Advanced Therapy Treatment Centres

Northern Alliance Advanced Therapies Treatment Centre

Tracking and storage considerations to maintain parameters during shipping & storage for different products

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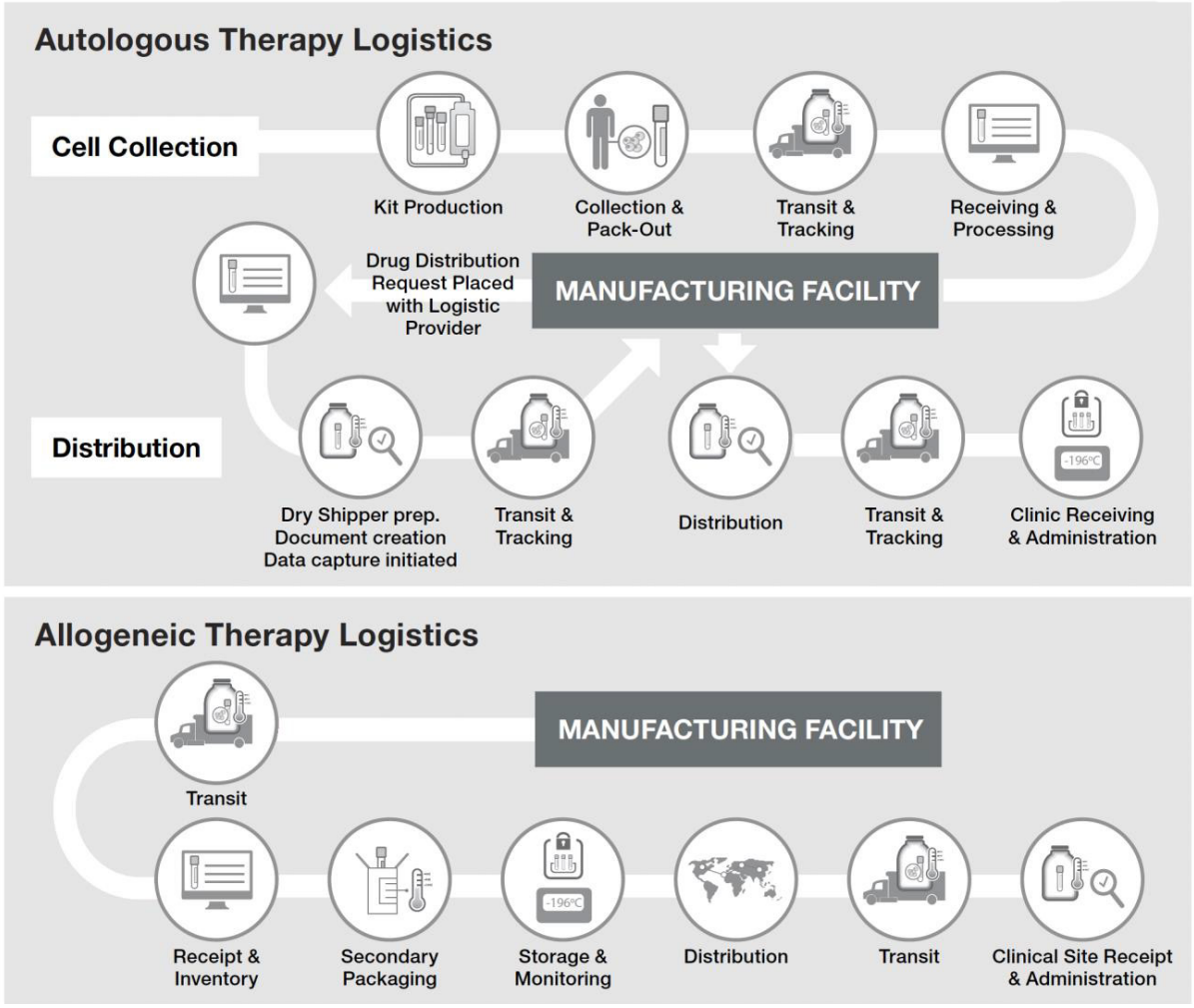
Introduction

Much of the discussion in the advanced therapy medicinal products (ATMP) industry today focuses on the complexity of manufacturing and the unique characteristics of each dose. However, the ultimate success of an ATMP rests on the ability to deliver a viable, potent product to the patient. Ensuring this living drug is delivered to the right patient at the right time, location, and temperature is essential to patient safety and product effectiveness. Having a sound logistics strategy is critical to achieving this goal.

In comparison to small molecule therapeutics and currently available biologics, the logistics management of ATMPs is drastically more complex involving multiple organisations often across different geographies and requiring rigorous quality standards, strict temperature control, regularly involving ultra-cold temperatures and coordination between the clinic, biorepository, and manufacturer. ATMPs require a comprehensive logistics strategy with standardized processes and procedures along with validated workflows to manage these and more, to avoid unwanted variations during storage and shipping.

The purpose of this document is to provide insight into the complexity of the ATMP supply chain and the aspects that need consideration when developing a logistics strategy, such as presenting chain of identity, chain of custody, shipping and storage aspects, that require consideration when developing an ATMP supply strategy.

The Unique Complexity of the ATMP Supply Chain



At a high level, manufacturing an ATMP requires that patient or donor material be collected and transported to a manufacturing facility, where they will be processed and developed into a drug product, and finally distributed to the clinic for patient administration. The movement and storage of cells and drug product is conducted at various temperatures, from 2°C to 8°C to cryogenic temperatures, depending on the material.
The supply chain will look slightly different for autologous therapies, which uses the patient's own cells in the manufacturing process, and an allogeneic product, which typically relies on donor cells and can be administered to a broader patient population.

Both require cell collection from multiple sites, shipments at multiple temperatures, and strict chain of custody documentation throughout the entire process, but each product will require unique adaptations of the supply chain in order to ensure successful delivery to the patient.

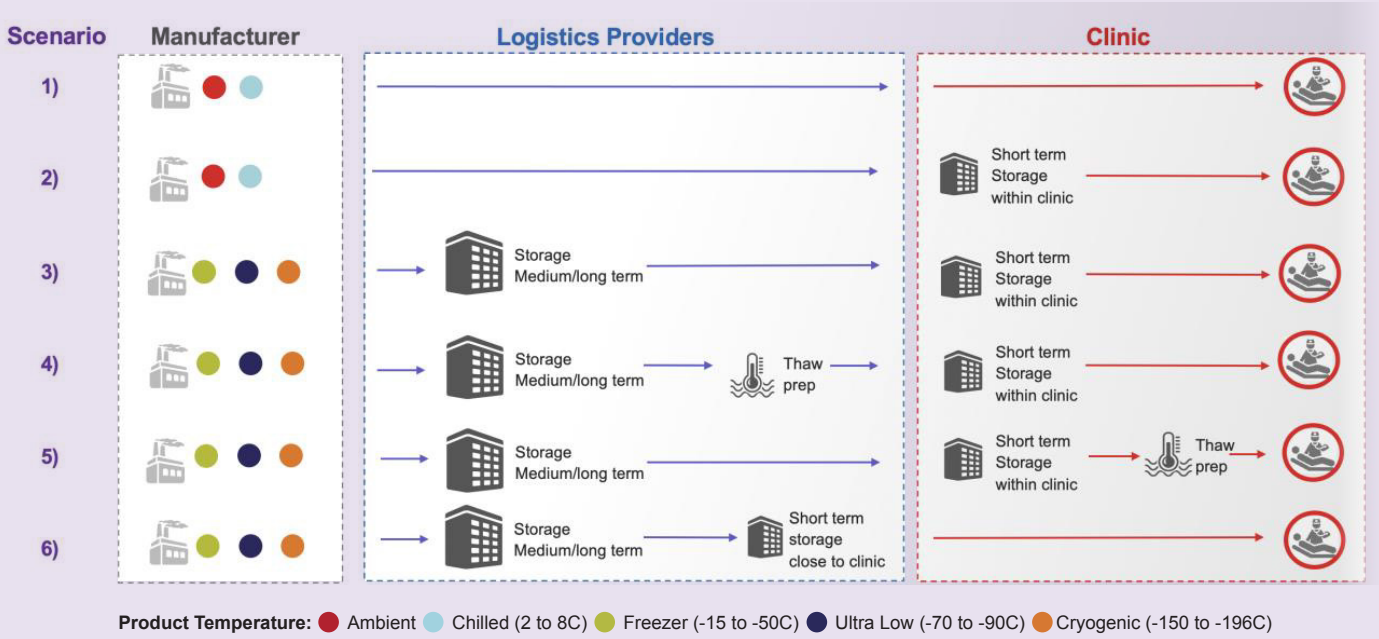
The following sections outline a number of these variations and the relevant considerations that need to be addressed to ensure that product reaches the patient in the right condition at the right time.

Chain of Identity and Chain of Custody

ATMP characteristics influence the way in which their supply chain is managed and the risks that need to be addressed to ensure consistent compliant supply. Broadly speaking there are three categories of ATMP:

- Autologous, the drug product is made from the patient's own starting material
- Matched Allogeneic, the drug product is generated from starting material taken from a donor who has been selected based on biological characteristics which need to match the recipient (e.g., HLA profile)
- Universal Allogeneic, the drug product can be administered to any patient regardless of their tissue type/antibody profile

Although the pathways from manufacture to clinic could be the same for each category Chain of Identity (COI) and Chain of Custody (COC) considerations are different. To illustrate this, six supply chain scenarios are detailed below, presenting different possible pathways depending on product temperature requirements.



Chain of Identity and Chain of Custody

Although the pathways are not ATMP category dependent the COI & COC considerations are different for each scenario, as detailed in the following tables:

Autologous

Scenario	Considerations
1	Chain of Identity (COI) & Chain of Custody (COC) required, one exchange to courier, one exchange to clinical site. COI to confirm that the product has been generated from the patient's own starting material. Assuming the drug product has a short shelf life, all assets for treatment are required on day/day after drug product arrives at the treatment facility.
2	Considerations of scenario 1 + Control steps associated with short-term storage at the clinic may be controlled/managed by sponsor in a clinical trial. Clinical storage for commercial products may not be as closely managed by the therapy owner, once the drug product has been received by the hospital/clinic title transfer will take place and so the consequences associated with 'local storage' problems will be the responsibility of the hospital/clinic. There will be an increase in risk of the wrong patient receiving the wrong treatment if 2+ autologous/matched allogeneic therapies are being stored at the clinic at any one time. However, if these sites operate to approved industry standards (e.g., JACIE accredited centres) then the risk will be reduced due to established procedures for patient identification and administration being followed.
3	In theory the controls in place for <24 hrs storage will be the same as medium/long term storage. However, longer storage parameters will suggest that orchestration systems used are integrated with electronic stock management systems. Consider moving beyond COC management and detail drug product location as part of orchestration. Short-term cryogenic storage may require dedicated devices at clinics.
4	Thaw to order will need close coordination with third party storage site and treatment sites. Thawing a drug product when any of the assets needed to administer the drug are not available may result in the drug product going past its expiry date/time (which tends to be very short once thawed).
5	Thaw/Prep at clinic will make it easier to ensure the patient/clinical team is ready to administer the drug before product preparation begins. Drug preparation must not cross the GMP Rubicon.
6	Additional storage sites will need closer COC/inventory management. A slight increase in risk due to more movements of the drug product.

Chain of Identity and Chain of Custody

Matched Allogeneic

Scenario	Considerations
1	COI & COC required, one exchange to courier, one exchange to clinical site. COI to confirm that the match is correct. Assuming the drug product has a short shelf life, all assets for treatment are required on day/day after drug product arrives at the treatment facility.
2	Considerations of scenario 1 + Control steps associated with Short-term storage at the clinic may be controlled/managed by sponsor in a clinical trial. Clinical storage for commercial products may not be as closely managed by the therapy owner, once the drug product has been received by the hospital/clinic title transfer will take place and so the consequences associated with 'local storage' problems will be the responsibility of the hospital/clinic. There will be an increase in risk of the wrong patient receiving the wrong treatment if 2+ autologous/matched allogeneic therapies are being stored at the clinic at any one time. However, if these sites operate to approved industry standards (e.g., JACIE accredited centres) then the risk will be reduced due to established procedures for patient identification and administration being followed.
3	In theory the controls in place for <24 hrs storage will be the same as medium/long term storage. However, longer storage parameters will suggest that orchestration systems used are integrated with electronic stock management systems. Consider moving beyond COC management and detail drug product location as part of orchestration. Short-term cryogenic storage may require dedicated devices at clinics.
4	Thaw to order will need close coordination with third party storage site and treatment sites. Thawing a drug product when any of the assets needed to administer the drug are not available may result in the drug product going past its expiry date/time (which tends to be short once thawed). This may be a challenging strategy if analysis of a patient's antibody profile is required prior to drug administration to ensure that the match is still valid.
5	Thaw/Prep at clinic will make it easier to ensure the patient/clinical team is ready to administer the drug before product preparation begins and review results of antigen profiling to ensure that the matched drug product is suitable. Drug preparation must not cross the GMP Rubicon.
6	Additional storage sites will need closer COC/inventory management. A slight increase in risk due to more movements of the drug product.

Chain of Identity and Chain of Custody

Universal Allogeneic

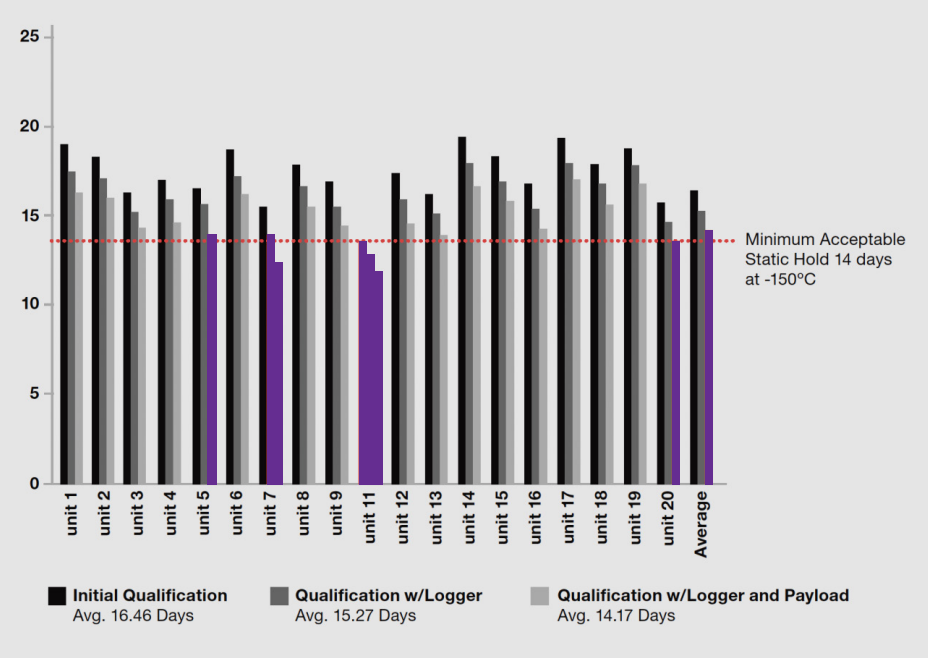
Scenario	Considerations
1	COC required, one exchange to courier, one exchange to clinical site. Batch/lot number can link back to batch's original donor material. It is assumed that the shelf life of universal allogeneic products is much longer.
2	Clinic may be able to store multiple doses due to the universal nature of the product.
3	Universal nature of the treatment could permit use of standard wholesaler dealer model for distribution, if the wholesaler dealer has the correct storage conditions.
4	Control not a critical, another product could be thawed if administration is not possible.
5	Thaw/Prep at clinic will make it easier to ensure the patient/clinical team is ready to administer the drug before product preparation begins. Drug preparation must not cross the GMP Rubicon.
6	Additional storage sites will need closer COC/inventory management. A slight increase in risk due to more movements of the drug product.

Shipping

Maintaining strict control of the environment surrounding a therapy whilst being shipped is paramount, with the most challenging aspect being temperature hold, which also has a direct impact on the maximum shipping time available.

Temperature hold during shipping is critical to ensure that therapies are delivered within their required temperature parameters and therefore the shipping solution requires qualification. This qualification should not be confused with blanket qualifications issued by the manufacturers. Manufacturers' qualifications can be useful in choosing possible solutions for testing but may fall short of the rigorous testing needed to make sure the material being shipped reaches its destination in perfect condition.

The graph opposite shows the static hold time for 20 brand new dry shippers, all the same model and lot. When these 20 manufacturer-qualified new shippers were tested after installation of the data logger and addition of the payload, five failed to meet minimum hold static time.



Temperature hold is affected by the thermal mass of the shipping device, which is also affected by other elements of the shipping configuration, such as data logger, rack, baffles, packaging, and the product. To get a true understanding of the expected performance of a dry shipper it must be validated with all elements in place.

Shipping

Beyond the shipper itself, there are situations that need to be considered when determining the hold time that is required:

Time needed for an international shipment to clear customs. While in most cases customs can be cleared in 24 to 48 hours, in some countries it can be considerably longer. Clearance times vary not only by country, but also with the volume being processed on a given day. Delays can be caused by documentation problems, local holidays, weekends, and inexperience on the part of the agent. A safety margin must be calculated into the temperature hold requirement.

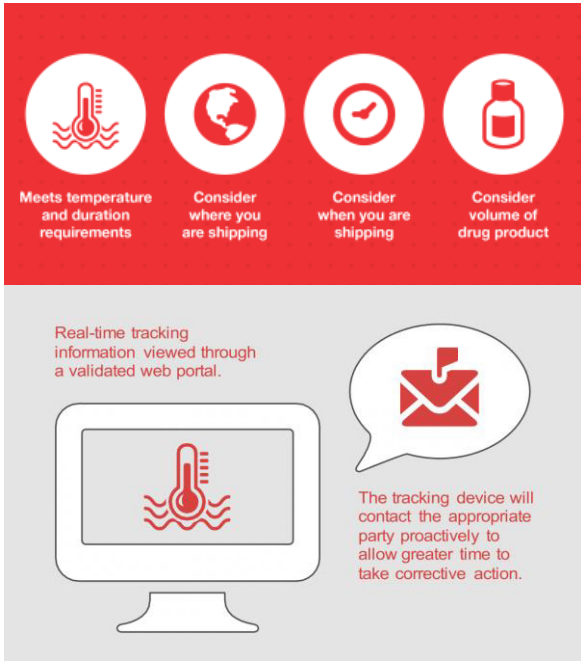
Outer packaging. Any supply of outer/thermal packaging for the purpose of transport will be calculated in relation to the size of the product/ tertiary box containing the samples/product, the type/classification of sample/product in line with the relevant regulations applicable to the mode of transport such as IATA for air and ADR for road and any local restrictions that may apply for example handing requirements for controlled drugs.

Amount of temperature hold lost in mishandling. Dry shippers are designed to be used in an upright orientation. Any deviation will rob the shipper of valuable hold time. For example, a shipper that is tipped over on its side for eight hours can lose as much as 50% of its hold time.

Knowing the detail. Understanding the detail of how product will be shipped is important as what may appear to be small details can impact the achievable timelines.

For example, smaller aircraft will result in space restrictions and the units possibly being tipped briefly on the ramp to load or routes requiring a transfer station so that the unit can be accommodated. This can alter the timelines achievable.

Using dry shippers for temporary storage at the site of administration. How much time is needed to prepare and administer the therapy to the patient once it arrives at the clinical site? What if the patient misses his or her appointment and has to reschedule for several days later?



Temperature Monitoring and Tracking. Verifying that the appropriate temperature has been maintained throughout the supply chain is an important aspect of COC documentation. There are data loggers available that will provide real-time tracking information viewed through a validated web portal. Sophisticated tracking technology can be set up with exception criteria. Exception criteria will allow acceptable windows to be set for conditions critical to the wellbeing of the product. If a parameter exceeds its critical window, the tracking device will contact the appropriate party proactively to allow greater time to take corrective action.

Corrective action could involve a phone call from a project manager to the airport personnel or courier to set the shipper upright, or it could involve preparing a second shipment, so the patient does not miss a dose. Corrective action is not always possible, but can be attempted with the help of real-time monitoring.

Geo-fencing allows the clinic or manufacturing site to prepare to receive the material. Through an online web portal, a radius around the delivery site is created. Once the shipment enters this radius, a specific person or group of people is notified. This will help ensure that the treatment is not left out on a loading dock and is processed immediately.

Storage Devices

Similar to the reasons for qualifying a shipper, storage equipment must also be qualified to perform in the specific way it is to be used relative to the material.

Specific equipment qualifications should be performed on all equipment used for the storage and handling of the drug product or any of the constituent cell products. This would include freezers, refrigerators, liquid nitrogen (LN2) vessels and CryoCarts.

As an example, say a finished drug product has a maximum storage temperature of -150˚C and will be stored in a vapour phase Dewar. However, there are variations in the temperature of any vapour phase vessel; the temperature is always colder at the bottom and warmer at the top. To determine the optimum storage location in the tank, it must qualify with multiple probes to determine the temperature gradient of the vessel. Only a portion of the vessel, the area at or below the -150˚C level, is appropriate for storage of the finished product.

Secondary Packaging, Labelling and Kitting

Secondary packaging and labelling are integral elements in the product supply chain. The following are several considerations for choosing the right label and packaging.

Secondary Packaging:

Secondary packaging has two functions: protect the product and hold the label. Most secondary packages are custom built to meet the specifications of the drug and application. The packaging can hold as many drug containers as is deemed necessary for delivery to a single patient or centre.

The final step in the process is the marriage of container and vial. This process must be conducted under a Batch Record process. The Batch Record process begins with the creation of Master Batch Record (MBR). The MBR is the set of instructions that are approved prior to execution. The MBR governs the actions, temperatures, equipment, relevant SOPs, and documentation of the process. Each individual instance of packaging and labelling will be documented through an individual Batch Record whether it is a lot of 10,000 or a single autologous dose. Batch records are issued based on Quality-approved MBRs. The conditioning of the carton, removal of the drug from storage, quality checks and vial insertion are all performed based on MBR instructions and batch record documentation. Once packaged, the drug product can be inventoried as packaged product or sent to distribution for transit to a clinic.

Secondary Labels

Labels must meet the requirements of the regulatory agencies in the countries where the product will be administered. Once this requirement has been met, the size of the label needs to be considered. This is dependent on both the size of the secondary package and the volume of text. Labels will need to be printed in the local language and some countries may require multiple languages.

Label stock also needs to be considered to ensure that the label remains in place when subjected to the relevant temperature. For example, under cryogenic conditions the label should be applied at least 48 hours prior to packaging to ensure the adhesive has adequate time to cure and adhere to the package.

Kitting

The use and production of kits can be a very effective tool in standardization, driving consistency. The use of a kit ensures that the same materials are used across sites, instructions are available for each procedure, labelling is consistent, and in the case of collection kits, makes certain that a qualified shipping solution is used for the transit of the critical patient cells after collection.

Kitting can also provide significant benefits for manufacturers managing consumables in the production cycle.

Manufacturers use significant labour resource during the pre-production phase to undertake a wide range of tasks including; procuring, receipting, storing, maintaining, collecting, cleaning, labelling and QC checking of consumables used in the manufacturing process. Each ATMP run may consist of up to 100 individual items, each having to be cross referenced to a specific 'pick list'. Although these activities are critical, they are of relatively low value compared to the core manufacturing activities.

Tailored kits, which can be temperature controlled if required, can be supplied that contain all consumables required to carry out a specific step within the manufacturing process i.e. broth bottle, alcohol pads, needles, manifold tubing, transfer bag, interconnecting lines and sterile sample line. All kits are uniquely identified and traceable, removing the need for additional checks of raw material receipt at the manufacturing location.

Summary

The development and adoption of ATMPs is a challenging space that is constantly evolving and having a basic awareness of the supply chain issues is essential for ensuring the success of any program. This document has been created to provide insight into a number of the aspects and considerations when developing and qualifying a robust logistics supply chain for an ATMP. The document does not aim to be exhaustive and individual therapies will each require and have their own specific variations. Experienced logistics partners can help to develop and deliver a seamless supply chain from the initial collection of cells to the delivery of the finished dose back to the waiting patient.

Logistics Considerations	Aspect	Requirement	Consideration
	1. Transit temp range	1. CRT, 2-8C, -20C, -65C, -150C	1. Excursion allowance
	2. Shipper size	2. HSE manual handling	2. Payload efficiency
	3. Shipping lane	3. Intra-UK, international	3. Origin / desitination
	4. Service level	4. < 24 hours intra-UK	4. Ground, air, next flight out
	5. Import / export	5. Custom clearance (add 12 hours)	5. Paperwork preparation
	6. Storage temp range	6. CRT, 2-8C, -20C, -80C, -170C	6. Redundancy, lead time to scale up
	7. Location	7. Capacity & accessability	7. Distance to major air / ground hub
	8. Receipt / dispatch volume	8. 12 hour lead time	8. Staffing
	9. Kitting	9. BOM, Just-in-time option	9. Inventory management
	10. Secondary packaging	10. Clinical & commercial	10. Secondary packaging
	11. Labelling	11. Printing, translation, & application	11. Temp excursion, manual vs. automate

This document has been created as part of the Northern Alliance ATTC project with input from Thermo Fisher Scientific, Cytiva, TrakCel and World Courier.

[i] Thermo Fisher Scientific internal data