e.g. CAR-T needs to be kept at  $-150^{\circ}\text{C}$ ), impacting the supply chain capabilities beyond those of traditional pharmaceutical products. As a result there needs to be an increased focus to maintain product veracity and process timeliness even in case of unplanned events, like the most complex procedures such as organ and cell transplantations.

#### **Capabilities Required**

CGT supply chains must achieve reliable cryopreservation with seamless cold chain and cold storage within the specifications of the product. For the temperature to be guaranteed, stakeholders involved should plan for contingency work process flows, for e.g., case of shipment delays or unplanned changes, without directly handling the product. Additionally, "control tower" capabilities are essential to provide full visibility throughout the transportation process to track and trace the product movement, temperatures and to coordinate the delivery of the therapy with the treatment centers. Treatment efficacy is also assured with appropriate storage and handling, including consistent thawing, at the treatment center. The ability to translate technical and

complex handling requirements into user-friendly instructions and education is hence crucial for CGT success.



#### **Complexity 2: Closed-loop supply chain**

Unlike traditional pharma products which begin their journey at the point of manufacturing, shipped to storage warehouse and distribution centers before final delivery at treatment sites, the CGT journey begins and ends with each individual patient. For Gene therapies, this closed loop value chain could begin with a unique diagnostic test (Antibody testing for specific viral vectors for gene therapies) and for autologous therapies, apheresis of cells at the treatment site or a specialized apheresis site. In addition, with each product being unique and individualized to each patient, every product batch needs to be monitored, tracked across the closed loop supply chain to maintain Chain of Identity and Custody leading up to final delivery and infusion.

#### **Capabilities Required**

The CGT supply chain needs to be supported by sound technological capabilities to maintain steady and continuous communication channels for product track and trace. Adopted technology solutions should provide the capabilities to coordinate Chain of Identity and Chain of Custody in real-time (e.g. precision recording and documentation methods to allow full traceability and key safety checks to track material labeling accuracy), linking geographic tracking data with temperature monitoring data solutions to maintain visibility into patient specific product batches and infusion schedule (e.g., active management of patient's attendance on site, coordination and timing of pre-treatments).

**Complexity 3: Low volume, high value**

Being patient specific and currently centered around rare diseases or last-lines of therapy, CGT often serve limited patient populations compared to traditional pharma products, due to low disease prevalence or a strict patient eligibility criteria.

The low volume combined with a highly complex manufacturing process translates into the high value pricing of CGT products. The cost for manufacturing one batch of a CGT product typically varies between \$500,000 and \$1m, confirmed by the price tags of some of the currently marketed CGT products.

The significant financial burden associated with CGT pose an unprecedented challenge, to biopharmaceutical companies, supply chain partners, treatment centers and payers. The cost forces to fundamentally rethink the traditional commercialization models including pricing and contracting modalities.

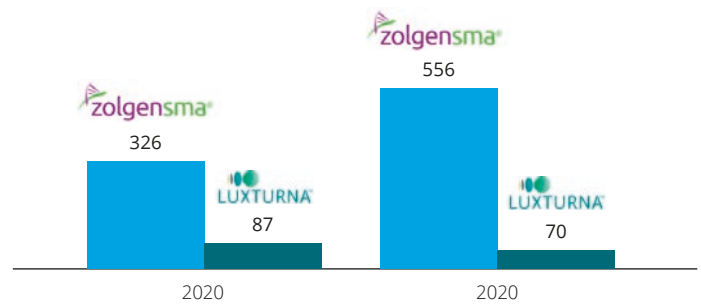
**Capabilities Required**

The uniqueness of CGT products' distribution and handling, requires differentiated capabilities compared to traditional biopharma distribution needs. In addition, the high value makes the financial ownership and liability for CGT products a major challenge. All of which magnifies the risk involved in the supply chain and hence the need for robust mitigation strategies and contingency plans. Successful commercialization also relies on the development of new contracting capabilities that enable payers to manage the financial impact on healthcare budgets, supported by strong patient outcomes capturing to demonstrate efficacy.

**Complexity 4: Make-to-order**

Due to the high value, patient specific nature and ultra-short shelf life of CGT products, and cell therapies can be manufactured after collection and shipment of of patient apheresed blood cells to manufacturing site (autologous therapies) or in the case of in-vivo gene therapies, only allow for very limited inventory of finished products. In the case of make-to-order gene therapies, labelling of the end-product can be a two steps process: a product label is affixed once the product vial batch is manufactured and a second one tailored to the individual patient during fulfilment. The second label could contain highly specific patient details, with COI and COC and prepared to a weight-based dosing. Hence, these supply chain requirements necessitate close coordination between treatment centers and biopharma companies, within the same country or across international borders.

**Figure 6. Five main CGT complexities**



**Figure 7. Price points of selected CGT products**



Source: 1. DRG; 2. Cell & Gene; 3. Drugs.com; 4. BiopharmaDive

**Capabilities Required**

The make-to-order set up requires seamless transfer of orders from treatment center to apheresis and cryopreservation (for autologous therapies) or treatment center to diagnostic center (for gene therapies) to manufacturing and final drug product sent to treatment center, with a clearly articulated hand-off among the stakeholders in the value chain. This requires communication, management, logistics and delivery underpinned by technology. Tightly linked to patient schedules at the treatment center, CGT just in time shipments need to be precise yet agile allow for variations in shipping schedules due to unscheduled order cancellations/ delays and other disruptions, while maintaining the product handling requirements. Coupled with limited to no inventory in the supply chain, this makes accurate demand forecasting and tight stakeholder coordination pre-requisites for quick turnaround.

Adequate infrastructure and systems support are critical to ensure the right manufacturing processes are followed to guarantee the right turn around time per patient. Patients are dependent on the exact timing of the 'just in time' or 'make to order' capabilities.



### Complexity 5: COI/COC and end-to-end visibility

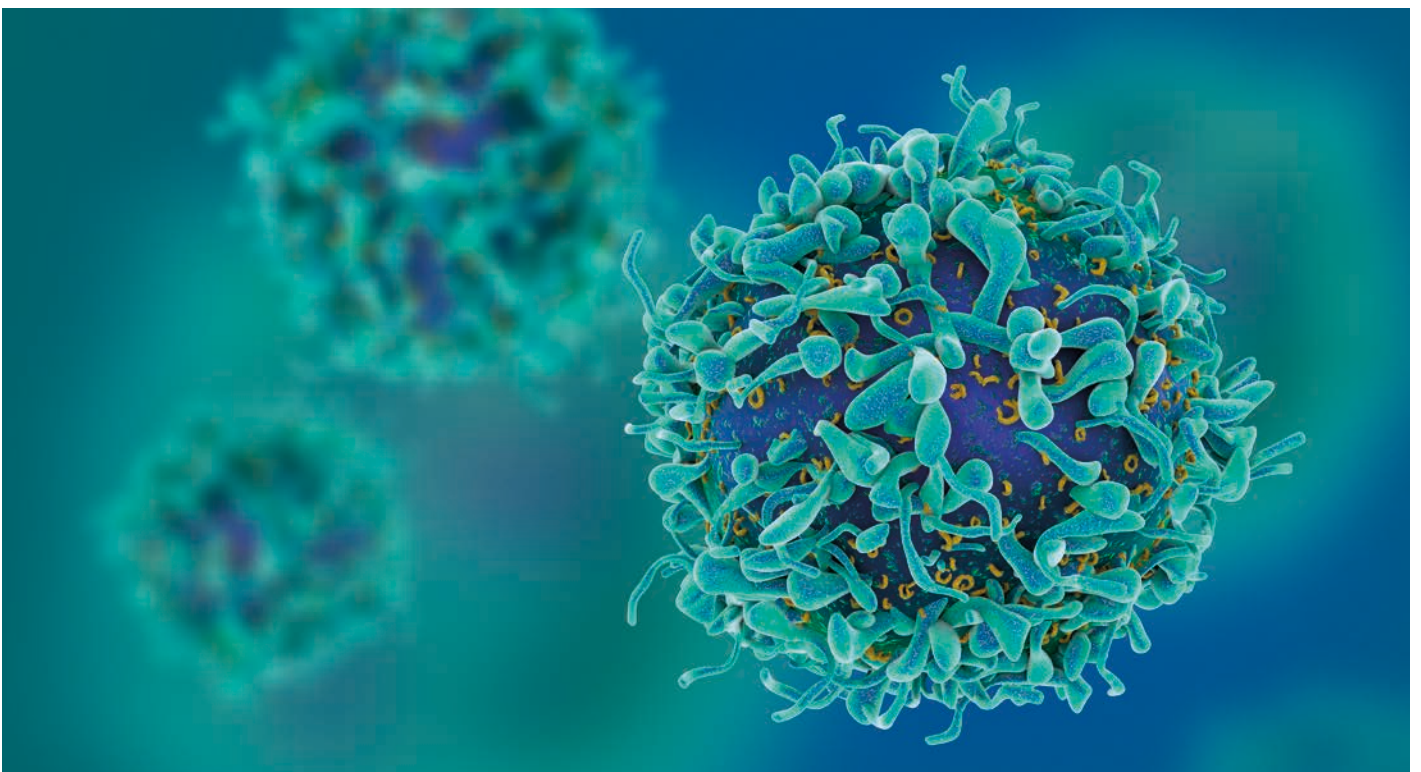
**Chain of identity (COI)** refers to the end-to-end traceability of a drug right from raw materials sourcing (which in the case of autologous cell therapies refers to the patient) to preparatory steps leading to manufacturing and finally delivery and infusion. A COI being established often refers to the unique identifier generated at patient enrollment, and this identifier being visible and traceable throughout the treatment journey. For instance, as part of the COI, an autologous donor's patient number should be associated with their unique donation number (Donor identification number/DIN or SEC number) and the manufacturing batch number.

**Chain of custody (COC)** refers to the ownership/stakeholder 'in-custody' of the cells or drug product, at any stage of the value chain. COC often includes reporting several critical parameters (if required to regulators) to health care professionals who look out for the quality and integrity of the cells/drug-product at every step of the journey. COC often supports decision making on out-of-spec products with reading on concentration of cells, temperature, pressure and qualitative parameters such as abnormality in color, sedimentation when not intended to happen etc.,

### Capabilities Required

Chain of identity and chain of custody in CGT are more than a 'cell-tracker' mechanism. For autologous cell therapies, they are critical for safety, quality and to ensure the right patient is matched with the right donor cell to the right product. Once the therapy is administered, the COI/COC become part of the health system and provide complete traceability over the patient's lifetime and ensure patient safety for multiple products and doses.

Adequate infrastructure and systems support are paramount to all four complexities in order to ensure the right product is available in time for the scheduled administration at the right treatment center. Technology must support coordination of last mile deliveries with treatment centers and supply chain partners, track temperature and location in real-time, guarantee chain of custody and chain of identity and ultimately facilitate invoicing and payment collection.



# 3. Cell and Gene Therapy Ecosystem

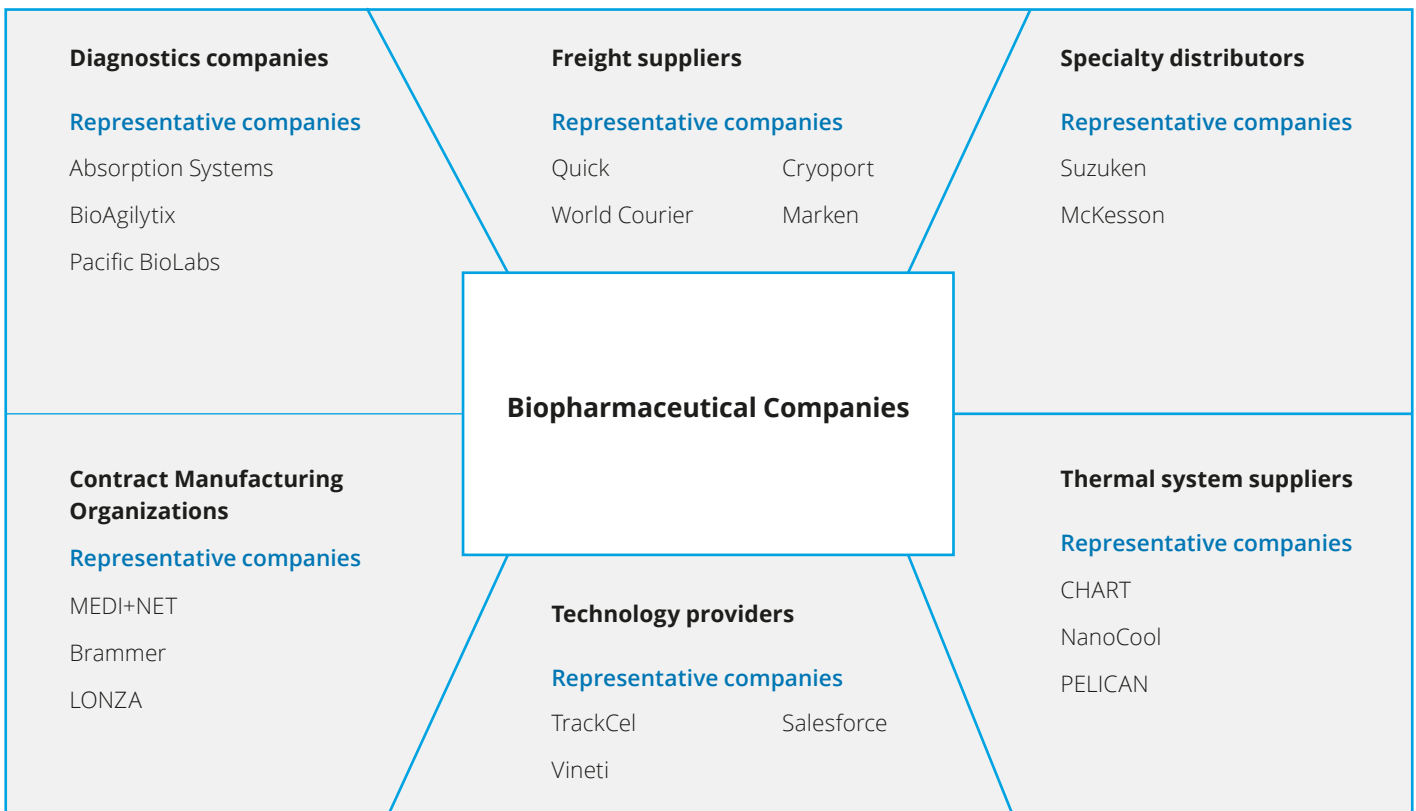


# 3. CGT Ecosystem

Managing end-to-end CGT supply chains requires biopharma companies to effectively develop and collaborate in an ecosystem that jointly delivers the full set of CGT-related capabilities

With CGT stretching the supply chain requirements far beyond the complexity of traditional therapies, pharmaceutical companies are faced with unique challenges related to adequate capability building to manage the risks inherent to the distribution of these products. Biopharma companies are building dedicated ecosystems to cover the breadth of specialized expertise required to set up a robust supply chain and manage the risks involved in the go-to market. While the increasing importance of being able to develop and collaborate in ecosystems is not unique to CGT, these therapies require a unique set of actors that consolidate and collectively possess the relevant capabilities, outlined in this chapter.

**Figure 8. CGT ecosystem**



### 01. Biopharmaceutical companies

A diverse range of players is active in the CGT development and commercialization, from large incumbent pharmaceutical companies to niche players specialized in CGT only. Collaborations, M&A and licensing of products and capabilities are increasingly becoming common among key players in this space. As owners of the CGT asset, they oversee the end-to-end supply chain and are the central point in the ecosystem, ensuring seamless collaboration and monitoring performance.

### 02. Diagnostic companies

Diagnostics companies play a crucial enabler role in the eligibility screening of patients. As CGT require specific anti-drug antibody assays to ensure safety and efficacy, these diagnostics are often performed by specialized labs with the required capabilities. For the sake of cost efficiency and fast response time, these diagnostics are often outsourced to few, selected third party labs.

### 03. Contract Manufacturing Organizations CMO

With CGT requiring specialized raw materials (even patient cells) and unique manufacturing techniques, biopharmaceutical companies often collaborate with CMOs for efficient manufacturing environments and capabilities to coordinate the specialized packaging and labelling of CGT products.

Different manufacturing models are being adopted in the CGT space: Large, established CGT organizations tend to outsource only the manufacturing of critical raw materials (e.g. plasmids) or drug substances (e.g. viral vectors) to CMOs, for various strategic reasons, including protection of intellectual property and higher manufacturing visibility and control. On the other hand, smaller biopharmaceutical companies, with limited investment and manufacturing capacities, tend to outsource manufacturing and storage to a greater degree.

### 04. Freight suppliers

A core capability insourced by biopharmaceutical companies is the shipping of products. Such partnerships are commonly set up at global level to cover the international leg of transportation, as well as locally for last mile delivery to treatment centers and to meet local market requirements. Key capabilities include the management of storage and shipping for CGT products from one point to another while keeping the (ultra) cold chain intact, with the help of liquid nitrogen, dry ice, phase change materials etc. Distributors should also be able to maintain the product viable even in case of delays or exceptional circumstances.

### 05. (Specialty) distributors

Specialty distributors have traditionally been key actors in the commercialization of traditional pharmaceutical products, with strong customer relationships with hospitals and existing infrastructure for order management, invoicing and payment

collection in their respective geographies. In some countries like the US, specialty distributors also play a key role in the patient journey due to the typically close ties between specialty distributors and specialty pharmacies, such as Cardinal Health (distributor) and BioMatrix (specialty pharmacy). They may help manage the financial impact of CGT by taking on product ownership and risk and cater to local markets with distinct requirements and regulation, such as Japan, that are often difficult to serve via global freight suppliers. First reference cases of partnerships between global freight suppliers and local distributors are emerging, indicating the value of specialty distributors in achieving truly global reach.



#### Industry Spotlight

#### Partnership between Suzuken and World Courier to Enhance CGT Logistics in Japan

The collaboration between Suzuken and World Courier offers Suzuken's Japan-based customers the opportunity to utilize World Courier's global cold chain network to extend their CGT supply chains worldwide. World Courier customers will benefit from improved access to the Japanese market and more domestic routing options, improving supply chain efficiency. Here the biggest challenge will be a close collaboration to ensure cell visibility.

### 06. Thermal system suppliers

Adequate shipping of CGT products relies on the tailored transportation solutions that meet the (ultra) cold chain requirements. Thermal system suppliers provide a range of storage dewars, with commonly multiple thermal systems being included in the regulatory filing to ensure continuity in terms of supply shortage or need for urgent replacement. Leading freight suppliers and distributors have experience with all qualified thermal systems in current CGT use and typically source and supply the selected system due to the need for adjacent capabilities such as cleaning and charging of the dewar.

### 07. Technology providers

Real-time control tower capabilities including Chain of Identity, Chain of Custody and close communication with partners and treatment centers are crucial for CGT. A few leading technology providers have established themselves in the CGT space and are increasingly partnering with both biopharmaceutical companies as well as freight suppliers/distributors to manage complex data systems along the end to end supply chain.



### Partner selection

With more and more companies entering the CGT space, the selection of value chain partners becomes a fundamental question that can make or break success in a context where reliability and precision are essential. The selection is typically driven by geography and product specific criteria and aims to identify suppliers that can support both the clinical trial and commercial phase. If clinical trial suppliers have shown a solid performance record, this relationship and expertise is usually leveraged in the commercial setting.

A key consideration for biopharmaceutical companies during the partner selection is whether to follow a single or multi-partner strategy in building their bespoke CGT ecosystem.

### Single partner strategy

Single partner strategies leverage one supplier with the capabilities and expertise to deliver one or multiple elements in the supply chain. Provided this supplier can offer a large geographic coverage, this strategy is valued because it allows for focused capability building and process improvements, close long-term relationship with one partner as well as lower coordination effort than in a multi-vendor ecosystem. On the other hand, the full dependence on one supplier for a specific supply chain capability creates significant risk in case of business disruptions or quality issues. In addition, a single partner strategy may have limitations in specific geographies that the supplier may not be able to serve as well due to local requirements/regulation or a lack of local footprint.

In the CGT supply chain, M&As are very common to ensure a strong geographical presence and/or set of activities. Alternatively a single partner strategy is typically followed for the selection of a CGT platform provider like TrakCel or Vineti, to facilitate collaboration through a single system and avoid duplication of the technology investment.

### Multi-partner strategy

In contrast to single partner strategies, multi-partner strategies make a conscious choice for multiple suppliers to provide a particular capability. The key driver is the very risk referred to above, for which contingency plans and back-up suppliers are essential for certain capabilities along the supply chain. Moreover, this strategy allows for the selection of best in class partners in each geography, thereby increasing reach to each target market. Nevertheless, it implies a larger ecosystem and hence requires higher collaboration appetite.

The multi-partner strategy is recommended for the management of international shipments, the core of the supply chain and critical to success given the reliable just-in-time delivery expected by treatment centers and patients. Contingency plans must be in place to ensure timely delivery, even in case of shortages, disruptions or other issues of a particular supplier. As a result, biopharmaceutical companies typically leverage multiple global freight suppliers for reliable service on the international leg and to major markets.

The CGT ecosystem mapping illustrates that collaboration and supplier management are crucial to the success of the CGT supply chain. To organize for success and select the most suitable partners, it is imperative to systematically assess product specific requirements along the supply chain and what capabilities shall be delivered in-house versus in-sourced. The choice between a single or multiple distributor partners ultimately boils down to the level of risk and collaboration appetite of the biopharmaceutical companies.



#### Industry Spotlight

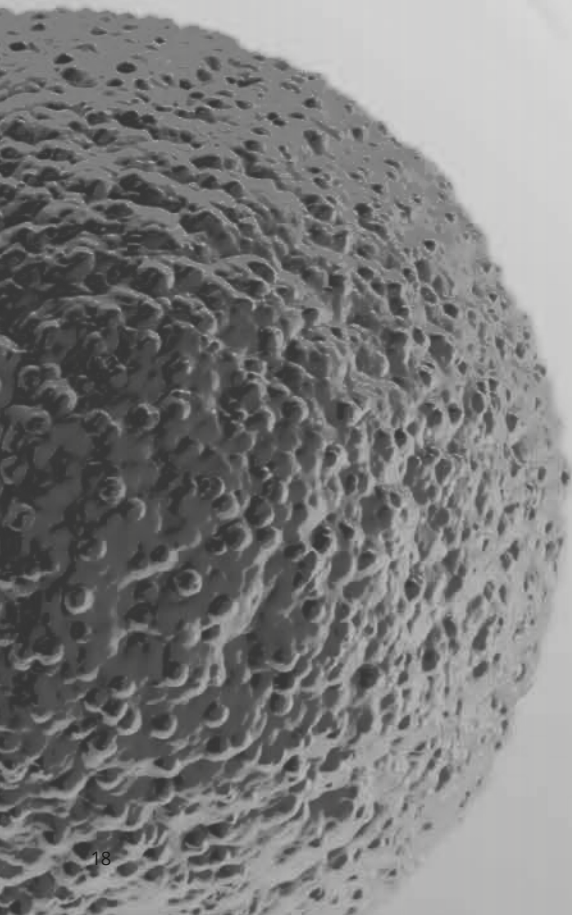
##### **Eakin Group acquired Pelican**

to transform activities into a state-of-the-art manufacturing and distribution center

##### **Biolife Solutions acquired EVO**

to strengthen market position as a developer of smart precision shipping containers

# 4. Gene Therapy (GT) Distribution Models



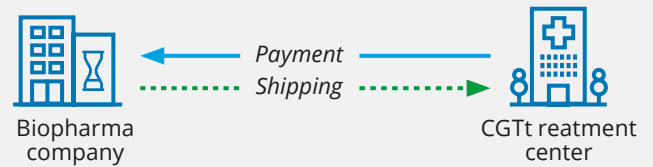
# 4. Gene Therapy (GT) Distribution Models

Managing end-to-end CGT supply chains requires biopharma companies to effectively develop and collaborate in an ecosystem that jointly delivers the full set of CGT-related capabilities

With product distribution being the core of the Gene Therapy supply chain, this section outlines the strategic options for biopharmaceutical companies. These options define how physical product flow and information exchange (incl. order management and invoicing) are handled and hence lay out the role of freight supplier or (specialty) distributor in the process. Based on Deloitte's experience, three main distribution models for GT are discussed: **direct delivery model**, **distributor-led model** and **hybrid model**.

The type of treatment modality plays a major role in determining the complete value-chain. However, the focus of the distribution model here is to highlight specifically how the **manufactured drug product (i.e. irrespective of whether it is autologous or allogenic) once it leaves the manufacturing site is distributed to the treatment site**.

## Model 1 > Direct distribution model



## Model 2 > Distributor-led model

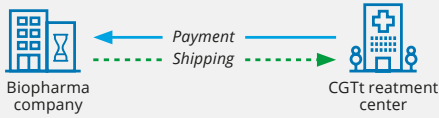


## Model 3 > Hybrid distribution model



**Legend:**

- Shipping without product ownership via a courier
- Shipping with product ownership via a distributor
- Payment flow

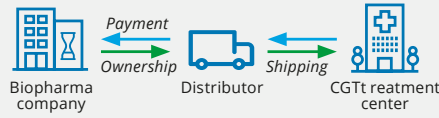


### 01. Direct distribution model

#### How does it work?

After order receipt from the treatment center, the biopharmaceutical company ships the product directly to the center via a freight supplier.

The biopharmaceutical company is responsible for coordinating product manufacturing and information exchange directly with the treatment center, and with the freight supplier involved in the transportation of the physical product on behalf of the company.



### 02. Direct distribution model

#### How does it work?

The commercialization and end-to-end distribution in a given geography is fully owned by the distributor, with financial liability borne by the distributor as of the product hand-over by the biopharmaceutical company.

Hence, the distributor is the point contact for treatment centers for order placement, fulfillment information and payment. The biopharmaceutical company supplies CGT products based on forwarded orders and provides manufacturing and distribution information to enable seamless interfacing with the treatment center.



### 03. Hybrid distribution model

#### How does it work?

As a hybrid between the direct and distributor-led distribution, this model leverages a directly managed physical product distribution through the distributor acting on behalf of the biopharmaceutical company.

While the distributor does not bear financial liability, its local administrative capabilities and infrastructure are used to handle order management and payment collection – paid by the treatment center or by the payer directly (typically passing on funds rather than upfront payment).



#### Industry Spotlight (Hybrid Model)

In Japan, the pharma company Novartis has an agreement with wholesaler Suzuken to distribute the CAR-T cell therapy Kymriah across the country.

In many instances, manufacturing capabilities for cell therapy may happen at 1 or 2 sites located globally. For those specific cases, distribution may need to enter a regional distribution center (for quality or regulatory reasons), before they are couriered to the treatment site. This could also be true for gene therapies, whereby a local distribution center (either the local OpCo or distributor) is involved for legal/tax/other packaging and labelling reasons

#### What is the rationale?

A direct distribution model allows to keep full visibility and control of the end-to-end supply chain. In addition, hand-offs are minimized, ideally to a single transfer to the freight supplier delivering the product to the treatment center. This set-up may be preferred due to the high risk and high value of CGT. local players that possess the required CGT capabilities.

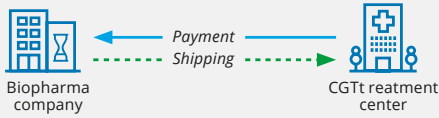
#### What is the rationale?

Distributor-led models typically are most suitable for markets where the biopharmaceutical company does not have the necessary local/regional presence to manage direct distribution. Instead, commercialization relies fully on the distributor's footprint, stakeholder relationships and market activation.

#### What is the rationale?

This hybrid model combines the tight control over the supply chain with leveraging local capabilities of the distributor. This may be preferable in geographies where distributors own the customer relationships and biopharmaceutical companies do not wish to build the administrative infrastructure.

Equally, some countries have regulatory requirements in place that mandate the involvement of local distributors in the process.



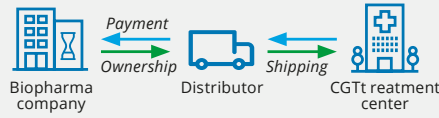
Towards customers, biopharmaceutical companies act as the central point of contact and service provider for orders, product and delivery information as well as payment. This direct contact may reinforce the customer relationship and competitive positioning.

**Who are the partners?**

For the direct distribution model to be most efficient, pharma manufacturers seek to collaborate with international/global freight suppliers with presence across the major markets. These suppliers should have strong experience in CGT and ideally be able to facilitate the customs processes.

Their capabilities can be limited to transportation without further involvement in administrative processes.

As discussed in the previous chapter, several suppliers are typically contracted to ensure business continuity in case of disruptions and issues. Where necessary due to regulation or geographic footprint, these suppliers are complemented with local players that possess the required CGT capabilities.



While the position of the company towards the treatment centers may be diminished, this model has also shown to be attractive where financial risk can be transferred to the third party to collect payment from a single stakeholder and, depending on the contact, potentially even upfront rather than as per payer reimbursement.

**Who are the partners?**

The ability to bear product ownership and financial risk will be a key criterion and challenge for distributors to meet, given the high price tag of CGT. Pharma manufacturers are heavily dependent on the distributor and hence and hence seek to collaborate with leading distributors in each target market that have strong commercial capabilities, but equally importantly, capabilities and experience in managing the supply chain. As the distributor-led model transfers significant control to the distributor while the ultimate responsibility for safety, efficacy and compliance remains with the biopharmaceutical companies, risk mitigating factors have a major influence on the selection.



With distributors being hesitant to take on financial liability given the high value of personalized therapies; this model may also be more feasible to implement.

**Who are the partners?**

Like the distributor-led model, biopharmaceutical companies typically opt for a distributor with strong local footprint and the suitable infrastructure and processes to provide administrative support.

CGT distribution experience and capabilities should be provided by the distributor, without financial risk or liability implications. Otherwise, a local freight supplier needs to be involved which further complexifies the local processes, collaboration and ecosystem coordination. yet do not imply liability and risk bearing for the partner.

The **direct distribution model has shown to be the most preferred one for CGT supply chains of biopharmaceutical companies** (irrespective of autologous or allogenic therapies).

This is primarily driven by:

- A strategic intent to maintain control as well as the customer relationship in the launch phase
- And secondly, to maintain close contact with treatment centers for faster responsiveness and to build a strong competitive positioning in this new space.

In those markets with distinct market requirements that make global/regional distribution a challenge, a hybrid distribution model is commonly used to ensure regulation, customer requirements and infrastructure needs are adequately addressed with the help of a local distributor. Although the distributor-led model has been pursued in a few cases, biopharmaceutical companies have been most hesitant to this go-to-market option due to the lack of experience with CGT and the key success factors both in terms of physical distribution and customer service. This may be a barrier making full reliance on an intermediary distributors a high-risk option and explain why some biopharmaceutical companies have decided to delay the launch in these markets and re-assess the additional complexities at a later stage based on the insights from the first pilot markets.

# 5. Value-added Services



## 5. Gene Therapy (GT) Distribution Models

While logistics and distribution is considered the core capability for distribution partners, some have actively been building broader CGT capabilities to provide value added services of varying degrees of proximity to their core business to biopharmaceutical companies.



### Treatment awareness

With the advent of new CGT, it is crucial to raise awareness and educate not only patient but also professionals. This awareness and education needs to span the benefits, risks and implications of the new therapies to key stakeholders to drive referral and uptake for CGT among the most suitable patients and authorized centers. While this is currently largely performed by biopharmaceutical companies, distribution partners can step in to play a role in this effort, leveraging upon their CGT knowledge and stakeholder relationships.



### Industry Spotlight

Cryoport provides comprehensive training covering their products, services and technology. In addition, they also provide standardized and clear-cut SOPs as essential documentation to establish and sustain a robust Quality System.



### Industry Spotlight

Marken, together with pharma and biotech companies, ensure that CGT are brought to the market successfully by addressing logistical complexities already within the clinical supply chain. As a result, Marken can seamlessly provide CGTs through each stage of the pharmaceutical journey.



### Patient support

Some CGT players, typically those acting as distributors/wholesalers in the traditional pharmaceutical space, have expanded even further beyond their traditional role and provide patient support programs. The latter includes education, patient counselling, reimbursement assistance and many more services that help patients address the clinical, financial and emotional challenges along the post-infusion patient journey to enhance the experience and minimize risks.



### Treatment center readiness

Successful launches, especially of CGT, rely on advanced capabilities and infrastructure at the treatment centers for safe handling within specifications and treatment efficacy. Specialty distributors are taking up this responsibility, especially in distributor-led models, which aims to ensure the center is well equipped to receive and store the product and has full knowledge on handling and administration.



### Industry Spotlight

McKesson has set-up a Patient Support Center which is fully online. More than 1,500 people are trained and employed to support patient access and support services.

“Integrated patient support programs need to be customized for different types of therapies and are highly customized for orphan drug therapies.”



### Outcomes monitoring

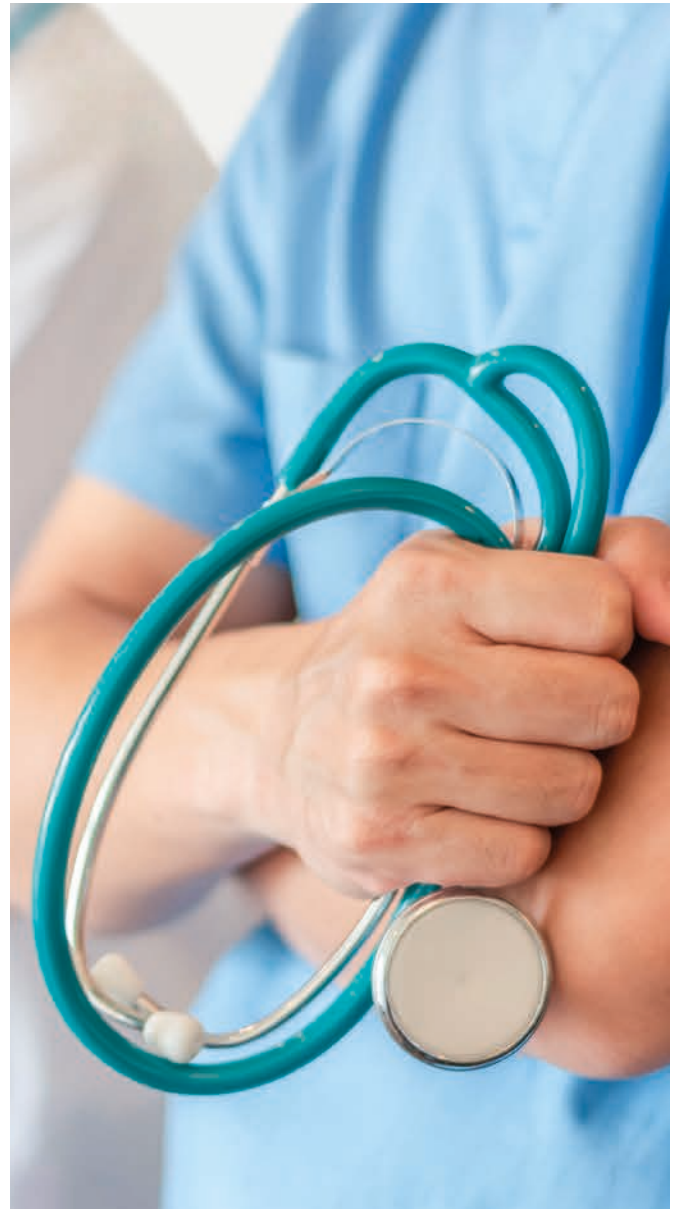
Given the criticality of patient data capture and outcomes reporting, it comes as no surprise that distribution partners are starting to explore opportunities in this phase of the patient journey. The services provide the necessary infrastructure to monitor patients, report adverse events as well as to capture and analyze real-world evidence/outcomes to demonstrate efficacy and secure attractive pricing and reimbursement. This support is not limited to the clinical trial setting but extends into the commercialization phase. In that way, distribution partners are actively contributing to the expansion of the CGT market together with biopharmaceutical companies.



### Industry Spotlight

McKesson has developed the electronic healthcare record iKnowMed for oncology indications, which tracks and stores patient outcomes over a certain time period. This database centralizes patient information and enhances collaboration as well as physician efficiency in clinical trial and commercial setting.

In a nutshell, distributors are willing to offer additional services than simply transporting products. There is a strong willingness to co-shape the CGT supply chains and co-create processes jointly with biopharmaceutical companies to further manifest the competitive positioning in this space across patient, product and payment flows.





# Conclusion



CGT have the potential to revolutionize the health care industry and raise hope that patients with certain diseases, which had been considered almost incurable until recently, may soon be able to enjoy a substantially higher quality of life. These innovative therapies require biopharmaceutical companies to master supply chain complexities that are nearly unparalleled among traditional pharmaceutical products, with the exception of organ transplants and similarly critical procedures. The complexity is driven by the time and temperature sensitivity, the patient-specific closed-loop supply chain, the high value of CGT as well as the make to order manufacturing and fulfillment. The set-up of the supply chain and related partner ecosystem is hence crucial for success.

Three main distribution models emerge in the CGT space, with direct distribution managed by biopharmaceutical companies in collaboration with freight suppliers being the most observed strategic choice. This model lends control over the end-to-end supply chain and a position for biopharmaceutical companies to build close(r) relationships with treatment centers. However, two alternative models are adopted in the CGT space: a fully distributor-led model in which the partner takes ownership of the product and related risk, as well as a hybrid model leveraging a local distributor in selected geographies with distinct market needs to in-source freight carrier services and utilize the partner's existing customer relationships and infrastructure to support the order, invoicing and payment processes.

With a promising market opportunity in sight and the ambition to add value in the CGT supply chain, distributors and freight suppliers are expanding their capabilities beyond the traditional storage and transportation of goods, towards adjacent product (handling) education, as well as patient support and even patient data and outcomes reporting. It remains to be seen to what extent biopharmaceutical companies will leverage these capabilities or develop them in-house, given the sensitivity of patient-related services in building the competitive advantage.

With its unique challenges and dynamic ecosystem of players, eager to shape this innovative space, CGT provides the ideal setting for companies to co-create and jointly organize for success.

These innovative therapies require biopharmaceutical companies to master supply chain complexities that are nearly unparalleled among traditional pharmaceutical products, with the exception of organ transplants and similarly critical procedures.

## Biopharmaceutical companies

### Understand the specificities of your CGT product

Organizing for success requires a deep understanding of the particular needs and challenges of the CGT across the patient, product and finance flow, both in terms of technical requirements as well as the impact on treatment centers and patients.

### Build a robust ecosystem

The product specificities and internal capabilities should drive the CGT ecosystem and partner selection. As high value implies high risk, investing in mitigation strategies and contingency plans is key, in the overall ecosystem design as well as process design with individual partners.

### Explore co-creation opportunities

With many players developing adjacent capabilities to add value beyond their traditional logistics services, new opportunities arise to jointly develop a competitive advantage in supply chain and services.

### Map out regulatory and local quality requirement

As the CGT is provided and distributed across the globe, the choice for the right operating model and distributor partners must also ensure the compliance with local regulation.

## Freight suppliers & distributors

### Demonstrate specialized CGT capabilities

Given the unique complexities, distribution partners need to develop specialist expertise and be able to showcase their ability to understand key challenges and requirements along the end-to-end supply chain.

### Gain a foothold in clinical trials

Typically, biopharmaceutical companies work with distribution partners during clinical trial and commercialization phase. Hence, involvement in clinical trials for new therapies is an important gateway to longer-term collaboration, as it provides a smaller scale platform to demonstrate the required capabilities.

### Expand market expertise and geographic reach

Global reach is high on the agenda in the quest to reduce complexity in a by default highly complex supply chain. Partnerships between global and local players indicate how the dynamics could change, leveraging cooperation rather than competition for CGT success.

### Manage risks within the complex distribution models

Implementing new and rather sophisticated processes while being able to save many human lives, brings up also some risks. In order to mitigate these risks solid documentations (e.g. quality) and trustable partners are a must.

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# Endnotes & Readings

# Endnotes

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