Digitalization: Is It Worth It?

Although advanced therapies (ATMP) have the incredible potential to cure devastating illnesses, this innovative therapeutic field faces unique manufacturing challenges. As with other drug molecules, ATMP's have to comply to the Good Manufacturing Practice (GMP) guidelines, which require the meticulous assessment of both quality and consistency of the end product. For ATMP s however, it is impossible to characterize every detail of the final product as they are based on living cells and tissues that are inherently variable and dynamic. This adds a fundamental complexity to the ATMP manufacturing and scale-up process that is not present in the production of most non-biologic therapies.

To be able to demonstrate safety, control is key. Controlling raw materials, controlling the quality of donor material and controlling the manufacturing process are essential to the evaluation of the consistency, efficiency and potency of a product. This need to carefully monitor the entire manufacturing process is both a challenge and an opportunity for the ATMP field. Investing in efficient, innovative, reliable, automated, digitally monitored processes, will position ATMP as a frontrunner within the pharmaceutical sector, attracting additional funding and making way for improvements in other product areas. Yet, contrary to what one might expect, developers today are often not embracing automation or even digital transformation. The monitoring of processes and collection of data is often done manually, on paper or in spreadsheets, a labour-intensive approach prone to human error. Why? A quick survey of developers indicates 3 main hurdles with regard to digitalized monitoring and record keeping: time, security and cost. Let us take a closer look at the concerns.

1. Digitalization is time consuming

The vast majority of ATMPs are developed within an academic context with limited resources and a strong focus on the product. With regard to monitoring the process and keeping

> *"Just like many other sectors, the biotech sector is subject to Digital Transformation. Our company is digitally transforming to improve the business operations and become more competitive in the future. The most critical part is the digitalization of the R&D and GMP production process. Manufacturing processes related to ATMPs or extracellular vesicle biological drugs especially are linked to the final product characteristics. Any significant change in the production process might have an influence on the product's properties. Therefore, we believe that a digital production platform must be implemented early in the development of the drug substance, preferably at the stage of non-clinical R&D. In the long run digitalization will allow improving GMP manufacturing process efficiency and will provide affordable therapies for the patients. The main challenge for us as a start-up biotech company is the relatively high cost of digitalization at the beginning. Yet, we believe it is a good and necessary investment."* Marcin Jurga, ExoBiologics

records, the use of paper or spreadsheets is common. Only when research proceeds into clinical trials does the process receive due attention. However, that next step of ensuring compliance with GMP guidelines necessary to obtain FAGG accreditation, is stressful and time consuming. It is the kind of endeavour that many researchers, though well aware of the advantages, do not want to complicate further by digitalizing operations. But to delay digitalization, is to deny it; once accreditation is granted, the enthusiasm to adjust the process will only decrease. Conclusion? It is critical to implement digitized processes at the earliest stage, avoiding even the pre-acceptance of paper-based processes.

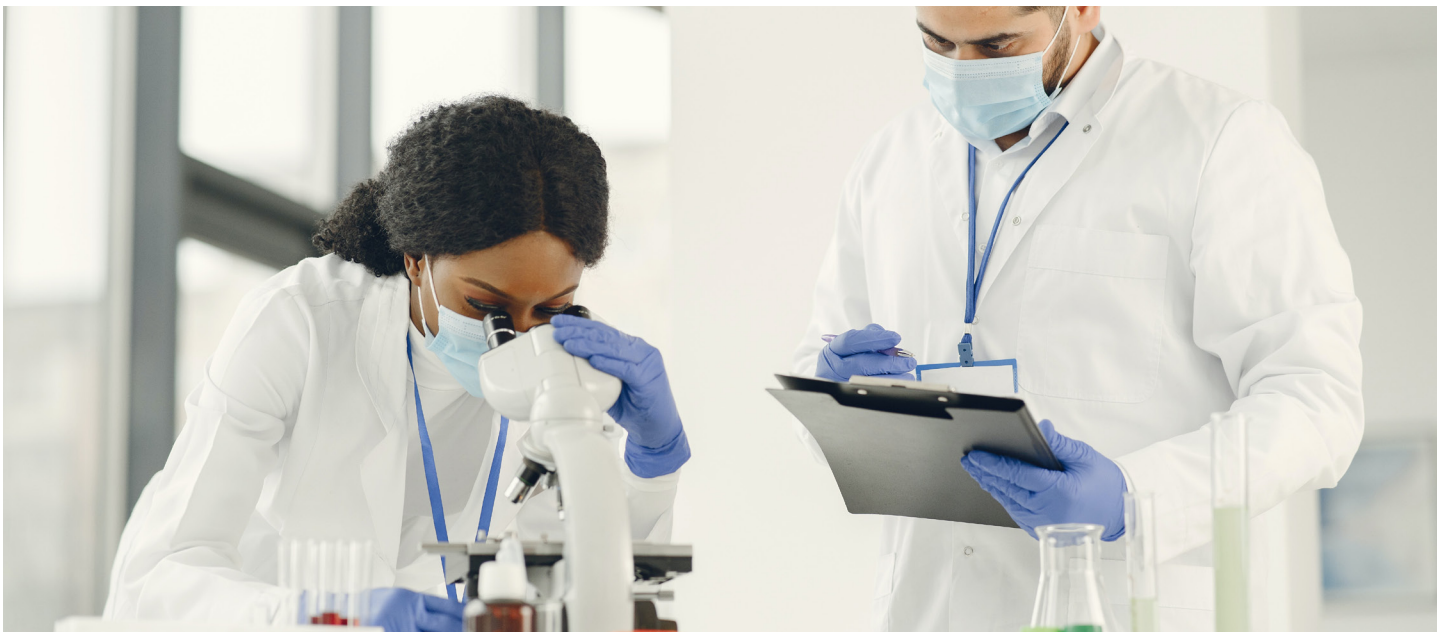
"The regulatory guidelines determining the safekeeping of digital data date back to the nineties, but regulatory bodies such as FDA are pushing hard on the importance of Data Integrity, encompassing both security (safe storage) and traceability (exchange of data). With regard to security, there are clear standards, though companies are often reluctant to host sensitive data in the cloud. In my opinion, for young biotech companies the cloud is probably the safest place to work in. Often start-ups and small companies do not have the IT profiles to harden the exposure profiles of your computer system, whereas the big players (Amazon, Microsoft,...) have the teams in place to provide the necessary security. The cloud today is perfectly capable of handling the significant privacy, security, and compliance challenges that ATMP developers face. People have to realize this." Sven Mus, Ordina

2. Digitalization is a security liability

Another common concern regarding the use of digital solutions is the safe storage of data. Especially cloud storage is often perceived negatively and associated with an increased risk of hacks, damage or loss. A risk analysis of the practice of manual data keeping, however, indicates potential problems of a far graver nature, such as the complete and irrevocable destruction of records as a result of a fire, flooding, or a loss due to poor management. Creating backups for paper documents is not easy and time consuming, for instance when documents are copied or have to be scanned and stored. An archive of paper documents requires good discipline to organize and takes up a lot of space. Storage of data on local servers gives a false feeling of security, for they are subject to the same risks of destruction and loss, and they require specialised IT knowledge to maintain uptime and security. Young biotech companies in particular often do not invest in the IT profiles or support necessary to guarantee the security of data management, ultimately making cloud storage for most companies probably the safest solution available when hosted by reliable cloud computing services.

3. Digitalization is expensive

Although paper document management and spreadsheet applications also come at a cost, digital systems are considered to be more expensive. However, the financial costs of digitalization must be related to the time savings, error prevention, data analytics potential and ease of regulatory compliance.



A McKinsey report[1] on digitalization in the pharmaceutical sector indicated an increase of productivity of almost 80%, as well as 65% reduction in deviations, after applying a combination of digitalization and automation. Moreover, it is a lot easier to prove compliance when using a digital system with a built-in audit-trial. Yes, digitalization comes at a cost, but the hidden expenses of time-consuming record keeping, rework after a preventable mistake and performing manual checks upon manual checks are far greater.

"MyCellHub, a spin-off company of KULeuven, has developed a system to digitalize lab and cleanroom workflows specifically for GMP processes such as ATMP production. The platform we developed addresses two major challenges for an ATMP manufacturer; how to ensure the quality and consistency of the process, and how to efficiently manage and interpret the abundance of process data. MyCellHub's application serves as a GPS that guides an ATMP manufacturer through the complex GMP processes, such as scheduling the different tasks, providing step-by-step work instructions, assisting with calculations and data collection. Digitalizing the GMP workflows allows to centralise all critical processes data with seamless data traceability and provides manufacturers with a comprehensive overview of what is going on in their facilities as well as automated reporting and analytics. By specifically focusing on the ATMP niche, the software and its standard library of process operations can be deployed in a similar timeframe as a paper-based system. In order to allow biotech companies to focus on bringing their therapy to the patient, we offer a Software-as-a-Service or "SaaS" solution that is hosted in the cloud. In this way we unburden the customer of activities like software validation, hosting, regulatory compliance, maintenance and backups. Data safety and integrity is obviously critical as we're dealing both with GMP-related data and GDPR-related data (i.e. personal data related to the operators and certain links to patient ID's). Therefore, we make sure that each customer has its own private cloud and the physical location(s) of the server and the backups can be tailored to the (regulatory) needs of the customer." Toon Lambrechts, MyCellHub

Reference: https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/digitization-automation-and-online-testing-the-future-of-pharma-quality-control

Yet, having debunked the common misconceptions on digitalization does not entail that any software solution related to data management is well suited to keep track of the ATMP manufacturing process. Traditional enterprise IT systems can be expensive, difficult to work with and therefore time-consuming to implement. Many software solutions simply lack the flexibility required to follow up on the variable production cycles that are typical for ATMPs. A suitable solution should be able to (1) accept and document many deviations throughout the process from raw material to finished product, (2) allow for easy adaptations and evolve along with the product into a definitive process and (3) be open to fluid integration with software platforms of other stakeholders such as CDMO's. As stated earlier, it is important to implement such a software solution early on, creating a digital spine in the product and process development that will result in a dynamic knowledge library.

In short, taking into account the complexity of bringing an ATMP to the patient, a strong case can be made to invest early in the development process in digitalization, avoiding paper-based data managing altogether. Also noteworthy in this regard is that the FDA is shifting its stance from 'Computer System Validation' (CSV), focused on elaborate documentation of each and every aspect of an application, to the more industry friendly guideline 'Computer Software Assurance' (CSA). This should allow manufacturers to embrace automation and digitalization. An excellent idea!

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This article is the summary of a workshop on 'digitization of processes in the ATMP manufacturing: hurdles and opportunities', organized by at.las with the following participants: Advipro, anicells, EXO Biologics, EY Belgium, Four&Five, Gevers, MyCellHub, Ordina, Radiomics, UZA

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