Successfully managing the unique demands of cell therapy supply chains

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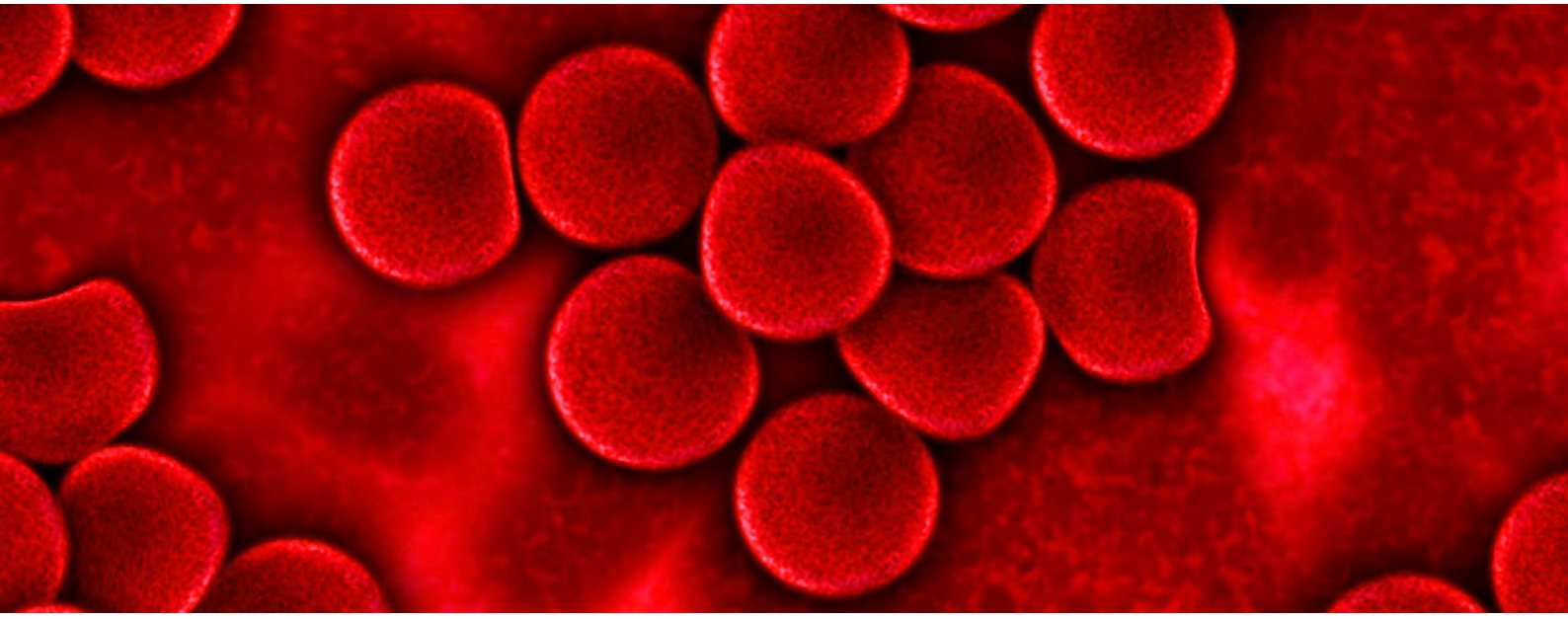

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Cell therapy professionals joined a specialist webinar by industry experts from PCI Clinical Services and TrakCel, addressing the unique complexity of an autologous therapy supply chain. Hosted by European Pharmaceutical Manufacturer magazine, the webinar was delivered by Rachel Griffiths, Associate Director, Technical Services, PCI Clinical Services, and Dr. Matthew Lakelin, Vice President, Scientific Affairs and Business Development, TrakCel . Here, we present the white paper from that webinar event.

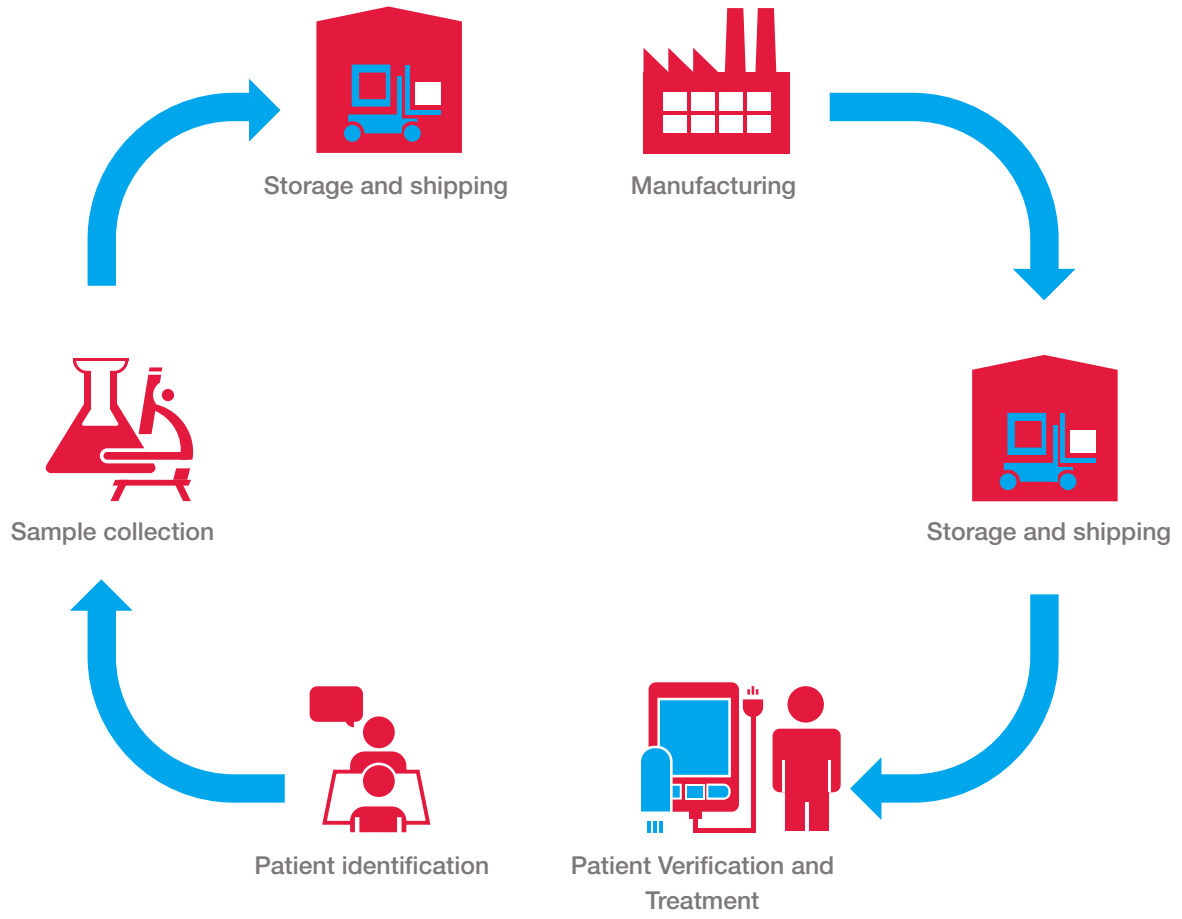
The industry

The cell therapy industry is advancing at significant pace with these novel therapies providing curative treatments to patients who previously had little hope of survival. The complexity associated with manufacturing a 'living drug' should not be underestimated and it is important to consider that although some general principles can be applied to cell therapies, each product will have its own specific challenges and complexities for managing its generation, manufacture and delivery.

There is a panoply of technical and scientific challenges associated with cell therapies but the patient's wellbeing should always be at the centre of the decision-making process throughout the product's development lifecycle. However, such is the technical complexity of the treatment process that the supply chain and manufacturing model may encounter risks which need to be addressed and actively managed to ensure consistent quality of product and safe treatment of patients.

To manage these risks, a robust understanding of the full cell therapy process and the consequences of out-of-scope activities is required. Identifying these consequences is not something which should be done in isolation; a multidisciplinary approach is required, involving all stakeholders – treating physicians, manufacturing experts and developmental scientists. Together these risks can be quantified and adequate mitigation steps developed to successfully manage the complex supply of these cell therapy products that may be difficult to manufacture and manage, but are so key to patient outcomes.

While cell therapy is playing an increasingly important role in the treatment of a variety of conditions, the real challenge in



In the flow diagram (above), the starting point is patient identification which will lead through to sample collection. From there, material can go into storage or be shipped directly to the manufacturing site. Following manufacture, the treatment then goes back into storage and will finally be returned back to the patient where it must be verified prior to the start of treatment.

delivering it successfully is not necessarily in the manufacturing protocol alone, but in the administration and co-ordination of the complex supply chain as a whole. Therefore supply chain risk management (SCRM) becomes an essential part of the process. Risks associated with production and transportation need to be assessed in advance and formulated into a robust risk assessment strategy.

The efficient management (see image above) of both the incoming apheresis units and the final product is imperative due to their short shelf-life. An effective risk strategy needs to be employed to manage the chain from collection of cells through production to a final product and back to the patient.

A thorough and robust risk assessment can influence the approach in managing the cell therapy supply chain and help to identify which factors in that chain might in turn influence manufacturing decisions. Factors to be taken into account might include, for example, the decision as to whether to have centralised or localised manufacturing strategies; whether the planned supply chain is logistically feasible; any import and export requirements; and of course time scales.

There are a number of considerations for effective supply chain risk assessment, based around different product characteristics and how they might affect the analysis of risk:

> **Sensitivity of the product** - the starting material, manufacturing intermediates, and final therapy, as well as the sensitivity to time, temperature and influences such as vibration.
> **Complexity of the manufacturing process** - whether the process is convergent or divergent, and where raw materials are coming from and their availability. Manufacturing assets will need to be examined and their availability identified before starting material collection, and a decision taken on the challenge posed by simultaneously manufacturing multiple therapeutic products.
> **Patient location** - where patients are located and whether local or global systems for control are in place. For autologous products, consider whether the sites of donation and treatment are separate, and what the physical distance is between treatment centres and manufacturing sites.

Building a risk map means looking at different types of process steps and analysing the risks associated with them.

The key process steps of:

- obtaining starting materials
- logistics
- manufacturing
- product release
- therapy logistics
- treatment

need to be set against the risks associated with:

- patient identification
- sample identification
- time excursion
- resource allocation

Case Study

As an example, consider an autologous material that requires one collection of starting material resulting in one manufactured batch returning back to the patient. The material is to be shipped between 2-8°C and has a short shelf-life of approximately six days from sample collection to point of entering into manufacture. Treatment centres are located in the EU, but manufacture will be in the USA. Once the treatment is manufactured it will be returned to the patient at -20°C under dry ice. At this stage the product has a medium-term shelf life of up to four weeks.

The risks associated with each key process step would be:

Obtaining starting material

For high through-put autologous therapies, **patient identification** can be high risk. Patient identifiers such as name and date of birth may not be sufficient. Methods used need to be complex enough to prevent errors, but simple enough to be used at multiple sites.

Sample identification requires the linking of analytical samples and starting material to patients. It is of paramount importance and potentially an area of high risk in the supply chain. The manufacturers may want their unique batch number affixed to the starting material at the point of collection to aid identification.

If outbound movement of the starting materials is the responsibility of the logistics provider then the risk of temperature excursions could be considered low at this stage.

Time excursion can be considered to be of medium risk, but the handover from the collection group to the logistics provider needs to be managed to prevent the risk of time excursions.

Resource allocation can be a high risk activity. All constituents of the supply chain must be able to demonstrate available assets and resources for processing patient material prior to the scheduling of the start of material collection.

✚ **Mitigation:** To manage these risks, robust recording and documentation methods need to be evident to manage patient

records at multiple sites allowing full traceability of starting material collection. Prior to this, all constituents of the supply chain must be able to demonstrate available assets and resources for processing patient material. This is a critical step for products which must be engrafted shortly after manufacture.

It is important that collection methods are standardised so that the variability between starting materials is influenced only by the biology of each donor and not by the way in which the product was handled during collection.

Starting material logistics

Patient identification is not critical at this stage however sample identification is vital, and must be identifiable back to the patient – and for any shipping and customs paperwork required during transportation.

Temperature excursion is critical and it is absolutely essential that the required shipping temperature is maintained throughout transportation. As a general rule, the colder the required shipping temperature, the easier it is to maintain.

Time excursion is also high risk for not only does the sample have to travel from Europe to the United States, it also has to clear customs. Pre-planning the route with the courier is essential.

For time- and temperature-sensitive materials, every part of the logistics supply chain must be in place and ready exactly when required. **Resource allocation** therefore has to be efficient and well thought through.

✚ **Mitigation:** The use of qualified preconditioned shipping systems delivered by the courier is advisable for the collection of starting materials, since starting material collection centres may not be equipped for the preparation of shipping systems or have adequate storage space.

Pre-planning of the shipping route is an essential element of the risk plan. Factors such as flight times can influence the time of sample collection. Customs paperwork can be pre-agreed and contingency plans need to be in place for unforeseen transport delays. Manufacturers should also be alerted to the fact that the sample is en route.

Manufacturing

Since there is no patient treatment involved in the manufacturing stage, patient identification is low risk. But if a sample is lost or damaged during shipment, the patient must be informed under HTA rules – or if there is a pre-treatment regimen that needs to be followed and is linked to the progress of a therapy's manufacturing cycle.

Sample identification is a critical strategy through all steps of an autologous supply chain and may become more complex during manufacture with multiple work in progress and with in-process samples to manage.

In a GMP environment, management of **temperature excursions** should mean this becomes medium risk. Similarly **time excursions** are also medium risk however robust workflow management may be required to prevent spikes of activity introducing additional risks.

Finally **resource allocation** is critical to ensure that all required assets are available for manufacture.

Mitigation: Manufacturing methods should be standardised in order to ensure that variability between batches is only influenced by the biology of the starting material and not by the way in which the product is handled during manufacture.

The chain of identity management becomes a great challenge when managing multiple products from multiple patients so close harmonisation with starting material collection can help to minimise the risk involved.

The impact of delays in manufacturing can be mitigated by a robust communications strategy which ensures all parties are notified of any change in timescales. This is particularly important where, for example, specialist assets such as operating theatres are involved in patient treatment. The planning for long-term storage and management of recovery samples must be considered for all treatments, but becomes critical for indications with large patient populations.

Product release

Patient identification is vitally important at this stage since there must be traceability from patient to manufacture and back to patient – clearly visible in the batch record. Similarly sample identification requires clear labelling of all samples and identification must be recorded in the batch documentation.

Temperature excursions can be considered to be of low risk, but any temperature excursions must be recorded in the batch documentation.

Allowable **time excursions** and the impact on the material must be justified and supported by documented evidence that it will not impact on quality.

Medium risk **resource allocation** requires the availability of QPs for time-sensitive material.

✚ **Mitigation:** In this example, the material must be delivered from the manufacturer into the UK facility where it will be stored until QP release. The QP should be familiar with the sample collection process, supply chain and manufacturing process. For autologous material, key checks will include ensuring the labelling of the material allows traceability to the patient. Staged release can be used where documents are released for review during the manufacturing process, reducing the time required for final release.

Therapy logistics

There is no requirement for **patient identification** at this stage – so it can be assessed as low risk. But **sample identification** is high risk since the product must be identifiable back to the original sample.

Temperature excursion is also a critical element. In this example, the shipping temperature of the product is below -20°C and it is essential that this temperature is maintained during transportation.

Time excursion becomes medium risk in the set example since the product has a shelf-life of up to four weeks from manufacture to patient treatment. Shipping and QP release should take no more than a week, with an additional two days to transfer from the site of QP release to the patient.

Resource allocation can also be considered to be of medium risk due to the time from manufacture to dosing, and since there is some additional time allowed for each step within the logistic process. However timing of resource for the shipment is essential to ensure there is no risk to the product.

✚ **Mitigation:** Using preconditioned shipping systems should mean that manufacturers are able to manage the shipping systems themselves. It is important that all customs paperwork and permissions are in order and in place and management of the final mile delivery will result in the therapeutic agent being delivered to the correct site, the correct individual and at the correct time.

For ‘fresh’ treatments, co-ordination of manufacture and treatment must be implemented. Therapies with longer shelf-lives can deliver additional flexibility providing the treatment centres have the capability to store the product. Once again, clear communications strategies will help effectively manage risk.

Patient treatment

Patient and sample identification are critical when treating a patient with an autologous therapy. There must be a clear chain of identity all the way from starting material to the final therapy at the patient’s bedside.

Temperature excursion at the point of treatment should not be a challenge unless there is a problem with final mile logistics or formulation steps. Time excursion is also medium risk unless presented with issues on final mile logistics.

Resource allocation can be very complex during patient treatment, particularly if specialist teams are required for engraftment and pre-treatment of the patient.

Mitigation: Ensure that there is a final opportunity to verify patient identity by establishing that the chain of identity is managed all the way to the patient’s bedside; that all therapeutic agents are correctly handled; and that no manufacturing steps are taken within dispensing that require a GMP licence.

Co-ordination is vital with some engraftment activities requiring specialist assets, such as operating theatres or ITU beds. Where long manufacturing processes are involved, the patient’s attendance may need to be actively managed on

site and any pre-treatments must be timed and co-ordinated. Notification of successful engraftment may be required to begin the 30-year timer for record retention.

Risk map

The effective risk map will look like the graph shown below, where red indicates high risk, amber medium and green low risk strategies.

In deciding whether to have centralised or localised manufacture strategies, the key areas for consideration are:

Stability data

- Is transit time suitable for centralised manufacture?
- Is the shipping system robust enough to meet the demands of cell therapies?
- If starting material is vulnerable to time and temperature excursions, but the therapy itself is stable, then centralised collection and manufacture can be an option. The patient could visit a collection site for donation of starting material and then be treated closer to home.

Wellbeing of patient

The patient's health may dictate whether or not they can be moved. The risk associated with moving a patient needs to be balanced against the management of starting material and final product if there is only one opportunity to collect material and treat the patient.

Post manufacture manipulation

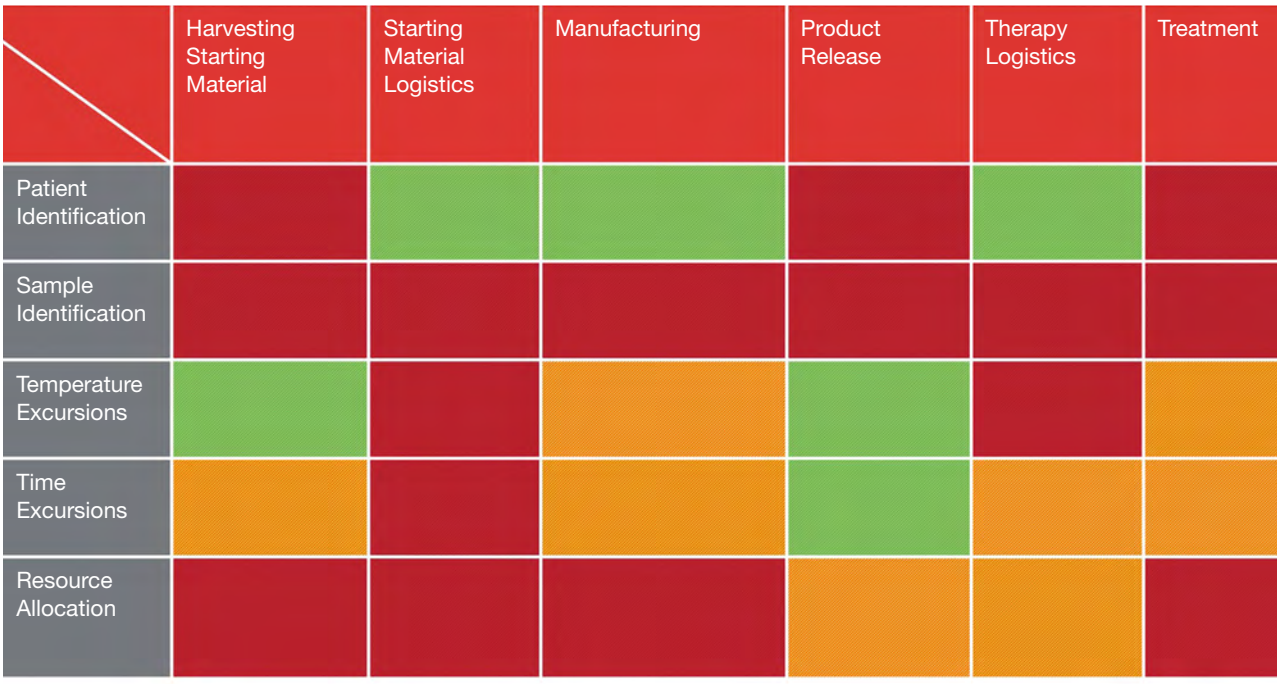
Some stabilisation methods for cellular therapies will require a thawing step which may also include washing to remove cryopreservation agents. It is important for decentralised manufacturing that dispensing steps do not cross the GMP Rubicon, or QP certification will be required.

Patient population

As patient numbers grow, it is conceivable that a number of manufacturing centres will be required in each country to support the use of cell therapies.

Manufacturing complexity

The challenge with cell therapies will always lie with the complexity of manufacture. Closed system automated



The effective risk map - red indicates a high risk, amber medium and green low risk strategies.

manufacturing may provide a simplification which could facilitate widespread manufacture, but specialists will still be needed to oversee the process.

Successful import and export of materials

The successful import and export of cell therapy materials depends on well thought-out, complex logistics, but customs intervention is uncontrollable so strategies should be put into place to minimise customs delay.

A template for customs declarations can be produced which can be reviewed with brokers and customs experts to meet requirements and sent in advance to the sample collection sites.

A test shipment could also be made to ensure that paperwork and the shipping route are not likely to cause any undue delays. However, any test shipment should use material as close to the finished product as possible, since dummy products have to be declared on customs' paperwork. Dummy products cannot be shipped and declared as the real material.

'Wheels up clearance' can also be used, whereby brokers submit paperwork to customs the moment the aircraft has taken off with the sample material – gaining the hours while the material is in the air.

For time-critical samples, careful planning of routes is critical to success. That means thinking about when material needs to be collected so that it can be transferred and made available for shipping without undue delays in as smooth an operation as possible.

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