



TRANSPORTATION SOLUTIONS FOR CELL AND GENE THERAPY SUPPLY CHAINS



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The number one priority with cell and gene therapies during transportation is maintaining the integrity of the drug, as well as ensuring it arrives on time to its destination and within temperature specification.

The task of maintaining speed, temperature, and integrity becomes much more complicated with these drugs. Many gene therapies are moved at a minimum of minus 80 degrees Celsius, while many cell therapies are moved at cryogenic temperatures, which can be as low as minus 196 degrees Celsius.

In addition to these strict temperature and timing requirements, cell and gene therapy supply chains are more complicated than traditional life science supply chains. Coordination challenges exist in the manufacturing process, especially for autologous therapies, given the highly personalized nature of the medicine itself. It is essential to quickly and efficiently move material to meet the needs of often extremely ill patient populations. This includes ensuring sufficient supply and storage conditions for raw materials, collection and transportation of apheresis or other patient-derived starting material, and final distribution back to patient.

Maintaining temperatures for cold chain drugs requires strict coordination of the supply chain to ensure the material arrives on time to its destination and within specification. Therefore, developing a strong supply chain both in terms of the raw material up front and the ultimate distribution of your cell and gene therapy, can make your company a more attractive target for acquisition as well as a more competitive player in the commercial environment.



Key considerations for evaluating transportation partners

Before evaluating transportation partners, you should thoroughly define your logistics requirements and evaluate partners against them, even if you are planning to use your default transportation option. The result is a customized solution tailored to meet your product's needs. Some questions to ask that can help define your requirements include:

What is the scope and scale of your trial? Are you delivering to 10 patients at a single clinical site or 100 patients across multiple countries? What are your patient enrollment goals for later phases of your clinical activity? Consider how the decision you make now will impact your cost of goods sold as you approach commercialization.

What is the temperature and time sensitivity of your product? This helps determine what type of shipper you use, how and where the carrier positions the shipper in their network, and the speed and service level that are required to move the product.

How much control and visibility do you want into the movement of your product? Do you need just in time (JIT) pickups or deliveries within a specific time window? How much lead time do you have to move the product? Will you require GPS monitoring?

What are the geographic requirements? Crossing borders is going to increase the complexity of the move, and there may be country-specific requirements for importation, especially for clinical versus commercial product. You may also need intermediate storage while the product clears customs. Regarding control and visibility, if your product will be shipped to other countries, you will need access to global trade compliance expertise.



Evaluating potential partner capabilities based on service level expectations

Risk mitigation should be at the forefront of any process, but you should choose a partner who will lower risks while also remaining cognizant of any cost pressures that you may be facing. One of the most important factors in selecting the right partner for your project's needs is a clear understanding of the difference in service level expectations for integrators versus those of specialty carriers. This is an area where there are common misconceptions, and it is critical you understand the differences in not only how they deliver your product, but also how they measure up against your business needs. Below are a few critical questions you should ask to explore where your potential partner stands.

AN INTEGRATOR VERSUS A SPECIALTY COURIER: WHICH IS A BETTER FIT FOR YOUR NEEDS?

The biggest difference between integrators and specialty carriers is that an integrator is an asset-based provider, whereas specialty couriers generally are not. Integrators have their own planes, trucks, and a global network of distribution facilities. Conversely, specialty couriers do have their own global network of distribution facilities, or depots, but they likely have very few owned assets that physically move the material. Instead, they rely on an agent network, which is made up of qualified companies that a specialty courier will contract to move your material within a specific region. Whether a partner is asset-based or not impacts how materials are moved through your supply chain and the amount of flexibility that exists while doing so. A specialty courier functions like a taxi. If there are any disruptions in a route, they can choose an alternate path and still arrive on time. However, an integrator functions like a public bus system, where there are predetermined routes with regular stops from which they cannot deviate.

HOW DO THEY ENSURE GLOBAL TRADE COMPLIANCE?

All logistics companies should possess a quality and compliance program that drives their services. Some companies are more compliance and quality driven than others, so ensure you ask providers to review their compliance program when evaluating different options. Product classification is not typically a service that is offered by an integrator or a specialty courier. However, couriers do work with brokers within their network to review and approve required documentation prior to a shipment departing its origin. This pre-approval ensures timely customs clearance and delivery. Integrators, in most cases, rely on a consolidated manifest that is sent to customs in the destination country. Understanding how this works is important, as it could affect the timing of delivery depending on the urgency and complexity of your shipment.

HOW DO THEY TRACK QUALITY?

For any shipments within the life sciences industry, and specifically shipments within the cell and gene therapy space, you want to be mindful of how the company is tracking deviations, complaints, and corrective and preventive actions (CAPAs). There are several specialty couriers that have built their businesses around the life sciences industry, which means they are not only familiar with the industry's specific requirements but also that their quality assurance or quality management systems have been developed to support the level of rigor required by these companies. Integrators are primarily trying to maximize the efficiency of packages moving within their own networks, so they may not have this expertise. You will learn more as you evaluate any company in further detail, but early indications of a robust quality management system and an experienced quality team are an important start.



HOW DO THEY COMPARE IN COST?

You may be able to leverage better rates with an integrator, but you must also evaluate the risk trade-offs required to move your product. It is not uncommon for clients to initially select an integrator based primarily on price but then face issues with the level of service provided. For example, clearing customs can be far simpler using a courier that can work closely with the in-country broker. Oftentimes, specialty couriers can help with other supply chain functions that integrators may be slower to adapt to due to their existing networks, which may limit overall flexibility in supporting your therapy.

WHAT ARE THEIR PERFORMANCE DRIVERS?

Specialty couriers all leverage the same commercial airlines that you use for personal travel every day to move something from point A to point B. What impacts performance here, though, is the relationship the courier has with the airline, its personnel, and the ground handlers. All specialty couriers leverage network providers. Remember, most specialty couriers are not asset-based. When they need to leverage boots on the ground, this is largely provided by their agent networks. Developing a strong agent network requires robust training on standard operating procedures. With so many similarities between specialty couriers, customer service can be a key differentiator to help you decide which is best for your business needs. A partner with good customer service will have a plan in place to proactively notify you if there is a delay or change to your plan as well as if there are any unexpected excursions or deviations.



How couriers build your proposal

Once you have established your requirements and are ready to seek proposals, you will need to develop a transportation proposal. First, you must define the following:

- lead time
- product shelf life
- pack-out assistance
- temperature requirements
- origin/destination pairs
- consignee (receiver) of product if shipping to international locations
- shipper technology and temperature monitoring devices

The courier will begin by reviewing this information and should work backward from the destination to determine the best optimal path for on-time delivery, all while taking into account the lead time, shelf life, and temperature requirements. As you might expect, the origin and destination pairs drive the strategy. The shippers must be positioned in a way that allows them to reach the origin site as quickly as possible, making the services of an integrator or specialty courier crucial. Using a specialty courier can significantly reduce risk, due to the level of customization and high-touch customer service, which may not always be necessary if you have enough lead and hold time with your shippers. For example, shippers with a short hold time with extremely critical material inside will still likely move via a specialty courier, even if there is sufficient lead time based on scheduling the patient for a subsequent manufacturing run. Depending on the geography, you may have more flexibility, given that the shipper has a longer hold time and you could potentially do all three legs via an integrator.

Next, the courier determines how far the origin is from the destination point. For example, if the product is going between Boston and New York, it may make more sense to drive the four hours to reduce the numerous handovers when tendering to airlines and recovering the product at the destination airport. The fewer the touches on the product, the more you can control the risk. While this is not always an option due to cost considerations, it is certainly something to consider when possible. Onboard carry - where a courier physically carries the material on the plane - is the most extreme example of how to reduce touches. However, this is very expensive and largely not necessary, due to the infrastructure that exists today to support cold chain logistics, both domestically and internationally. If the destination is too far to drive, the courier will look at how many nonstop flights depart for the destination on any given day. The more nonstop flights going from your origin and to your different destination points, the more likely a delivery will be on time should the product not make it onto the first flight out. This can sometimes happen since passenger baggage typically takes priority over other packages on commercial airlines. Therefore, if one of your flight legs is a regional flight to a busy destination, your material could potentially get bumped.

If you are still considering your manufacturing strategy, location can be an important factor, as it can have long-term cost implications. Ideally, your manufacturing sites should be in close proximity to several major airports so that you have more flexibility within your supply chain. Manufacturing locations or collection points that are more remote require some form of a dedicated drive (again, consider how to mix in a ground strategy that can reduce turnover of the product). Depending on your position in between major airports, the courier may suggest using one

airport over another, even if one seems to be further from the origin site. Some factors that drive decisions like these include a better relationship with an airline and its ground personnel at a particular airport; or perhaps one airport has larger volumes of cargo shipments, making it is easier to get space on the plane.

Based on your destination, the courier may choose to send the material to a major hub airport that requires a longer drive to your destination versus a regional airport that requires a connecting flight. This can occur if the recovery of the product is easier at one airport versus another, if you are sending palletized materials that require use of wide-bodied planes that are too large to land at small regional airports, or if there is a potentially better interim storage or replenishment infrastructure at one airport versus another. Finally, the courier will consider which agents to use at the destination as well as what the relationships are with brokers in that country (if you are shipping internationally).

Regardless of whether the destination is domestic or international, couriers will want to obtain approval to ship the product prior to even leaving the airport. If there is a major integrator hub near the origin or destination points, then a hybrid strategy is certainly an option. This reduces costs while providing a higher level of visibility and assurance via specialty carrier for the recovery and final mile delivery. Once the courier has considered all the nuances of the geography and the product itself, they will then determine the primary, secondary, and tertiary next flight out options, assessing on-time performance, recovery times, and developing storage replenishment plans at the destination airport. These are all risk mitigation techniques to protect the product in the event of any unanticipated delays.





Balancing cost versus risk in your proposal development process

Risk mitigation is a key focus during transportation, but many of the methods to reduce unexpected issues and delays and/or temperature excursions also come with added costs. It is important you understand and consider this balance when defining the requirements for your transportation proposal. For example, shorter lead times or JIT deliveries can drive costs up, as can certain types of shipping technologies that are often used to increase reliability and flexibility, such as shippers using phase change material. The same applies to advanced shipper technologies or more customized delivery and pickup windows intended to provide better oversight of your delivery. From a geographical perspective, dedicated ground transport may be more expensive, but it can decrease turnover risk and the number of touchpoints the product encounters, which could be a helpful strategy depending on where you are shipping. While flying may end up being the most expeditious and cost-effective mechanism, it is worth asking about ground transport so that you understand your options as they relate to speed, security, and cost.

The EU presents a lot of opportunities for ground trucking, especially since goods can move freely within the region. In both North America and the EU, you can likely leverage some combination of integrators and specialty couriers. This is going to allow you a higher level of customer service through the courier and potentially save on cost with the integrator when your delivery windows are not time specific. In Asia-Pacific (APAC) areas of the world, you must be cognizant when using regional flights, as some of these package handlers may not be familiar with the materials being shipped. Your courier should be in constant communication with the agents that are going to be handling the shipment on the other side, as well. A dedicated drive is not much of an option within APAC, and packaging may not be as readily available.

While you want to make sure all shipments are planned well in advance, there are huge variations in infrastructure across countries, and hybrid solutions can still be an option depending on how close your manufacturing environment is to a major hub. In all of our discussions with current and potential customers, Thermo Fisher Scientific stresses the importance of key performance indicator (KPI) management. Your courier will already be tracking their on-time performance, but it is important to set up structures early in the process to monitor your own interactions with your partners. For example, depending on your provider, you may incur additional costs for rush orders, reprocessing, and cancellation. Putting KPIs in place early in your process helps identify issues quickly and efficiently and subsequently makes way for root cause analysis that will enable corrective action to take place.

CASE STUDY

Cell therapy phase III trial

A sponsor was conducting a global phase III trial, enrolling over 1,000 patients at clinical sites in the U.S., as well as 20 EU and 20 non-EU clinical sites. Thermo Fisher arranged JIT kit distribution to the treatment centers for collection of tumor cells to be used in the manufacturing process. Once the tumors were biopsied from the patients, Thermo Fisher arranged the collection of the kits back to its facilities for storage in a validated and client-dedicated minus 80-degree Celsius storage system for 30 hours.

When the client was ready for a manufacturing run, Thermo Fisher shipped the tumor material on dry ice to the CMO, where it would be processed into 10 to 14 vials of final drug and cryopreserved. Thermo Fisher then coordinated the return of the 10 to 14 vials of final drug product back to its facilities for storage in a validated and client-dedicated storage unit. Upon client notification of an order, Thermo Fisher shipped a single dose, or one vial of drug, for administration to the patient and coordinated the JIT dose distribution and administration kits to the treatment centers utilizing a validated and dedicated fleet of dry vapor shippers for this client.

Given the scale of patient enrollment across geographies, having detailed work instructions and a robust training program was extremely important to ensure the timely delivery of materials within specification. Because Thermo Fisher Scientific's dry vapor shippers are fully validated at cryotemperatures for 10 days, there was an option to adjust the shipping schedule. The patient dose was shipped several days in advance via an integrator using certain EU lanes to make sure it was still available for the patient's scheduled appointment. If the shipment arrived early, the shipper could act as a temporary storage device at the clinical site; if it was delayed by a day or two, the dose would remain within specification prior to patient dosing due to the 10-day temperature hold. Because of the number of shipments engaged in this trial, KPI management was essential to monitor and control costs and complete this phase of the trial under budget for the client.

Overall, the partner you work with for the shipment of your temperature-sensitive drug products must have extensive experience in this space, in order to manage the complexities of your trial. They must be able to holistically look at your supply chain and leverage their global footprint and network to help you mitigate risk and help you scale your business. Using KPIs, they can drive continuous improvement and ensure any issues are identified quickly and a corrective action plan is put in place. Investing in your supply chain up front to improve efficiencies and processes later allows you to protect your materials, your investment, and most importantly, patients.





