INTERVIEW

The Evolving CAR-T Therapy Supply Chain: Progress and Challenges

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Q What is the role of supply chain in the commercialization of cell-based therapies, in particular of autologous therapies such as CAR-T?

KLF With the increased focus on autologous therapies as potentially curative therapies, supply chain plays a key role in their successful commercialization. The complexity increases when it comes to autologous therapies compared to traditional pharmaceutical products or other off-the-shelf cell therapies, because the manufacturing starts with the patient's leukapheresis.

How the supply chain touches the patient is important both for the patient and healthcare provider experience. Examples of these touch points are highlighted in a few critical steps: (1) scheduling a patient for apheresis has to be linked to scheduling at the manufacturing site's shop floor; (2) communication between the manufacturer, the physician and various allied health care providers has to be timely from the time the cells are shipped for manufacturing and returned for infusion; (3) finally, supply chain has to ensure cycle times from vein to vein are quick, predictable and reliable. To enable these critical touches, supply chain's integration with commercial and marketing organizations for both design of operating model and interface will ensure a positive patient and healthcare provider experience.

Q What are some of the unique challenges across the supply chain of an autologous therapy compared to traditional biologics?

KLF The supply chain ecosystem for an autologous therapy faces several maturity challenges. First, the supply of critical raw materials is relatively unstable (either limited capacity or sole sourced). A robust and low-risk supply chain requires developers to identify backup suppliers where possible, and where backup options do not exist, work with suppliers to de-risk their supply chain. Manufacturers are using CMOs for certain critical raw materials that are capacity constrained which impacts both pricing and availability to service market demands.

Shipping is another challenge unique to autologous therapies. Throughout the cell journey, there are several handoffs and controlling the shipping conditions is required to ensure quality across the supply chain. De-risking includes early cryopreservation of leukapheresis or PBMC (peripheral blood mononuclear cells). Autologous therapy developers are working on logistics scheduling systems to manage the collection, shipment, cell processing and shipment back to the infusion site to ensure critical attributes of the incoming and outgoing materials are maintained.

Thirdly, how the patient's chain of identity (COI) is defined and controlled through the vein-to-vein supply chain presents a challenge that companies must address. There are no globally harmonized privacy regulations. As a result, manufacturers must ensure their COI systems includes unique patient identifiers which protects patient confidential information such as their name and date of birth throughout the cell journey. Technology enablers play a critical role in maintaining the COI throughout the autologous products.

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Finally, the manufacturers of these therapies have limited control within the apheresis or treatment centers because their systems are not electronically integrated. On the front and back ends, these centers use labelling and administrative procedures to control COI as the patient touch point.

Q What are the key considerations when developing a supply chain business model for CAR-T therapies?

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KLF Raw material sourcing and control is one consideration. A lot of the first-generation CAR-T processes have a high percentage of sole sourced critical raw materials. This limited supplier base that cell therapy developers can procure materials from, limits their power to secure the best prices. Therefore, the ecosystem that supports the industry must become more established, so that raw material sourcing is not a rate-limiting step.

Another area of consideration is introducing closed systems and automation into the manufacturing processes. Automation plays a key role in supporting product quality; increasing robustness and consistency; and decreasing contamination risk and operational costs. The manual cell therapy manufacturing processes must evolve beyond clean rooms with biosafety cabinets and be optimized for higher volume and faster throughput production.

Finally, how manufacturers engage and partner with regulatory agencies can accelerate reviews and speed to market. Early autologous entrants have received approval on early versions of their manufacturing processes. Health authorities may consider cell therapy platforms and leverage clinical trials from different components of those platforms to speed the integration of process improvements into next generations products.

Q Companies are now investing in developing kits as standardization tools to minimize process variation across the supply chain. Are such kits being used in the CAR-T supply chain?

KLF The goal of standardization tools is to reduce process variation and to ensure that clinical results reflect the efficacy of the product rather than variations in handling. It is important to standardize as many procedures as possible to develop a robust cell journey. Examples of such kits include cell collection kits, product administration kits, etc.

The value of such kits as standardization tools increases as the cell therapy product passes through the later stages of development into commercialization. Early stage trials usually involve a few clinical sites, thus allowing for close coordination to ensure material handling is consistent. But when these products move beyond Phase 2 towards commercialization, there are more interfaces with treatment sites which makes it more difficult to ensure that each site follows the same procedure for cell collection, processing and administration. That's where standard kits become important to enable consistency.

Most cell manufacturers are running various versions of kitting operations internally during the cell processing steps. Certain components can be kitted at external raw material providers and others are custom by the unique patient lots within the cell processing manufacturers.

Q Beyond standardization, what other areas are under active investigation to address current challenges in the CAR-T supply chain?

KLF For CAR-T processes requiring lentiviral vector, companies are working to shift from an adherent to a suspension manufacturing process for efficiency and cost improvements.

Optimizing the vein-to-vein cell journey to reduce cycle time and minimize risk includes improving how patients are scheduled to manage demand through the manufacturing facility and optimizing labor and equipment utilization while meeting customer service level requirements.

De-risking the use of single logistics and LN2 providers and ensuring alternatives courier services for healthcare providers is also an important development focus. Optimizing the packaging design is an area where innovation can lead to more reliable and traceable packaging configurations with smaller credo cubes and liquid nitrogen shippers.

Finally, the apheresis product labelling is not globally consistent. As a result, patient-specific kits sent from manufactures to the apheresis center or pull printing of pre-formatted labels at the apheresis center are options being used by manufacturers. As the industry matures, standardizing labelling nomenclature will improve robustness of chain of identify. During the clinical trials, several apheresis centers used hand-written labels, or pre-printed hang-tag labels from clinical trial sponsors. As more CAR-T drugs are approved, apheresis centers will see an increase demand where consistent "machine readable" coding

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and labelling for CAR-T blood products will reduce complexity and improve throughput with lower label related deviation rate at the apheresis centers.

Q How important is it for cell therapy developers, manufacturers, suppliers and clinicians, to work together to ensure the therapy is delivered successfully to the patient?

KLF Developers, manufacturers, regulatory bodies, suppliers, clinicians and patients are the key stakeholders in this pioneering cell therapy ecosystem.

It's important that developers and manufacturers continue to invest in making sure that safe and efficient first-, second- and third-generation products are released into the market. Although the initial investment is large and sometimes the return on investment is not as fast as the a company might want initially, it is worth the investment for patients with no other options. It's also part of pioneering the next pillar of medicine.

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From a supplier perspective, standardization where possible is required to ensure product consistency. Whether it's in the raw material or single-use items, getting them to be GMP-compliant is critical for the supplier ecosystem to truly support the successful delivery to patients.

Regulatory bodies are key stakeholders in the field. Commercial autologous CAR-T therapy is new and it's hard to fit under the same guidelines as biologics. We need additional guidelines on how to regulate this type of product. Developers and manufacturers will need to build a scientific case to the regulatory agencies, to justify product characterisation, comparability etc. Regulatory bodies have to build their internal expertise so that they can really understand the data supporting the new technologies.

From the clinician's or healthcare provider's perspective, making sure their voices are heard is critical. Healthcare providers have to articulate their needs and ideas for improvement to help manufacturers and developers meet the needs of their patients. That's how I see the whole ecosystem evolving.

Q Where do you see the next opportunities for optimizing the supply chain of CAR-T therapies over the next few years?

KLF Looking out, there is a huge opportunity to bring down the cost of manufacturing. Currently, companies are focused on speed of technology to market. Innovations will drive a reduction in cost of goods to allow for sustainability of this potentially curative value proposition.

One of the key things I am interested in influencing across the industry is pushing suppliers to make the right investment, to come up with solutions that manufacturers and developers require, to truly make this therapy accessible to the masses.

Our patients are waiting for combined cost improvements and early usage to solidify personalized medicines as our next pillar in medicine.

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