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Bringing treatments closer to patients: Can Point-of-Care Manufacturing represent the third viable business model?

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The landscape of autologous Advanced Therapy Medicinal Products (ATMPs) manufacturing is growing: new products are entering the market and Point-of-Care manufacturing (PoC) could play a significant role to bring them closer to patients. PoC manufacturing refers to the process of producing therapies at or near the location where they will be administered to patients. ATMPs demand highly GMP regulated manufacturing processes, specific skills, and infrastructures. One product batch is often linked to an individual patient, meaning that a scale-out model might be more appropriate than a scale-up one. In the attempt to bring therapies closer to patients, PoC manufacturing for autologous ATMPs is emerging in clinical settings as a potential solution to enable faster treatment initiation and improve access to ATMPs for those in need (1; 2; 3).

This article explores if Point-of-Care manufacturing for autologous ATMPs in the European Union (EU) can represent a third viable business model in addition to central and regional manufacturing.

Introduction

Advanced therapy medicinal products (ATMPs) are a category of medicinal products for human use, that include Gene Therapy Medicinal Products (GTMPs), Somatic-cell Therapy Medicinal Products (sCTMPs), Tissue-engineered Products (TEP) and Combined Advanced Therapy Medicinal Products (CATMPs) (4).

Cell and gene based ATMPs are often referred to as Cell and Gene Therapies (CGTs), and they have experienced significant growth (>2700 of developers, >1600 clinical trials around the world, and new products being approved in the US and/or EU markets every year) due to their potential to address conditions like severe immune system diseases, hematological cancers, and genetic disorders (5; 6). There are two categories for CGTs: autologous and allogeneic. Autologous CGTs require the collection of cells from the patient, followed by genetic manipulation outside the body to introduce therapeutic genes or correct genetic defects, and subsequent infusion of the modified cells back into the same patient. Allogeneic CGTs are, instead, a type of therapy where cells or tissues are collected from a healthy donor which will then be genetically modified in a laboratory to introduce therapeutic genes or correct genetic defects. Subsequently, they are expanded and administered to treat patients (Figure 1).

Both allogeneic and autologous products are based on temperature- and time-sensitive human material. Furthermore, in the case of autologous therapies, cells or tissue come from patients that have gone through multiple rounds of conventional therapies (e.g. chemotherapy, radiation therapy, etc.), hence the quantity and quality of patient materials might represent an additional constraint.

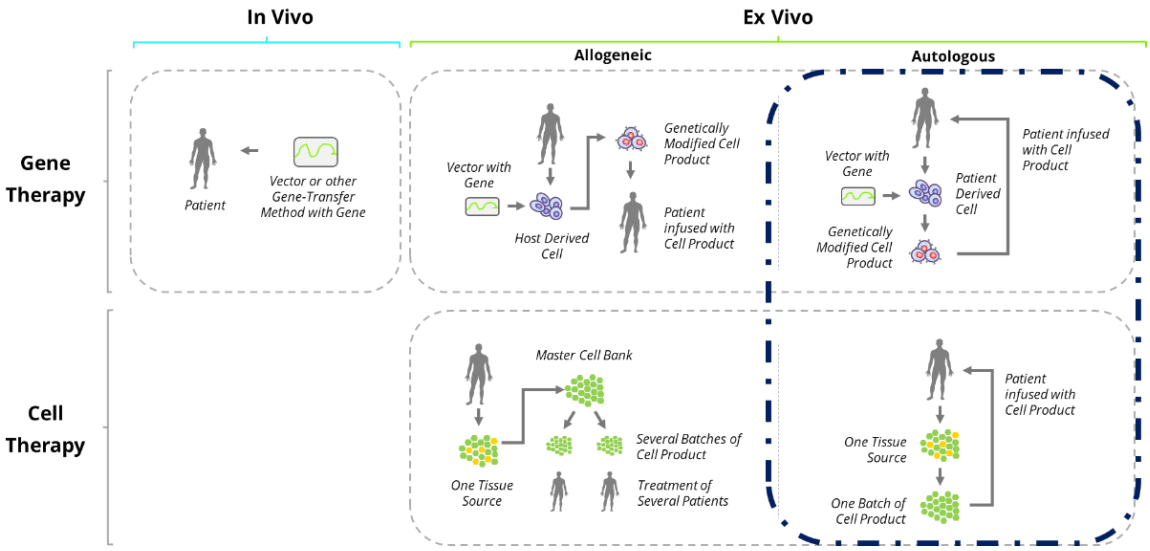

Figure 1. ***Allogeneic and Autologous Cell & Gene Therapies*.** Allogeneic and Autologous Cell and Gene Therapies are performed e*x vivo*. For autologous CGTs, cells are collected from the patients themselves, genetically modified and returned to the same patients. For allogeneic CGTs, cells are collected from a healthy donor, genetically modified and returned to the patient.

To date, autologous CGTs have mainly been manufactured in centralized sites, where patient material is delivered from hospitals (either fresh or cryopreserved) to the manufacturing site (7). The final product is then transported back (cryopreserved or fresh) to the hospitals, where it will be administered to the patient (Figure 2a). Preserving and transporting patient cells from hospitals to manufacturing centers, safely returning modified cells to patients, and ensuring CoI and CoC (Chain of Identity and Chain of Custody) add considerable time constraints and complexity to the end-to-end supply chain (1).

Figure 2a. ***Centralized Manufacturing.*** Centralized manufacturing of Cell and Gene Therapies starts with sample collection from the patient in the hospital/clinical center. The cryopreserved or fresh material travels via interfacility and interdepartmental transport to the central manufacturing facility. Final products are then again cryopreserved or freshly stored and transported back to the clinical center where they will be administered to the patient.

The adoption of PoC manufacturing, is being investigated as a potential way to face the constraints and complexities of the current traditional manufacturing approach. PoC manufacturing is based on the ability to produce therapies either directly within the hospital itself or at a nearby manufacturing unit. This approach results in a faster therapy administration, and it eliminates the need for complex transportation from a centralized facility to the patient's location. With PoC manufacturing units in place, there could be a reduced need for cell cryopreservation, lowering, for example, the risk of affecting cells' viability every time a product is frozen or experiences sudden changes of temperature (Figure 2b).

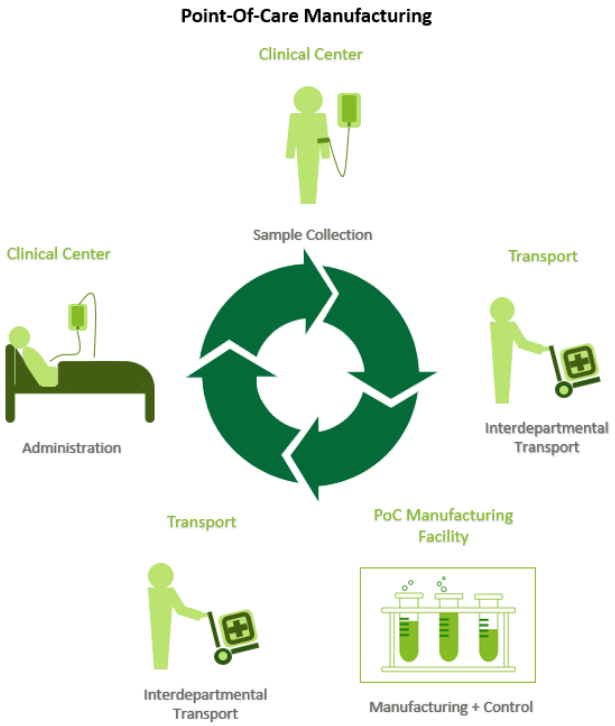

Figure 2b. ***Point-of-Care manufacturing.*** PoC manufacturing starts with sample collection from the patient in the hospital/clinical center. The material gets transported to a nearby manufacturing facility (or can also be manufactured in the hospital itself), and then the final product gets transported back to the clinical center, where it will be administered to the patient.

In the next section we present seven dimensions and some related key considerations to reflect upon when choosing to implement PoC manufacturing.

Navigating Point-of-Care Manufacturing: Key Considerations

The decision to opt for a specific manufacturing approach needs to be carefully evaluated by the Sponsor/Marketing Authorization Holder (MAH). At one end, there is a fully centralized manufacturing approach (one manufacturing facility serving worldwide), while on the other one, we have complete decentralization (manufacturing facilities placed directly in the treatment centers) (Figure 3). However, between these two extremes, the level of decentralization can be tailored to adapt PoC manufacturing to specific circumstances.

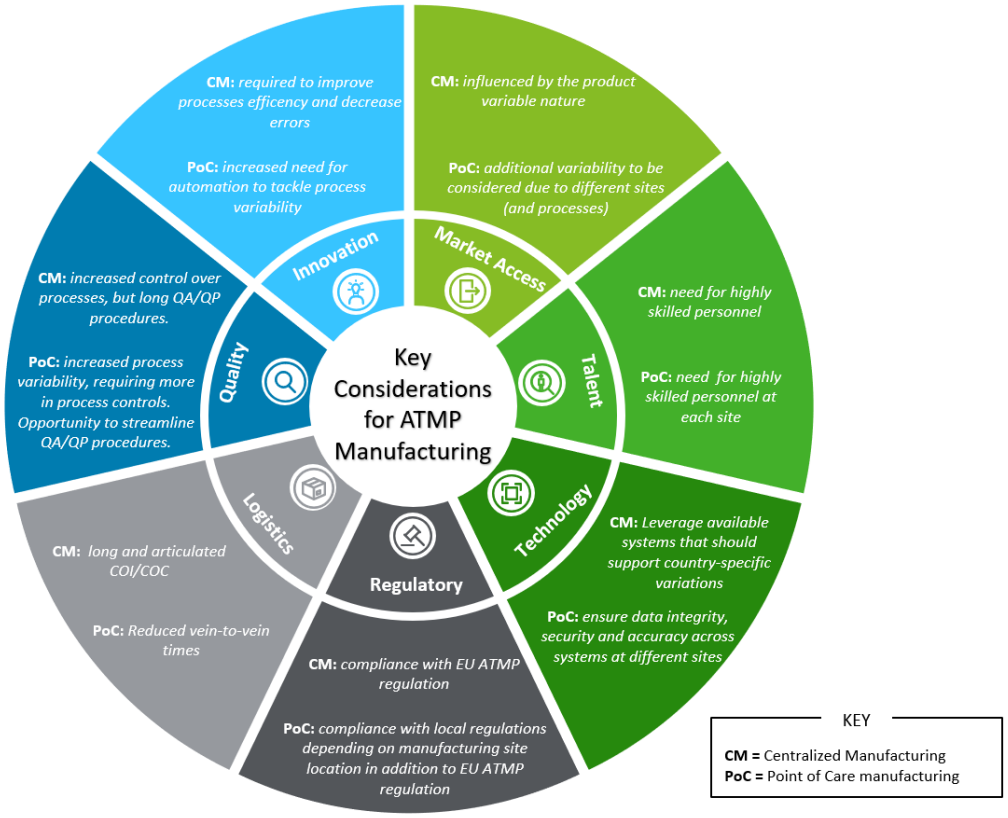

Figure 3. ***Key Considerations.*** High level overview of the selected seven dimensions with some examples of key items to consider when considering either central manufacturing (CM) or Point of Care manufacturing (PoC). The list is not exhaustive and has only an illustrative purpose.

Supply Chain

Moving to PoC manufacturing has the potential to remove several logistical obstacles. This transition offers some interesting benefits indicated in the list below.

- Simplification of the COI and COC due to a reduced number of parties involved in the supply chain.
- Reduced risk of temperature excursion due to shorter duration of transportation/ shipment.
- Reduced vein-to-vein times.

Nevertheless, it is essential to consider specific complexities alongside these benefits. PoC manufacturing demands that sponsors ensure that each manufacturing unit is provided the raw and starting materials required for the entire manufacturing process.

- Each manufacturing unit must establish an effective supply chain to source necessary materials.
- Each manufacturing unit needs inventory management and its own storage space that should meet the specific storage requirements.
- There might be an increased cost associated with storage facilities, transport and inventory management linked to the different PoC manufacturing sites.

Quality

When implementing a PoC manufacturing model with multiple manufacturing units, it is essential to ensure the presence of adequate quality controls. A list of aspects to be considered is available below:

- Controlling Good Manufacturing Practices (GMP) operations and performing quality investigations can be challenging.
- Variations in processes, equipment, personnel expertise make it more complex to manage and oversee quality operations (3).
- COI/COC becomes less complex when manufacturing is decentralized, but it is a regulatory requirement that needs to be implemented at each unit.

When looking at quality while implementing PoC manufacturing, it is key to define a clear governance structure where roles and responsibilities are detailed between Sponsor and Contract Manufacturing Organizations (CMO):

- A CMO, which is the PoC manufacturer (e.g., hospital and other life science/healthcare companies)
    - Is responsible for manufacturing the product according to the applicable EU and local regulatory requirements, the contractual agreements and Quality Agreement agreed upon with the Sponsor/MAH.
- A Sponsor/MAH
    - Ensures that processes meet regulatory standards and product specifications.
    - Approves and oversees the processes conducted by a CMO.
    - Ensures, after their regulatory approval, the allowance of legal production and distribution of the product by the CMO.
    - Sets the requirements for the CMO and prepares a Quality Agreement.
    - Could assist the CMO in seeking support to ensure compliance with the principles of GMP.

Embracing a decentralized approach implies that MAHs or sponsors, will interact with increasing numbers of PoC manufacturing sites. Consequently, this approach can result in the implementation of multiple Quality Assurance (QA) processes, which can translate in additional costs and resource needs.

Innovation

When exploring PoC manufacturing, it is crucial to consider the added value of using cutting-edge solutions to minimize human error and ensure control over the processes, for example through the use of automated technologies and/or closed-system manufacturing (8).

- **New automated technologies** slightly enhance efficiency and productivity, contributing to better control over the manufacturing process (8):
    - Streamlining of processes and optimization of resources.
    - Leading to faster production, improved efficiency, and cost-effectiveness.
    - Resulting in reduced human errors, ensuring consistent and high-quality ATMPs.
- **Closed-system manufacturing** minimizes contamination risks, maintaining product integrity (9; 10).

Market Access

Gaining market access to ensure that these new therapies can reach patients is vital. Due to its novelty, PoC manufacturing could require additional clarification when Marketing Authorization Application are submitted, but it also represents an opportunity to bring therapies closer and faster to patients.

Health Technology Assessment (HTA)
The HTA is a process used to evaluate therapeutic benefits and risks of new treatments, providing evidence-based information to support decision-making in healthcare (11; 12)**.** PoC manufacturing often brings variability regarding quality and standardization, which increases the uncertainty of HTA outcomes. Nevertheless, PoC manufacturing can deliver therapeutic solutions closer to patients affected by highly invalidating diseases, potentially at lower cost (13).

Outcome-Based Agreements (OBA)
OBAs (Outcome Based Agreements) are contracts between healthcare payers and manufacturers of medical treatments, implying that payment depends on how well the treatment works (11). CGT products are by nature subject to quality variability, when combined with the challenges in standardizing PoC manufacturing and finding workers with the required skill set at each manufacturing site, this introduces the risk of inconsistent clinical outcomes, impacting the payment deal.

Market access is hereby affected by quality issues impacting regulatory approval and workforce limitations leading to reduced reimbursement. Nevertheless, despite the variability, it is important to highlight that when the therapy proves to be successful, it can bring to a complete remission for patients, improving their quality of life and reducing their need for healthcare assistance.

Long-term data collection
Collecting data for an extended period of time helps to support the entry of a product onto the market. It can show that the product matches the expected quality requirements and has positive patient results, creating real-world evidence of the outcome (12). However, for personalized treatments (1 batch=1 patient), variability is an important factor to consider, especially if additional data noise can be due to differences in the type of manufacturing. This implies that models chosen for the analysis of such data need to be able to account for such variability.

Technology

ATMP manufacturing requires different IT systems to communicate with each other (e.g., customer-facing platform, APS, COI/COC, ERP, MES etc.) to ensure a successful manufacturing process. Therefore, some technical challenges are listed below.

Divergence in IT systems at different points of care

- For centralized manufacturing, sponsors/MAH can leverage the economies of scale of available technology backbones. Small, decentralized manufacturing models might prefer standardized solutions due to costs/resources constraints. Nevertheless, these might not be fit for purpose and require additional customizations, leading to non-standardized ways of working across different manufacturing points.
- Each system has unique requirements, making it harder for healthcare providers and technicians to maintain them and train end-users.
- Interoperability issues might be an obstacle to data-driven decision-making.

End to end (E2E) compliant and secure processes

- It is key to identify which systems should be owned by the Sponsor/MAH shared across the different PoC and the ones that shall be specific to the different sites.
- The presence of different IT systems (and potentially processes) across different sites and their integration represents an increased risk for data integrity, continuity, and security.
- A well-defined governance is fundamental to define roles and responsibilities across the different systems involved in the E2E processes.
- Clear issue and incident resolution processes should be established both at central and local level.
- Risks can be minimized through thorough testing and validation of the different systems E2E to ensure that the processes work as expected.

Talent

Acquiring the right expertise for the right roles is crucial (14). This holds true for the production of all ATMPs, but it is even more important when considering PoC manufacturing as such expertise should be available at multiple sites.

- Highly specialized teams are needed with experience in operation planning, material handling, aseptic operations, coordination of the different players and departments involved, and knowledge of regulatory requirements. Less experienced people represent a risk for quality.
- The talent distribution needed for manufacturing and the people required for various forms of support, both locally and remotely, should be considered when thinking about decentralized manufacturing units. To ensure successful outcomes, clear governance, supported by the available manufacturing sites, is required.
- Regular training of personnel is needed due to the innovative nature of these products and the related manufacturing technologies.

Regulatory

Complying with regulations and enforcing highly regulated processes, while ensuring consistent product quality, can become challenging when manufacturing occurs at multiple locations.

Manufacturing of autologous CGTs at the PoC falls under the EU regulatory framework for manufacturing ATMPs (15). The existing framework can be applied for a PoC manufacturing approach if efficacy is demonstrated, and quality is controlled and assured.

While the regulation addressing the manufacturing of ATMPs is well-established at EU level, the type of commercial manufacturing activities of ATMPs that a hospital is allowed to perform can be subject to additional national laws or requirements and should, hence, be verified before commencing activities. For example, the UK Medicines and Healthcare products Regulatory Agency (MHRA) is currently working on a new regulatory framework to address limitations associated with manufacturing of ATMPs at the PoC (16)**.** The proposed framework will not substitute centralized manufacturing and distribution but complement the existing regulations in situations where the current model is impractical. For example, it will address challenges such as the long times required for quality control testing and qualified person batch certification for products with short shelf-life, the need to inspect and authorize all individual manufacturing sites, as well as their preventive inclusion in the Marketing Authorization (MA) (15; 17).

An important sidenote worth mentioning is that within the EU, the European Medicines Agency (EMA) has established a specific provision known as "Hospital Exemption" in the ATMP Regulation (EC) No 1394/2007 to allow hospitals to manufacture and treat patients with ATMPs that are not (yet) granted with a MA (18; 19)**.** This provision enables the local production of ATMPs in the hospital or healthcare institution where the treatment will be given to patients, but this is applicable only on a non-routine basis. It is crucial to note that this exemption does not permit commercial manufacturing. Nevertheless, the application of this exception is left to individual countries' interpretation, leading to a lack of uniform approach.

Conclusion

In the world of CGT manufacturing, there is no one-size-fits-all. The PoC manufacturing model is complementing the centralized and regional ones, and sponsors have already started to look into it for clinical manufacturing. Thanks to the new emerging technologies streamlining and ensuring quality in every process, PoC manufacturing could further grow in the upcoming years, bringing the possibility to reach more patients faster. However, there are questions that need to be addressed before moving towards PoC, for example, what will be the roles and responsibilities of the different entities involved in the manufacturing processes? What are the capabilities required to implement PoC manufacturing? Should there be additional regulatory guidance on a national level?

Despite the numerous challenges, there are some good practices that should be considered for PoC manufacturing:

- Develop and implement risk management strategies to identify and mitigate potential risks associated with PoC manufacturing and update them regularly.
- Implement a quality management system (QMS) that can adapt to various manufacturing environments.
- Foster a culture of compliance and quality at each site through ongoing support and collaboration.
- Control towers combined with real-time dashboards controlling the entire manufacturing process will help continuous monitoring of processes reducing the risk brought in by variations due the implementation at multiple sites.
- The adoption of new automation technologies across the different E2E processes will enhance efficiency and reduce the probability of human errors.
- Thorough E2E testing and validation of chosen IT solutions at PoC sites to ensure data integrity, continuity and security.
- Identify and clarify regulatory differences and commonalities related to PoC manufacturing (e.g., compliance to local regulations/guidance).

References

1. *Point-of-care manufacture of advanced therapies: readiness measures for hospital, companies, and regulatory agencies*. Bicudo, E., Brass, I., Carmichael P. 2022.

2. *Delivering cellular and gene therapies to patients: solutions for realizing the potential of the next generation of medicine.* Elverum K., & Whitman, M. 12, 2020, Gene Therapy, Vol. 27, pp. 537-544.

3. *Challenges and advantages of cell therapy manufacturing under Good Manufacturing Practices within the hospital setting.* Iancu, E. M., & Kadalaft, L. E. 2020, Current Opinion in Biotechnology, Vol. 65, pp. 233-241.

4. European Commission. *Regulation (EC) No. 1394/2007 of the European Parliament and of the Council of 13 November 2007 on Advanced Therapy Medicinal Products and Amending Directive 2001/83/EC and Reculation (EC) no 726/2004*. s.l. : Ofiicial Journal of the European Union, 2007.

5. Cell and Gene Therapy Sector Snapshot: August 2023. *Alliancerm.com.* [Online] August 08, 2023. https://alliancerm.org/the-sector-snapshot-august-2023/.

6. *Advanced Therapy Medicinal Products and the Changing Role of Academia.* Priesner, C., & Hildebrandt, M. 3, 2022, Transfusion Medicine and Hemotherapy, Vol. 49, pp. 15-162.

7. Restore. *Roadmap of WP4 - Roadmap of the needs and strategy of the Implementation of new Advanced Therapies.* 2019.

8. *Centralised versus decentralised manufacturing and the delivery of healthcare products: A United Kingdom exemplar.* Richard P. Harrison, Qasim A. Rafiq,Nicholas Medcalf. 6, 2018, Cytotherapy, Vol. 20, pp. 873-890.

9. *Good design practices for an integrated containment and production system for advanced therapies.* Cristina Zanini, Franco Severina, Giovanni Lando, Carlotta Fanizza, Eugenio Cesana, Davide Desidera, Marco Bonifacio. 8, 2020, Vol. 117.

10. *Optical Spectroscopy for the Quality Control of ATMP fabrication: A new method to monitor cell expansion and to detect contaminations.* Bruno Wacogne (1), Déborah Legrand (1) , Christian Pieralli (1) , Annie Frelet Barrand (1). Malte : HAL Open science, 2020.

11. *A comparison of reimbursement recommendations by European HTA agencies: is there opportunity for further alignment?* Allen, N., Liberti, L., Walker, S. R., & Salek, S. 2017, Frontiers in pharmacology, Vol. 8, p. 384.

12. *The challenges of outcome-based contract implementation for medicines in Europe.* Bohm, N., Bermingham, S., Grimsey Jones, F., Gonçalves-Bradley, D. C., Diamantopoulos, A., Burton, J. R., & Laing, H. 2022, Pharmacoeconomics, pp. 1-17.

13. *Available tools to facilitate early patient access to medicines in the EU and the USA: analysis of conditional approvals and the implications for personalized medicine.* Leyens, L., Richer, É., Melien, Ø., Ballensiefen, W., & Brand, A. 5, 2015, Public Health Genomics, Vol. 18, pp. 249-259.

14. *Institutional and infrastructure challegnes for hospitals producing advanced therapies in the UK: the concept of "point-of-care manufacturing readiness".* Bicudo, E., & Brass, I. 10, 2022, Regenerative Medicine, Vol. 17, pp. 719-737.

15. *The UK's emerging regulatory framework for point of care manufacture: insights from a workshop on advanced therapies.* Bicudo, E., Brass, I., Carmichael, P., & Farid, S. 9, 2021, Cell and Gene Therapy Insights, Vol. 7, pp. 1005-1015.

16. Adair, J. E., Haworth, K. G., Sauvageau, G., Heimfeld, S., Hocum, J. D., Trobridge, G. D., & Kiem, H. *A Point-of-Care Platform for Hematopoietic Stem Cell Gene Therapy.* 2015.

17. Kawalekar, Omkar. Point-of-Care Manufacturing for Cell Therapy: Is the Industry Primed for a Transformation? [Online] Linkedin, August 14, 2023. [Cited: December 18, 2023.] https://www.linkedin.com/pulse/point-of-care-manufacturing-cell-therapy-industry-primed-kawalekar/?trackingId=YuAFwguFQ9GWaaKqT0nGfw%3D%3D.

18. Alvaro, D., & Challener, C.A. Bedside Cell Therapies: Point-of-Care Manufacturing is Slowly Becoming a Reality. *Pharma's almanac.* [Online] November 15, 2022. [Cited: December 18, 2023.] https://www.pharmasalmanac.com/articles/bedside-cell-therapies-point-of-care.

19. *REGULATION (EC) NO 1394/2007 ON ADVANCED THERAPY MEDICINAL PRODUCTS ("THE ATMP REGULATION") - GUIDANCE ON THE UK'S ARRANGEMENTS UNDER THE HOSPITAL EXEMPTION SCHEME.* UK Government. 2011.

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