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Challenges and advantages of cell therapy manufacturing under Good Manufacturing Practices within the hospital setting

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Academic medicine serves to advance the scientific field and provide the highest quality of clinical care. This applies to cancer where there is a continuous unmet need for innovation. In the last decade, we have observed a significant development of commercial cell and gene-therapy products with a rapid growth of the industry. Hospital-based Good Manufacturing Practice (GMP) facilities which support primarily investigator-initiated clinical trials, are increasingly involved in interactions with industry. Although the missions of academic and commercial GMP facilities are different, both are bound by industry standards and often engage in technology transfer with industry partners. The successful set-up of an academic GMP facility requires striking a unique balance between commercial and academic priorities. Here we review the role of academic facilities in the development of cellular therapies with a focus on cancer immunotherapy and we highlight some of the most challenging operational aspects and point to potential solutions.

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Introduction

Innovative treatments known in Europe as Advanced Therapy Medicinal Products (ATMPs) as per Regulation (EC) number 1394/2007 are composed of cells or tissues which have undergone significant manipulation. ATMPs include somatic cell therapies, tissue-engineering therapies, gene-therapies or a combination of the above. Personalized cell therapy treatments are a type of ATMP, manufactured specifically for each patient, using their own cellular material (e.g. blood cells or tumor tissues) [1,2,3••].

The manufacturing and testing of these personalized treatments is a complicated process compared to standard medicinal products and biologics. On the clinical side, the delivery of these therapies to patients is even more complex, as patients require care before, during and after receiving treatment and a lot of tight coordination between the manufacturing and medical teams [4]. Table 1 summarizes the main characteristics of ATMPs, highlighting also specific challenges that need to be overcome regarding manufacturing process, quality control testing as well as product release, in order for them to reach the clinic.

The complexity of these products comes primarily from the fact that they are composed of live cells from the starting point of isolation of the cellular starting material up to the final product and that the size of the manufactured batch is very small, often one batch equals one product only destined for a single patient. Since the live cells cannot be filtered nor sterilized at the end of the process before being administered to the patient, their sterility must be ensured throughout the manufacturing process. As a consequence, the entire manufacturing process and quality control strategy must be carefully designed using a risk-based approach in order to guarantee the quality and safety of cell therapy products [5]. Traditionally, the expertise of late stage development, manufacturing, quality control testing and release of medicinal products for human use lied mainly with the pharmaceutical companies [4]. On the other hand, hospitals and academic research institutions were the main drivers for scientific innovation, focused on proof of concept projects and early stage product development. Although early product development was taking place in both the academic and industry settings, only pharmaceutical companies possessed the required manufacturing expertise and resources necessary to drive late stage product development, scale-up and product manufacturing compliant to applicable laws. Pharmaceutical companies depended mostly on hospitals and clinics for the availability of patients required to run their clinical trials using novel products. However, over the past two decades, the field of immunotherapy has seen a revolution in this traditional paradigm with academic centers becoming significant contributors to the development and manufacturing of ATMPs [2].

Table 1

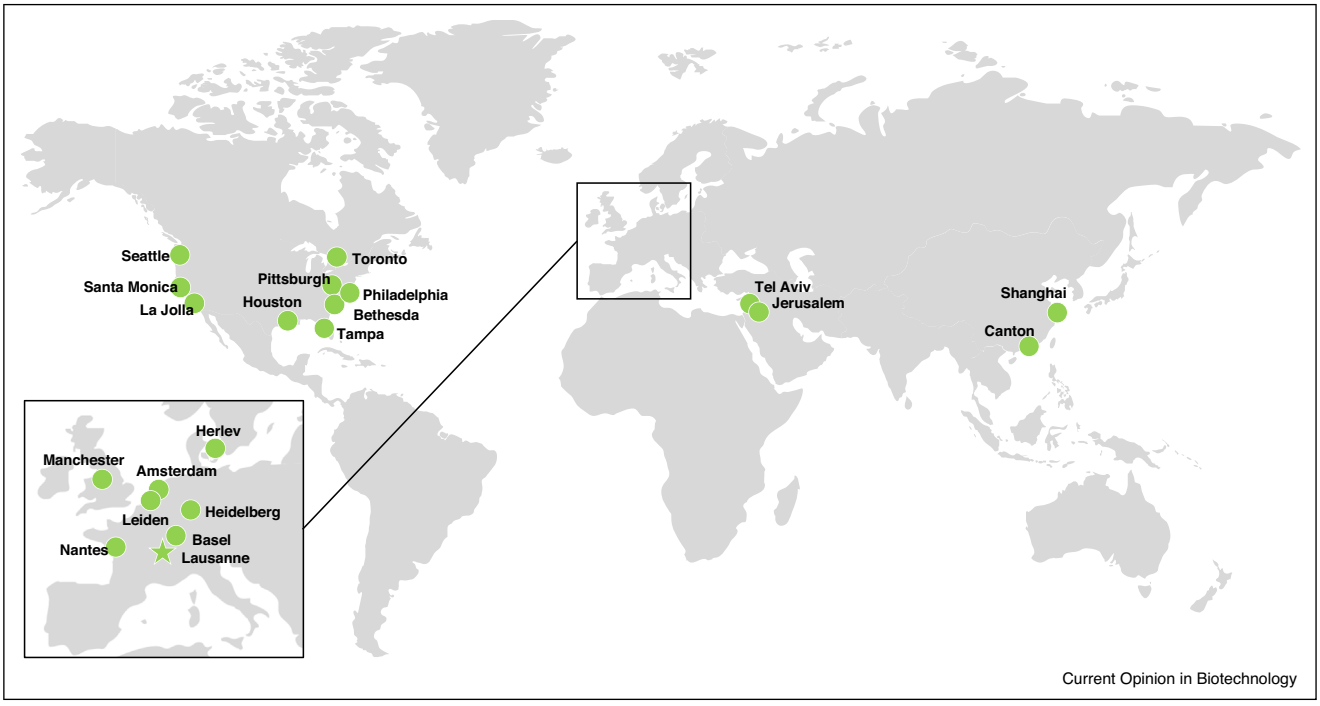
Common characteristics of advanced therapy medicinal products

Item	Advanced therapy medicinal products
Types of products	Autologous, personalized treatments. Cell-therapy products and vaccines. Cells may or may not undergo genetic modification.
Batch size	$N = 1$; one product for one patient.
Expiration time period	Short, varying from few hours to one year.
Traceability	Extremely important for all stages of the material procurement, manufacturing process, packaging, transport and storage.
Manufacturing process	Aseptic process; no sterilization or filtration step possible at the end of the process. Combination of open and closed system steps.
Automatization of the process	Possible for cell culture, cell processing and washing steps. Manual manipulation of starting material (i.e. tumor tissue) still required.
Variability of the process and the final product	Standardized manufacturing process, however variability is introduced in the manufacturing process by biological differences of the tissue and cellular starting material. Different growth kinetics, expansion potential and functional characteristics impact final product yield and quality.
Segregation of the production suite, in space and time	Line clearance required between each batch and each product, increasing significantly the number of cleaning activities per production suite.
QC test methods	Novel products may require the development of new quality control testing methods designed specifically to test their quality and functionality.
QC sampling strategy	Limited. Using a risk-based approach, the sampling strategy needs to be designed specifically for each product. The sampling volumes need to be decreased to the minimum required in order to prioritize the final product dose released for the patient.
Raw materials and consumables	Risk-based assessment of raw materials and consumables is required to meet GMP quality standards. Final product QC strategy may be impacted by the quality of the materials used in the process.
Process development	Extent of process development, technology transfer and scale-up before GMP manufacture depends on the maturity of the process being transferred from research laboratories. Process adaptation efforts need to focus on adapting the process to the manufacturing environment and equipment while minimising the open process steps and maximizing closed systems steps.
Batch certification	By a Qualified Person (QP) in Europe or responsible person (RP) in Switzerland.
Partial certification and release for use	Final quality control test results may not all be available at time of product release for use. The possibility to release the products using available results to date is allowed based on a risk-based analysis.
Batch rejection	Decision to reject a batch can be made by the sponsor (in clinical trials) or by treating physician based on risk-benefit evaluation for the patient. Since only one batch/one product is often manufactured for each patient, the availability of material to reperform manufacture is often limited.
Product recall	Possible, but since fresh products have a very short expiration period, the product may have already been administered to the patient when the recall can occur. Recall procedures of such products need to be complemented by risk-based evaluations and decisions by the medical team to ensure patient safety.

Indeed marketing authorizations from the European Medicines Agency (EMA) and Food and Drug Administration (FDA) were granted to several personalized cellular immunotherapeutics products stemming out of academic centers, including the chimeric antigen receptor T (CAR-T) cell products such as Tisagenlecleucel (Kymriah®, CTL019; Novartis) [6,7] and Axicabtagene ciloleucel (Yescarta®, Kita Pharma) [8] which were both approved in 2017 for the treatment of different hematological malignancies.

Throughout the world, several academic hospitals have started to build their own personalized patient treatment programs and with it to build their own in-house manufacturing capacity [9••]. For example, Tumor Infiltrating Lymphocytes (TILs) therapy, a type of immunotherapy used in clinical trials for the treatment of advanced stage cancer patients has been made accessible throughout the world by academic centers. Figure 1 provides a non-exhaustive map of academic centers in the world, including our Lausanne University Hospital, equipped today with their own Good Manufacturing Practice (GMP) facilities and who are actively manufacturing and treating patients with cellular immunotherapy products including TILs (based on search using ClinicalTrials.gov database). The number of centers worldwide would evidently be higher if all types of advanced therapy products would be added to the map. Similar to any other pharmaceutical company, these academic hospitals had to meet GMP requirements, including the construction of specialized facilities for product development, product manufacture, quality control testing and in parallel to establish a pharmaceutical quality system compliant to laws and regulations in order to

Figure 1



Academic centers in the world manufacturing TIL products for clinical trials.

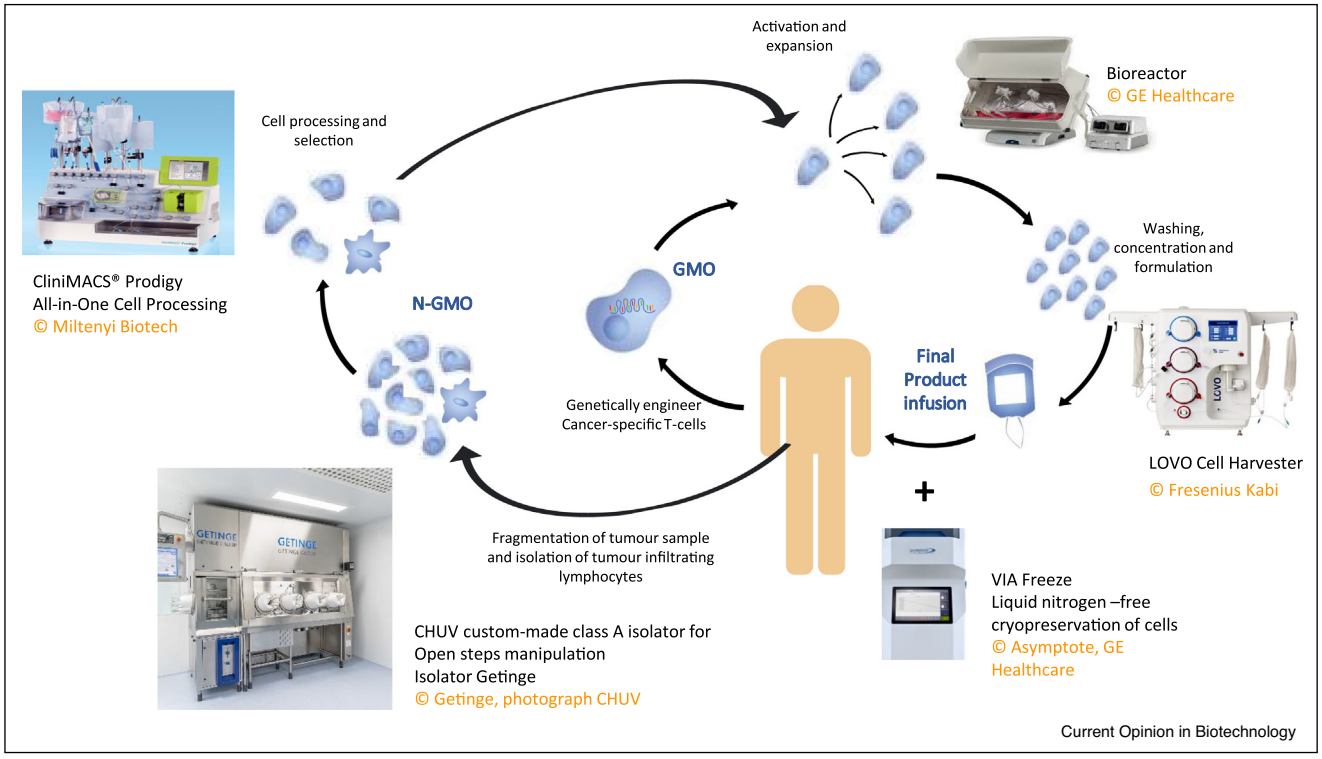
guarantee the consistent manufacture of products of high quality for patients [3••,9••,10••]. Most of such institutions also set-up in parallel effective clinical trial operational units in order to continue to run external sponsored trials but also allow in-house clinical trials using their own manufactured products. Moreover, each facility had to adapt their facility design and quality system based on differences in regulatory requirements that exist between different countries. In the European Union and Switzerland for instance, GMP requirements are expected for all stages of the clinical trials, including phase I trials where most novel ATMPs will fall. This, along other requirements such as product release by a qualified person, is not expected in the United States and Canada for phase I trials, making the development and patient specific ATMP manufacture more stringent in Europe [2,11].

In this remaining part of this review, we will highlight some of the advantages of building and running a manufacturing facility within a hospital academic setting and discuss the challenges that one may face in order to achieve these ambitious projects in an effective, compliant and successful manner. We base our conclusions on our own recent experience in building two manufacturing facilities for personalized cell and gene therapy treatments within the Center of Experimental Therapeutics (CTE) of the Department of Oncology, of the Lausanne University Hospital (CHUV, Centre Universitaire Hospitalier Vaudois) in Switzerland.

Manufacturing strategy and facility concept design

Personalized cellular products require small-scale manufacturing of $N = 1$ batch numbers. For example, in the case of cancer treatments using TILs, only one batch of TIL product formulated as one infusion bag of approximately 300 mL volume is produced and administered at one time to the patient (autologous treatment) [12]. Over the past years, the manufacturing process of personalized treatments has been improved by growing technological advances in the field of closed-system technologies combined with single use disposable consumables. Figure 2 outlines the use of some of the currently available closed system equipment for cell processing steps in the manufacturing of cellular therapy products such as TILs at our center in Lausanne Switzerland (Harari *et al.* 2020 manuscript submitted). Equipment such as the Xuri™ from GE, the Lovo™ from Fresenius Kabi and the CliniMACS® Prodigy from Miltenyi are now well-established closed systems that can be elegantly integrated into the manufacturing strategy for personalized cell therapy products [5,12,13]. Since each batch will require the use of such equipment at a

Figure 2



Manufacturing strategy using open and closed-system approaches.
An example manufacturing process sequence for cell-therapy products combining open and closed system approaches. The process can include genetically modified organisms (GMO) or not, (N-GMO). The manufacturing process starts with the patient and the manipulation of the turmor sample starting material under sterile conditions inside a class A isolator (i.e. an open-process step). Several cell processing, cell selection, activation, and expansion steps are then performed during the process using various closed-systems technologies. At the end of the process and before final product formulation for infusion back to the patient, the cell-therapy product is washed, concentrated and cryopreserrved if necessary; examples provided from Miltenyi, GE HeathCare and Fresenius Kabi.

time, the capacity of a facility will largely depend on the number of available closed system equipment. These closed systems have several advantages, including increased automation of the process, require less operator intervention and allow the concurrent manufacturing of multiple small batches destined for multiple patients. This integration of closed systems in the manufacturing strategy for ATMPs not only reduces the risk associated with direct product manipulation, but also allows an increase in the number of product batches that a production operator can control at a given time [13].

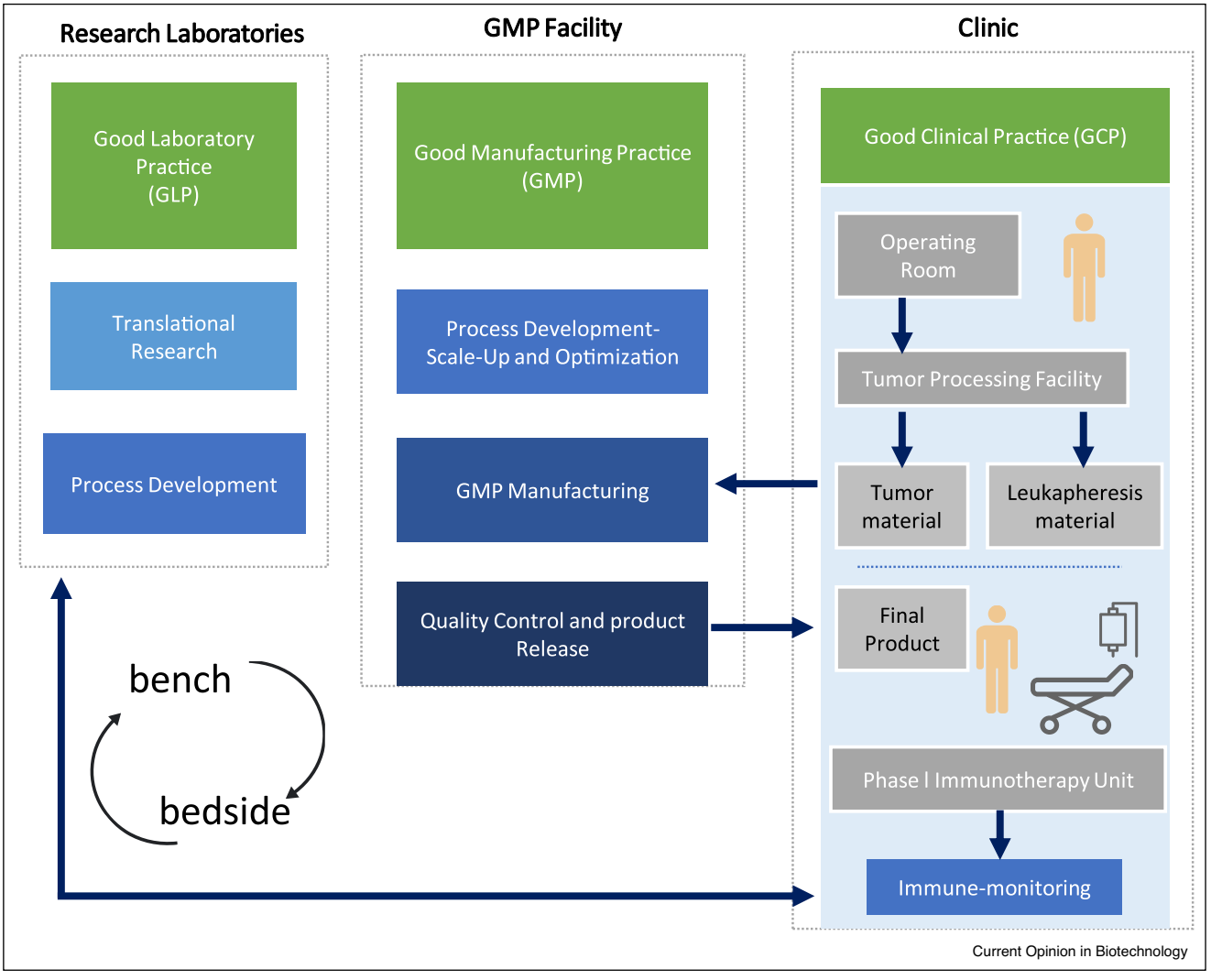
In combination with the closed system approaches, the use of the isolator technology has proved to be effective and sufficient to allow open step manipulations on the cellular material under sterile conditions (Figure 2). The use of isolator systems combined with closed-system technologies require clean room environments of Class C and D (ISO grade 7 or 8 equivalent), which in turn require less stringent ventilation, cleaning and gowning requirements compared to clean rooms of higher grades. Hospitals are often limited by the available space to build clean rooms. Therefore the combination of these approaches have allowed several hospital departments throughout the world to design efficient strategies that permit the manufacturing of multiple personalized products within a small size GMP facility on the hospital campus.

Advantages of hospital GMP facilities

There are several advantages of having an in-house GMP facility for a hospital. The main ones are lower cost, rapid supply of manufactured products in response to clinical demand and optimal organization and transport of cellular material. Once a request from a hospital clinical unit is placed for a given patient, all efforts from all the involved units are put together to prioritize the demand. The planning of a new batch becomes the priority of all GMP facility units including production, internal quality control performing the control testing in-house, and the quality assurance required for batch review and release for use. This internalization of all quality resources leads

to the quality control results being available fast and at lower overall costs per batch [4,13]. The other main advantage is attributable to the proximity of a manufacturing facility to the hospital operating rooms and the clinical units [10••]. Personalized cell therapy based treatments require fresh cells isolated rapidly as starting material. The proximity of our GMP facility to the CHUV hospital allows fresh tumor material to arrive at the manufacturing facility within few hours from the operating room thus eliminating the need to temporarily preserve the tumor by freezing (Figure 3). The same advantage of the proximity applies when the finished product needs to be delivered to the hospital clinical unit at the patient's bedside. Overall, the proximity of a GMP facility within the hospital significantly reduces the cost and complexity of the logistics required to deliver personalized medicines to patients, while in parallel decreasing the risks to the product's integrity and cellular product quality associated with product transport over long distances [4]. The advantage of an in-house facility is also evidenced in the flexibility of the planning of a batch. Close collaborations between the manufacturing team and the clinical team also ensure that any unforeseen modifications in the planning of a batch are rapidly taken into account. These can be due to events either stemming from the manufacturing side (e.g. production constraints or variability in cell expansion rates) or the clinical side (e.g. patient status not optimal to receive treatment). Overall, having an in-house facility dedicated to the hospital or even specifically to one department allows an overall state of control over the production planning, the cost and the

Figure 3



Bench to bedside process flow.

coordination of the various units involved in patient treatment.

Not only having an in-house manufacturing facility within a hospital center facilitates patients' treatments, but it also accelerates bench to bedside transition of innovative treatments. Figure 3 depicts the interaction between the research groups from University of Lausanne (UNIL) and Ludwig Institute for Cancer Research (LICR), the GMP facilities of the department of oncology and the Phase I immunotherapy patient treatment unit of the CHUV necessary in bringing novel treatment options to cancer patients. The proximity of the facility and the access to research institutions and early development scientists allows new processes to be taken very early from basic research environments and to be adapted to the manufacturing requirements for large-scale clinical grade production. The role of an in-house GMP facility in this context is to provide in-house expertise and quality support for research laboratories and investigators, thus improving and accelerating the transition from discovery to clinical translation [10••,14]. This shortens the time required for the transfer of technology and expertise from early product development stages. In addition due to the fact that different units are internal to the hospital, or that collaborations already exist in place, this is also performed in a more efficient way from a quality as well as legal perspective. Overall, this drives scientific innovation with bench to bedside proof of principle, all while providing patients early access to the latest innovative treatment options available.

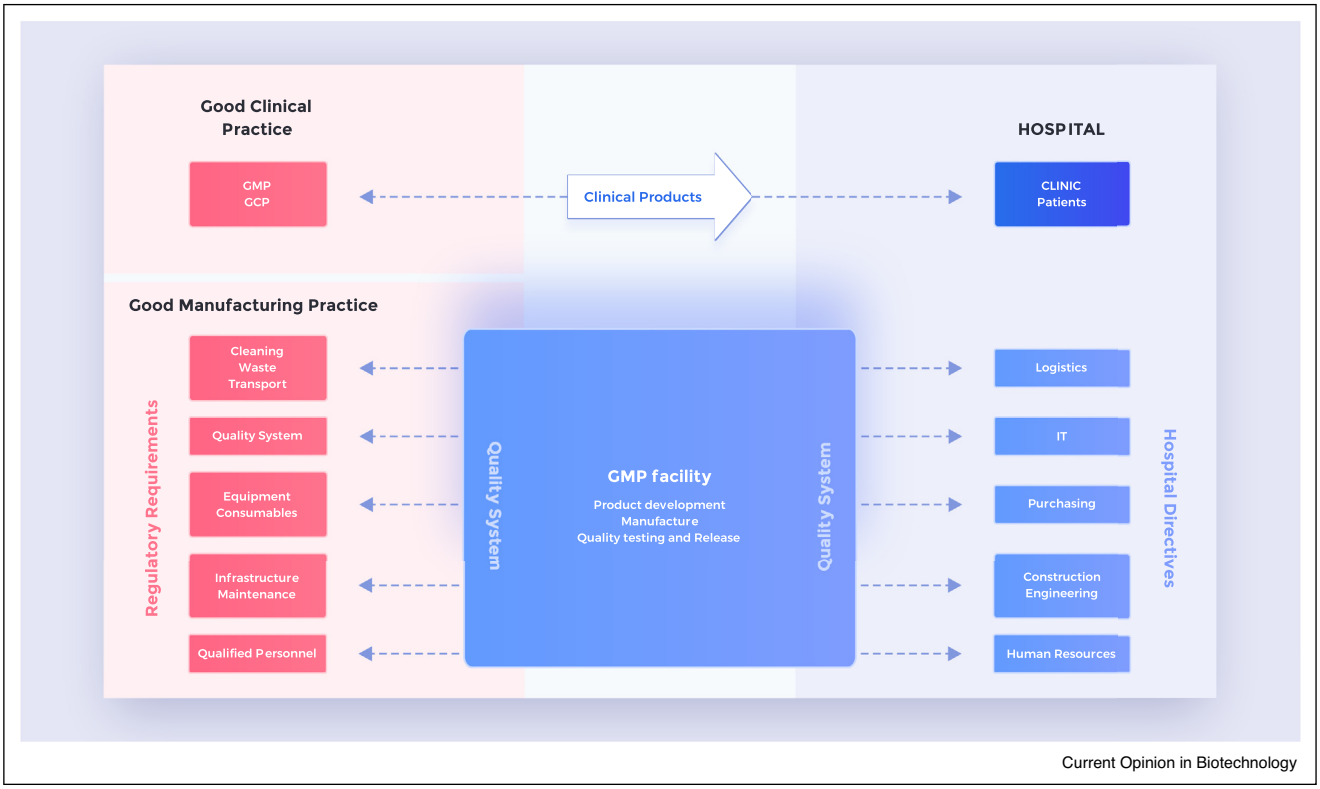
Achieving GMP compliance

In order to obtain the authorization to manufacture products for human use, a manufacturing facility has to demonstrate compliance to GMP laws and regulations. This compliance is required for the facility's quality system as well as for the facility's infrastructure and equipment. Setting up a new GMP compliant quality system is a highly time consuming endeavor, since all critical activities related to quality system management, production, quality control and infrastructure and maintenance have to be defined and documented [9••]. However, there is no right or wrong strategy to set up a compliant quality system, but its objectives have to be clearly identified. While the pharmaceutical quality system for a GMP facility has the objective to ensure that the manufacturing process guarantees the consistent manufacturing of high quality products, the quality systems of a hospital is generally intended to ensure the best performance of medical services to patients [3••]. Some of the important things to bear in mind during the set-up of the pharmaceutical quality system are also the types of activities being performed, the types of products being manufactured, whether the system is manual or electronic, how large is the department and how many employees will be using the system.

The development of a new therapeutic product from bench to bedside is accompanied by a transition in quality standards from Good Laboratory Practice (GLP) to GMP and Good Clinical Practice (GCP) as shown in Figure 3. This requires efficient communication and collaboration between the different teams to identify the unique challenges and regulatory pathway that each new product will need to follow in order to reach the clinic, including all the required pre-clinical and translational work. A good balance between quality and following established protocols as part of the quality system is therefore important to keep in mind for all GMP facilities within academic hospitals [10••]. A significant amount of time, money and effort may also need to be put during the process development adaptation and optimization stages if the reagents and consumables defined during pre-clinical studies are not of appropriate grade required for clinical product manufacture under GMP rules [14].

Procedures describing critical activities must be sufficiently detailed to provide clear instructions but not too extensive and lengthy that can lead to difficulties in respecting them on a routine basis, and thus potentially leading to a decrease in quality level. Therefore, the quality system must be established on a risk-based approach, focused on the quality of the data and the importance of the information that needs to be captured and not just solely on meeting compliance to regulatory requirements. The quality system of the new facility must also ensure that the hospital directives and applicable laws are respected and that any potentially divergent rules are clearly identified and negotiated to ensure GMP compliance. The challenges of building a GMP facility in a hospital environment thus comes from achieving the right balance between following the hospital internal rules and directives and putting in place procedures in order to meet GMP and GCP compliance. The main aspects that a GMP facility must balance between these two worlds are summarized in Figure 4. While applying the quality system by all facility personnel is a requirement to demonstrate compliance, this may often prove difficult to reach outside of the facility units, since other hospital departments may be either unaware of the requirements of GMP laws or perhaps unable to meet them for various reasons or lack of resources. In such instances, a close collaboration needs to be put in place between the GMP facility and each hospital unit involved in a critical GMP activity. First, the manufacturing facility must clearly **communicate** its requirements in order to meet GMP **compliance** and to ensure product quality and patient safety. Secondly, the parties must **collaborate** and **coordinate** the work required to meet those needs and **clarify** the responsibilities of each unit within the project. Once the collaborative agreements have been put in place, the GMP facility must perform a regular **control** to ensure that the quality level is maintained over time,

Figure 4



Academic GMP facilities are required to comply with both regulatory requirements and hospital directives.

Table 2

The 7Cs of success during the construction of a GMP facility

The 7 Cs	Explanation
Communicate	Communicate the user requirements in a clear and detailed manner, including the quality objectives of the project
Compliance	Ensure compliance to institutional directives, country specific laws and international rules and regulations throughout all stages of the project
Clarify	Clarify the roles and responsibilities of project personnel and units; identify a responsible party for each project activity or deliverable
Collaborate	Collaborate with multidisciplinary teams in order to identify project risks and create innovative solutions
Coordinate	Coordinate efficiently all project activities between different parties, with particular focus on management of interfaces and prevention of potential gaps
Control	Control regularly that the project timelines, budget and project milestones are respected with no impact on quality requirements
Check	Check at regular intervals that the user requirements, quality objectives and compliance to GMP requirements is assured at all stages of the project

with the final **check** being the verification that the project has met the requirements and quality standards defined in the beginning. Therefore, these '7 Cs' can be used as a guide to success during these challenging projects of building a GMP facility (see Table 2).

The second aspect that needs to meet GMP compliance in order to obtain authorization to manufacture is the infrastructure. Unless a new facility can benefit from the construction of a new site with newly designed and built facility systems, building a facility within a hospital environment often will require modification of an existing ventilation and gas system and refurbishing of the existing spaces. International Standards Organization (ISO) and GMP standards for facility design and air handling units vary based on the type of products intended to be manufactured in the facility [10••]. Careful attention must be given during the design of facilities intended for aseptic manufacturing processes of ATMPs which lack terminal sterilization processes, and where microbiological safety is the most important quality attribute [3••]. The design of such facilities needs to take into consideration the technical design but also all the other GMP requirements regarding space segregation, and flows of materials and personnel. Regulators will also expect to show evidence via risk assessments that the design of a multi-product facility including genetically modified products will have taken into

account the necessary segregation requirements for production spaces, ventilation systems, material and personnel flows in order to minimize cross contamination risks.

Careful attention must be given to the materials used for the facility construction, since GMP expectations will often exceed those of the other hospital spaces [9••]. The qualification as per GMP requirements as well as the maintenance of its facility systems and equipment is also of utmost importance in ensuring compliance. The success of the construction project will largely depend on two main factors. The first is the quality of the facility design to meet the department's manufacturing objectives and at the same time be compliant to increasing regulatory demands and future technological advancements. The second is the level of technical and GMP expertise of all the personnel responsible for the execution of the construction work and qualification activities. Building a GMP facility is a rigorous project associated with a significant level of documentation at every step of the process. For an academic institution, the required documentation and attention to detail may seem extensive at first, however specific GMP training along with a close collaboration of the various units involved are the key to success of such a project. Moreover, upfront consultation with local regulatory agencies during the early phases of a GMP facility project has been shown to be a key indicator of success by many groups, including ours [2].

Cost and other challenges

The cost associated with building and maintaining a manufacturing facility is substantial and has been clearly identified by many groups in different countries [9••]. While everyone is aware that minimizing those costs is crucial for the success of late stage clinical trials and future commercialization, estimating the costs of the facility construction and the required equipment correctly is not an easy exercise as multiple factors need to be taken into account in the calculation [3••,15,16]. Whether the financial investment comes from internal (e.g. institution) sources or external sources or both, it is the first milestone in getting the project started. The cost of construction of a manufacturing facility will evidently depend on its size, but often require several million dollars even for smaller facilities. Unlike other laboratories or other specialized facilities within a hospital, the cost of qualifying and subsequently maintaining the facility's infrastructure and equipment is also significantly high. This is mainly due to the execution of specialized tests and controls that must be performed frequently on the facility's critical systems and equipment and also due to the quality documentation requirements that are normally associated with all such activities. These costs must be clearly identified at the start of the project and sufficient funding sources must be found before the design and construction phases have started, then the costs need to be re-evaluated at different stages of the project.

The other main challenge in the success of a facility project is the availability of qualified personnel [9••]. Internal GMP facility resources particularly senior management, are required early in the project as the infrastructure and the quality system are being built. When the project is finalized and the facility licensed for manufacturing, the available team must also be sufficiently trained on the processes and the operation of the facility to ensure product quality and safety. Since many of the personalized ATMP processes being developed are new to the field, previous experience of production and quality control operators with similar products and technologies is scarce or non-existent. A previous experience in a GMP environment is often the minimum requirement for a good candidate, since he/she will be already very familiar with a GMP quality system and with the procedures associated with working in a clean room environment. The availability of resources from units outside of the GMP facility itself should not be underestimated either. Setting up a facility will require significant time and dedication from multiple units within the hospital, including the construction and engineering teams, the bio-medical engineers, the cleaning service, the gowning service, the purchasing and the legal departments (See Figure 4). In short, building a GMP facility is a project for the entire hospital not just the respective department and its success will largely depend on the dedication and collaborative efforts of the entire hospital units.

Conclusions

A dedicated GMP facility within a hospital setting has many operational advantages and allows patients access to innovative treatments that are personalized to their needs. At the Department of Oncology of the CHUV we have successfully set up two facilities, one small facility in close proximity to the main hospital building where patients undergo surgery and treatment, and another which is a short distance away but has a large manufacturing capacity of multi-products including genetically modified products. Being able to develop new products from the research laboratories, to adapt those processes to the manufacturing requirements, produce, test and release those products for human use, and then study their safety and efficacy within the scope of clinical trials, is a pure demonstration of bench to bedside, all under one institution. In addition to using an in-house GMP facility to manufacture a product from start to finish, there are many other uses of a GMP facility. Some of those include setting-up of collaborations with other internal units or external partners for the storage of various materials or products as well as the manufacture

of intermediate products. Such collaborations allow further scientific advancements which in turn will allow faster development of innovative treatment options for patients. The example of the TIL therapy now available worldwide is thanks to the many academic centers who have been able to successfully overcome these challenges of building a GMP facility within an academic center. It provides hope that in the future we will continue to see novel advanced therapies for cancer and other diseases emerge from academic centers, thus bridging the gap between science and clinic and between the laboratory academic environment and the pharmaceutical environment.

Conflict of interest statement

Nothing declared.

CRediT authorship contribution statement

Emanuela M Iancu: Writing - original draft, Writing - review & editing. **Lana E Kandalaft:** Writing - original draft, Writing - review & editing.

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