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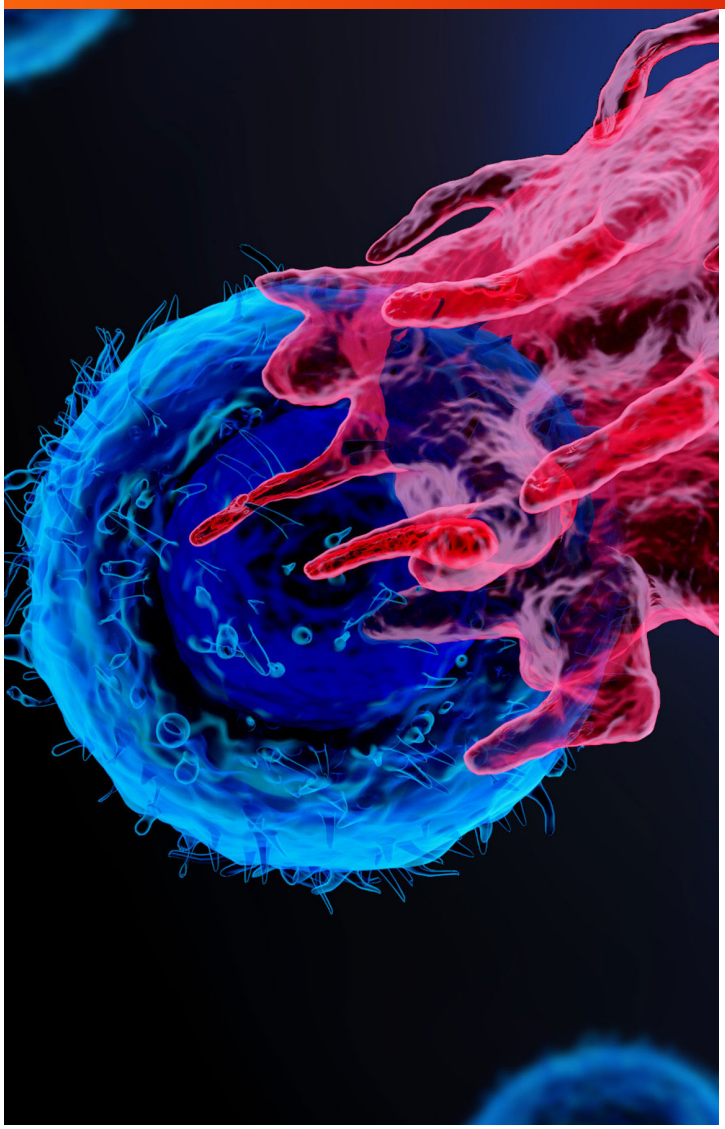
ATTC Advanced Therapy Treatment Centres | Northern Alliance Advanced Therapies Treatment Centre

Whitepaper



Exemplar Fresh in Fresh Out Autologous Process

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Autologous treatments are at the forefront of advanced therapies, the approval of Kymriah, and Yescarta demonstrates that autologous treatments with complex supply cycles can be commercialised.

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Introduction

The Northern Alliance Advanced Therapy Treatment Centre (NA-ATTC), formally established in March 2018, is a consortium of twenty industry, NHS and academic organisations led by Newcastle Hospitals and the Scottish National Blood Transfusion Service (SNBTS).

The purpose of the centre is to develop the systems and infrastructure required to support the delivery of cell and gene therapies with the ultimate aim of increasing patient access to advanced therapy medicinal products (ATMPs) on a national level.

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Exemplar Fresh in Fresh Out Autologous Process

TrakCel was established in 2012, all of the cell therapies that were encountered by the company for the first few years were primarily fresh-in-fresh out. That is, both the starting material and the drug product were not substantially preserved (e.g. cryopreservation) so that shelf lives of starting material post collection and of the drug product post manufacturing were relatively short, typically between 24-72 hours. The short shelf-life reflected proof of concept development work, the maturity of the cell therapy industry and also the manufacturing strategies employed when most manufacturing occurred close to the patient's location.

The 'fresh in fresh out' (FIFO) nature of cell therapy manufacturing strategy pressurises the supply chain. 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 in manufacturing the drug product, transporting starting material to manufacturing or transporting the drug product to the treatment centre and administering the therapy to the patient may lead to the drug product or starting material 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, cryopreserved drug products with longer shelf lives will permit a pause in the process providing that the drug product is thawed only when the patient is ready and able to receive the therapy.

FIFO products influence the release procedure where therapies are administered in the EU QP release is undertaken in two phases. Phase one is based on reviewing batch documentation and any available analysis, but final product release can only take place once sterility results have been reported, typically within one week after manufacturing has been completed and usually after the FIFO therapy has been administered. This is known as 'parametric release' and is commonplace for radiopharmaceutical products and is now used for some FIFO ATMPs.

General Considerations

Aristotle (and Mary Poppins) have been attributed to the quote 'Well begun is half done.' This is important for FIFO treatment where once starting material is obtained there is little opportunity to pause in the process or address delays due to the short shelf life. Thus, prior to collection of starting material all aspects of the supply cycle need to be addressed and confirmation is needed that all parts of the supply cycle can be undertaken at the correct time and all necessary raw materials and equipment are available to complete manufacture of the patient's therapy.

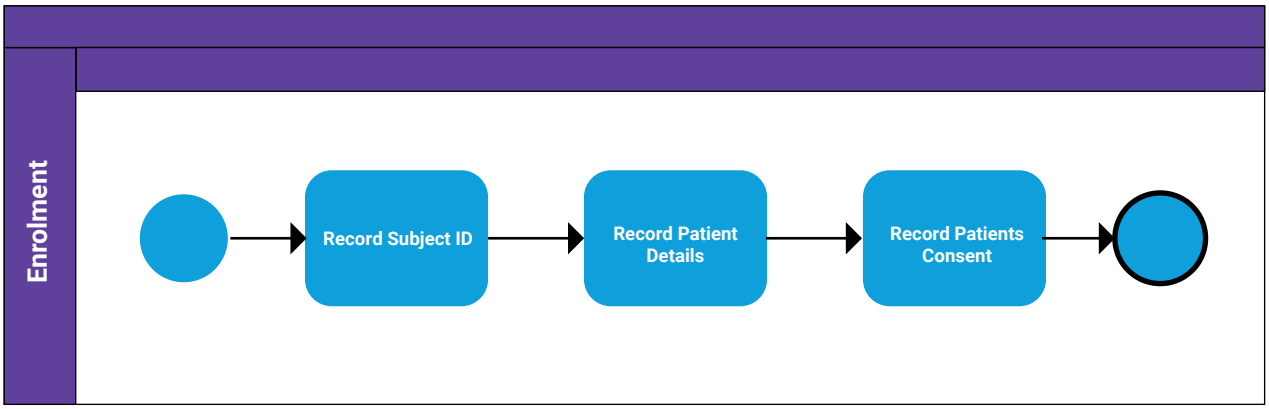
In most cases the patient will make themself available; receiving a beneficial treatment is all the motivation an individual requires to clear their diary. However, the patient must be made aware of the manufacturing process and the constraints associated with a FIFO process to ensure that they are punctual for starting material collection and drug administration, if all, or part of the process is undertaken on an outpatient basis. When scheduling collection of starting material, it is important to confirm that all other activities in the supply cycle can be undertaken and dictated by the manufacturing schedule, coordination is key.

Where transportation of drug product from manufacturing and transportation of starting material to manufacturing is required serval factors must be considered, the latency period from booking a collection to one being made, the time it takes to precondition and shipping systems and also weather conditions which might influence the ability for couriers to move consignments. Where possible weather forecasts should be reviewed for both logistics steps prior to collection of starting material, snow can cause widespread transportation problems, in some cases grounding all flights at airports for days at a time.

Enrolment:

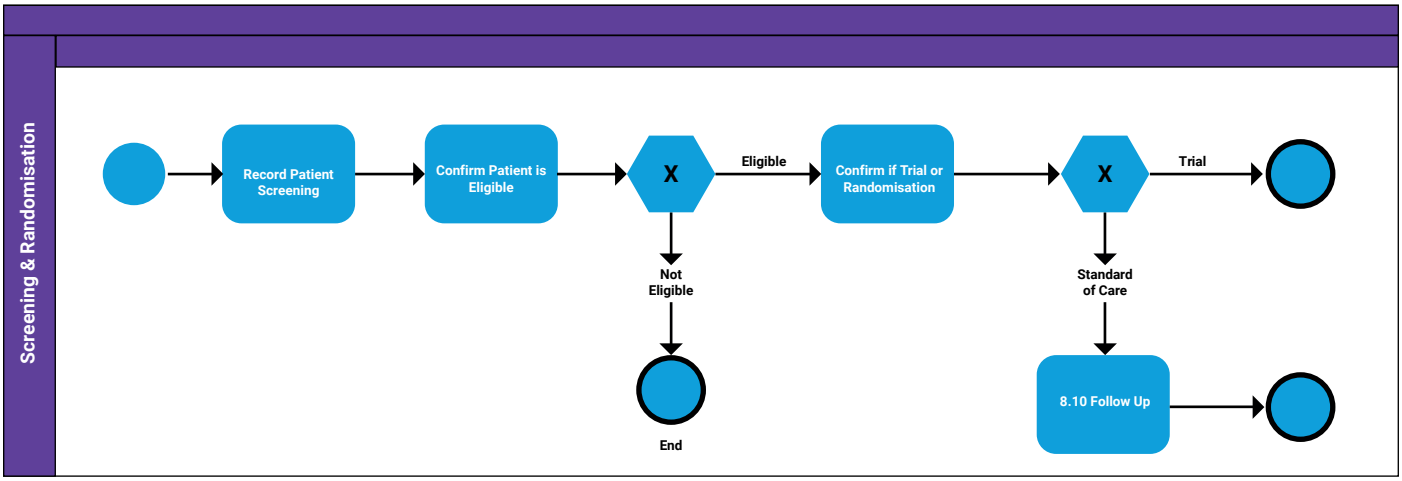
Where electronic systems are being used to manage patients and the supply chain consider what data needs to be shared outside of the hospital environment to permit traceability, try to use pseudonymised identifiers (identifiers that are easily attributed to the individual but do not directly identify the individual) for data that is exchanged outside of the hospital. Thus, when recording patient information, most data will be stored locally with perhaps only the pseudonymised identifier used by external systems.

It is important to verify that all subject identifiers are unique and attributable to the patient.

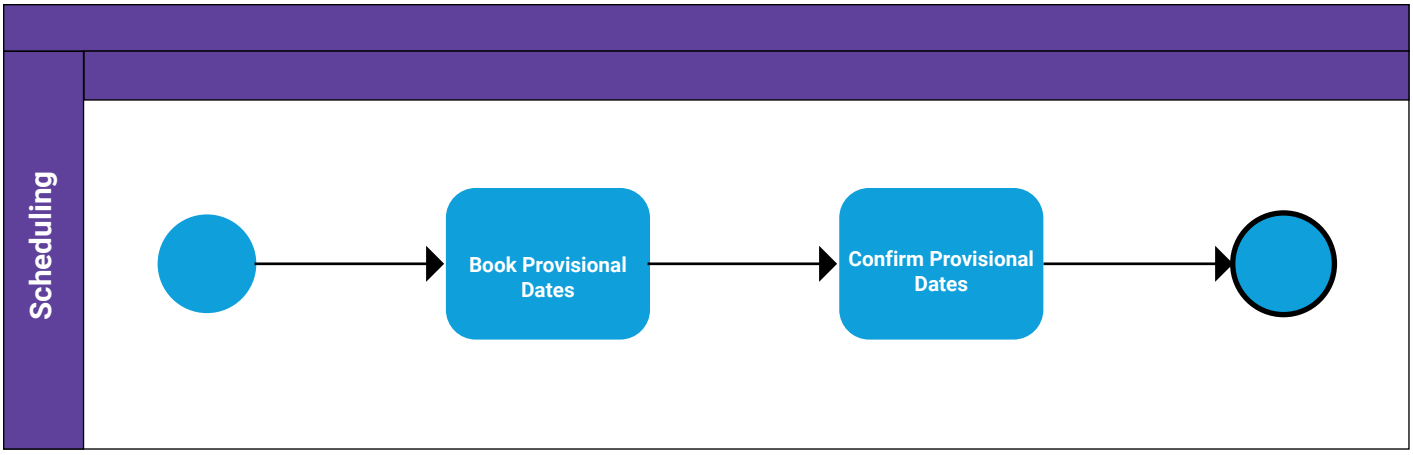


Screening and/or randomisation:

Details of the Patient's attendance at screening need to be documented; for clinical trial use, meeting the study's inclusion/exclusion criteria should be included. However, to manage traceability avoid recording details of these tests in orchestration software, simply record that these criteria have been met. If an Interactive Response Technology (IRT) system is being used to randomise patients onto different treatment arms of the study, the patient's study number should be used as the identifier and not their name. Typically, only patients who meet inclusion/exclusion criteria will proceed to receive the treatment. However, there may be opportunities to treat a patient on a compassionate basis if they do not meet the study's requirements.



It may be possible to administer the therapy to patients who do not meet inclusion/exclusion criteria on a named patient basis, (EC 726/2004) however, these treatments must not be reported as part of the clinical trial's results.

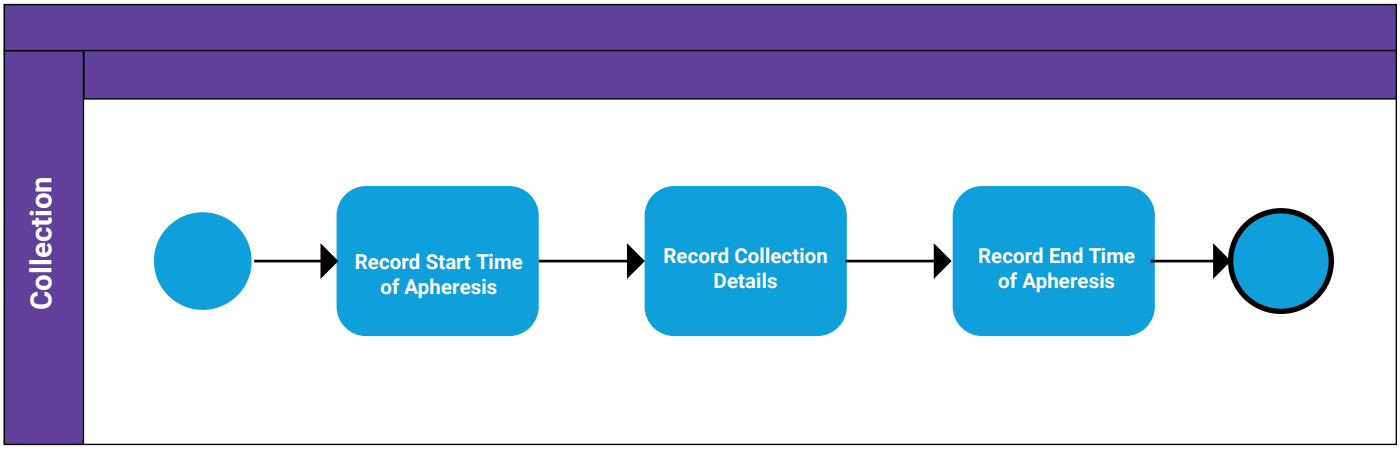


When distilled into its simplest form the scheduling diagram seems simple, book provisional dates and then confirm provisional dates. However, there are many factors to consider when scheduling a FIFO process. All constituents of the treatment and manufacturing cycle need to be sure that they can undertake their allotted tasks at the allotted time or else the patient's therapy may not be administered as planned or even at all.

Collection	Logistics	Manufacturing	Administration
Is the patient available on the required date?	Does the proposed collect date allow enough time for a courier to be booked to collect the starting material?	Does the proposed manufacturing date match up with clean room capacity?	Is the patient available on the required date?
Is there appropriately trained staff available to collect the starting material?	Is there appropriately trained staff available to collect the starting material consignment?	Will therapy-specific equipment be available for the manufacture of the product?	Is there appropriately trained staff available to administer the treatment? Is there a QP available to release the drug product?
Does the collection require any special equipment, will these be available?	Does the courier/transporter need specialist shipping systems, does the proposed date provide enough time to precondition shipping systems	Will all therapy-specific raw materials be available for the manufacture of the product?	Does the administration require any special equipment, will these be available?
	Have external factors been considered such as weather and customs clearance times when calculating shipping times.		For CAR-T and other treatments with the opportunity for serios adverse events, are there ICU beds available?

Once the schedule has been agreed for a patient's treatment cycle it is recommended that all groups associated with the treatment cycle provide evidence of their approval, if an orchestration system is being used this can be executed using electronic signatures from authorized individuals.

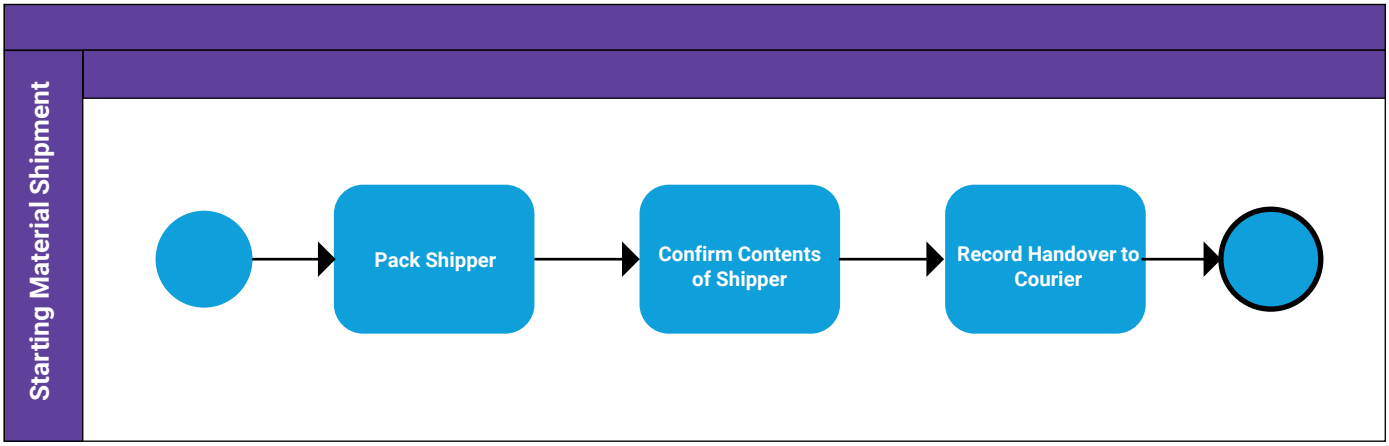
Collection of starting material:



Before collection of starting material, it is worth considering if there were any risk areas identified when the schedule was agreed. For example, if there was a risk of inclement weather affecting logistics steps or low stock levels of critical raw materials then the therapy owner/trial sponsor may wish to implement one additional check with supply cycle partners before starting material is obtained.

Typically, collection of starting material will be specific for the therapy type e.g. blood centre for apheresis material. Collection may follow the collection centre's own standard procedures or allow for a treatment-specific collection SOP to be followed. Recording data in other systems may be necessary for the purpose of traceability (associating the patient's treatment ID with the starting material's collection ID)and provision of data to manufacturing units. Where collection can take hours, the start time and completion time of collection is recorded, and there must be provision made for the possibility of several separate units of starting material collected. This may be because a second blood bag is required due to a blocked line during apheresis or multiple samples being available for tumour starting material. For blood products this is managed with split numbers and for tumour material is important to record from which tumour the samples are obtained, and the number of samples taken from each tumour location.

Starting material shipment:

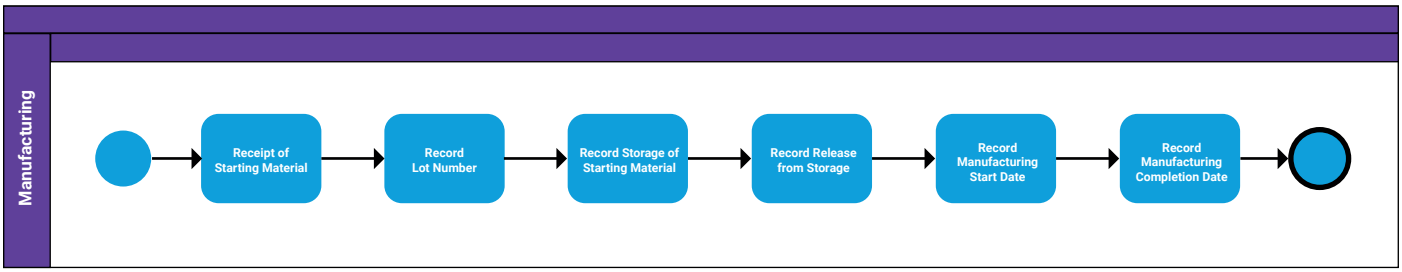


Whether the starting material is carried down a corridor for further processing or if it is handed to a courier for international transportation, certain principles must be observed. The Chain of custody must be documented, so when custody of the starting material or drug product changes a record of this change is made. The use of temperature control shipping systems is also recommended even for short journeys, the shipping equipment used must also meet biohazard regulations due to the nature of starting material. It is also advisable to monitor the temperature of the starting material during shipment. When arranging collection of starting material, it is important that explicit instructions are given, typically hospitals have labyrinthine designs and these instructions will aid couriers unfamiliar with the layout to collect the starting material. Furthermore, where possible avoid associating collection centre employee's names with collection of starting material, in practice it is better to use a job role title, because staff rosters can be unpredictable.

When using a courier and an electronic orchestration system, it is advisable to administratively associate the waybill number (a unique alphanumeric identitifier) with the starting material identifier. So that at the point of dispatch it can be verified that the correct starting material has been placed into the correct shipping system. It is recommended to use a tamper evident seal for the shipping system; time is of the essence for FIFO processes and starting material should be transferred to the manufacturer with haste.

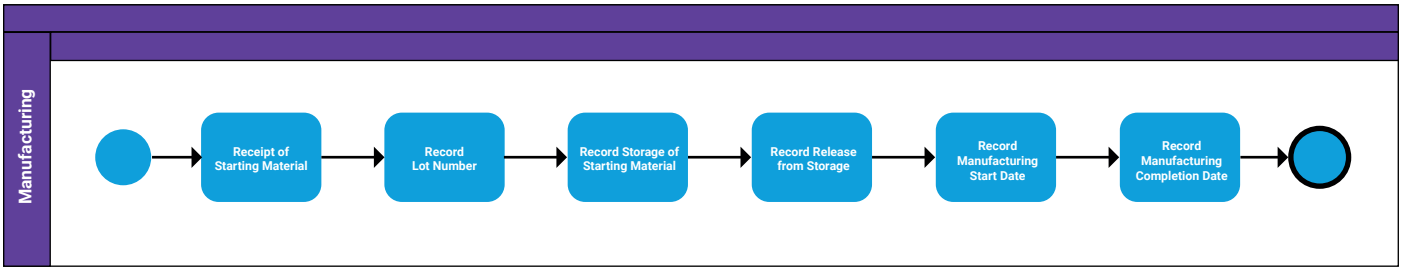
Manufacturing:

For FIFO processes manufacturing equipment and clean rooms may be prepared in advance of the starting material arriving to optimise the supply cycle. Typically, this may begin once it has been confirmed that the patient has arrived at the collection centre or the starting material has been dispatched depending on the transit time associated with the starting material. Receipt of starting material must be recorded to demonstrate its change in custody. Following receipt, the unique patient identifier, the starting material's collection identifier, and the lot number should be associated to ensure chain of identity fidelity. If the starting material is to be stored prior to manufacture the location, time into, and out of storage should be recorded cross referencing with any temperature records of the storage area.



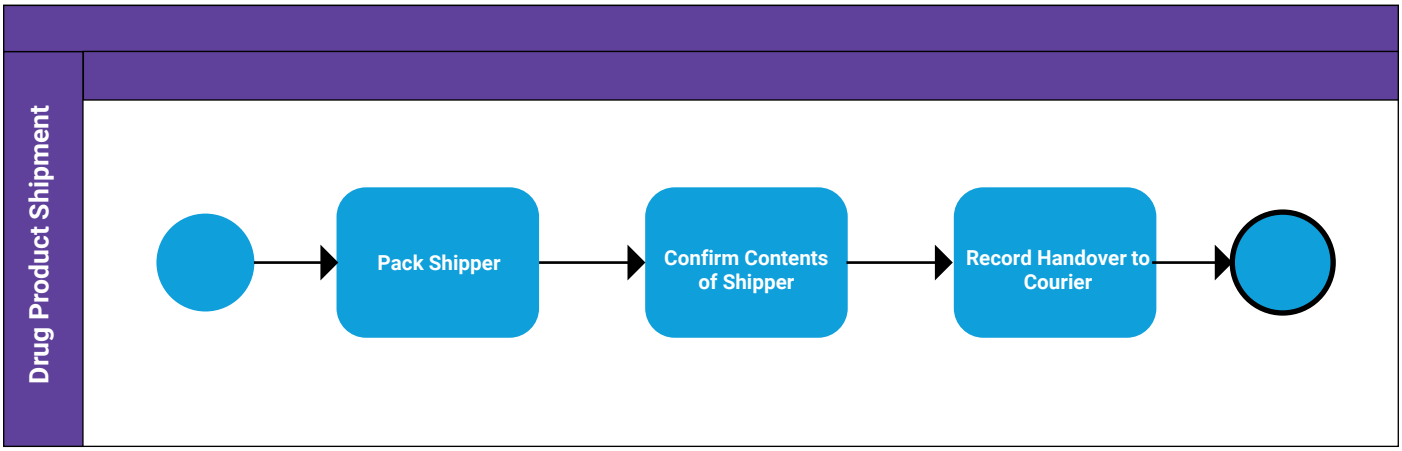
For FIFO processes it is worth considering notifying the group that will administer the treatment when key milestones are met during manufacturing, keeping them informed of the progress of manufacturing. Most treating physicians are reluctant to begin precondition patients for cell therapy administration until the drug product has arrived at their hospital, this may be problematic for FIFO therapies.

Product Release



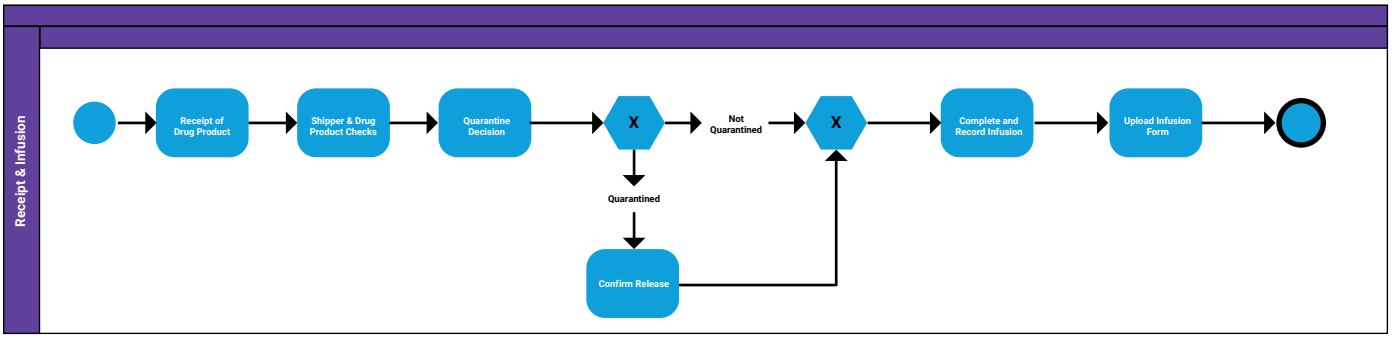
During manufacturing of FIFO products real time review of batch records and any deviations will expedite product release. The release procedure may be in two phases with final release of the drug product not occurring until after administration of the drug product, this is an acceptable practice for FIFO products (ENTR/6270/00 Parametric Release). Typically, a QP certificate for EU-based products will be provided in two stages, stage one once the first set of analytical results have been reviewed and approved and secondly after sterility results have been obtained.

Drug Product Shipment



Temperature control and monitoring is more important for efferent logistics than afferent logistics. The effect of temperature excursions on starting material can be detected during in-process and release testing analysis during manufacturing. However, the effect of temperature excursions on the quality of the drug product may be difficult to detect prior to drug administration. Close attention should be given to the shipping system selected for the drug product, the ambient temperature during the drug product's transit may affect temperature control, some temperature-controlled shippers have summer and winter configurations. Using a temperature monitor which provides an obvious indication of a temperature excursion is advised to ensure that the group receiving the shipment can identify if an excursion has occurred and can seek further information. The change in custody should be documented when the drug product is handed to its courier.

Receipt and Administration



Receipt of the drug product must be recorded, including results of a visual check of the transport container, if a security tag has been used the number must be recorded and cross referenced with dispatch information. The waybill number can be used as an identifier upon point of receipt providing it has previously been associated with the drug product lot number. However, prior to administration the drug product lot number is the primary identifier used to cross reference with the patient identifier to ensure the correct product is administered to the correct patient. These verification steps need to be undertaken quickly because if the transit time for the drug product is several hours then the drug product may be reaching the limit of its shelf life. Typically, all of the drug product is administered to patients for FIFO products. However, it is advised that reconciliation and destruction procedures be in place should some of the drug product remain after administration.

Discussion

FIFO cell therapy products are difficult to manage due to there being no opportunity to pause the manufacturing and treatment cycle once starting material has been obtained. However, FIFO products were the first to be developed and to demonstrate the curative nature of cell therapies. Most developers have moved on from the FIFO model and have introduced a cryopreservation step into their process to provide flexibility and accommodate unforeseen delays. Indeed, some developers have introduced two cryopreservation sets into their processes, one after starting material collection which reduce the time pressures associated with shipping starting material to manufacturing sites and one after manufacturing is complete. Nevertheless, when correctly controlled FIFO therapies can provide safe treatments to patients.

(EC 726/2004) Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-4/pdfs-en/v4an17_en.pdf

About TrakCel

TrakCel is the market leading developer of integrated technologies specifically created in 2012 to manage the international autologous and allogeneic cell, gene and immunotherapy supply chain. TrakCel's platform has been developed in collaboration with, and increasingly adopted by leading companies in the cell, gene and immunotherapy industries.

TrakCel's software delivers real-time control over the entire therapeutic supply chain, from sample collection through manufacturing to treatment delivery. The TrakCel platform accelerates global scale-up and scale-out of cell and gene therapy products, increasing efficiency and decreasing complexity, while maintaining treatment collection to administration compliance and traceability.

About Northern Alliance Advanced Therapy Treatment Centres

The ATTC network is a world-first, national system of Advanced Therapy Treatment Centres operating within the NHS framework and coordinated by the Cell and Gene Therapy Catapult to address the unique and complex challenges of bringing pioneering ATMPs to patients.

The centres include:

- Innovate Manchester Advanced Therapy Centre Hub (iMATCH)
- Midlands-Wales Advanced Therapy Treatment Centre (MW-ATTC, comprising Birmingham, Bristol, Cardiff, Leicester, Nottingham and Swansea)
- Northern Alliance Advanced Therapies Treatment Centre (NA-ATTC, comprising Edinburgh Glasgow, Leeds and Newcastle)

The CGT Catapult is playing a central coordination role for the network and provide support to manufacturing, supply chain logistics, regulatory affairs, clinical trial capability, R&D support and upskilling via specialist training and development.

Coordinated by CATAPULT Cell and Gene Therapy

The network is initially supported by the UK Research and Innovation's Industrial Strategy Challenge Fund.