WHITEPAPER

Enabling Decentralized Manufacturing of Autologous Advanced Therapy Products: A Review of Emerging Technologies

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Abstract

Advanced Therapeutic Medicinal Products (ATMPs), particularly Cell and Gene Therapies (CGTs), are pivotal in regenerative medicine. However, there's a significant shortage in manufacturing capacity for these therapies. This paper discusses the transition from Centralized Manufacturing Model (CMM) to Decentralized Manufacturing Model (DMM), which could reduce costs and logistical complexities, especially for autologous ATMPs. The introduction of Automated Closed-System Processing Units (ACPUs) is explored as a means to standardize manufacturing processes and reduce contamination risks. The paper also delves into the challenges of tracking and transporting sensitive material in the supply chain, proposing solutions like real-time tracking devices and drone technology for remote areas. Additionally, the importance of electronic document management for regulatory compliance and efficient data handling is highlighted. Lastly, the paper touches upon quality control and product testing at the point-of-care, emphasizing the use of modern equipment to ensure safety and consistency of ATMPs.

Introduction

Advanced Therapeutic Medicinal Products (ATMPs), including Cell and Gene Therapies (CGTs), have become a core segment in the growing field of regenerative medicine. However, despite more than 20 autologous and allogeneic ATMPs on the market, there is an estimated 500% shortage of manufacturing capacity compared to the demand [1, 2]. In fact, research suggests one fifth of eligible cancer patients waiting on a CAR-T therapy don't survive the waiting period for a manufacturing slot [3]. For autologous ATMPs, challenges associated with their unique scaling restrictions being made-to-order rather than made-to-stock are especially limiting to their widespread distribution [4]. While traditional manufacturing practice, known as the Centralized Manufacturing Model (CMM), is suited to supply patient-specific, autologous ATMPs to local health centers in high-infrastructure regions, scaling them for global and rural markets is significantly more expensive and logistically challenging than scaling their allogeneic counterparts [4]. Transitioning to the Decentralized Manufacturing Model (DMM) would bring down cost and complexity associated with the distribution and logistics of ATMPs, especially when considering rural and global markets [4]. The DMM may also be implemented in parallel

or in partnership to the existing CMM in high-infrastructure regions to bridge the manufacturing shortage and provide regional manufacturing services and reduce travel requirements for rural patients. While considering the associated challenges with the DMM, such as ensuring regulatory requirements, consistent environmental parameters across sites, and reliable supply-chain and document management, recent developments in modern technology can both provide solutions to these challenges and reduce current treatment cost to patients [4]. Here we will review some areas of emerging technology that can facilitate the advent of widespread decentralized manufacturing for autologous ATMPs.

Automated Closed-System Processing Units

Obtaining more control over the ATMP manufacturing processes is a major initiative within the industry. Additionally, upholding regulatory requirements across multiple sites in a DMM is a potential challenge to manufacturing at the point-of-care. A solution to standardizing manufacturing processes is adopting end-to-end manufacturing equipment such as Automated Closed System Processing Units (ACPUs). These ACPUs can be automated and digitized, are a closed system, require minimal operator interaction, and minimize batch to batch variability [6, 7]. Examples of ACPUs are the Cocoon® (Lonza, Basel, Switzerland) and CliniMACS Prodigy® (Miltenyi Biotec, Bergisch Gladback, Germany). These units can operate in a lower grade ISO 7 (Grade C) cleanroom, as opposed to an ISO 5 (Grade A or B) cleanroom which are traditionally used in open-system manufacturing sites in a CMM [8]. ACPUs can operate individually as a stand-alone unit or may be linked together to allow flexibility in the number of patient samples that can be processed in one cleanroom space [9]. The closed-system design of ACPUs minimizes contamination risk because they protect the patient material from environmental exposure, use sterile and single-use components, and enable sterile collection of in-process samples [6, 9]. Additionally, automating the manufacturing process reduces operator interaction and has demonstrated improvement in product consistency and process repeatability while lowering labor and space requirements [6, 7, 9]. ACPUs can be placed both at the point-of-care or at a centralized facility, and their closed-system, automated, reduced operator input design decreases labor and manufacturing cost of ATMPs as compared to traditional, open-system manufacturing [9].

Tracking and Transport Logistics

Other pain points in manufacturing autologous ATMPs are the logistics involved in transporting the patient material to the manufacturing site and back to the patient. Key risk factors include reliable packaging and storage, trackable shipping, maintaining equipment validation, and upholding chain of custody documentation [4, 10]. ATMPs such as CAR-T therapies are sensitive to temperature and stress, so experience in handling during transportation is critical for product stability and safety [10]. Capturing data in real-time is also essential for both the clinical and manufacturing teams. A solution to monitoring the environment can be achieved by early-phase devices such as Pebble Trackers (IoTeX Blockchain, San Francisco, CA). The trackers are equipped with an expansive array of sensors — internal and external GPS, environmental monitoring (temperature, humidity, air pressure, air quality), motion changes (acceleration, angular velocity), and light intensity [11]. Monitoring a chain-of-custody for human material that is encrypted and tamper-proof ensures the right patient receives the right treatment at the right time, while also guaranteeing it was maintained at the right conditions. [5]. Real-time tracking and tracing of material by clinical and manufacturing teams also informs decision making in the event of delays or contamination, and this real-time data may serve as a tool for early communication to ensure the patient and clinical team can prepare for a safe and seamless treatment schedule.

Another challenge in creating a dependable supply chain, particularly in low-infrastructure regions, is managing disruption in conventional transportation systems such as adverse road conditions or vehicle access barriers. Incorporating drone technology as a tool to sustain global supply-chains can also remove limits accessing previously isolated patient populations and reduce time required to replenish supplies in developing regions. Small aircrafts in early-phase development such as those developed by Wingcopter (Wingcopter, Darmstadt, Germany) and Matternet (Matternet, Mountain View, CA) are currently in use and validated to transport medical supplies [12, 13]. With further cold chain transport development, these airborne vehicles may facilitate access to remote regions and allow for widespread, global manufacturing of autologous ATMPs.

Electronic Document and Quality Management

The unique logistics associated with delivering autologous ATMPs has made optimizing and streamlining document and quality management critical across multiple sites. Under the DMM, manufacturing may occur near the clinic and patient, but to ensure proper documentation and validating the standard of care across sites and regulatory requirements, there is a need for a digital platform to integrate and coordinate between the clinical team and the manufacturer. Specifically, there is an opportunity to enable cloud technologies and blockchain [13]. ATMP specific enterprise software and operation platforms such as Tulip (Tulip, Somerville, MA), Vineti (Vineti, San Francisco, CA), and Lonza MODA-ES (Lonza, Basel, Switzerland) are cloud based, digital systems that manage ATMP data and traceability, and are critical to documenting and validating regulatory requirements at the point-of-care. The patient-specific paradigm of autologous ATMPs requires confidential, patient-specific tracking and management of data from product release testing to ensure the right patient receives the right therapy, safely and efficiently [14, 15]. An example of a software platform is Tulip, which integrates multiple hardware devices and sensors into a customizable dashboard to create and execute electronic batch records which can be used at any site with the software available [15]. Using apps and integrative software increases access to data and visualizations across users on all ends of the process to better inform decisions and manage sites and product chain-of-custody [15]. Other platforms such as Lonza MODA-ES can use information generated by the manufacturing process to streamline the process itself and let systems adjust, rather than operators [17]. Integrating cloud-based platforms for document management in the manufacturing process assure details like starting materials, in-process manipulations, in-process sampling, and tracking up to the end-product delivery to the right patient are visible in real-time to those involved [16].

Quality Control & Product Testing

Finally, when manufacturing products for human treatment, safety is first. Autologous ATMPs undergo In-Process and Final Product Release testing to ensure that the end-product meets all the predetermined critical quality attributes (CQAs) [17]. The challenge when considering a DMM is how to properly and efficiently perform these tests at the point-of-care where access to labs for analytical testing may not be consistent across sites and the product has a short shelf-life. However, modernized sensors and analytical equipment are now able to accelerate Quality Control assays and protocols to streamline product testing regardless of where the lab is [17]. Measuring product identity via flow cytometry in the manufacturing process can be measured through the integration of MACS® Flow Cytometry (Miltenyi Biotec, Bergisch Gladback, Germany) and CliniMACS Prodigy® allowing for a streamlined finish of the final drug product. Other product identity testing options like a Benchtop Flow Cytometer (Accellix Israel, Jerusalem, Israel) can produce results as quickly as 15-30 minutes with minimal training and calibration to operate [18]. Other QC evaluating tools, like products from bioMérieux (bioMérieux, Marcy-l'Étoile, France), can evaluate product sterility and levels of endotoxin and mycoplasma in automated units with low operator requirements and release results in just a few hours [19]. These are just a few examples of analytical technologies to show how a DMM can integrate analytical capabilities and speed up delivery of drug products to patients. Some of these technologies are new and require further validation before they can be used as part of GMP compliant final product release testing protocol, but developing technology to uphold and validate GMP regardless of existing lab infrastructure could facilitate the full potential of a DMM for autologous ATMPs.

Summary

Adhering to traditional manufacturing methods for a product as novel and complex as autologous ATMPs has created a considerable deficit in manufacturing slots for patients, up to 500% [3]. Adopting an alternative Decentralized Manufacturing Model to the traditional Centralized Manufacturing Model may be the solution to bridging the gap between manufacturing slots and patient demand while removing accessibility and financial barriers to global and rural markets. Although there are inherent challenges associated with enabling manufacturing at the point-of-care, new ideas and innovative technologies may be the solution

to ensuring regulatory requirements are met across all sites, ensuring environmental parameters are maintained during the manufacturing process, and ensuring the most reliable and traceable supply-chain and document management so that new and established ATMPs can continue bettering the lives of the patients they serve.

References

1. Rader, R. Cellular and Gene Therapies Face a Manufacturing Capacity Crunch. *BioPharm International.* September 2020.
2. Paglia, M., Eaker, S. Fueling The Genetic Revolution With cGMP Manufacturing And Training. *Cell & Gene.* May 2022.
3. Coppens, D., Hoekman, J., et al. Advanced therapy medicinal product manufacturing under the hospital exemption and other exemption pathways in seven European Union countries. Cytotherapy. Volume 22, Issue 10 (592-600). Sept. 2020.
4. Papathanasiou, M., Stamatis, C. Autologous CAR T-cell therapies supply chain: challenges and opportunities? *Cancer Gene Therapy*. January 2020.
5. Triantagyllou, N., Bernardi, A. A digital platform for the design of patient-centric supply chains. *Nature Portfolio*. 2022.
6. Lonza Cell & Gene. Cocoon® Platform: The Next Step in Cell Therapy Manufacturing. www.*lonza.com.* 2012.
7. TerumoBCT. Quantum® Cell Expansion System: Product Confidence. Process Scalability. *www.terumo.com*. 2015.
8. Cell Therapy Handbook. *ThermoFisher Scientific.* 2021.
9. Miltenyi Biotec. CliniMACS Prodigy® T Cell Transduction Process. www.miltenyibiotec.com. 2020.
10. Discover IoTeX. *Take control of your data with Pebble.* www.iotex.io. 2023
11. Matternet. *Applications: Healthcare.* www.mttr.net. 2023.
12. Wingcopter. *Drone Delivery Solutions.* www.wingcopter.com. 2023.
13. Mooraj, H., Kawalekar, O. Cell and gene therapies. *Deloitte Insights.*
14. Vineti. What is the Vineti Personalized Therapy Management® (PTM) cell therapy platform? *Platform Overview.* www.vineti.com. 2023
15. Tulip. *Building the Premier Frontline Operations Platform*. Tulip.co. 2023.
16. The Cell and Gene Therapies Journey from Translation to GMP Production and Commercialization. *PharmaIntelligence Informa.* June 2021.
17. SCB Regenerative Medicine. Project: Chain of Custody/Chain of Identity. www.standardscoordinatingbody.org. 2023.
18. Accellix. *Accellix Instrument & Software.* www.accellix.com. 2023.
19. Biomérieux. *Pharma Quality Control Diagnostic Testing.* www.biomerieux-industry.com. 2023.