

## CELL & GENE THERAPY INSIGHTS

AUTOMATION: MIGRATION FROM  
MANUAL PROCESSES TO  
CLOSED-SYSTEM AUTOMATION

SPOTLIGHT

### EXPERT INSIGHT

# Automating decentralized manufacturing of cell and gene therapy products

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Decentralized, or redistributed manufacture, is likely to be the manufacturing approach of choice for some cell- and gene-based therapies, in particular, personalized therapies. Such an approach will ultimately depend on the business model and will take into account the regulatory and supply chain factors. Advances in technology and integration of automated production platforms have demonstrated the potential for decentralized manufacturing, however there is a need to extend the scope of automation across the entire process including the cell isolation, distribution, tracking, administration, quality management systems and development of automated analytical techniques to facilitate real-time release. For decentralized manufacture to be successfully integrated for cell and gene therapy production, lessons from other accepted healthcare-associated models of manufacture can provide useful insights and perspectives to make informed decisions. Such models share similar characteristics to decentralized manufacture in that they are patient-specific and have a limited time-frame for administration. These existing approaches, which have successfully incorporated aspects of automation, can provide a blueprint for success and may expedite the decentralization of patient-specific cell and gene therapy manufacture.

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Since the industrial revolution, the manufacturing paradigm has changed from a localized, decentralized means of production toward an increasingly centralized operation.

Such an approach has facilitated cost-savings through economies of scale and scope. However, for certain cell and gene based therapies, in particular autologous products, it is

likely we will witness a reversion to a redistributed, decentralized manufacturing approach. This is coupled with recent advances in technology that have permitted reproducible,



repeatable and reliable manufacture of highly specialist products at a small scale [1-5]. Equally important, however, are the advances in real-time monitoring and quality management systems (QMSs) which ensure that these small-scale manufacturing platforms are continuously monitored even in the absence of skilled human operators.

As technological progress in small scale manufacturing has advanced, the potential to manufacture inherently unstable, personalized cell and gene therapy products has become close to being realized. Rather than the large-scale manufacture of products with accompanying well-connected shipping and distribution networks, the regulatory, clinical and commercial requirements of personalized therapies will benefit from a redistribution of these facilities, decentralizing them towards a range of smaller manufacturing units able to respond in an agile manner by producing smaller batches of advanced, customer-specific products.

### DEFINING REDISTRIBUTED MANUFACTURING

As with many newly coined terms, the definition and scope of “redistributed manufacturing” is still fluid. Recent white papers and focus groups from leaders in the field have examined the scope this encompasses [6,7]. Current understanding is that redistributed manufacturing will be local to the patient, flexible and reproducible whilst at the same time being more sustainable than centralized manufacturing due to its efficient use of resources. With distribution of manufacturing, particularly of advanced

healthcare products, there is a regulatory requirement to ensure that the products manufactured at the distributed facilities are equivalent and meet the same specification. For this reason, the manufacturing process or system must be robust, resilient to external or internal challenges (such as changes in supplier of manufacturing equipment and changes in staff, respectively) and able to re-configure (e.g. increase or decrease the number of commissioned manufacturing units) in order to meet demand.

### Blueprints for success

Whilst no ‘ideal model’ of redistributed manufacturing currently exists for cell and gene therapy production, there are a number of accepted models of manufacture currently being utilized in the market that can provide a useful perspective for decision making and from which lessons can be drawn when considering this approach. These include the manufacture of radioactive pharmaceuticals for nuclear medicine, personally-titrated anti-cancer agents, total parenteral nutrition products and blood and platelet supplies. These operational models have many of the characteristics of the redistributed model for advanced therapeutics in that they are responsive to local clinical requirements, personalized to the patient, delivered (often before full analytical characterization) within a narrow time window and, in some cases, require aseptic manufacture.

Whilst there are some notable differences between the manufacture of more conventional healthcare products and cell and gene therapies, there are a large number of instructive parallels that can be drawn. These parallels are summarized in **Table 1**. By examining these

**TABLE 1** Comparison of current decentralized healthcare manufacturing paradigms that are relevant to cell and gene therapy redistributed manufacturing.

	Cost of infrastructure	Product stability	Transport window	Risk of product loss due to supply chain failure	Degree of product customization
<b>Nuclear medicine</b>	<b>High</b> Technetium-99m manufacturing infrastructure very high and subsidised by states. Cyclotron production feasible but requires significant investment.	<b>Low</b> The technetium-99m precursor is stable for days but must be purified prior to end use. Radiopharmaceuticals for PET imaging are stable for a matter of hours.	<b>Hours-Days</b> The transport window ranges from ~2 hours for cyclotron produced PET imaging radiopharmaceuticals to days for the technetium-99m precursor.	<b>Medium-High</b> PET tracers have a very short window for use but have short travel time making local co-ordination easier. Technetium-99m must be transported over long distances / internationally reconstituted and used within a short time span. Delays more likely.	<b>Medium</b> Due to half-life degradation, technetium-99m product must be purified at, or close to point of use which is challenging. Overall product is not fully customized to patient.
<b>Total parenteral nutrition</b>	<b>Low</b> Cost of production of constituents relatively low. Generic drugs, nutrients and macromolecules require cGMP aseptic production.	<b>Medium-High</b> The constituents for TPN are relatively stable drugs, nutrients and macromolecules. Some may require refrigeration but generally they are stable products.	<b>Days</b> Constituents of TPN are stable at ambient - low temperatures. Shipping is neither costly nor challenging. Largest difficulty is having available all potential variations but stockpiling is possible.	<b>Low</b> Stable products which can be stockpiled. Several key constituents are listed as in short supply which could make shipping decisions more challenging if triage decisions are required.	<b>Low-High</b> Products for TPN can be almost entirely off-the-shelf, pre-made formulas or entirely bespoke formulas made up for the patient on the spot.
<b>Blood supply</b>	<b>Medium</b> The large collection and distribution is expensive but built on tried and trusted technologies. The process and products are well understood.	<b>Medium</b> The stability ranges from 5 days (platelets) to 42 days (red blood cells) and plasma and cryoprecipitate (1 year). Blood can be used as a raw material for human derived products with longer shelf lives.	<b>Hours-Days</b> Blood product stability and storage conditions vary. Triage must occur and certain products expedited to destination. Stockpiling can occur and excess product used as raw materials for protein products.	<b>Medium-High</b> Supply chain must expedite certain products and handle shipping between locations if there is a glut in one location. Current management is challenging and it is suggested better modelling can reduce supply chain failures.	<b>Medium-High</b> Over 100 products can be derived from blood. Most blood products are semi-customized type-matched to the patient.
<b>Anti-cancer medicines</b>	<b>Low-Medium</b> Custom medicinal formulas are currently off-the-shelf combinations of existing therapies. Emerging anti-cancer therapeutics may have a higher infrastructure cost attached to them.	<b>High</b> Off-the-shelf medications have a high degree of stability. Emerging treatments and therapeutics may have a more advanced production and storage chain depending on the formulation.	<b>Days</b> Constituents of customized therapies are stable at ambient - low temperatures. Shipping is neither costly nor challenging. Stockpiling is possible. Emerging therapies may have slightly more challenging characteristics.	<b>Low</b> Current drug combinations are stable products which can be stockpiled making supply chain failure unlikely. Future therapies may need to be less off-the-shelf in nature and be at higher risk of supply chain failure.	<b>Low-Medium</b> Therapies can range from a single pharmaceutical to a customized combination prescribed by clinician. The degree of customization fits in to a framework of understanding. Future therapies may have a higher degree of customization.

four paradigms we can begin to understand the requirements that are necessary for a cell and gene therapy product or manufacturing solution to align with the existing market constraints. These otherwise hidden costs of adoption are likely to be of higher significance than the technical features of any single manufacturing solution, or the efficacy of any product, in terms of their effect on market penetration. Anything new must fit within, or only just outside current practice. If too large a change to practice in procurement, stock management, prescription, dispensing or administration is required before a product or solution can be adopted then the change will be resisted.

For a decentralized manufacturing system to succeed, the technology must be robust and reproducible and there must be significant process and product understanding [8]. The relationship between the variation in properties of the starting material, the control strategy for manufacture and the product features must be well understood. With the progression in manufacturing solutions for cell and gene therapies, as well as an enhanced understanding of their mechanism of action, there is renewed optimism that patient-specific therapies can be a clinical and commercial success.

The manufacture of cell and gene therapies will undoubtedly incur high costs for changes to infrastructure, requiring significant investment. This cost has traditionally been spread over large numbers of product units by using large centralized facilities but, as PET radioisotope production demonstrates, high cost products can be manufactured in a distributed manner close to the end point of use. By manufacturing

perishable goods (in the case of radioisotopes this means goods with a short half-life) locally, the risk of product loss due to inefficient transport networks is also reduced.

It is possible, particularly for allogeneic cell products, that a combination of central and local preparation is suitable for optimal manufacturing, with an intermediate product being prepared at a central facility and forwarded to local facilities for finishing as small campaigns for immediate application to patients [9]. This has the dual advantage of enlarging the transport window by shipping the intermediate at low temperature (allowing some flexibility in shipping dates due to its stable form) and manufacturing the Drug Product in its final formulation on-site, similar to the way that technetium-99m radioisotope purification takes place. This also reduces the risk of supply chain failure as patients are not dependent upon the long-distance shipping step, but merely the local supply where delivery timing is more easily controlled. This solution also potentially offers a higher degree of customization at or near to the point of use whilst maintaining economies of scale for production of master stock (the intermediate) at a centralized facility [9].

### EXISTING MANUFACTURING & DISTRIBUTION SOLUTIONS

Development of successful distributed manufacturing platforms for cell- and tissue-based therapies has the potential to provide huge benefits to the health of society. Realizing these goals will, however, require a

substantial improvement in available technology not only for manufacture of products, but also for analytical and monitoring purposes to facilitate real-time release. Many experimental approaches for scalable manufacturing and online and non-invasive monitoring demonstrate great success in this area.

Whilst the growth of such well-established cellular platforms as Chinese Hamster Ovary (CHO) cells in scalable, automated bioreactor systems is well established [10], the scalable culture of adherent cells has proved more challenging [11–14]. Adherent therapeutic cells such as dermal fibroblasts, chondrocytes or mesenchymal stem cells, are typically produced using planar technologies (flasks). By adding multiple levels to each flask this production method has been scaled up to progress several allogeneic cell therapy products into mid- to late-stage clinical development. This however limits culture area for planar culture to around of 3–5 million cm<sup>2</sup> per lot, translating to total cell production batches of 100–400 billion cells for most adult primary cell types [11,14,15]. This approach has been used successfully for around 30 years and could theoretically be a template for how manufacturing of cell and gene therapy products could be automated [16–18]. Indeed such automated manufacturing approaches for adherent cell processing for vaccine production have been used for clinical and commercial success [19,20].

The default strategy for maximizing lot size in planar vessels is to adopt a scale-out approach, i.e. to increase the total surface area that is to be manipulated per unit operation and then replicate production in multiple units.

However for many clinical indications, achieving lot sizes of several hundred billion to trillions of cells will be imperative for commercial success; utilizing high-density bioreactor manufacturing platforms, such as stirred-tank bioreactors in conjunction with microcarriers, is likely to be the only way to accomplish this [21–25].

As our process and product understanding increases and we improve our knowledge of the mechanism of action of therapeutic biologics, we can begin to investigate methods to facilitate process intensification with increased confidence. Centralized production allows for a reduction in costs in numerous areas (mainly the fixed overhead costs) by locating many aspects of the product development life-cycle centrally [9]. The decision to move to decentralized production will forego this simplicity and requires a comprehensive economic assessment in each case, which will include a clear understanding of who the potential customer is and where they are located in the value chain before undertaking significant investment decisions [9,26].

In order for decentralized manufacturing to succeed, effective procedures for managing and automating procurement of starting materials and consumables, tracking of work in progress, release of product and overall administration must be prepared. The burden of cost when this is done on a product-by-product basis is extremely high. By developing generic operations into a series of standards that can be adopted by new businesses at a pre-competitive stage of business development, this cost and responsibility can be reduced and barriers to investment in the field can be lowered.

### AUTOMATION OF ADMINISTRATION

Automation of manufacturing processes has the potential to enable adoption of decentralized manufacturing through smart and online control. It will also provide greater oversight through tracking and will aid administration of manufacture. If current manufacturing approaches employ a centrally managed QMS, how could we move to a distributed QMS which would require an alternative to traditional oversight? Automation of manufacture in a decentralized network can enable QMS changes to be rolled out across all sites via changes in operating software, thus ensuring mandatory compliance across sites. This ensures all sites, regardless of where they are located will be working to the same procedure all the time. This process could allow for QMSs to be partially decentralized, permitting cost-saving measures to co-exist with current regulatory requirements.

Knowledge of how the dominant features of manufacturing may alter the functionality of biological products is critical to any success with decentralization and will facilitate automated manufacture [5,9]. It is anticipated that the adoption of automated manufacture will decrease variability in the quality of manufactured cell products, resulting in more consistent clinical outcomes that exhibit both reproducibility and, importantly, dose-responsiveness. Poor understanding of the link between potency and product characteristics makes it challenging to develop a series of assays which reliably predict the result of a batch *in vivo* [27,28]. This situation is further complicated by the fact any assays of a fresh-preserved product must be completed rapidly as non-frozen cell-based

products are not stable. This is not a problem in radiopharmacy where PET radioisotopes are assayed very rapidly as the half-life of the product is measured in hours. However, biological potency tests can take days or even weeks to yield results which make “at risk” release of batches unavoidable.

Product release should depend ideally on rapid quality control testing and as biological testing practices advance this is likely to become a reality. For testing to be effective however, there must be a series of standards with which to compare to the product. Manufacture of standards of simple biological products could improve this situation dramatically and the nature of the standard may not necessarily require full replication of the product analysis. For example, could the therapeutic potential of cells in which the mode of action involves release of lipid vesicles be assayed by comparing the vesicles in the batch to a standard and if so what would this standard look like? By manufacturing simple, relatively stable biological products such as liposomes to a prescribed protocol known to generate a batch of predictable characteristics, a range of simple standards could be established that could be used as comparators.

As the product moves through the manufacturing and distribution supply chain, automated online tracking and monitoring will be an advantage. Decentralized manufacturing increases this challenge for such tracking as material movement is complex yet compliance must still be demonstrated. Cell and gene therapy products can usefully ‘piggyback’ on the existing infrastructure such as the blood product supply network not only to provide

a template for success (blood transport wastage is estimated at ~2%) but also to minimize transport costs as barrier to adoption. Automated, online monitoring systems and full chain of custody recording will be an absolute necessity for decentralized manufacturing in order to comply with Good Distribution Practice. This will not only minimize the opportunity for loss and mix-ups, but will also ensure process compliance and aid detection of any problems that occurred during supply that may result in inadequate efficacy of a product unit. This final point could be critical for identification why a specific biologic did not work as expected in any given patient.

### TRANSLATIONAL INSIGHT

With technical capability of cell and gene manufacturing systems advancing rapidly, the promise of large-scale, small-footprint redistributed manufacturing is becoming a reality. Whilst there are still gaps in automation of manufacture and supply which may not currently be filled without a human operator, there are promising automated solutions emerging which should be able to fit into existing manufacturing platforms. Current analytical quality control systems are often limited by the rate of throughput of samples and many are destructive or sample-altering in nature. A range of measuring systems for cell- and tissue-based products are needed that are non-destructive and near real-time in measurement [27].

Shipping and automated tracking of cell and gene therapy products is still a nascent area, ripe for innovation and development. With the pressure on innovative companies to reach clinical trials early there has been little opportunity

for developing an understanding of how the product should be shipped and handled or how this could affect cell function. Automation and tracking of the upstream scheduling and downstream production for cell and gene therapy products will be critical for managing material across distributed sites. Perhaps more important than this however are the insights into correct shipping and handling procedures for these biological products.

As challenging as the technological requirements are the radical changes that redistributed manufacturing will bring to the role of the operator. These involve a substantial change in the organization of labour and roles for human operators, increasing the number of manufacturing staff across a network but lowering the level of skill required because of the extent to which the automated platform replaces expert knowledge. As the burden of responsibility shifts from operators to machines, a system is required that maintains regulatory compliance but is still similar enough to the current QMSs to be acceptable from a societal standpoint.

Decentralized manufacturing has the potential to revolutionize the way we manufacture cell and gene therapy products. Patient needs can be met locally by a system which digitally manages and monitors patient and product requirements as part of an automated platform. In order to reach this state however there are a number of technical objectives that must be met. In order to create a system which is both flexible and replicable, significant progress in online monitoring and culture automation must be achieved. Progress in these areas is promising, particularly for a large

central facility, but providing all of these in a small footprint with minimal staffing is currently not feasible.

Products manufactured at each facility must be equivalent in quality, every time. In order to meet the challenge of a local distributed facility at geographically diverse locations, each distributed facility must meet the same rigorous specification. Automation on the product manufacturing side is a component of this, but automation of the administration, tracking and QMSs is an equally important share. Solutions for these already exist in other healthcare sectors and these paradigms can provide blueprints on which to base decision-making. Finally, it is important to remember that technical success of a manufacturing solution is not the sole indicator for success; even the most brilliant products must sit close enough to the limitations of the current marketplace in order to overcome the invisible barriers to adoption.

## FINANCIAL & COMPETING INTERESTS DISCLOSURE

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