ADVANCED THERAPIES INVESTMENT REPORT 2017

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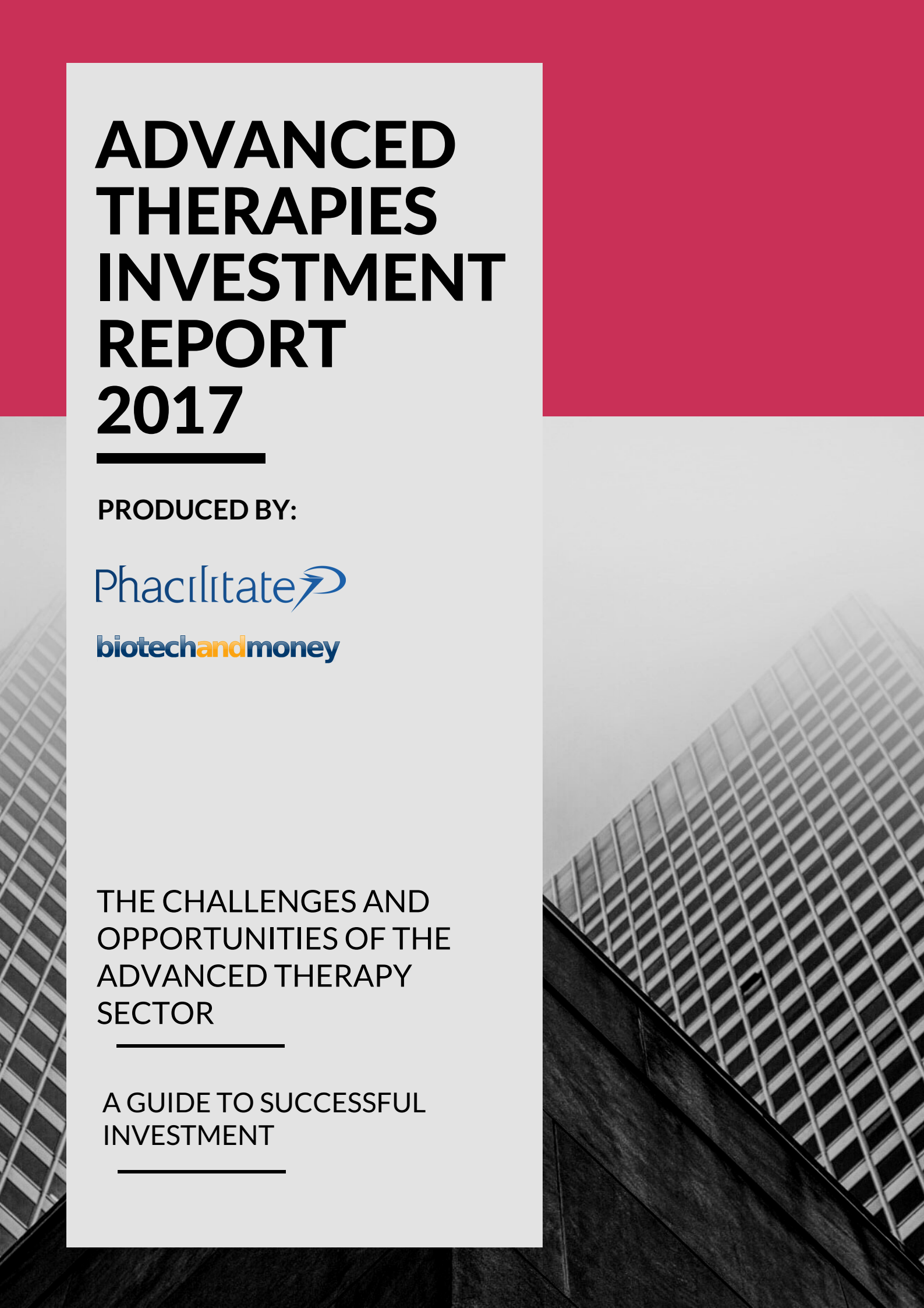

THE CHALLENGES AND OPPORTUNITIES OF THE ADVANCED THERAPY SECTOR

A GUIDE TO SUCCESSFUL INVESTMENT

MANUFACTURING COMMERCIAL OPERATIONS AND SUPPLY CHAIN

Chapter 4

4.1. Summary of Chapter 4

Advanced therapies are characterised by a high degree of technical complexity and face substantial challenges for their scalable manufacture. The novel nature of cell-based therapies and an associated lack of precedence presents a particularly unique set of challenges; bioprocessing equipment options are limited, and many available platforms are imported and adapted from blood product processing, research-scale cell culture, or antibody production, and are therefore suboptimal for scalable manufacturing. Cell and gene vector bioprocessing can be divided by expansion phase into upstream and downstream halves, each involving a series of unit operation steps. The immaturity of the advanced therapy manufacturing ecosystem in combination with rapid growth means that raw materials are often in short supply. Securing backup suppliers is therefore a vital requirement in de-risking the supply chain.

A growing number of stakeholders are offering advanced manufacturing and supply chain solutions, including GE Healthcare, Invetech, PCT, and Lonza. Twelve further manufacturing organisations were identified. Each of these offers either virtual-model (development and) manufacturing services, bespoke integrated manufacturing solutions, and/or off-the-shelf bioprocessing equipment. Advanced therapy manufacturing in high-profile companies is generally achieved primarily by the the latter two at present, with many leading advanced therapy companies opting either to out-source manufacturing to CMOs with deep experience in cell bioprocessing, or contracting custom-built integrated manufacturing solutions. Smaller or earlier-stage biotechs infrequently have the financial resources for these strategies.

Automation in cell bioprocessing is a major driver for cost-effective manufacturing, and should generally be implemented early in clinical development to avert high-risk late-stage process modifications. Single-use and disposable manufacturing systems often constitute major components of scalability. Automation can play a key role in supporting product quality through increasing robustness, consistency, and decreasing contamination risk, while decreasing operational costs. Manufacturing may be centralised to a single site or distributed; contributory factors include product shelf life and other characteristics, market potential, and cost. A number of leading cell therapy developers are opting to delay implementing automation until their second-generation product, restricting the manufacturability of their first-generation product.

Expert Insight

Timothy Moore,
Executive Vice President, Technical Operations, **Kite Pharma**

The cell therapy industry is embarking on the first phase of an exciting journey with a goal to bring life-saving treatments to patients with hematologic cancers who have no other options. There is a growing sentiment that the potential for cell therapy will flourish once the trail has been blazed. As we carve out this new path to reinvent cancer therapy, it was imperative to establish the first generation of cell therapy manufacturing and supply chain processes. This work is not trivial as the next generations must be built on a solid foundation. At Kite, we believe we have created a solid manufacturing and supply chain platform that is built to evolve and embrace new technology. This foundation is designed to address the needs of the here and now, while on balance, successfully embrace inspired collaborations that will allow us to bring next generation manufacturing and supply chain breakthrough technologies to the industry.
The success seen to date in cell therapy has inspired entrepreneurial thinking industry-wide. This is most evident by the number of companies investing in this transformational therapy space, both in the manufacturing and supply chain environment, to continually evolve solutions aimed at

improving cost, quality and reliability. Together, we plan to advance the manufacturing processes in collaboration with key industry suppliers to develop highly automated manufacturing unit operations, deeply integrated IT solutions to support knowledge management and continuous improvement, as well as efficient supply chains to ensure chain of custody and chain of identity are maintained throughout the end to end supply for autologous CAR-T/TCR products.
We believe that over the next five years, automation, process equipment, and supply chain management will make substantial advancements that can greatly impact the cost, quality and most importantly, the speed with which a patient receives therapy. At the end of the day, that is what drives innovation because every day matters in the lives of these patients.

Expert Insight

Robert Preti Ph.D.
Chief Executive Officer and President, PCT

PCT Cell Therapy Services, LLC
A Hitachi Group Company

Cell therapy, like every innovative industry that has come before it, has its own set of unique challenges. And just like these other industries, cell therapy solutions are forming directly along the challenges that are being presented.
The journey of a cell therapy, from conception to commercialization, is long, complicated and resource intensive. In order to reach success, a cell therapy product must be manufactured to high quality standards using a robust, cost-effective process that will be able to scale up and remain sustainable over the commercial life of the product.

To best ensure this success, cell therapy developers must plan ahead for the future of the cell therapy product, no matter what phase they are currently in. A common mindset for cell therapy developers is to focus on what they need in order to complete the current clinical phase and to enter the next phase of development. The most thoughtful among developers create strategic manufacturing plans to avoid costly, time-consuming roadblocks that could ultimately reduce the potential for commercial success.

In an ideal world, it would be most beneficial for cell therapy developers to set objectives for quality, cost of goods, scalability and sustainability before proof of concept clinical trials. In reality, this is not always possible before some clinical data is established. Given that the quality of the cell therapy product is so closely connected to the manufacturing process, any changes to the process, no matter how small, have the potential to create comparability risk. This can lead to additional costs and delays if such changes are introduced late in clinical development.

Personalized cell therapy (or patient-specific cell therapy), because of its individualized nature, carries a unique set of manufacturing challenges as compared to both off-the-shelf- cell therapeutics and traditional pharmaceutical and biologics. The main challenges include finding a method to manufacture cell therapies for clinical and ultimately commercial use in a way that considers cost of goods, quality, scalability and sustainability.

Current cell therapy manufacturing processes rely on a great deal of time, manpower and cleanroom space, all of which can lead to burdening cost of goods with the overhead operating expenses associated with idle capacity stemming from uneven demand over time.

In a traditional cell therapy manufacturing model, a developer invests much time and resources into creating a dedicated manufacturing facility intended for the manufacture of one or two therapies. In the case of cell therapies, the operation costs, inability to scale appropriately to meet demand and

other challenges can be daunting, creating insurmountable obstacles to commercial viability.

There needs to be an industry-wide effort to apply innovation and engineering to cell therapy, thoughtfully rebuilding unit operations for cell therapy from the ground up, to transform cell therapy manufacturing processes and test methods in a way that achieves true scalability and sustainability.

To allow for the long-term viability of the cell therapy industry, cell therapy manufacturing processes must be slowly taken out of the cleanroom and sent into production spaces more suited for high-volume production. In addition, automation, closed systems and integration will play a critical role in achieving this new manufacturing environment. When this occurs, then, cell therapy manufacturing will begin to see commercial success.

4.2. Typical stages of advanced therapy manufacturing

Cell bioprocessing is generally segmented into a series of discrete unit function steps which may differ between cell types and according to the specific needs of the product. A typical cGMP process for cell-based products follows these steps:

- Receipt of starting material and accessioning (e.g. apheresis or bone marrow, or possibly cell line/cell bank for allogeneic therapies)
- Cell processing- Washing to remove bulk of unwanted cell types
- Selection/enrichment- Target cell selection or enrichment
- Cell engineering- Activation, genetic modification
- Cell culture- Static or bioreactor platforms, typically 1-30 days

Upstream

- Cell processing- Washing to remove impurities
- Product formulation- Volume reduction, formulation and potentially cryopreservation
- Final product storage/shipping to clinical site for patient infusion

Downstream

cGMP gene therapy manufacturing processes generally involves fewer and often simpler steps:

- Vector amplification and cell expansion
- Bioreactor cell/vector expansion- Bioreactor culture

Upstream

- Cell disruption- Transduction
- Purification- Chromatography, DNA removal
- Polishing- Microfiltration/ultrafiltration
- Fill & finish- Transfer to storage, cryopreservation

Downstream

4.3. Major challenges in advanced therapy manufacturing

Medicinal product manufacturing environments are globally subject to GMP protocols, regulatory mandates enforced by national level agencies but internationally harmonised that aim to ensure production of high quality products that pose no risk to the consumer or public. ATMP manufacturing in particular requires a stringent and carefully controlled bioprocess to control for the intrinsically complex and variable nature of cell therapy products.[70]

The value chain for advanced therapies in 2017 places notable emphasis on novel manufacturing solutions. The industry is now limited by the usefulness and scale of available manufacturing solutions; innovation of scalable bioprocessing solutions is crucial for the commercial success of

advanced therapies over the coming 5-10 years. Existing bioprocessing solutions are largely adopted from biopharmaceutical manufacturing or blood product supply chains, and are usable but wholly sub-optimal for long-term commercial sustainability due to high failure risk, high costs, and poor flexibility for optimisation. Early advanced therapies are manufactured through manual, labour-intensive processes which limits their supply, demands high production costs, and ultimately curtails ROI. The unsustainability of this model is becoming increasingly apparent as technology developers realise the importance of innovative manufacturing solutions; multiple leading advanced therapy companies are commissioning exclusive and customised supply chain solutions from major manufacturing stakeholders (e.g. Kite Pharma and GE Healthcare), while a fertile bioprocessing industry is rapidly developing new commercially-available solutions.

Designing advanced manufacturing solutions early in product development is crucial to de-risk development. Any modifications to the manufacturing process implicate comparability studies to demonstrate equivalence, and major unforeseen alterations can be highly disruptive to timely completion of strategic development goals. Comparability studies are time consuming, require ongoing cash burn, and where reasonable comparability cannot be demonstrated, clinical trials may need repeating.

Upfront process development and manufacturing optimisation before the major value inflections offered by clinical trial results is an understandably high-risk investment, compounded by a relatively long time to ROI. Further, there are limited viable options for full-scale bioprocess solutions, and manual elements of manufacturing may be justifiably present at market launch. However, it is clear from historical and ongoing case studies that manufacturing remains central to costing a therapy, and therefore bioprocess optimisation to reduce therapy price remains central to commercial success.

4.3.1. Impact of suboptimal manufacturing: Provenge

The need to optimise manufacturing scalability is well demonstrated by Provenge, a dendritic cell cancer vaccine developed by Dendreon and authorised for marketing by the FDA approved in April 2010 and EMA in June 2013 for the treatment of advanced prostate cancer. Within a month of launch it became clear that manufacturing bandwidth was limiting revenues; Dendreon announced that only 2% of eligible patients would be able to receive treatment. Despite at that time also announcing a $400 million investment into a new manufacturing plant, stock prices fell by 36% over a two-month period. In November 2010, Dendreon secured a new increased pricing point of $93,000 with Medicare, and stocks remained relatively stable for the next 8 months. However, the need for this price rise as a result of manufacturing complications ultimately undermined clinician's desire to prescribe Provenge. Reimbursement issues were also a major contributor to the products failure; physicians did not want to front payment for the expensive therapy at risk of being denied reimbursement by the patient's insurer. Dendreon filed for bankruptcy in in 2014.[71] Ultimately, Provenge failed for a number of interrelated reasons centring around meeting market demand and cost, both issues addressable through manufacturing solutions.

4.3.2. Capacity shortfall

There is increasing understanding that research-scale manufacturing solutions are insufficient for the commercial launch of ATMPs, and resolving this issue requires substantial manufacturing expertise. In pursuit of this, numerous service providers offer either bespoke solutions for integrated manufacturing, or CMO-style virtual manufacturing models. Some of the major manufacturing stakeholders are PCT, Cobra Biologics, Invetech, Lonza, GE Healthcare, Oxford Biomedica, PharmaCell, MaSTherCell, and Apceth. Many other CMOs or service providers exist and the

ecosystem around ATMP manufacturing is rapidly expanding, offering increasing opportunities for ATMP manufactures to 'shop around'- but the availability of manufacturing solutions is counterbalanced by the sheer diversity of ATMP manufacturing needs and the depth of expertise required for successful manufacture.

Expert Insight

Brian Hampson

Vice President, Global Manufacturing Sciences and Technology, PCT, A Hitachi Group Company

For cell therapies to truly become commercially viable, the industry must begin to think of developing a very different future state of manufacturing. Cell therapy manufacturers will need to start shifting their model, moving away from the cleanroom and toward putting their processes into production spaces that are much more suitable for high volume production.
Automation, integration and closed processing systems can result in a simpler manufacturing space that is used for multiple processes at one time. This leads to a healthier bottom line, ultimately helping cell based therapies become globally accessible.

4.3.3. Raw materials shortages

As a young and emerging industry, the supply of starting and raw materials such as cell culture media is relatively volatile. Creating a robust and low-risk supply chain requires developers to identify backup suppliers where possible, and where backup options do not exist, work with materials suppliers to de-risk their supply chain in turn. The lack of competition for materials supply also impacts product pricing, and the use of high-cost media can significantly contribute to COGs.

Expert Insight

William Montieth

Chief Operating Officer, PCT, A Hitachi Group Company

Scott Oppenheim

Director, Supply Chain, PCT, A Hitachi Group Company

Given that cell therapy is still in a state of infancy, there are a number of unique supply chain considerations that haven't been fully addressed yet. Obtaining high-quality raw materials is one of many reasons for the high COGS seen in cell therapy products. There's a very limited supplier base that cell therapy developers can procure materials from, which limits their power to secure the best prices. In some cases, there is only one source for a specific material.

4.3.4. Shelf life and distribution

Small molecules are usually manufactured at single sites for global distribution, made possible by a long and undemanding shelf life. Biotherapeutics may require refrigeration, but tend to have shelf lives sufficient for cold distribution and local storage for use as necessary. In stark contrast, organs for transplant cannot (to date) be stored, and must be delivered fresh from the donor to the recipient within a matter of hours. The limitations presented by an inability to store donated organs cannot be overstated, and the infrastructure in place around managing this need is extremely costly. Cell based therapeutics lie somewhere in-between these extremes.

ATMPs have wildly varying shelf lives, depending primarily on whether they are cryopreserved. Holoclar (Chiesi), an autologous limbal stem cell product indicated for ocular chemical burns, provides a clear example of where short shelf life and an autologous supply chain has presented logistical barriers.[72] Patient biopsies are taken in a clinical setting, shipped fresh to the Holostem facility, and cryopreserved to await patient preparation. When the patient is ready the product can be thawed for undergo secondary culture, a process could take between 5 and 9 days depending on how the cells respond. Upon release, the product must be transplanted to the patient within 36 hours. The patient and clinical team therefore need to be prepared for delivery within a 4-day window. Holoclar's shelf life and associated logistical concerns have majorly impacted its price.

Expert Insight

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Transportation has to be considered as a unique challenge for cell therapies. At the earliest stages of process development, it's critical to assess whether the cell therapy product needs to be cryopreserved or refrigerated, as this will impact the ability to deliver it in a timely manner. Logistical considerations for a refrigerated supply chain of short dated or cryopreserved products can significantly impact COGS. For example, the use of courier service and cryo shippers to assure the maintenance of proper and timely storage conditions are a necessity. In addition, cell therapy developers will need a logistics scheduling system to manage the collection, shipment, processing and shipment back to the infusion site to ensure the critical attributes of the incoming and outgoing materials are maintained.

Furthermore, there are a limited number of suppliers who perform the specialized delivery services needed for cell therapies. Not only is maintaining a certain temperature a concern, but timing is also important. For example, there is usually a limited time to deliver the apheresis product to the facility for manufacture and then back to the patient for infusion. The courier chosen must have the ability to deliver these time- and temperature-sensitive products in a consistent, safe manner.

Expert Insight

Martin Lamb

Executive Vice President, Sales & Marketing, TrakCel Ltd

The Impact of Cellular Orchestration Platforms on Cost of Goods

Cellular Orchestration Platforms (COPs), such as TrakCel, are designed to improve supply chain performance for cell and gene therapies (CGTs). This is achieved by:

- Providing full traceability of therapies from donor to recipient – this is especially important for autologous cell therapies, where following modification and expansion at a manufacturing site, starting material derived from a patient must be infused back into the same patient. As the number of therapies being received, processed and shipped by clinical sites, manufacturers and logistics providers grows this will become increasingly challenging.
- Driving compliance with regulations, the trial protocol and Sponsor SOPs at clinical sites, through the implementation of prescriptive 21 CFR Part 11 compliant workflows. Again, as the number of parties involved in cell therapies grows in late stage clinical development and

commercialisation, the need for consistency and control increases.

- Capturing Data from multiple parties in the supply chain, giving Sponsors a single-system view of needle-to-needle supply chain performance allowing for analytics and performance optimisation.
- Scheduling of activities in the supply chain to ensure upstream tasks occur only when there is downstream capacity available for subsequent process steps. For example, providing apheresis centres with visibility of manufacturing capacity so starting material is collected only on days when capacity is available for cell modification and expansion.
- Simplifying QA release processes and supporting product quality by providing Quality Staff with all the information on a product's chain of custody required to certify it is safe for infusion into a patient.

Through the above functionality, COPs can significantly reduce Costs of Goods during clinical development as illustrated below. Savings in this table are based on the following estimated costs for a clinical trial (based on standard pharmaceuticals/biologics – for CGTs, we would expect the cost to be at the high end of this scale, if not higher):

- Phase I $1.4M - $6.6M
- Phase II $7.0M - $19.6M
- Phase III $11.5M – $52.9M

Major cost drivers include clinical procedure costs (15-22%), study administration costs (11-29%) and clinical site monitoring (9-14%). For illustrative purposes, and based on the complexities of CGTs, we will use the higher figure in these ranges for CGTs.

Cost driver	**Estimated Cost**	**Potential savings and rationale**
Clinical site monitoring	$0.6M at PhI, $2.7M at PhII, $7.4M at PhIII	Up to 25% - COP enforces compliance, which in turn should reduce the monitoring effort, supporting risk-based monitoring
Clinical procedures	$1.5M at PhI, $4.3M at PhII, $11.6M at PhIII	Up to 10% - COP workflows should make this more efficient. Integration with other systems eliminates duplicate data entry. Scheduling ensures procedures performed at the right time.
Study Administration	$1.9M at PhI, $5.7M at PhII, $15.3M at PhIII	Up to 15% - Automated data capture removes paper records/transcription errors and reconciliation challenges vs if data is captured in multiple systems

Further supply chain challenges, and associated costs, need to be captured in each therapy's Cost of Goods (COGs). While a COP may not directly impact on these processes *per se*, data captured by the system allows Sponsors/Developers to take a holistic view of their supply chain and identify opportunities for optimisation. These include:

- **Logistics** – COPs can provide logistics providers visibility to future needs, allowing for better forecasting and utilisation of courier services and improved management of specialised

shipping system inventories, which in turn can reduce costs. Also, data captured can be used to analyse courier performance, route selection and potential points of failure.

- **Manufacturing/QC testing** – In many cases, scheduling is performed manually across the supply chain. Automating this process can enhance utilisation of manufacturing assets, which has a significant impact on the cost of goods. Integration with manufacturing equipment allows for a more efficient review of manufacturing data at the time of release.
- **QA/QP release** – This is a major cost and process bottleneck for even traditional pharmaceutical manufacturers. Capturing data and documentation across the entire supply chain, from multiple sources (as is often the case for CGTs) can be challenging and adds significantly to release timelines – particularly for initial batches. By capturing key data, COPs can help alleviate this – one QP we spoke to quoted up to 40 man hours at a cost of $10,000 to release a first batch of product when compiling data from multiple stakeholders, which can fall by around 85% if all information is available in a single system.

TrakCel's experience to data has been focused on supporting our clients' products through clinical development. We are well aware of the challenges ahead when products are commercialised. One client we spoke to when compiling this paper cited that, in order to justify their current market capitalisation, larger autologous CGT developers will need to sell 5-10,000 treatments per year. This in turn equates to 40-60 batches of product released every day. How is this going to be possible using manual traceability and supply chain orchestration? What will the labour cost of achieving this, let alone the risk of product failures in terms of lost material and damaged reputations, amount to? COPs were developed to *enable* cell therapies to reach their potential – this will not happen without traceability, consistency across all stakeholders, automation and holistic data-driven decision making across the supply chain provided by these systems.

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http://journals.sagepub.com/doi/pdf/10.1177/1740774515625964

4.4. Designing scalable manufacturing systems

Expert Insight

Brian Hampson

Vice President, Global Manufacturing Sciences and Technology, PCT, A Hitachi Group Company

For a commercially successful cell therapy, developers need to meet several manufacturing criteria, including consistently high product quality, reasonable cost of goods, production that meets demand and sustainable capability throughout the commercial life of a product. To meet these criteria, it's critical for developers to think about manufacturing as early as possible in their development of a cell therapy product. Those who address manufacturing needs too late and then find out they need to make changes to achieve economically viability face a huge risk with regard to comparability of products made by original vs new processes. Investors are unlikely to agree to changes to the manufacturing process that may help to ensure profitability if they require that clinical trials be repeated.

4.4.1. Single-use technologies

Single-use and disposable manufacturing tools offer low-risk bioprocessing solutions. Traditional stainless steel bioreactors used in biopharmaceutical manufacturing typically require deep cleaning between batches, and Commonly used in academic or R&D contexts, single-use technologies can accommodate for the variable needs of cell bioprocessing, and are becoming increasingly adopted in commercial-scale supply chains. Lonza's largest viral gene therapy manufacturing facility, announced

June 2015, uses single-use bioreactor bags to manufacture 2,000L of viral gene therapy product across eight cleanrooms, demonstrating the growing movement towards disposable manufacturing solutions.

4.4.2. Automation

Expert Insight

Thomas Heathman

Business Leader, Technology Development, Manufacturing Development & GTP Services, PCT, A Hitachi Group Company

It is critical for cell therapy developers to start as early in the product development cycle as possible and understand how scalability can be achieved, be it off-the-shelf or patient-specific, and minimize the cost per dose as the production rate increases. This includes rigorous characterization of bioreactor platforms for off-the-shelf therapies at the small scale, so that comparability of the physical environment can be maintained as the scale increases throughout development.[115]

In addition, cell therapy developers should work closely with their manufacturing partners to leverage their knowledge and expertise, helping to ensure that the process, including supply chain and logistics, is scalable and will be commercially viable for the future. The timing, cost and comparability risk of modifying process steps during clinical development should be carefully managed and balanced against increasing cost advantages, to ensure the future sustainability of the cell therapy product.[115]

Automation offers step-change improvements to several manufacturing challenges. By automating otherwise manual steps, manufacturing becomes more scalable, robust, reliable, and consistent, and product quality can be enhanced. Human error is consistently identified as the highest risk element of the manufacturing process, responsible for the majority of protocol deviations and therefore batch failures. Automation mitigates these risks by offering repeatable and reliable bioprocessing.

Automating manufacturing opens opportunities to further refine the product process. Implementing in-line, on-line and at-line process testing allows up or downstream feedback, enabling compensation for batch variability, early identification of failed batches, and generation of a wealth of process data that can be leveraged for ongoing process optimisation.

Implementing automation technologies does require upfront capital investments, but this is a necessity to reducing long-term manufacturing costs, and to producing a commercially viable product, therefore offering an indirect return on investment.

4.4.3. Quality assurance and quality control

In Section 2.5: *Understanding and characterising* cellular products we discussed the critical need to fully characterise advanced therapies in de-risking product development and downstream commercialisation. A widely-implemented solution to this need, further to developing a battery of batch-release/ end-stage assays, is to implement in-process testing to monitor and control each batch as it is manufactured. Integrating in-process testing can obviate separate QA/QC processing, currently a major barrier to optimisation due to time constraints associated with the necessary tests, to facilitate greater manufacturing throughput and increase product shelf life.

Expert Insight

William Montieth

Chief Operating Officer, PCT, A Hitachi Group Company

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Currently, most patient-specific cell therapy manufacturing processes are manual. There isn't the economy of scale that is seen with the more traditional small molecule environment, where large batches of product with multiple doses can be made at one time. Cell therapies are produced manually in a traditional cleanroom, which means that capacity will become a limiting factor when attempting to scale up (or, in this case, scale out).

In order for cell therapies to reach commercial viability, companies will need to introduce appropriate automation and closed system processing into their manufacturing processes. Automation doesn't just mean faster – it will also greatly reduce costs once the process is taken out of the cleanroom and moved into a closed system. This drastically lowers infrastructure and support costs as a validated closed system can be housed in a controlled non-classified (CNC) environment versus a Grade B or Grade A cleanroom environment. Once this migration out of the cleanroom occurs, multiple products can then be run in one room. Concerns over cross contamination, sterility risk through the environment or human manipulation is minimized. Investing in automation before commercialization may have a significant long-term effect on reduction of costs and profitability.

4.4.4. Reducing COGs

Cost of goods sold in advanced therapy production may be substantially higher than in biopharmaceuticals, due most significantly to high cost of materials, high labour costs, and the need to maintain validated cleanroom space. Reducing production costs could involve degrading cleanrooms to Grade D, possible only with a completely closed process; reducing labour costs through automation; and simplifying the manufacturing process by excluding unnecessary steps. Manufacturing costs may be particularly elevated in autologous processes, which do not benefit from economies of scale.

Expert Insight

Brian Hampson

Vice President, Global Manufacturing Sciences and Technology

PCT, A Hitachi Group Company

Automation and the related opportunity for integration will play a larger role as these new types of factories come into existence that will justify the investment in the development of automation technologies and platforms. Integration of multiple unit operations (steps) into a single unit operation presents benefits including lower labor and material costs as well as quality advantages associated with less transfer of cells between unit operations. However, there is still an unmet need for cell processing platforms that can perform a variety of cell manipulations across a range of scale – but this innovation is starting to happen.

Having deep knowledge of the technology landscape ensures developers are able to choose automation platforms that offer the best available solutions for their specific process requirements. Automation strategies need to address a range of considerations, including:

- Process automation, such as closed-loop control of a culture process
- Task automation, such as a cell selection step, or coupled wash and formulate steps
- Test automation, such as a compendial safety test method
- Factory automation: for information such as electronic batch record; for execution such as manufacturing execution systems

Expert Insight

David Sourdive

Co-Founder, Executive Vice President, Technical Operations, Cellectis

How will bioprocessing improve in the next 5 years?

Cell therapy is now transitioning from the world of grafts, where it has been confined for decades, to the world of pharmaceutical products. In the coming decade, off-the-shelf cell therapy will become a reality that will have a broad impact on the field. Standards and regulations will evolve with that revolution.

Cellular systems will be both better defined and more extensively and precisely engineered. Gene-editing transformative potential will also start materializing with designer cells and systems tuned for therapeutic applications.

Expert Insight

William Montieth

Chief Operating Officer, PCT, A Hitachi Group Company

Scott Oppenheim

Director, Supply Chain, PCT, A Hitachi Group Company

Managing cost of goods sold (COGS) for patient-specific cell therapies (PSCTs) has unique challenges when compared to traditional biologics. The greatest differentiator: PSCTs are manufactured one batch at a time for one patient. As a result, this limits the cost savings from traditional economics of scale. Current high COGS for cell therapy products are driven by a combination of several factors – labour intensive manual manufacturing processes, high infrastructure and support costs, expensive raw materials as well as lack of economy of scale. And because these therapies are patient specific and the health of the patient impacts availability for collection of starting material, scheduling variability can inhibit the efficient utilization of planned resources. This can result in a higher waste stream due to aborted processing runs. An additional impact on COGS is the associated cleaning and segregation requirements when viral vectors are used in cellular processing for the transduction of cells.

As cell therapy processes mature, the need to drive down COGS to achieve commercial viability becomes critical. COGS for cell therapies must be reduced through technology optimization utilizing such methods as automation, isolator technology and closed system processing which reduce the infrastructure and support cost of a traditional Grade B or Grade A clean room environment and results in reduced sterility and processing errors through human intervention.

Near and long-term planning is critical to mitigate supply chain risks in cell therapy manufacturing. By performing this type of analysis, the cell therapy developer has a road map for their manufacturing strategy, process improvements, required capital and raw material costs. Without performing COGS analysis in the process development stage, it is difficult to predict if and how the manufacturing process can be fully optimized for commercial viability. As regulatory filings proceed, changes may become more difficult to make and cell therapy developers could end up locked into certain material suppliers and more costly processes. Regulatory agencies have shown support for comparability study between manual and closed system/automated processing during the clinical and post approval life cycle of a product, thus providing a pathway for this change.

4.5. Centralised and decentralised manufacturing models

Advanced therapy supply chains must be intelligently designed to maximise product availability. Owing to long shelf lives and simple distribution needs, small molecules can be manufactured in a single manufacturing site and readily shipped across the world. For cell therapy developers, opting for single or multiple manufacturing centres will depend upon the preferred business model, regulatory, economic, and supply chain factors.[73] Autologous therapies in particular may benefit from multicentre manufacturing solutions, particularly where bioprocessing can be confined to black-box systems installed within the healthcare setting. Multicentre manufacturing models are subject to substantial comparability requirements, where centres must demonstrate the precise replication of products between centres, but can offer logistical advantages. Different elements of the supply chain have various levels of associated risk (Figure 4) and this must be considered when designing a manufacturing model.

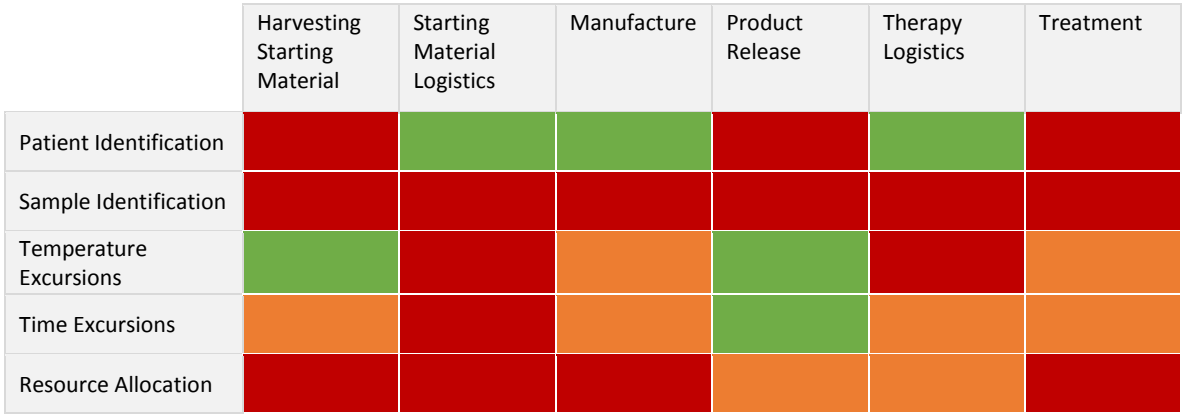

Figure 4: Risk heat map for autologous cell therapy supply chains. Red indicates high-risk, amber medium, and green low. Adapted from 'Successfully managing the unique demands of cell therapy supply chains' white paper, Rachel Griffiths and Dr Matthew Lakelin.[74]

4.5.1. Shipping and logistics

Transporting advanced therapies can be a high-risk aspect of the supply chain, particularly for fresh product cell therapies which often suffer from short shelf lives and can be extremely sensitive to environment factors such as temperature, gas concentration, and even vibration. Logistics complications such as delays to customs release or within airports due to air traffic or unforeseen circumstances can incur time exclusions. Minor process changes such as moving to a cryopreserved final shipped product can substantially mitigate these risks, and shipment condition tracking devices should be employed to validate the post-transport quality of each batch. Provenge provides a clear example of the importance of shelf life management, where an initial decision to ship fresh was later overturned following unsustainable costs and high wastage, and a cryopreservation process modification implemented.

Chain of identity management becomes a high-risk demand with autologous therapies, as products must be effectively tracked throughout their manufacturing, analysis, release, and shipment to ensure that a high-quality product is delivered to the correct hospital and administered to the correct patient. Batch identification through patient initials and date of birth is considered insufficient, but labelling must be simple enough for use across sites. Supply chain management tools such as TrakCel and Vineti (previously Vitruvian Networks) aim to manage this risk.

Where appropriate, the use of qualified and trained personnel in receiving the shipment can be critical to ensuring proper handling upon receipt. Collection centres may not be equipped with adequate storage space and mitigating the risk of batch waste in this case requires competence on the part of the clinical establishment.

4.6. When to invest in manufacturing?

Deciding on the stage and degree of investment in manufacturing is a strategically important decision. We searched for press releases between 25/04/17 and 01/01/2016 announcing manufacturing decisions (Table 11), finding the most common manufacturing investment period was in preparation for phase II trials. Several companies also invested prior to pilot clinical trials, plus some expansions to manufacturing resources in anticipation of commercial launch. Press releases listed include both integrated infrastructural development and virtual model out-licensed manufacturing agreements.

Date	Company	Announcement
18th April 2017	Cobra Biologics	£15m gene therapy manufacturing expansion to meet increasing ATMP CMO needs
11th April 2017	GE Healthcare; Asymptote	GE acquires Asymptote for undisclosed sum to support enhanced cell ATMP manufacture and cold supply chain
10th April 2017	GE Healthcare; Cellular Biomedicine Group	Strategic collaboration between GE and CBG to develop CAR-T and stem cell manufacturing industrial process controls
28th March 2017	Nohla Therapeutics	UC Davis to manufacture NLA101 stem cell product on behalf of Nohla ahead of clinical trials and market
18th January 2017	Erytech; Invetech	Invetech to develop custom scalable automated manufacturing system for Erytech ahead of phase II trials
18th January 2017	Servier; MaSTherCell	MaSTherCell to develop CAR-T commercial manufacturing system for Servier ahead of phase II trials
9th January 2017	Orchard; PharmaCell	PharmaCell to provide manufacturing services for Orchard *ex vivo* gene therapies ahead of phase II trials
15th December 2016	Bluebird Bio; Apceth Biopharma	Apceth to continue manufacturing support for European commercial-scale production of gene therapy candidate
13th December 2016	Kite Pharma; Vitruvian Networks	Collaboration to develop logistics and data analytics software for commercial scale CAR-T production
19th September 2016	PCT, a Hitachi Group Company; Adaptimmune	PCT to manufacture T-cell products for Adaptimmune over 5 years, ahead of late-stage trials
1st August 2016	Atvio Biotech (Orgenesis); MaSTherCell	Atvio to provide contract development and manufacturing services to support MaSTherCell expansion
1st August 2016	Pfizer; Bamboo	Pfizer acquires Bamboo Tx, including phase I/II gene therapy manufacturing assets
21st June 2016	Kiadis Pharma; PCT, a Hitachi Group Company	PCT to manufacture Kiadis' products for phase III trials
20th June 2016	Kite Pharma	Kite Pharma opens T-cell manufacturing facility ahead of late-stage clinical trials
17th April 2016	Freeline Therapeutics; Rentschler Biotechnologie GmbH	Freeline Therapeutics acquires AAV gene therapy manufacturing platform from Rentschler Biotechnologie ahead of clinical development

15th March 2016	TxCell; PCT, a Hitachi Group Company	PCT to manufacture regulatory T-cells on behalf of TxCell for early-stage clinical trials
10th February 2016	Lonza; Renova Therapeutics	Lonza to manufacture gene therapy products on behalf of Renova for pivotal phase 3 clinical trials
2nd February 2016	Invetech; Ceylad	Invetech to develop and supply stem cell manufacturing systems for Ceylad product commercial launch
21st January 2016	Asterias; Cancer Research UK	Cancer Research UK to manufacture stem cell product for Asterias for phase I/II clinical trial
19th January 2016	Cellectis; CELLforCURE	CELLforCURE to manufacture CAR-T products for Cellectis ahead of phase I trials
13th January 2016	GE Healthcare; FedDev Ontario; Centre for Commercialization of Regenerative Medicine	GE Healthcare, Federal Economic Development Agency for Southern Ontario, and the CCRM, to build CAD$40m advanced therapeutic cell therapy manufacturing centre

Table 11: ATMP industry announcements since 1st January 2016 regarding manufacturing. Blue fill indicates integrated manufacturing; green fill indicates virtual model manufacturing agreements; no fill where N/A.

4.6.1. Portfolio strategy in automation investment

Investors traditionally prefer to delay investing in drug manufacturing optimisation until a product is sufficiently far through clinical development (and therefore low-risk and valuable enough) to justify dedicating the required resources to enhance manufacturing scalability. However, it should be well understood that upscaling advanced therapy manufacturing can be economically impossible without modifications to the process, in particular where manufacturing is particularly labour intensive. Any modifications to the manufacturing process will require comparability studies, and these can be extensive; more dramatic modifications to the manufacturing protocol may even require re-authorisation or clinical trial repetition. Investors must commit to early-stage process development to achieve sales, cash flow and ROI from their first-generation product.

However, many investors have shown a preference to authorise a first-generation product with a manual and poorly scalable process, before investing in scalable, automated second-generation product. Investors must be aware of the limitations on ROI for the first-generation product when adopting this strategy.

4.7. Major manufacturing stakeholders

4.7.1. GE Healthcare

GE Healthcare are a subsidiary of General Electric and produce a significant range of medical equipment, predominantly imaging devices and other hospital services. The company have interest in cell-based drug screening through three core collaborations: a cell analysis research alliance with BGI (2012), a license to Cellular Dynamics' drug screening platform (2012), and a license to CRISPR-Cas9 technology with the Broad Institute (2014).

GE Healthcare produce cell bioprocessing equipment for commercial use, with the Xuri technology family their flagship platform. GE Healthcare have shown considerable interest in growing their cell therapy capabilities, signing co-development agreements with LeukoDx in 2016 and with Zenith Technologies in 2017. They also acquired cell bioprocessing company Biosafe Group in 2012 and cryogenics supply chain solutions company Asymptote in April 2017.

Further to commercial manufacturing solutions GE Healthcare directly supports over 100 clinical stage companies across its various product lines, including in advanced therapies.[75] GE Healthcare

are developing bespoke manufacturing solutions for two CAR-T companies, Kite Pharma (2015) and CBMG (2017).

In January 2016 GE Healthcare announced a $31.5 million co-investment with the Canadian government (through the CCRM) to open BridGE@CCRM Cell Therapy Center of Excellence, a research institute aiming to accelerate the development and adoption of cell therapies. GE Healthcare and Mayo Clinic co-established Vitruvian Networks in April 2016, aiming to develop software infrastructure to bring "the internet of things" to advanced therapy manufacturing.[76] The platform aims to coordinate and de-risk the entire supply chain network while incorporating business intelligence and data analytics capabilities.

GE Healthcare is engaging with the advanced therapy industry through several angles, not only producing commercial bioprocessing equipment but also supporting the research ecosystem, developing an advanced supply chain management platform, and providing bespoke bioprocessing systems to two CAR-T companies.

4.7.2. Invetech

Invetech are a large manufacturing company with interest across a range of engineering exploits. Invetech specialise in automation, providing bespoke solutions to clients across medical, industrial and consumer markets. Through their Cell Therapies Group (established in 2004) Invetech have completed over 35 projects for more than 25 advanced therapy companies, including Argos Therapeutics (2014), Ceylad (2016), NanoCellect (2015), NeoStem (a Caladrius subsidiary) (2015) and Erytech (2017). They do not offer contract manufacturing services but work directly with technology developers or manufacturing organisations to integrate bespoke and often automated bioprocessing solutions.

4.7.3. PCT*, A Hitachi Group Company*

PCT, one of the most widely used CDMOs, having agreed manufacturing contracts with Orchard Therapeutics (2017), Adaptimmune (2016), TxCell (2016), Kiadis (2016), Kite Pharma (2015), IRX Therapeutics (2015), Immunocellular Therapeutics (2015), Medstar Georgetown University Hospital (2013), Hackensack University Medical Center (2013), Baxter (2012), and Sotio (2012). PCT also announced a collaboration agreement with supply chain management platform TrakCel and one with instrument developer Invetech, both in 2015. PCT has 55,000ft^2 of development and manufacturing space across two separate US facilities (Allendale, New Jersey on the east coast, and Mountain View, California on the west coast), and announced in October 2016 a $17.5 million CDMO facility in Yokohoma, Japan, to be constructed by parent company Hitachi Chemical and to be fully operational by April 2018.

4.7.4. Lonza

Lonza offer manufacturing solutions across chemical, water processing, consumer, agricultural, pharmaceutical, and other industries. In the advanced therapy sector they manufacture a range of off-the-shelf bioprocessing solutions, but also engage directly with technology developers as a CMO. Lonza currently have two advanced therapy manufacturing facilities, a cell therapy suite in Walkersville, Maryland, and a 2,000L, 100,000ft^2 viral therapeutics facility in Houston, Texas. In the advanced therapy sector Lonza have agreed manufacturing contracts with Selecta (2017), Renova (2016), bluebird bio (2016), Massachusetts Eye and Ear centre (2016), Benitec (2015), TiGenix (2015), Regneus (canine cell therapy) (2014), and Celladon (2014). Lonza were awarded a $9.5 million contract from the NIH to develop and manufacture clinical-grade iPSCs, plus the associated manufacturing infrastructure (2016), and are collaborating with Nikon to build a cell and gene therapy manufacturing facility in Japan (2015).

Lonza are a major manufacturing organisation across the globe and are heavily engaged with the advanced therapy community, offering commercially available bioprocess instruments and widely used virtual model manufacturing services.

4.8. Other manufacturing organisations

Numerous contract development and manufacturing (CDMO) organisations exist globally, some of which with integrated product pipelines for their own therapeutics. Table 12: **Non-exhaustive list of CDMO organisations focusing on EU and US geographies.** Table 12 lists clinical and commercial scale C(D)MOs not included in the above sections.

Company	Geography	Public partners	Notes
Apceth Biopharma	Germany	Bio Deutschland, Dechema	Also developing an integrated MSC immuno-oncology portfolio
PharmaCell BV	Netherlands	Orchard Tx (2016), Immunocellular Tx (2015)	Experience in clinical trial manufacturing with commercial-scale resources
Cobra Biologics	Sweden	Undisclosed	Provides range of goods & services across range of therapy types
Oxford BioMedica	UK	Manufacturing agreement Novartis (2013). Gene therapies out-licensed out to Sanofi (2009), GSK (2006), Immune Design Corp (2012).	Substantial lentiviral manufacturing facility used to develop Novartis' CTL019. Integrated gene therapy pipeline commercialised through out-licensing partnerships.
Roslin Cell Therapies	UK	Advanced Cell Technology (2011), Lonza (2010)	Specialists in iPSC and ESC development and manufacturing.
Cancer Research UK Biotherapeutics	UK	Asterias (2014)	300m^2 manufacturing facility; Asterias phase I/II trials contract.
Sartorius	Germany	N/A	Produce bioprocess equipment, no CMO services
Atvio	Israel	None announced	50% owned by Orgenesis
MaSTherCell	Belgium	TxCell (2015), Servier (2017)	Wholly owned by Orgenesis
Cell*for*Cure	France	Cellectis (2014)	1,400m^2 semi-automated cGMP facility with space for 8 different products. LFB Group subsidiary
SAFC (Sigma-Aldrich)	US	Applied Genetic Technologies Corporation (2014)	Wide-ranging bioprocessing products. Manufacturing agreement with AGTC
Cell Therapies Pty	Asia-Pacific	PharmaBio, Peter MacCallum Cancer Centre, Medipost	Major Asia-Pacific CMO with presence in Japan, Australia, Malaysia, South Korea

Table 12: Non-exhaustive list of CDMO organisations focusing on EU and US geographies.

- Are your follow-up times sufficiently **long term**? How can you ensure any projected or forecasted clinical outcomes are **valid**?
- Where are you going to undertake your trial and what are the **market access implication** of this decision?
- Have you fully considered the **optimal patient subpopulation** to treat?
- Does your clinical trial strategy fully capture the **value** of your product?

6.10.4. Pricing and reimbursement

- Do you understand the **cost of the disease** including its current economic burden and indirect healthcare costs sufficiently to justify your pricing strategy?
- Does your clinical trial generate sufficient data to **justify** your pricing strategy?
- Have you analysed the risk of achieving reimbursement, and have you **approached payers or industry associations** to inform this assessment?

6.10.5. Commercial

- What is the (current and future) **competition** in this disease space and how might it be mitigated?
- How well **protected** is your technology? How comprehensive is the IP, and when does it expire? What other protection strategies may be relevant?
- What are the **regulatory risks**? How can you leverage **expedited development pathways** (e.g. PRIME, breakthrough status) to de-risk product development?
- How do you plan to **exit**? What role might biopharma organisations have in this?

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