TrakCel

Whitepaper

Maintaining an Efficient and Safe Cell Therapy Supply Chain

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Over forty cell therapy products are commercially available and over five hundred are undergoing assessment in clinical trials[1].

Unlike traditional pharmaceutical products, which have linear supply chains, autologous therapies have circular supply chains where the first step is to obtain cellular starting material from the pateint[2].

Should an error occur in an autologous therapy supply chain, resulting in a patient receiving a therapy manufactured from another individual's cellular starting material, there is a significant risk of graft versus host disease (GvHD) and other unwanted responses[3].

Supply chain complexity is exacerbated when considering the time and temperature sensitive nature of these products.

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Furthermore, some autologous cell therapies require invasive procedures to obtain cellular starting material[4], thus supply chain errors could result in patients having to repeat these uncomfortable procedures.

Regulations

The manufacture of allogeneic products does not require harvesting of tissue/cells for processing from the therapy's recipient, however, regulations state that it must be possible to trace the therapy to the original donor of the cellular starting material[5]. Allogeneic therapies present their own challenges for scale up; take a DMSO cryopreserved product as an example, scaling up to larger batches will increase the time between addition of DMSO to the cells and completion of fill finish and subsequent chilling to sub-zero storage temperatures. Although a tried and trusted cyropreservative, the deleterious effects of DMSO when exposed to cells at room temperature[6] are documented and prolonged exposure due to scale-up led process modifications may affect cell viability.

Scale up and Scale Out

Typically, manufacturing of cell therapy products is labour-intensive, requires continuous communication between treatment centres and manufacturers to coordinate manufacturing and treatment; products tend to be separated so that only one patient's therapy is contained within a clean-room to prevent cross contamination.

To efficiently scale up and scale out cell therapy products, clear strategies need to be developed for scheduling management, logistics management, product stability and closed systems manufacturing. To commercialise Provenge an autologous treatment for prostate cancer Dendreon had to develop an IT system (Intellivenge) to assist with coordinating treatments and logistics management[7]. Once a prescription of Provenge is made Intellivenge examines manufacturing assets to identify the next available manufacturing slot and schedules a manufacturing exercise for the patient's therapy. It then schedules collection of cellular starting material at an apheresis centre close the patient's home as well as arranging the transportation of cellular starting material to and the final therapy from Dendreon's manufacturing facility.

Not all cell therapy developers will have the luxury of stabilising cellular starting material and the final therapy by cryogenic preservation, however, any opportunity to increase a product's, or an intermediate's shelf life, should be examined during the early stages of development to improve the product's chance of obtaining a Marketing Authorisation and also to reduce the unit cost of manufacture. There are clear guidelines available on the requirements and testing required in order for a cell therapy to gain approval[8].

Flexible Manufacturing Strategy

A therapy with a limited shelf life will either require localised manufacturing assets or the movement of patients over long distances to collocated treatment and manufacturing centres. There are some therapies currently undergoing clinical assessment when stability data allows transatlantic transportation of cellular starting material from EU treatment centres; in these cases the study sponsors avoided the need to build EU manufacturing

> some treatment centres may be reluctant to thaw samples prior to treatment

assets or outsource manufacture to European CMOs, driving down the cost of generating clinical data in the EU. Although this strategy may not be wise for commercialisation it does demonstrate that increased stability data can permit a more flexible manufacturing strategy. Furthermore, a patient missing a treatment appointment may not require the manufacture of a new batch if a new treatment date can be scheduled within the product's shelf life. A simplified view is that the longer an autologous therapy's shelf life, the fewer manufacturing assets will be required for meeting post-approval market demand.

For cryopreserved products there is a conundrum for the manufacturer; ship a cryopreserved product to treatment centres or thaw the product and then dispatch. Some treatment centres may be reluctant to thaw samples prior to treatment and in some cases may not have the capability. However, thawing at the site of manufacture may require supplementary analytical steps in addition to the original lot release but will negate the need for shipping in dry nitrogen shippers.

Both strategies have their advantages and their pitfalls and full final user engagement is required when developing a strategy. Pluristem Therapeutics Inc. developed a thawing device[9] to enable uniform thawing of its PLX cell product at the point of care. However, Fibrocell Technologies Inc. preferred to thaw, wash, formulate and then ship Azficel-T[10] at 2-8°C to prescribing physicians due to concerns that the treatment centres may not be willing to undertake these steps.

> one company was prepared to charter aeroplanes to guarantee patients' treatments

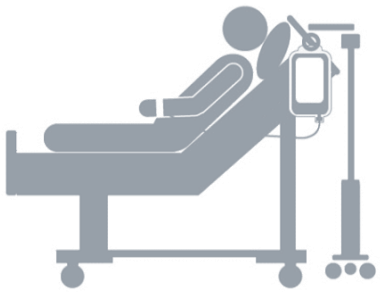
Scheduling management is a key consideration for maintaining an efficient supply chain during scale up. Depending on the manufacturing process, after standardisation, some flexibility in the proposed duration of manufacture may be required to allow for patient-specific cellular dynamics. An active scheduling system should be considered so that at the point of treatment approval the treatment centres and manufacturing asset's resources can be assessed so that cellular starting material will not arrive for processing when manufacturing slots or resources are unavailable. The scheduling system must also be able to respond to unforeseen changes, delays and then automatically notify all the parties involved. It is worth considering linking inventory control with scheduling management to ensure that stocks of raw materials are available to meet demand.

Logistics management

A robust transport procedure needs to be in place, allowing cell therapies to be delivered efficiently to treatment centres for clinical programmes and post-approval.

The World Health Organisation outlines that every activity in the distribution of pharmaceutical products should be carried out according to the principles of GMP, good storage practice (GSP) and good distribution practice (GDP) as applicable[11].

Anecdotal evidence suggests that one company was prepared to charter aeroplanes to guarantee patients' treatments, although a redoubtable sentiment, such shipping strategies will erode product profitability. Risk-based management needs to be employed to identify shipping strategies, tools such as Failure Modes Effects Analysis should be employed to identify weak points in logistical systems and mitigation plans should be developed which may need revising as product demand increases.



The most efficient method for moving temperature sensitive products is to use validated shipping systems; robust validation negates the need to monitor all shipments. However, it is questionable if this approach will work for all aspects of the supply chain. Complications arising from a temperature excursion of a cellular starting material shipment to a manufacturing facility may be identified by the facility's own QC analysis but treatment centres may not have the facilities to analyse incoming shipments and this should be considered when assessing logistics options.

For the movement of susceptible products, using temperature monitors in shipments is the most effective way to monitor the product in transit and to record the product's temperature during shipment. However, even with robust mitigation strategies, temperature excursions do occur; using conventional temperature monitors the recipient will only discover a temperature excursion once the shipment has been received. Temperature monitors are available that can supply real time data and issue warnings should shipping temperatures exceed pre-set parameters., To effectively use real time data, strategies need to be formed for addressing temperature warnings during shipments.

To effectively use real-time data the following needs to be considered:

- If access to the shipment is possible, how will the current custodian be notified should a temperature warning be issued?
- What can be done, or what equipment is required to return the shipment to the desired temperature at each step of the journey?
- What resources are required to continuously monitor the shipment?

> batch recording will need to be assessed and new strategies developed

Employing such strategies is difficult and resource intensive but may be the only way to protect patients from having to be subjected to additional invasive procedures following temperature excursions.

Release Testing and Manufacturing Batch Records

As scale up and scale out progresses, release testing and batch recording will need to be assessed and new strategies developed. Some autologous treatments which are currently undergoing clinical assessment have the potential to treat many thousands of patients per annum in North America alone[12]. Technically, each treatment will be a separate batch requiring its own record of manufacture[5]; paper-based batch records will not be suitable for such a high number of recorded treatments.

Considering that harvesting cellular starting material and movement of cells between treatment centres and manufacturing sites will have to be recorded to produce a full custody record as part of the batch document, it seems unlikely that using paper-based document control will be an option. Integrating automated data capture at treatment centres, logistics providers and manufacturers in a regulatory compliant manner will not be simple. Such a system, however, will drive down the unit cost of a cell therapy significantly, reducing the resources expended to document the manufacture of each batch. Batch release can be a resource hungry beast for autologous therapies and as patient populations increase reviewing each set of batch records will strain even the most efficient of quality departments. Consideration should be given towards batch approval, which follows a release-by exception strategy. Using automated data capture during manufacture, attention should only be directed to events that are observed outside specified limits for the process [13].

All batches manufactured that meet these specified limits required limited quality-assurance review.

Validating release by exception is a complex and challenging process but has a long-term payoff when batch volumes increase to justify the expense and the complexity. ■

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