CELL & GENE THERAPY INSIGHTS

SUPPLY CHAIN MANAGEMENT: PoC CONSIDERATIONS, PRODUCT TRACKING & DATA MANAGEMENT

SPOTLIGHT

EXPERT INSIGHT

Delivering cell therapies to patients: clinical and logistical challenges past, present and future

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Cell therapies present the opportunity to change the lives of patients with previously untreatable conditions, most recently a child with epidermolysis bullosa [1]. Nevertheless, if they cannot be delivered, both clinically and logistically, then their benefit is irrelevant. Indeed a robust, efficient supply chain can differentiate products and therapies. The traditional pharmaceutical development cycle is 10 years, however Kymriah went from clinical trials to market in 5 years and many innovators are talking about times shorter than this. Therefore, robust delivery systems have to be developed now, as the industry does not have the time for a more organic progression. This paper will investigate the evolution of the industry, identify seven delivery barriers (both logistical and clinical) and suggest strategies to ensure continued industry growth and patient benefit.

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The cell therapy industry has gone through a Gartner Curve-like evolution; early promise attracting investment, but then drifting away with the slow development of clinical evidence, then rising again in view of strong clinical data – primarily in oncology – with several commercial therapies now on the market (namely Provenge®, Strimvellis™ & Kymriah™) [2,3].

There have been many reasons for the changing fortunes of cell therapies, most notably the manufacturing process and associated cost of goods. Probably the most significant element to support the current success and interest in cell therapy relates to the strong benefit it is delivering to previously incurable and hopeless clinical situations. The modest speed of regenerative approaches is being supplemented by harnessing the immune system via the use of lymphocyte-based therapies to deliver unprecedented patient benefit. However, the

delivery systems, both clinical and logistical, must now become a key focus for the industry to survive and mature.

CASE STUDIES

To give context to the discussion, two generic case studies have been created and aim to highlight the key challenges that, to date, have been 'minor bumps in the road', but as the industry expands will become impassable potholes (Table 1).

CHALLENGES

Patient numbers & geography

These are the drivers of complexity within the system. In early stages of therapeutic development, a developer will have limited patients who are often located relatively close to the manufacturing base. The developer can therefore use whatever resources (people, equipment, clinical protocols, etc.) are available to manage deliveries. However, as patient numbers increase, geographic spread also rises and the sheer volume of activity means that new technology and systems are required. In addition, as the therapy internationalizes, additional issues such as language, regulations, differing ports of entry, among others, multiply the challenge.

In order to grow, developers therefore have two choices:

- Build internal business units that proactively manage the complexity; accepting that there will be peaks and troughs of activity and therefore productivity,

OR

- Utilize external organizations to control the areas in which they have expertise (storage, logistics, packaging, tracking, etc.), which enables the therapy developer to focus on their key skills of development, manufacturing and other functions.

Inbound

The source donor material is the key raw material for any cell therapy, as without it there can be no product. With allogeneic therapies, although significant expense has gone into locating, consenting and collecting the initial donation, it is a 'one-off' shipment and therefore relatively simple to coordinate. However, for autologous patient material procurement, the shipment can be more problematic than the delivery of the final therapy. This is due to the fact that it is often only able to be moved at relatively warm temperatures (controlled ambient or 2–8°C) and therefore has a very short shelf life, while most final products are, or will eventually be, shipped and stored frozen.

The impact of these stringent requirements are increased supply chain costs, or that the manufacturing site has to be near the donation/patient site. An alternative is to move the patient to the therapy, which is the approach adopted by GSK for Strimvellis, to the extent that they have created a 'concierge' service that looks after the patients' families so that they can stay nearby and live in Italy. However, as most of the patients being targeted for treatment with cell therapies require a high level of clinical supervision this is a difficult and expensive solution.

There have been publications on the viability of donated cells, post-thaw, that have been shipped

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TABLE 1

Illustration of growing complexity.

	Allogeneic			Autologous		
	PhI/II	Early market supply	Commercial	PhI/II	Early market supply	Commercial
Patient numbers (yr)**	20	150	50,000	20	2,000	5,000
Geography (number of countries)	1–5	1–5	5–10+	1	1–5	5–10+
Inbound (donation)	20	150	50,000	1	5	5
Outbound (therapy)	20	150	50,000	20	2,000	5,000
Clinical samples*	200	1,500	250,000	200	10,000	25,000
Cryostorage	X	XX	XXXX	Unlikely	Possible	Ideal
Secondary packaging and labeling	X	XX	XX	X	XX	XX
Real time tracking	X	XXX	XXXX	X	XXX	XXXX

* Assumed 10 samples per patient within clinical trials, dropping to 5 in commercial stages.
**Patient volumes taken from ISCT Webinar: Outsmart Commercialization Pain-Points Before They Happen, September 19, 2017, and market announcements around CAR-T therapies.
X indicates volume of input/complexity.

cryopreserved [4]. This is an improved solution to the inbound supply chain as it removes the time constraint. However, as many therapies have reached the later stages of development without this manufacturing step, companies are unlikely to revalidate their processes as it may delay commercialization. It will therefore be some time until this opportunity is tested at scale.

Outbound

Cryostorage of master and working cell banks – components of allogenic therapies – enables these therapies to be shipped cryopreserved. For autologous therapies this is more of a challenge, yet there are more therapies, such as Kymriah, being developed that have the ability to be shipped cryopreserved. This improves on the shipping from the manufacturing viewpoint. However, it pushes the challenge into the supply chain, and critically the clinician.

Traditionally cryopreserved shipments have utilized dewars/dry shippers; however, these were invented decades ago and are not fit for purpose, at scale. From a logistics point of view, this is because of their large size and the fact that their capability rapidly declines if they are tipped. This can incur significant costs, and may even push the therapy's cost over the reimbursement threshold and prevent patients from benefiting. At the clinical site this is compounded by the challenges of receiving a large (c1m^3), heavy container, full of a potentially hazardous gas that requires specialist handling skills.

In addition to these product flow challenges, one has to consider issues associated with storage. The manufactured therapies usually require extra low temperatures (-80°C and cryogenic) that are not normally available at the clinical site. Once stored, they need to be handled and thawed under tight time and

regulatory constraints. The thaw is often done in water baths; however, these are difficult to control and present a significant contamination risk.

At present, with a handful of patients being treated, this challenge is manageable through utilizing contract research organization (CROs) and controlling processes. But as the market expands and cell therapies are approved for larger indications, the issue will only become more pronounced. Already Kymriah is targeting 5,000 patients, and if we assume that all the CD19 targeted therapies have similar patient volumes you can quickly see that the number of deliveries and thawing cycles will quickly surpass clinical capability, compounded with other potential products in the pipeline.

Solutions are beginning to appear with the Asymptote (GE Healthcare) and Medcision automated thawing devices, which are moving the principles of GMP into the clinic by enabling automated warming cycles. In addition, the dewar has been re-engineered by SAVSU to create a smaller, lighter system, which can be tipped during transit. Taking advantage of these innovations is critical to the cell therapy industry being able to commercialize and treat the number of patients required.

Cryostorage

If therapies have the ability to be cryopreserved, this improves the challenge of shelf life. However it does present the issue of where to store the product. At present the volume is low enough that stock can be held in manufacturing and/or clinical sites. However with the specialist infrastructure required, combined with the volume predicted, this is a short-term solution. Storage of frozen material can be done centrally or at the clinical site. Central location has the advantage of proximity to the point of manufacture, or geographically relevant locations, and the ability to use an extensive range of temperatures. Nevertheless, this adds additional pressure to the logistics system as an extra shipment is required. Alternatively, storage at the clinical site obviates these challenges but can create different problems concerning volume/space requirements and very low temperature needs.

This challenge could be an opportunity; the current conversation focuses on where to locate manufacturing (i.e., central vs near-patient) but instead of distributing manufacture, there is the potential to distribute storage and we can see evidence of this is already beginning to happen.

Autologous therapies are still limited by the inbound/donation shelf life. However if this storage distribution model is followed for allogeneic, it will allow developers to limit the number of manufacturing sites while enabling their therapies to be available and close to the patient.

Clinical samples

This is often the 'forgotten' logistics challenge. Throughout clinical trials, and potentially into commercial application there is a need for blood and patient samples to be taken and sent for analysis. Many of these samples require bespoke analytical expertise and therefore cannot be managed by laboratories close to the clinical setting. In addition, frequently, they can not be frozen and thus have a short shelf life. Although important, these shipments do not

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have the same patient impact as the donation; however, the shipping conditions and short shelf-life mean that they can be just as expensive to ship. Additionally, donations can be timed to coincide with flight times; however clinical samples are driven by a medical timescale and so may not fit in with logistical capabilities.

To date, the primary way of flying a shipment is on a passenger airline, to ensure speed and safety. This adds to the cost and often limits the times you can utilise this option as most people, and therefore planes, want to fly during the day. While the freight network can offer more flight options – including at night – and can be more cost-effective, this option often fails as the oversight provided by premium couriers is missing and there are challenges with reliability through a network that ships thousands of different items daily. Premium couriers who manage shipments on both passenger airlines and freight carriers offer one potential way of addressing this this challenge.

Packaging & labeling

In early-stage trials, packaging and labeling is driven by regulatory and clinical demands. However, as the therapy reaches the market, additional commercial considerations come into play, such as branding and cost.

As the industry grows competition will increase, not only from equivalent therapies but also from the number of cell therapies that a clinical site has to deliver on a daily basis. Therefore to drive adoption, developers will have to think about ease of use with packaging for example. It is critical that the developer adapts to the market needs so that market adopts the therapy.

In our daily lives, we are confronted with products that have more packaging than valuable content, and can be incredibly difficult to get from the box into a useable format. Clinicians face the same challenge. As these cell products scale, there needs to be packaging systems developed that enable clinical teams to quickly access the primary packaging, thaw (if required) and utilize the therapy.

In an ideal world, the therapy would be delivered in practical formulations such as pre-loaded syringes, so that post-delivery manipulations are minimized and administration made as easy as possible. In the long term, this may be achieved by creating therapies with stability at higher temperatures, but in the short term developers need to think about the end user and make their life as easy as possible.

Tracking

Initial clinical trials are often delivered close to the manufacturing point, sometimes with the patient and the GMP facility being in the same clinical center. At this stage, the therapy can easily be tracked manually. However, as patients are recruited further away from the manufacturing center, the supply chain becomes more complex, and the risk of failure increases.

In many cases, visibility is provided by automated texts and email messages being issued as the therapy reaches various checkpoints (airport, crossed border, arrived at clinical site, etc.). If this manual paradigm continues, the risk is that as the number of therapies increases so will the number of messages, and developers will quickly reach a point where they are overwhelmed with the quantity of information, that

the value of that information is lost. In addition the current systems rely on data-loggers that need to be analyzed before the therapy can used, which takes up time within already shelf-life-limited timeframes.

To maintain control at scale, automated tracking and robust dashboards that visualize movements are essential. The developments of systems like TrakCel are enabling this, but to make them effective for logistics the shipping containers must be able to report in real time. This means that tracking technology needs to be built into shipping units (e.g., SAVSU).

Tracking is critical for all modalities of cell therapy, both autologous as well as 'off-the-shelf' allogeneic, for the control and safety of the product, despite the fact that the implications for the recipient patient may be different depending on the source material. As these technologies are used, future logistics systems will allow developers to see what is happening to their therapies and therefore address issues in advance, adjusting manufacturing slots in real time, reducing the need for data-logger analysis at point of care (as the readings have already been transmitted and approved) and therefore allow patients to be treated faster.

CONCLUSION

There are a number of barriers to the commercialization of cell therapies, but the potential to offer life-changing therapies off the back of compelling clinical data, is driving the industry forward. From a logistics view point the industry has evolved from seeing shipping as a last minute phone call, to something that impacts on quality, reimbursement and patient value.

There are seven challenges identified here that companies should think about during the development of their therapies. The key is to manage complexity, which is created by increasing patient numbers and the therapy being provided across wider geographies.

To achieve this, new and improved shipping and thawing technologies should be utilized, whilst designing packaging and labeling that is simple for the end user to adopt. In addition, logistics providers need to continually develop their service lines to provide in/outbound and sample shipping solutions that enable the industry to keep moving forward. Indeed there is potential to move beyond logistics to create inter-linked services that take the burden of coordinating the supply chain from therapy developers.

These factors should be at the forefront of the developers concerns from day one. Supply chain, like process development, should not be an afterthought or late-stage consideration, but an already integrated part of therapy development considerations.

FINANCIAL & COMPETING INTERESTS DISCLOSURE

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