Northern Alliance
Advanced Therapies Treatment Centre

Advanced Therapies: Gap Analysis of Challenges in the Supply Chain

Advanced Therapy Medicinal Products (ATMPs) are based on genes, tissues or cells using very complex and variable processes, this includes the supply chain where seemingly minor alterations in the process could impact delivery of the final product to the patient. The model for delivering traditional pharmaceutical medicines uses a centralised manufacturing approach, involving manufacturing hundreds of thousands of doses, distributing these to well-defined hubs, then into pharmacies, and from the pharmacies to patients. This is not possible for Advanced Therapy Medicinal Products (ATMPs), and certainly not for autologous cell therapies, which are patient-specific products, with a batch size of one.

Taking autologous immune cell-based cell therapies as an example, the supply chain pathway of the medicinal product for such ATMPs actually starts when the patient has their cells harvested, creating the starting material. This occurs in a clinical (or apheresis) facility. Manufacture of the ATMP usually occurs at a location remote from this clinical facility. Indeed, this location may even be on another continent. Once the ATMP has been manufactured, it has to be returned to the clinical site, and ultimately to the patient bedside. The pathway finishes with administration of the final drug product to the patient. Many processes take place between the collection of starting material and administration of the medicine and it is essential that a chain of identity/chain of custody is in place, and can be evidenced, all the way through the ATMP manufacturing pathway.

The complexity of all these moving pieces in a supply chain and the blending of the manufacturing and administration phases is relatively new territory, and has been a paradigm shift for both healthcare providers and ATMP manufacturers which influences the work flow in a completely different way to that of traditional medicines.

A number of challenges exist in the supply chain, specifically around growing volumes and scaling up; destinations are changing as manufacturing sites are established in new locations, for example, the Middle East, APAC and Latin America - possibly driven by ATMP short shelf lives which require local manufacturing sites, or influenced by economics i.e. cost of goods. Product temperature, storage and shipping conditions are also being evaluated. The industry is learning how to balance the biological constraints of these products with the increasing need for a longer shelf life to fit the growing distribution networks that come with globalisation. A move towards cryopreserved starting material and final products is one result of this evaluation.

Standardisation is critical to the supply chain, with automation vital to mitigate the risks. This gap analysis highlights where the challenges and gaps are currently in the complex supply chain world of advanced therapies. It is a working document which reflects the professional views of clinicians, manufacturers, and various organisations involved in specialty logistics, supply chain management systems and supply of equipment. Its purpose is to provide a focus on what gaps need to be addressed, in particular for clinical sites which may have had little exposure to ATMPs, and also for manufacturers who are becoming more aware of the impacts of factors such as shelf-life on the process of the product. Collaboration is key, to work with experts in each field to reduce or eliminate these gaps.

GAP ANALYSIS			
	Current state	**Desired state**	**Action required**
1	**Collection and delivery**		
	Autologus products are dealt with by 3 separate teams: collection from CAU->manufacturing centre->infusion centre, and each clinical site will have a different procedure for receiving therapies or handing over donations. All teams will have different ATMP knowledge, resilience, shift systems. Leads to potential confusion/difficulties in changing drivers/nurses as they don't know the procedure. The organisation of the delivery reception area varies. Some lack of control or monitoring. Some clinics have products leave in the shipper, some prefer to transfer to internal storage.	Single location to deliver to in clinic (first/last 100m) Fully integrated batch system. Integration with electronic systems and through bar codes (ISBT 128). Minimum specifications for reception area e.g. monitoring system, WiFi. Suggest compiling a list of which tasks need to be consistent e.g. temperature monitoring. Use list to prepare best practice guidance document for sites. Knowing exactly who is doing what by means of a process map/assigning responsibilities between all parties, and making use of technical agreements	Connectivity/Process/ Training/Integration
2	**Thawing process**		
	There are units that currently offer controlled thaw, but these are not widely used. Water baths are prevalent, but have the associated problems of poor-sterility and lack of control. Clinical sites often don't record critical steps such as thawing/adminstration time.	Thaw in theatre as standard. Digital recording of thawing process. Suggest developing best practice documents / standard template detailing particulars which need to be recorded e.g. thaw time / administration time. Work with clinicians to ensure documents are practical. Needs to be attributable, times, temperatures with a log or more automated.	Process/Integration
3	**Managing clinical uncontrolled thaw (in clinic transport)**		
	Most clinical cryo-stores are in the basement of hospitals, which leads to a minimum 30min transfer time between storage and patient. Potential risk within manufacturing and may lead to therapy failure. Often reliant on manual systems through alarms.	Standard, validated process e.g. CryoPods or small transfer dewars to ensure that the therapy stays at cryo-temperatures during that time. Temperature trace has the ability to be downloaded which should be utilised.	Process/Training
4	**Connection to manufacturing (forecasts to logistics orders)**		
	Therapy developers know, potentially, weeks in advance when they are going to recruit a patient or when a manufacturing batch will complete. Many logistics shipping is booked the day before. Technology platforms like TrakCel's can address this challenge by harmonising patient management with logistics management.	Integrating clinical and manufacturing planning will reduce delay, complexity and cost, whilst producing a better service for patients and therapy developers.	Connectivity/Training
5	**Lack of understanding around criticality of logistics**		
	Logistics is perceived to be an online booking system and there is limited understanding around limitation. Dewars, for example, take 24hrs to charge - it is therefore impossible to order one the day before. There needs to be work to support developers in understanding the constraints around logistics, which needs to be echoed so that logistics experts can understand the therapy developers contraints. Customer currently rings customer services to find out where product is.	Cultural understanding regarding the nuances around ATMP shipments. Online booking and tracking is an expectation through an app or website.	Training/Connectivity
6	**Silos**		
	Similar sets of data are held by all the stakeholders in the supply chain but are not shared. This is being overcome, in part, by systems like TrakCel, but there are still areas where information sharing and standardisation will remove complexity. NHS sites aren't aware of any deviations until the manufacturer advises.	Detailed data map of information which is needed to be shared across an ATMP's supply cycle and an assessment of what data can be shared from a regulatory perspective.	Connectivity/Integration
7	**Tracking**		
	This is still manual. SAVSU and VIAShipper are changing this, but further integration is required to give actionable information.	Full tracking is only useful if a premium courier is being used, realtime monitoring is only of value if resources are available to monitor the shipment around the clock and access the shipment should a temperature excursion occur.	Connectivity/Integration
8	**Sharing best practice**		
	JACIE is very clinical and high level. Detail of process and overcoming these gaps needs to be widely disseminated. Established processes need to be widely disseminated.	Gap analysis could be redone at the end of the project - the desired states above should be in place for all Northern Alliance sites.	Training