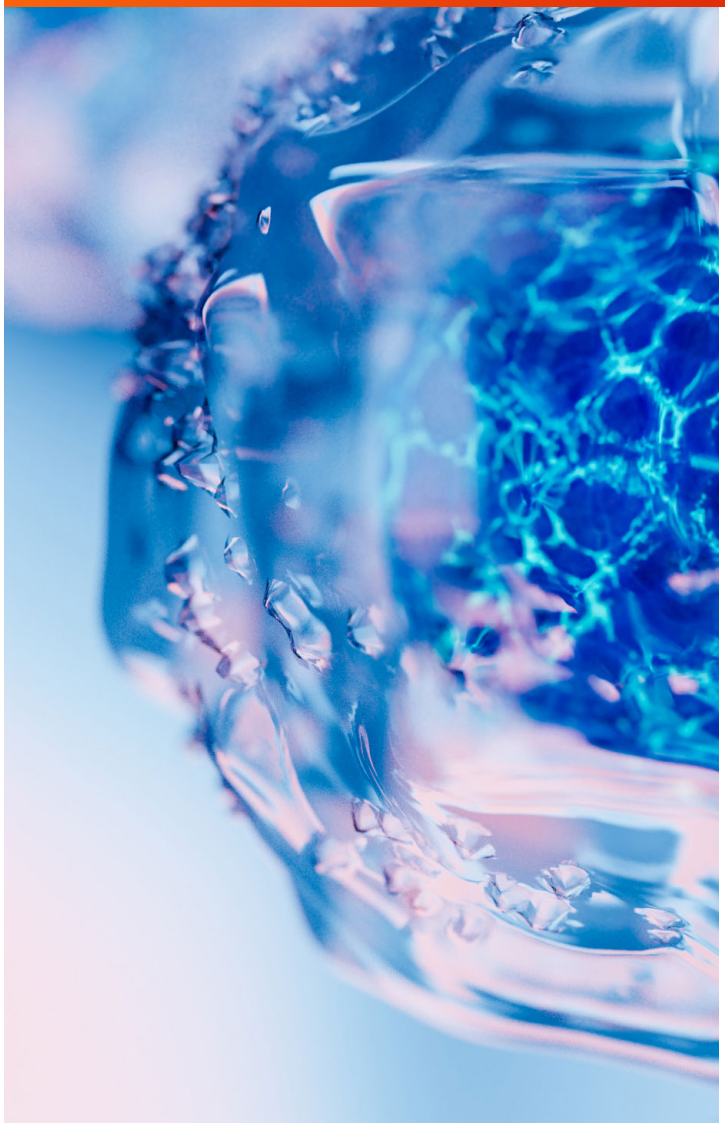
TrakCel

Whitepaper



ATMP supply chain product-centric and patient-centric review

Dr Matthew Lakelin PhD
VP Business Development & Scientific Affairs
TrakCel

This white paper examines the challenges of addressing patient-centric and product-centric needs for advanced therapy supply. The supply of three different advanced therapies are reviewed to highlight the challenges of delivering cell therapy drug products efficiently, compliantly and safely in a cost-effective manner.

Introduction

In 2017 InnovateUK set a challenge to industrial, academic and National Health Service groups in the UK; build consortia to prepare the UK's healthcare infrastructure for advanced therapy medicinal products (ATMP).

ATMPs are categorised as gene therapy medicinal product, a somatic cell therapy product or tissue engineered product; ATMPs are not standard pharmaceuticals and typically deviate from standard supply and management paradigms.

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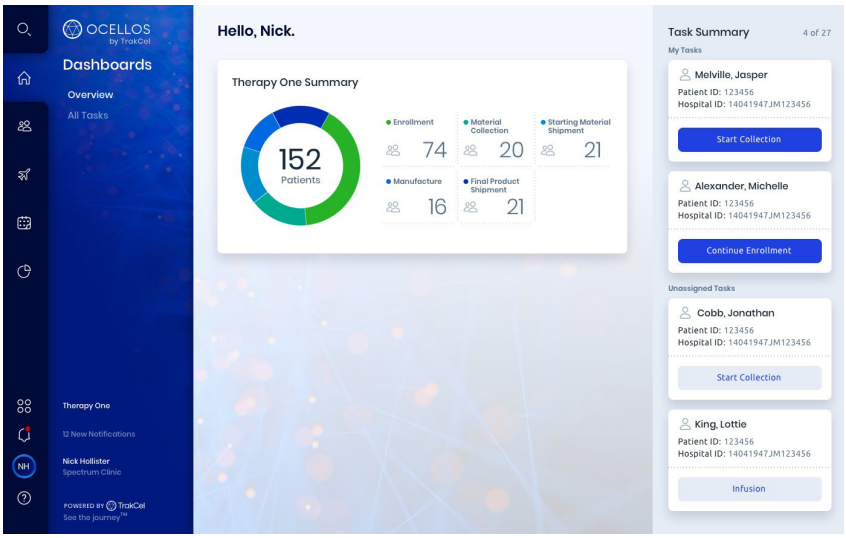
Table 1: A comparison of Small Molecule, Biologic and Cell Therapy product characteristics

	Small Molecule	Biologic	Cell Therapy
Raw Materials	Long shelf life, multiple suppliers available. Consistent and controllable specifications.	Long/Medium-term shelf life available. Consistent and controllable specifications.	Patient-specific agents, short shelf life. Patient-specific variability in starting materials.
Manufacturing	Large batch sizes possible. One batch can be manufactured for multiple countries.	Living entity to generate therapeutic agent. Large/medium batch sizes possible.	Potentially one patient one batch. Living treatment requiring specialist handling and manipulation. Potentially, just one opportunity to manufacture the product.
Analysis	Well defined chemical analysis available.	Well defined chemical and biological analysis available.	Functional assays in infancy, small batches limit samples available for testing. Conditional released of some products.
Distribution	Large batch sizes allow network of wholesalers to be used for international distribution.	Large batch sizes allow network of wholesalers to be used for international distribution.	Patient-specific distribution, products may have a shelf life measured in hours.
Treatment	Well defined treatment practices and dosing.	Well defined treatment practices and dosing.	Therapies may need specialist dispensing activities which may not be familiar to most pharmacies.

Table 1 outlines some of the challenges facing ATMP developers regarding availability of raw materials, manufacturing, analysis, drug distribution and administration of therapies.
It was recognised by InnovateUK that ATMPs products present a new challenge to healthcare in the UK, the advanced therapy treatment centres were set up to develop knowledge, pathways, processes and best practice for the administration of ATMPs.

The aims of the ATTCs:

- Increase patient access to ATMPs on a national level
- Establish best practice for the safe and effective delivery of ATMPs to patients
- Establish best practice for the manufacturing and final preparation of ATMPs using Good Manufacturing Practice (GMP) within a clinical setting
- Establish robust connected supply chains for the manufacture and delivery of ATMPs
- Create systems to allow traceability and tracking of ATMPs. These must be compatible wit current regulations and be suitable for applying across the NHS
- Establish best practice for patient follow up and data capture



TrakCel has been focusing its activities on developing connected supply chains and traceability and tracking solutions as part of its ATTC work.

TrakCel has reviewed the supply and administration of several ATMP products as part of its work with the ATTC network. This was a dual aspect review, examining the needs of the therapy at the clinical sites and the needs of the therapy manufacturers. Autologous (where patient-specific starting material is used to generate a treatment) and Allogeneic therapies were used as exemplars, thus, collection of starting material was also reviewed for the relevant products. Collection of several different types of starting material and different administration methods were reviewed to give a broad view of the types processes required to support ATMPs.

Allogeneic purified stromal cell isolated from human umbilical cord

This therapy is a universal allogeneic product and so no tissue/blood matching is required between the drug product and recipients of the drug product. Furthermore, the product is being assessed for efficacy in multiple indications providing a test of several logistics and administration routes (local and systemic) for the product. This presents an interesting challenge, whereas most ATMP products are developed for specific indications (or groups of illnesses like haematological malignancies), this ATMP is administered by several different clinical groups that need to appreciate the intricacies associated with administering the product.
The drug product is cryogenically stored (≤150°C, typically liquid nitrogen LN2 storage), most hospital pharmacies do not have access to cryogenic storage facilities, preventing most clinical sites from storing supplies of this ATMP and requiring vials of the drug substance to be shipped to order. However, one clinical site (Birmingham) has LN2 storage available, so separate dispatch protocols were required depending on whether local ATMP storage was available (storage collocated with treatment) or hub storage of the ATMP was necessary with the drug product shipped to clinical sites on demand. The dispatch protocols consider transit time and storage time limitations (10-14 days) of cryoshipping systems*.

**Footnote, Cryoshippers used for ATMPs are typically dry nitrogen shippers, these are dewars that have porous walls which adsorb and retain LN2. When prepared correctly the dry shipper does not contain any free liquid nitrogen, but the transported ATMP's temperature is retained at ≤150°C. Cryoshipper's typical validated shipping time can be 10-14 days, and so can be used for short-term storage at treatment sites where cryogenic storage is not available. Although dry shippers are useful for short term storage, the shipper needs to be collected once the therapy has been administered and procedures are required when therapy administration is delayed and the shipper is at risk of exceeding its validated shipping/storage time.*

The advantage of a universal allogeneic product is that the drug product administered does not need to be matched to recipients and can be used to treat any patient regardless of their HLA profile or tissue type. Nevertheless, traceability from donor to patient is required (EU Commission Directive 2006/17/EC) and there is a necessity to retain these records and possibly undertake a recall on a donor-specific basis.

The interesting nuance associated with this human umbilical cord-derived therapy is that the starting material is generated from pooled umbilical cord samples, thus requiring several donors to be associated with each batch produced and therefore increasing the (highly unlikely) probability of a product recall being triggered due to subsequent donor-related medical conditions.

Extending this clinical trial to other sites in the UK will need significant planning to accommodate the short shelf life of the starting material and drug product. The 'fresh in fresh out' (FIFO) nature of the product also adds pressure to the scheduling and execution of activities in the supply chain, the availability of manufacturing, drug administration and transportation assets must be guaranteed prior to collection of starting material.
Any delays associated with:

- Manufacturing the drug product
- Transporting starting material to manufacturing
- Transporting the drug product to the treatment centre
- Administering the therapy to the patient may lead to the drug product or starting materi al passing its expiry date. Most of these elements can be controlled, but should a patient not report for treatment or be too unwell to be administered the drug product then the whole manufacturing exercise will be in vain.

The FIFO nature of the product influences the release procedure of this product. Qualified Person (QP) release is undertaken in two phases. Phase one is based on review of batch documentation but final product release can only take place once sterility results have been reported. Typically, sterility test results are available one week after manufacturing has been completed, and also after the treatment has been administered to the patient, this is known as 'parametric release' and is commonplace for radiopharmaceutical products and is now used for some classifications of ATMPs.

REX-001 (Rexmyelocel-T)

REX-001 is a cell suspension of autologous bone marrow mononuclear cells composed of several mature cell types (lymphocytes, monocytes and endothelial cells), as well as progenitor cells for the treatment of chronic limb-threatening ischemia (CLTI) in patients with diabetes mellitus. The starting material for this therapy is obtained by bone marrow aspiration, like the MATCH product this is a fresh in fresh out (FIFO) treatment. Because of the FIFO nature, scheduling of all activities is critical for success. Once manufactured REX-001 is infused directly into the arteries below the knee by vascular surgeons or interventional radiologists. The therapy is designed to promote neovascularisation and immune modulation in patients to aid recovery from critical limb ischemia.

Unlike other autologous therapies where there may be an association between the collection of starting material and other standard of care treatments (bone marrow transplant), clinical staff who collect REX-001's starting material, bone marrow aspirate (haematologists), typically have little interaction with the clinical team that are managing the patient's condition (vascular and endocrinology departments). Thus, communication between collection and treatment departments for this FIFO product needs to be meticulously planned, to ensure, as detailed before that once starting material is obtained, manufacturing and drug substance administration can be undertaken within their required time constraints. This should be emphasised, bearing in mind that obtaining bone marrow aspirate can be an uncomfortable procedure for the patient.
Furthermore, obtaining an adequate amount of bone marrow aspirate can be challenging, presenting manufacturing groups with difficult decisions. Should a batch be manufactured when less than the optimal amount of bone marrow is obtained, or should the starting material be discarded after subjecting the patient to an unpleasant collection procedure?

Another idiosyncrasy associated with this treatment is that the screening procedure potentially requires patients to undertake a second round of serology tests, due to the time elapsed between patient screening and starting material collection. Serology analysis is required for human blood and tissue samples that are being processed, to protect and manage the risk associated with individuals handling potentially infectious tissues and blood products. Standard practice (EU Commission Directive 2006/17/EC) dictates that serology samples must be taken within 30 days of starting material collection. Should 30 days elapse from serological analysis to collection of starting material then another serology sample is required.

Summary

Even when using just three different therapy examples it is obvious that a single supply paradigm will not work for the current crop of ATMPs. Each therapy in this report has its own idiosyncrasies that need to be addressed by manufacturers and care teams to deliver these therapies safely. Over time it is expected that several standard supply patterns will be developed, e.g. standard TIL and CAR-T pathways will evolve. However, in the short-term each ATMP will have to be assessed and managed according to its unique characteristics. Nevertheless, ATMP products have been shown to have curative properties and demonstrating profound clinical responses from patients with few other treatment options. The immeasurable value to patients will motivate developers and clinicians to accommodate the needs of these therapies. The work of the Advanced Therapy Treatment Centres is providing guidance, support and leadership for the administration of ATMPs and further work will ensure widespread access to these novel therapies.

Parametric Release

Commission Directive 2006/17/EC