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# Producing Off -The- Shelf Cell and Gene Products.

Expert Insight eBook

CELL & GENE THERAPY MANUFACTURING

# Top Challenges: Manufacturing Commercialised Cell & Gene Therapies

The international regenerative medicines market – which includes the likes of cell therapies, gene/gene-modified cell therapy and tissue engineering – is set to climb to around $67 billion by 2020.[4] Alongside, discovering therapies that will treat cancer and orphan diseases, many in the industry are hungry to land grab market share and produce the next blockbuster product. However, there are many challenges that stand in the way of producing commercialised cell and gene products - whether they are allogenic or autologous. Autologous therapies will require separate manufacturing batches for each patient therapy. Those therapies can be hard to transfect. Whereas, allogenic therapies will take the altered cells, expand them as to create a large volume of them to be used by patient demographics.[2]

The rise of personalised medicines has led to the focus on small scale manufacture with a key challenge being that lots of the same element will run through a facility at once. Randomised trials with complex gene therapies- which target a small number of patients often in regards to orphan diseases can encounter various manufacturing hurdles. Also, evidence is needed to prove efficacy against historical controls with Phase II trials. This of course requires several years of data which is limited, incurring implications on cost and time to market.

Clinical results stand as a key challenge for product developers to meet. Dieter Hauwaerts, VP Operations, Celyad explained that in order to show really outstanding and reliable clinical results there needs to be truly outstanding manufacturing processes and technologies that are consistent and have a very high degree of quality built into them. Besides generating those breakthrough clinical results, pharma and biotech companies need to consider how they are going to manufacture, release and ship those products at a significantly larger scale than that being conducted currently. Dieter Hauwaerts believes that there always will be a place for cell and gene therapy products in smaller indications, but the true maturation of the field only will come when the industry can show results from a clinical and a commercial point of view in larger indications. Typically, that is where the CAR-T field is moving towards.

Ahead of the Cell and Gene Therapy Manufacturing conference Pharma IQ examines the various challenges that complicate the route to producing off the shelf cell and gene products.

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## Scientific Awareness Of Production

While it is essential that companies have a detailed knowledge of the regulatory/legal requirements surrounding these therapies, it is also critical that companies understand the science and details of producing an effective and high quality cell and gene therapy product. This includes decoding the relationship between technology, science and regulation. Understanding the quality aspects behind the cells and biology is key to creating effective therapies.

In regards to reaching process excellence in the production of these therapies, Elena Meurer, Head of Pharmaceutical and Technical Development at apceth GmbH & Co.KG sees two major routes towards improvement. For small autologous products - develop a strategy to produce everything at the patient side in the clinic, so a closed automated system will allow manufacturers to avoid the use of a clean room. It is however not possible if the manufacturing of a cell product is lengthy due to a cell expansion phase. In this case, a simple, robust process should be developed to ensure the product's success, as the patient material is valuable. The adoption of allogenic manufacturing in huge batches would allow for the cost minimization.

## Limited Appropriate Manufacturing Platforms

According to some this stands as one of the greatest challenges for the market. Many manufacturing platforms exist for cell-based products, like for antibodies, vaccines and so on where cells take part of the process. However, Elena Meurer notes that the solution landscape for automisation and monitoring is completely different when the process needs to harvest living cells that are still potent and can still provide therapeutic agent.

Some manufacturing platforms can impose limitations on scale and cell density in the production of these therapies.[2] Some have mentioned that electroporation technologies can act as good non-viral alternatives.

When asked for his predictions on likely manufacturing trends for cell and gene therapies as they progress over the next few years, Mark Woodyer, Technical Lead, Manufacturing Sciences and Technology at Oxford BioMedica said: "As more cell and gene therapies progress into late stage clinical development, commercial success will require manufacturing breakthroughs to provide a step change in manufacturing output. The manufacturing trends will most probably focus on maximizing process output per unit volume, thereby minimizing ultimate batch sizes. In addition, new manufacturing modalities will

come to the fore, with greater use of integrated closed manufacturing technologies, with the potential use of continuous processing to improve efficiency. Such developments will require sophisticated logistics, greater automation and implementation of process analytical technologies (PAT). These trends have been evident in earlier technologies, such as antibodies."

There is a marked need for manufacturing platforms to support larger scale manufacturing for example with automation, bioreactors and related process technologies.

Also, Dieter Hauwaerts notes the need to progress towards more integrated manufacturing platforms. Existing solutions for the different steps within the manufacturing process are not always interoperable from a product flow perspective as well as from a data perspective. He stresses that success may be found in reaching standardised platforms that are connectable.

## Quality By Design

Dr Ryan Guest, Director of Cell Production from cell therapy manufacturer Cellular Therapeutics highlighted that general lack of scientific product quality awareness and meaningful functionality tests makes manufacturing in a QbD space difficult. For example, viral vectors with modified cell therapies need processes that are gentle as to preserve the cell's quality.

Looking ahead to the future for the market, Dr Ryan Guest believes that as part of manufacturing QbD approach the manufacturer should consider the impact the process has on the final product and this includes consideration of box technologies with their plug and play style to implementation. He confirms that this is certainly a fast moving field for the cell and gene industry with tech manufacturers trying to chase this market. He believes that these plug and play technologies are likely to be adopted on varying levels depending on the complexity of the cell therapy and the financial impacts.

## Quality Assurance

As previously mentioned, the development and manufacture of cell products requires intensive quality control (QC) to preserve the product's end quality. Of course the further through the process a product advances through to release, the more stringent the QC measures become. Bart Vaes, PhD, David Craeye and Jef Pinxteren mentioned in an article about using a tiered strategy for QC –measuring cell identity by marker genes and protein expression using " quantitative real time polymerase chain reaction (QPCR), enzyme-linked immunosorbent assay (ELISA) and flow

cytometry." They added that added epigenetic assays can be conducted to prove the quality of the product.[1]

Preserving the quality of the cells throughout the process demands arduous precautions and monitoring measures within the manufacturing and supply chain stages. The lengthy cryopreservation process has limited vessels of choice. C. Challener notes the challenges in preserving the quality and stability of the master cell bank regarding disease contamination.[2]

**Autologous**: Dr Ryan Guest highlighted a few of the emerging solutions for quality assurance hurdles in the UK. He said: "The UK Human Medicines Regulations 2012 and similar approaches in other EU member states enables an approach to allow MS specials/ Hospital exemptions manufacture for a patient specific need, where there is available efficacy data. [This] has helped significantly with proof of principle to de-risk investment and allow patients access to cell & gene therapy medicines."

He added: "To date the most success has been seen with close partnerships where each party has key experience and evidence of delivering results in the cell & gene therapy field."

## Cost Efficiency

Stable funding is hard to access with the lengthy R&D timelines and changing regulatory parameters that surround cell and gene therapies. Challenges encountered in manufacturing cell and gene therapies cause costs to surge. With the emergence of new methods and technologies, hopefully these issues that are currently expensive to rectify will become more economical for the industry. Dr Phil Vanek notes the potential cost effectiveness of moving from clean rooms to closed systems.[3]

Methodologies are still not as cost effective as they could be, one good example concerns cell type isolation - for this accessing automated closed bioreactors is very difficult. C. Challener notes that the process of droplet-based flow sorting is still very manual, open, technique-sensitive and unsuitable for the large-scale commercial production of many thousands of doses annually. In addition to this it is labor-intensive, time consuming and subject to errors.[2]

Automation can decrease clean room time by lowering the manual labour efforts needed, which stands as a major cost. However, with more automation comes less flexibility, Elena Meurer notes: "One should also

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consider that in this case, once [the process is] decided, it's difficult to change it. It's much less flexible. The more automatisation one undergoes, the less flexibility is left. So, actually the only thing which has to be considered, [is] that one decides on final solutions early enough."

Timing for automated continuous processing is vital in regards to when it is implemented into the process. Manufacturers need to ensure they don't attempt to implement automated continuous processing when it is too early for them to be fully aware of what their process will require, but equally manufacturers shouldn't implement automated continuous processing when they are too far into trial stages or too advanced in how the product is described in regulatory findings.

To produce autologous therapies in a consistently cost effective way, the industry will need to invest in sharing information and knowledge to propel the field's progression.

## Scalability ( Up And Out )

A scale-up can change some characteristics of a cell and therefore it is important to decide whether it is essential or not. Elena Meurer said: "[It] is a very known case when a company performs first clinical studies in the small scale and then change[s] for larger-scale within later clinical stages. As an example, the larger scale might require a prolonged cultivation of cells thereby providing older cells, which might result in the change of product potency. So, that is a pitfall [to look out for]: if you change your cultivation technique during scale-up, that the product [may not be] potent any longer."

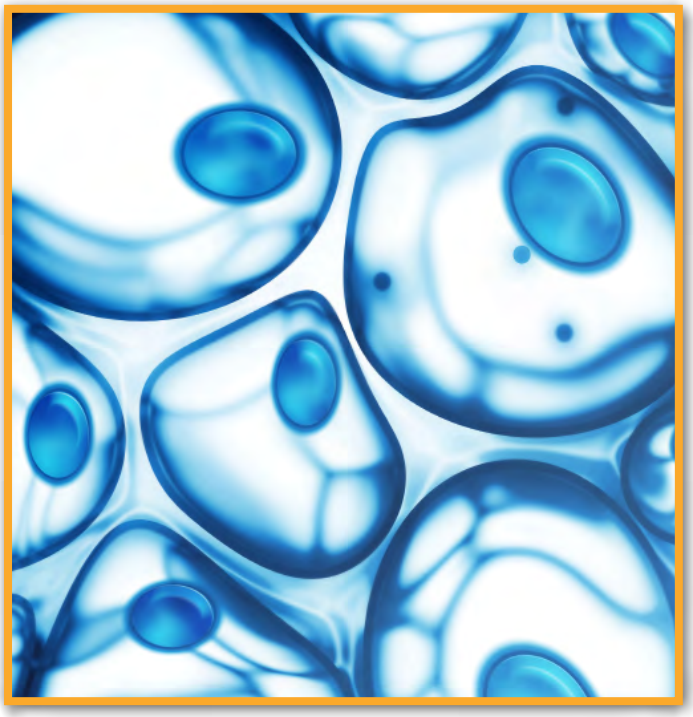
Downstream processing times that are elongated can have a direct impact on cell quality as the scale is upped. Also, as the scale increases the cells are exposed to toxic cryoprotective agents for longer periods during cryopreservation. C. Challener adds that formulation to maintain quality becomes crucial in these cases. [2] On this subject, Elena Meurer commented: "The tip would be to decide early enough what are critical parameters in the quality of the final product, so what has to be assessed and what has to be monitored and what is [the reality] of the influence to conclude about the quality."

**Allogenic:** The commercialisation problem that cell and gene manufacturers encounter is the scale out jump from treating 150 – 500 patients to 500,000 – 1 million [3]. Especially when large scale bioreactors are scarce in supply.

Challenge of population cell size becomes apparent with the high volume manufacturing of allogenic therapies. For instance, C. Challener states that a patient can need hundreds of millions of cells per treatment [2]. Cells have

finite expansion capabilities, which complicates meeting this quota.

**Autologous:** There is a lack of monitoring technologies when it comes to cell expansion – the process of creating a large number of cells on a consistent basis. 2 In addition to this, cells can react to the reagents that enable the material to instruct the cells. Cell isolation



without encountering foreign particles can be a challenge. [2] Scale-out is thought to mostly apply to autologous products to produce an individualised medicine for one particular patient. In this instance the quality of starting material is very important.

"If one thinks about [a] robust process based on small autologous process, the starting material has to be prioritised very well and has to be decided early enough, which is critical to make sure that a good product is resulting from the study material."- Elena Meurer
When upscaling cell and gene therapies, very high numbers of materials need to be handled. When dealing with large volumes of these therapies, Dieter Hauwaerts highlights that logistically there are many challenges to navigate. This involves multiplying the number of containers, shipments, deliveries coming into and going out from a manufacturing site when you have thousands or more of shipments occurring a year.

## Quality Of Starting Materials And Influence On The Efficiency

Raw material can be challenging to manage – in a recent article, it was noted that cytokines and growth factors are often unavailable, costly or can't be reached under the right conditions. [2] Stages such as waste removal can be high risk regarding mistakes. The use of viral vectors can be a great blockage to the upstream process when editing the cells to modify them for use. They need virus particles which C. Challener notes are extensively complex raw materials.[2]

**Autologous:** The sourcing of usable starting material from a patient or donor can be complicated as it is highly variable. Collection is hard to standardise as it is conducted at various sites so therefore there is differing variables in play. [2] Quality of cells can be impacted by the extent of the condition at hand and any previous treatments. Therefore, evaluation tests against clear quality metrics for these materials are vital.

## Regulations

The task for authorities is to assure and verify the safety, quality and efficacy of the therapies they are licensing and simultaneously avoid blocking innovation in product or process from accessing the public or commercial sectors via short timescales and cost efficient means. (5)

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The lack of harmony in regulation regarding the GMP validated production and approval of these therapies presents many obstacles. Companies are still approaching each national regulatory agency independently which results in delays. Using orphan drug status programmes and early adoption schemes where available can speed up a product's route to the patient.

Regulators do acknowledge the complexities of these products and that they are too complicated to assure quality through merely testing to specification. Regulations are focused on the controls and the routines of the manufacturing process due to their direct influence on the end performance of the product [5].

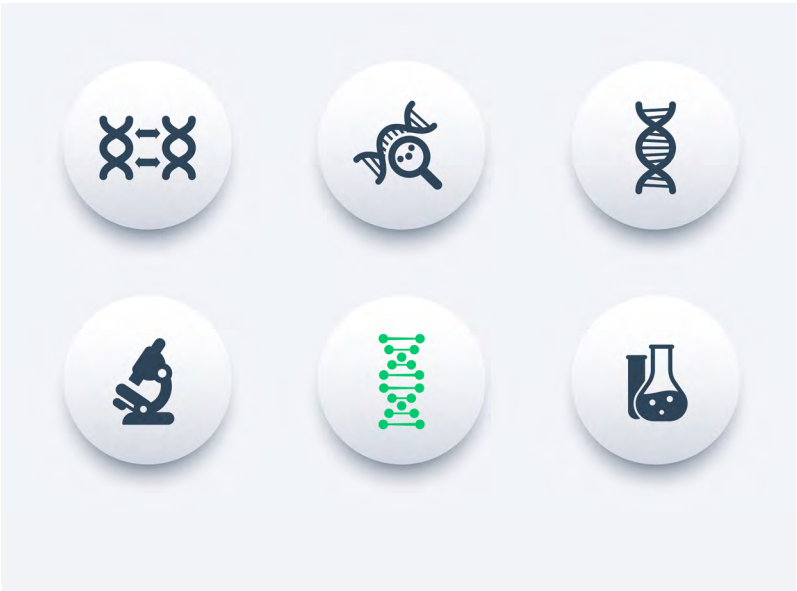
Dr Ryan Guest noted that one emerging method is to deploy cumulative trial design to reduce delays between trial and approval and allowing trials to build on each other. By looking at approaches that are adopted in the market and appreciating that the EU requires good clinical data, producers can look for a rapid single phase trial to reach the level of efficacy that is needed.

There have been a few products that have managed to get the green light for authorisation according to Hourd P, Chandra A, Medcalf N, et al. South Korea approved PharmiCell Co. Ltd's HeartiCellgram®-AMI a bone marrow-derived mesenchymal stem cell (MSC) autologous product, as well as "the world's first allogenic off-the-shelf MSC-based product (Cartistem®; Medipost Co. Ltd)." [5] New Zealand granted approval to allogeneic MSC product from Osiris Therapeutics Inc. – Prochymal.

Industry experts note that allogenic and autologous therapies are handled in almost the same manner regarding compliance. With specific autologous cell therapies, the regulatory concerns focus on their intended clinical use, method of clinical delivery and manufacture.

Dieter Hauwaerts notes that for allogenic therapies, there are still outstanding questions to prove the combination of safety and efficacy at clinical level. There is very promising data at pre-clinical stage, but as of today, limited evidence in the clinic. So to get to a true off-the-shelf therapy, there is still quite some work to be done in the allogenic field.

The EU's Advanced Therapy Medicinal Product (ATMP) Regulation covers Europe's cell-based medicinal products and enforces that all products deemed as ATMPs should undergo a centralised marketing authorisation procedure and comply with Directive 2003/94/EC regarding GMP for medicines. The regulation was



praised for aligning with that of the member states. Individual states hold autonomy regarding the approval of clinical trials and have jurisdiction to block products if deemed necessary in some cases. [5]

There are differences in how the EU and US regulate cell and gene products, which include the following areas:
- The management of starting materials
- Sterility testing
- Monitoring of GMP suites
- Language used
- Levels of particulates
- Detection of microbial contamination.

These differences can complicate the process of parallel distribution in various markets.

## Closed System Processing

Single use closed system processing is a vital part of the commercialisation of these therapies. The untapped knowledge of the blood processing industry in regards to the equipment, materials available and compliant devices required provide a much needed fit for cell and gene manufacturers.

Dr Ryan Guest said: "Bioprocessing has largely come out of industrial pharmaceutical manufacturing with classical bioreactors and was not designed for small scale personalised medicines."

"However the blood processing and apheresis industry, which has been in existence for nearly a century, has a lot of experience and knowhow - which can be adopted by the cell therapy industry.
"A lot of cell therapy companies have come out of blood and cell processing where materials and equipment are largely available off-the-shelf and are manufactured under the medical devices regulations complying with the requirements for direct contact with patient material."

### How are you navigating around traditional challenges faced by the industry in regards to scaling up and extractables and leachables?

**Carol Knevelman, Senior Manager for Process Research and Development of Oxford BioMedica**: "OXB recognized at an early stage the need to develop technology platforms as part of its manufacturing strategy and to adopt single-use technologies with more emphasis on closed processing and automation. We have used Lean systems to help refine our adherent 2D cell culture production systems to be more robust and to reduce the possibility of processing errors and opportunities for product contamination. Our process scientists and engineers have developed a serum-free suspension 3D cell culture platform that is scalable to 200L (and beyond) that can support the rapid commercialisation of these therapies, whilst targeting acceptable cost of goods.

We are also able to apply and leverage the specialist expertise, processes, analytics and know-how that has been developed over many years in order to facilitate the development of products that are being developed by our strategic partners.

**Mark:** "Oxford BioMedica has developed in-house expertise in the design and

implementation of single use technologies throughout its production platforms to help minimise any potential extractables and leachables (E&L) issues. We use a riskbased approach to assess the potential for E&L to enter the product process stream similar to that advocated by the Bioprocess Systems Alliance, and endorsed by the regulatory authorities."

There is a need for closed-system automation solutions that enable commercially viable manufacturing of viral vectors. Some of the technologies that are emerging onto the market include sensors that remotely monitor culture conditions and can make automated adjustments in closed system environments. [2]

Another gap in the market is the level of bioreactors that can expand isolated cells from low amounts to a large volume and simultaneously allow for the starting material's variations due to patient sourcing. [2]

Single use systems in biomanufacturing can greatly simplify the path to market. This is due to the reduction of sterilisation time and spend, lowered labor efforts, swifter set up times, lower cross contamination levels and reduced operating costs in the production of biopharma products. As a result, many are implementing more single use systems within their production lines.

## Supply Chain Collaboration

Live materials need to be transported safely on time within the correct temperature range from the lab to the right clinical sites to ensure their survival. These high volume – high value shipments will be obstructed by weather extremities, delays, road conditions, climates, customs regulations temperature controlled packaging issues.

Validated track and trace systems will be required for transporting these therapies as well as close collaboration with partners. World Courier noted that it works with its partners years in advance in order to calibrate a highly personalized supply chain for cell and gene products. [4]

Niche supply chain hurdles are imposed by the unique logistics infrastructure required by cell and gene therapies (Patient > Manufacturer > Patient). Sascha Sonnenberg, President of Global CTD Sales & Operations at Marken presented a session on this topic at last years Cell and Gene Manufacturing Conference.

The dominant consideration is to, of course, transport the right product to the right patient at a reasonable cost of goods. For this the location of the patient population in comparison to the manufacturer is pivotal. The delicate stability of the products which require tight turnaround times and their expensive price points mean that mistakes in logistics cannot be afforded. In executing transit correctly and efficiently attendees at the meeting last year considered whether patients should be brought to the production site rather than bringing the cell to them. It was mentioned, however, that some subjects requiring these treatments are in critical conditions and so international travel is not always possible.

### Local infrastructure

Local infrastructure is relied upon heavily in the production of these therapies so the

regional capabilities of airlines and airports need to be considered - flight connections, frequencies, seasonal operating patterns, loading capacities and shipping and storage restriction considerations. For example, if dry ice is being shipped there could potentially be restrictions, in some instances the pilot makes the decision on these limitations. If the shipment is unloaded then the process would need to be restarted and materials could be lost. QP release when importing to the EU can cause delays in transport and cause materials to be lost.

## Partners & stakeholder support

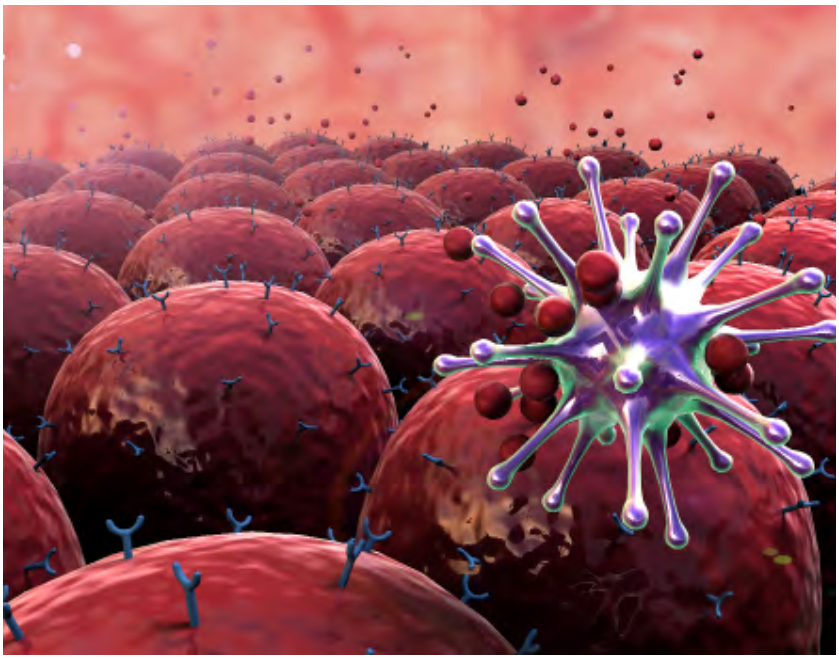
The location of sourcing partners for materials is another factor to account for the process. Also, their capabilities and experience to adequately support producers needs to be assessed as cell and gene medicines are complex to produce and transport. Training may be needed also for instance to prevent non-sterile raw material microbial contamination. Suppliers need to be audited and quality agreements need to be agreed upon.

Partners need to support in managing the chain of custody and identity with constant communication. With separated communication channels, there is a danger that information could be missed like upgrades in packaging requirements. Some firms use procurement as a template for biosample handling.

## Logistics Systems

Documented lane verification and administration for transit and customs clearance timelines are very influential on the success of transporting a cell and gene therapy. With the handling of systems, authorisation of access to systems needs to be delegated. Automation should be applied wisely to aid workload without harming the precision of efforts. Firstly, an enhanced level of visibility of integrated systems is needed to enable automation. Ordering tracking and system interfaces can assist with the transit of these products.

The reverse logistics attached to some temperature control containers and dewars can act as a large blockade for some pharma firms. With closed loops being a necessity, reverse logistics apply additional costs and operational burdens.



In response to burdens of reverse logistics Jeroen Janssens, Senior Manager, Vaccine Distribution & Cold Chain, GSK Vaccines reminds: "We are here to manufacture pharmaceutical products, not to organise logistics flows of empty containers." In

response to this sort of opinion and with greener cold chain packaging solutions rising in popularity, the suppliers of these packaging solutions, or even LSPs, have started to include the reverse logistics in the rental costs for units. One attendee at the event noted that volumetric changes could be made to the packaging of the therapies to reduce cost burdens on the supply chain. Ancillary investments can be applied to incur savings in the overall shipment for example using plastic instead of glass vials can make significant savings. Especially if thousands of shipments are being made.

In regards to contamination requirements, packaging needs to maintain the stability of the product and have the ability to be frozen. Contamination control should apply sterile over wraps on the therapies as well as validating the stability and integrity of thermal cycle and cleaning the containers used for transit.

Contamination can occur at any stage. One case discussed at the conference noted the presence of a bug living inside the wrapper of an iVbag which was found to have infiltrated the product once it gained entry into the critical production area. Improvements are needed in the industry concerning conflicts on how contamination is handled with policies and procedures by the bedside.

## Materials

The more stable the product's materials are, the greater the delivery flexibility. In Sascha Sonnenberg's session it was noted that the product stability in fact directs the distribution and manufacturing strategy. For instance, in the selection of a centralised single site model or a multi site approach. This also stretches to the temperature management solutions chosen. Perhaps by avoiding using liquid nitrogen or dry ice can manufacturers can sidestep adding weight and costs later on. He added that it's important to remember with cell therapy it isn't about shipping, but handling a chain of identity and custody so that materials are maintained.

In preserving the chain of identity, firstly, materials need to be qualified and validated, therefore the suppliers will need to be audited also. Contamination of the designed cells can occur at any stage. Qualification must start with the raw biological material. Samples of material need to be tested at procurement. Quality of what is being put in needs to be assessed as well as the final packaging to see if it is suitable for the product's life cycle and process. A slip up in this area can have adverse consequences. The whole process should be designed to ensure that the product has the most minimal risk of contamination.

## Commercial Scale-up & Scale-Out Considerations

When going commercial with a cell and gene therapy, members at the conference noted that

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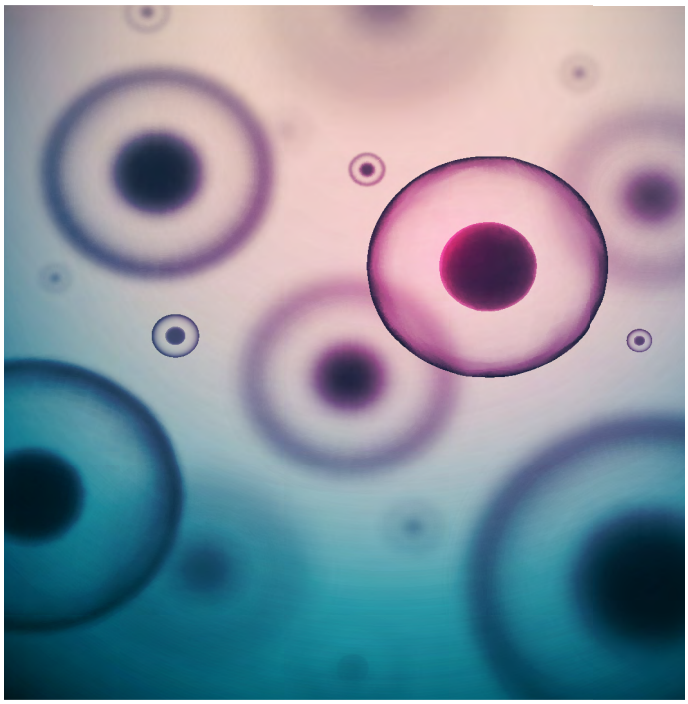
it would be a mistake to view it as a brand new supply chain. Instead, scaling up, scaling out and the robustness of the supply chain need to be considered from the primary stages. When scaling up the additional weight incurred by the therapies is a significant change has a large influence on budget. It was mentioned that manufacturers can expect 60% of budget to go on to the logistics of the cell and gene therapy.

Automation is very productive for the commercial scaling up stages. System integration is similarly important when uplifting volumes. These points will ensure that the right cells are transported to the right patients with a reasonable cost of goods.



## Take Action And Attend:

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**Attend this Year to:**

- Determine what needs to be considered when **moving from the research stage to commercial production,** identifying the opportunities and challenges in ATMP
- Look at the different challenges surrounding both **open and closed system processing** and identify the best approach to enhancing your system
- Understand the best method for improving **logistics and product stability at the final stages** of the bio manufacturing process allowing you to start creating the optimal system
- Study what the opportunities and barriers are when looking to **scale up production** allowing you to plan ahead for your manufacturing process

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Resources:

1. http://www.bioprocessintl.com/manufacturing/cell-therapies/quality-control-during-manufacture-of-a-stem-cell-therapeutic-328530/
2. C. Challener, "Cell and Gene Therapies Face Manufacturing Challenges," BioPharm International 30 (1) 2017.
3. http://insights.bio/cell-and-gene-therapy-insights/?bio_journals=visualizing-the-cell-and-gene-therapy-supply-chain-of-the-future
4. http://www.biopharmadive.com/news/global-logistics-supply-chain-strategies-for-cell-gene-therapies/436182/
5. Hourd P, Chandra A, Medcalf N, et al. Regulatory challenges for the manufacture and scale-out of autologous cell therapies. 2014 Mar 31. In: StemBook [Internet]. Cambridge (MA): Harvard Stem Cell Institute; 2008-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK201975/ doi: 10.3824/stembook.1.96.1