Just-in-time logistics

Introduction

Thermo Fisher Scientific is proud to be a member of the Innovate UK funded Midlands & Wales and Northern Alliance Advanced Therapies Treatment Centre programmes, which have funded this work jointly. The network of Advanced Therapy Treatment Centres (ATTCs) has been set up to enable collaboration across industrial and NHS partners to develop ways of working within and across centres that smooths the path to Advanced Therapy Medicinal Products (ATMPs) adoption into routine medical practice and support the dramatic increase in clinical trial activity across the country. They also present an opportunity to place the UK at the forefront of this technology and for the country to be the place to bring these treatments to patients as they move from clinical trial to marketed products.

Just-in-Time (JIT) delivery is a well-understood operational strategy in many sectors including Automotive and Fast-Moving Consumer Goods, used to increase value and reduce costs. Due to the complexities and specifics of the supply chain it is not possible to simply apply JIT procedures from another sector to this one. Optimising the flow of commercial scale ATMPs along the supply chain can though provide the following benefits, which are the drivers behind this work:

- Reduced inventory
- Better responsiveness
- Faster deliveries
- Reduced wastage
- Lower cost-of-goods
- Improved patient value

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The project reported here examined three significant aspects that will aid the quantification of the value proposition and further development of JIT delivery:

- Creation of a model to identify and examine potential cost savings JIT delivery to clinics
- Distribution service models that could enable JIT delivery.
- Future innovations that could support the supply chains' move towards optimised JIT delivery.

The outputs from this 6-month project are valuable in raising awareness of the opportunities that JIT delivery could provide and forms a strong foundation for follow-on activity to develop, pilot and demonstrate benefits of JIT delivery models. It is hoped that such activity will form part of the ATTC phase 2.

The Unique Complexity of the ATMP Supply Chain

Much of the discussion in the 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.

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.

At a high level, manufacturing an ATMP frequently requires collection and transportation of patient or donor material to a manufacturing facility, where they are processed 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 designed to be administered to a broader patient population.

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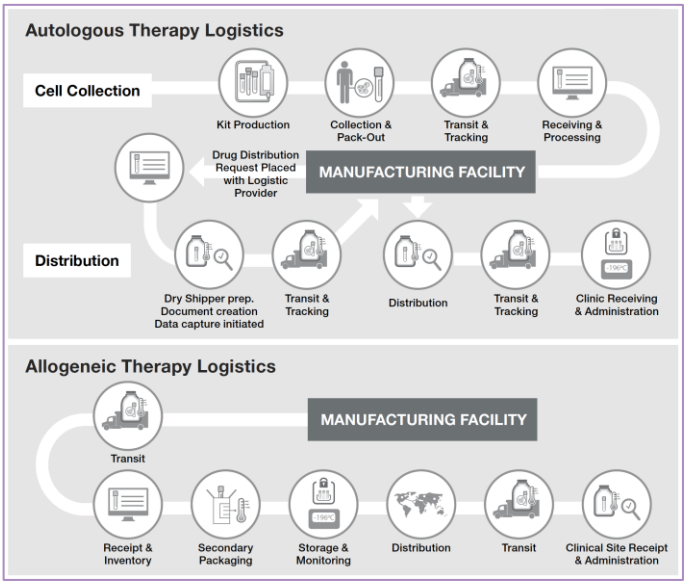
Both require cell collection from multiple sites, shipments at multiple temperatures, and strict chain of custody documentation throughout the entire process, but each product will require unique adaptations of the supply chain to ensure successful delivery to the patient.



It is recognised that the ATMP supply chain is still relatively immature, relying heavily on labour-intensive processes with limited automation or digital assistance. This currently manifests itself through single patient batches being delivered at times and locations decided post manufacturer QP release, with long-elapsed time between request for a therapy from storage to patient infusion, typically 4 to 5 days, with transport only accounting for approximately 10% of this time. This sub-optimal and costly chain model causes further issues at clinics with many already reporting congestion at receipt locations.

This project focused on the final distribution, transit, and receipt at clinical site (final three stages of the above pathways), linking to and complimenting the work undertaken by the M&W and NA-ATTCs identifying and examining the issues relating to the first and last 100m of ATMP logistics at clinics. The work also compliments the other ATTC supported JIT activities developed by Thermo Fisher Scientific, including Kitting Services for ATMP Manufacturers and Late-stage Customisation of packaging and labelling.

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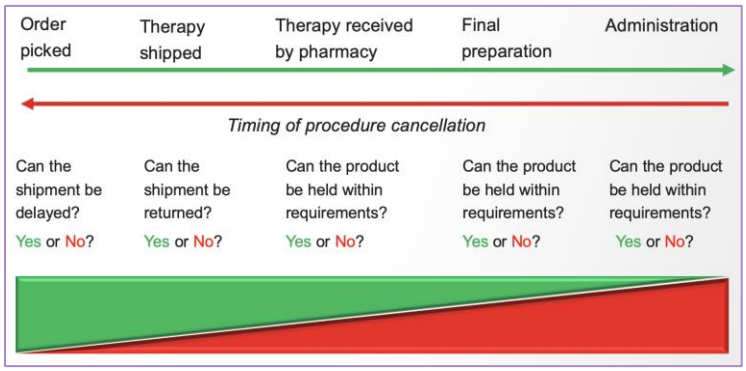
Modelling the costs of ATMP wastage due to cancelled procedures

Due to the complexity of the ATMP supply chain, the long lead time between a dispatch request and delivery at the clinical site means that if a procedure is cancelled after a product is dispatched there is a risk that its viability cannot be maintained and may have to be destroyed, which can represent a significant financial loss.



To gain an understanding of the magnitude of costs due to cancelled procedures and the potential savings that could arise from JIT delivery a model has been created to enable costs, operational scenarios, and savings to be examined.

Model Logic and Overview

The model was initially to be based on data collected from clinics, however an initial review highlighted that there was little consistency across clinics. This was also a finding of the "Addressing-issues-for-ATMP-logistics" that had identified "Most hospitals had grown organically over time, no two hospitals alike" and that "Cell/gene therapies are still new to most hospitals" (Briggs, June 2020). To overcome this, the model created has a framework with a high degree of flexibility with customisable inputs, enabling it to be adapted to examine an individual clinic or group of clinics.

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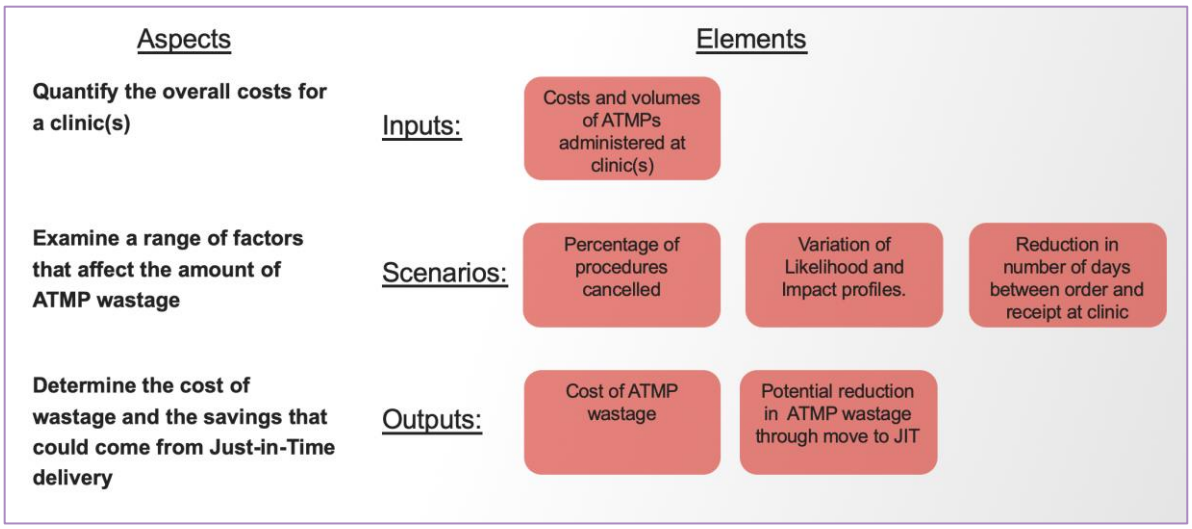

The model enables a range of inputs, factors and scenarios to be examined, which are:

- Therapy type
- Therapy name
- Source of cost information
- Cost per infusion
- Infusions per month/year
- Percentage of infusions cancelled
- Likelihood and impact of cancellation on ATMP viability
- Delivery time reduction (from order to receipt)
- Potential cost reduction through JIT delivery

The model does require further development and has been constructed so that this can continue beyond the close of the Runway project as more data and insight is gained.

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Model Walk Through

This section outlines the current state and functionality of the model.

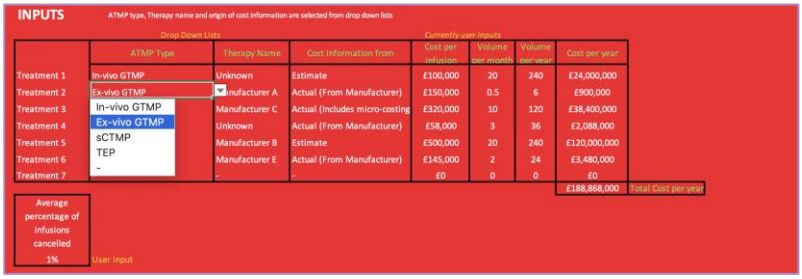
All inputs are entered on the front page, which also presents the outputs. Modifying scenarios, Drop down menus, scenario profiles and calculations can be accessed and modified through the relevant tabs.

Inputs

Due to the limited duration of the project and availability of data the model currently contains representative data and input labels to demonstrate its functionality. These can be modified and updated to make them specific to a particular clinic or grouping of clinics as required.

The following screenshots show the range of drop-down menus and user inputs.

Therapy type – the types shown here are consistent with those available within the MW ATTC Micro costing tool kit



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Therapy name

Source of the cost information – a variety of sources can be selected, including from the

Micro costing tool kit.
Cost, volumes administered per month/year and average percentage of infusions cancelled are direct user inputs.

Cancellation Likelihood and Impact Scenarios

Maintaining the viability of a therapy through the supply chain depends on a range of factors, which also affect its ability to be returned if required. For example, the challenges associated with a fresh product manufactured close to a clinic versus a cryogenically held product that requires international shipment to reach its destination have different constraints.

The reason for a procedure being cancelled is also likely to be varied, which could include unavailability of staff, infrastructure, or patient. As a result, the timing of when a procedure might be cancelled is likely to vary, with the greatest cancellation notice having the least impact on wastage. Whereas a cancellation within 24hrs of the procedure is likely to have the greatest impact.

These two factors combine to affect the ability to maintain a therapy's viability. The model considers these two independent factors which have been termed Impact and Likelihood.

The model allows different profiles to be created for impact and likelihood. Currently the model has a number of built-in scenarios to demonstration functionality. These scenarios are

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though only estimates and data is required to construct appropriate scenarios.

Outputs

The model calculates the cost of ATMP wastage based on the user inputs.

The user is able to review savings due to a reduction in the number of days between order receipt and arrival at clinic, through a drop-down menu.

No commentary of any findings from the use of the model is provided in this report as the data currently within the model is unrepresentative and has been used solely to check the functionality of the model. When good quality data is available, the outputs can be used to determine the scale of the savings that may be made through reduced delivery times. This information can be used to inform and support the value proposition of new or modified distribution models.

The model can also be used to understand the impact of innovations that could affect the impact and likelihood scenarios. For example, a new shipper technology could reduce the impact of wastage. Accounting for this by modifying the impact profile as appropriate would quantify the scale of any saving.

Although the model is primarily aimed at supporting decisions within the supply chain, it could also be used by clinics to understand the costs of cancellations and the opportunities to reduce this.

Further Development Work

The functionality of the model has been tested; however, there is further development work that is required to provide greater functionality. Shortfalls in model include:

- Model applies a uniform cancellation percentage across all treatment types due to lack of data.
- Model does not specifically consider different temperature hold requirements.
- Model currently does not consider different return times for different therapies. For example, transport times, which may be different due to therapies having to be returned to different locations, are not considered.

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Evolving distribution service models

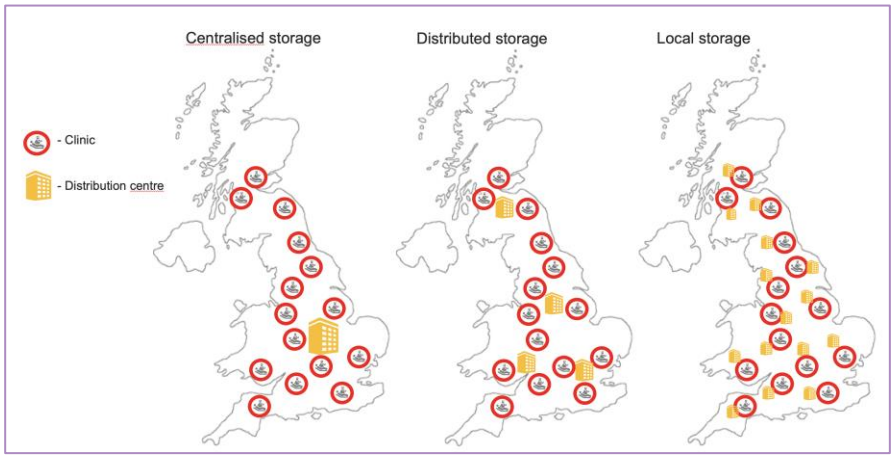
The ATMP industry is undergoing a huge expansion in the number of treatments required for future clinical and commercial supply. Global investment in ATMP development in 2019 totalled $9.8bn (Alliance for Regenerative Medicine Annual Report 2019) with manufacture of ~100m ATMP doses forecast by 2025 (Phacilitate Advanced Therapies Investment Report 2017). This rapidly expanding sector is predicted to be worth £10bn to the UK economy, supporting 18,000 high value jobs by 2035 (Cell and Gene Therapy Catapult Annual Review 2019/20).

The supply chain and associated distribution models need to develop and mature quickly to handle the predicted volumes without throttling the opportunities presented by ATMPs.

The industry has the opportunity to learn from other sectors to understand the characteristics and benefits of a highly developed and mature supply chain, whilst adapting them to the specific needs of the ATMP sector. For example, the use of distributed consolidation centres is often seen in highly responsive supply chains with short order to receipt times.

Digital based developments are key enablers for new commercially viable distribution models to be considered. Orchestration platforms such as that being developed by TrakCel, provide the ability to accurately forecast therapy demand, whilst real-time location and condition monitoring provide insight for all relevant parties, including those at the clinic awaiting delivery.

Currently the majority of therapy distribution is either direct from the manufacturer or from centralised locations.



The rapid growth in ATMP volumes means that the use of storage and distribution centres will grow significantly. However, to provide the greatest responsiveness and minimise the time between therapy request and availability on-site at a clinic ideally requires stock to either be held on-site or to be held as close to site as is practical in local storage. With the varied and complex nature of storing ATMPs, along with ownership and reimbursement considerations holding stock on-site clinics is not favoured. There is therefore a balance to be considered between the operational benefits

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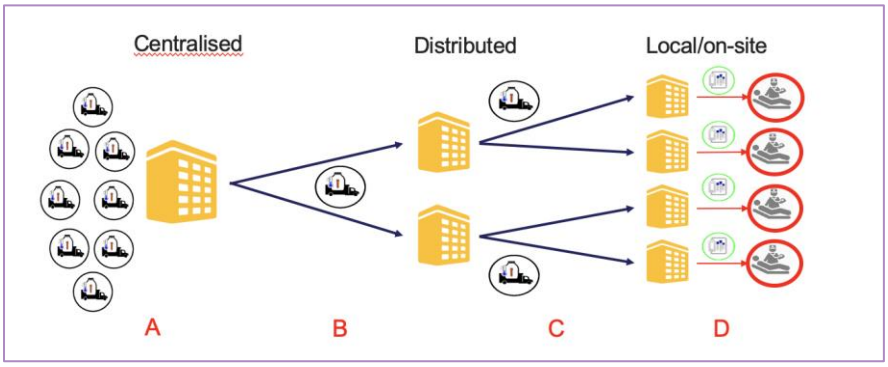
and costs of centralised versus local/on-site clinic storage or of a hybrid making use of intermediate distribution centres.
The optimum delivery solution for a clinic will be affected by a range of factors including, geographic location, therapy types, volumes and temperature control requirements.

This example shows how all three elements of storage and distribution could be combined to provide JIT delivery to clinics.



A) Large volumes of therapies from multiple manufacturers are held in a centralised medium to long-term storage facility.
B) Therapies and required kits transferred on an infrequent basis from central storage to a geographic consolidation centre for medium term storage based on predicted clinic requirements.
C) Therapies and patient specific kits made up and consolidated for delivery to local/on-site hold at clinic. Frequency and timing of deliveries optimized and standardized based on forward orders from clinic, such as through orchestration platforms.
D) Daily requests for ATMP product from clinic with rapid delivery.

The development of novel distribution models could lead to new ownership, responsibility and reimbursement models being created. Currently the dominant distribution model is “Direct”, where a manufacturer maintains ownership and ultimate responsibility of therapies until their receipt at clinic. The supply chain activities used to deliver the product being provided on a service basis to the manufacturer.

Creating and operating a delivery model such as that presented above could be “Distributor” led, possibly with ownership and responsibility passed on from a manufacturer to a distributor. This may allow the distributor greater flexibility in where therapies are stored to provide the fastest response to clinic requests delivery.

These examples are just some of the possibilities that should be considered as the ATMP supply chain matures. The development of any new distribution model is not trivial. Determining the viability, implications, benefits (such as cost savings identified by the model) and wider impacts

of any new distribution models requires significant further work drawing together the wide array of relevant stakeholders to explore, develop and pilot options. As such, this would be best delivered as part of future ATTC activities.

Continued Optimisation of the Supply Chain

The move towards JIT delivery to clinics does not solely rely on the development of new delivery service models. It requires the continued development and optimisation of the supply chain.

In this section Thermo Fisher Scientific have worked with our ATTC supply chain partners, Cytiva, TrakCel and World Courier, to briefly identify a number of new technologies or processes that could reduce therapy delivery times.

The list presented below is by no means exhaustive and is put forward to highlight the range of activities and, in particular, how sector wide developments could provide the greatest benefits. These sector wide areas reinforce the continued need for pre-competitive collaboration and stakeholder engagement, which the network of ATTC s has been so successful in developing.

Company Specific Developments:

- Automation of cryogenic picking and packing from storage
- Creation of distributed and local storage centres
- Placement of packaging through a dedicated hub over designated offices for the broader non-office served locations.
- Automation of scanned in and out inventory management & refurbishment status process
- Automated alerts outside of the standard touchpoints emails and reach to SMS etc.

Sector wide Developments:

- New shipper designs able to hold higher volumes of product with reduced overall dimensions and mass.
- New packaging designs that require reduced or no conditioning and incorporation into site specific processes.
- For cryogenic shipments the adoption of smart, LN2-free shipper technology
- Adoption of RFID identification of primary, secondary packaging and shippers
- Regulation change to allow multiple autologous therapies to be transported in the same shipping container

- New formulations of products ensuring stability at higher subzero temperatures or positive temperatures
- Facilitate the reception of therapies at clinical site and transfer to patient ensuring required pharmacy, QA and clinical oversight.
- Automated receipt of therapies at clinics that is not reliant on staff being present, allowing 24/7 drop off
- Eliminate final therapy preparation requirements at clinic.
- Build a transferable model to enable new sites to adopt ATMPs easily.
- Removal of duplicated paperwork efforts sites may have to complete for licenses
- Increase knowledge of ATMPs for government agencies such as Customs and Pharmacological authorities to facilitate and expedited clearance of shipments at borders.
- Standardisation of handling SOP's.
- Further review of the *Do Not X Ray* status requirements.

Conclusions

The project has examined three aspects to aid the quantification of the value proposition and further development of JIT delivery:

- Creation of a model to identify and examine potential cost savings JIT delivery to clinics
- Distribution service models that could enable JIT delivery.
- Future innovations that could support the supply chains move towards optimised JIT delivery.

Although this project has not been able to explore in as much detail as originally planned, it has provided a number of valuable outputs that can be used to further inform and accelerate the development of optimised and cost-effective JIT ATMP delivery. Along with realising the sector wide benefits of:

- Reduced inventory
- Better responsiveness
- Faster deliveries
- Reduced wastage
- Lower cost-of-goods

This work has shown the potential for JIT delivery and forms a strong foundation for continued work to develop, pilot and demonstrate benefits of JIT delivery models as part of a larger ATTC phase2 project. Without the continued support and availability of the ATTC network it is not clear how the required developments will proceed. If they do they are likely to be slower and fragmented as the current momentum and access to all relevant stakeholders is lost.

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