Health by Advanced Therapies

D 2.4
Strategy paper on various issues of manufacturing (including automation) of advanced therapy medicinal products (ATMPs)

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1. Deliverable's description

Deliverable D2.4 is a strategy paper to identify common principles among the highly variable and dynamic landscape of GMP manufacturing of advanced therapy medicinal products (ATMPs).

We at RESTORE believe that sophisticated GMP manufacturing will help to significantly improve patients health by increasing Safety, Efficacy, Access and Acceptance of ATMP treatment all over Europe.

This strategy paper will shortly introduce and reflect on the current GMP manufacturing strategies among authorized ATMP treatment in Europe and indicate weaknesses and bottlenecks.

In the following chapter: "Putative solutions" sophisticated and beyond state-of-the-art GMP manufacturing strategies will be outlined and weighted according to their impact to improve the aforementioned cornerstones of successfully improved ATMP treatments of European patients.

Finally, the RESTORE consortium will give a summary of the innovatory activities which promise the highest impact on patient health and how RESTORE could help to overcome current and future challenges in ATMP treatment within an adequate time window.

2. State of the art, challenges and Limitations

The clinical breakthrough and the subsequent market approval of the revolutionary CAR-T ATMP treatments from Novartis (Kymriah) and Kite/Gilead (YESCARTA) set a new horizon for (bio-) pharmaceutical development and manufacturing in the ATMP space[1]. Especially the entering of the major pharma players has induced a tremendous global wave of activity and hope at all ends of the ATMP value chain including academia, biotech, pharma industry, hospitals, regulators, legislators and patients. It can be expected that further technological waves (e.g. stem-cell/iPSC based therapy) will follow and thus additional market opportunities will arise whilst other, more outdated, ATMP technologies could vanish very quickly.

Although the market share for ATMP products is still at a very low 1% of the total pharma portfolio, ATMP products account for 12 percent of the industry's clinical pipeline and at least 16 percent of the preclinical pipeline showing the strong growth potential of this business[2]. While the number of clinical trials remained stable in Europe over a 4-year period the global situation looks quite different with a significant growth of more than 32%[3]. Beyond these figures, it is obvious that AMTP production is not only a leap in therapeutic

treatment of patients but also a game changer in how fast novel drugs have been developed, tested in clinical trials and approved by the regulatory authorities.

Despite this initial success a closer and more careful look at the current state-of-the-art situation shows that we are just at the beginning of a probably infinite game to improve the health of (European) patients by using innovative ATMP treatments.
Due to the few and very recent market approvals and the relatively small number of ATMP treated patients (Kymriah: app. 300 in 2019, YESCARTA: app. 500 in 2019) we still lack comprehensive data to thoroughly evaluate **safety** and **efficacy** but also control aspects under real world situations including massive upscaling and parallelization during GMP manufacturing[4]. Moreover, all commercialized CAR-T treatments are only approved for a very small subset of liquid tumors while clinical (autologous) CAR-T studies in solid cancers only show mixed results[5]. Another important issue is the control of unwanted side-effects including severe cytokine release syndromes and neurotoxicological effects which have been observed in a significant subset of CAR-T patients[6]. Due to the increasing complexity of ATMPs and the lack of sufficient pre-clinical test systems to reliably predict side-effects of such personalized therapies strong efforts should be made to close this "pharm/tox gap" as soon as possible. Other, e.g. Stem-cell based therapies are either approved in (ultrarare) orphan diseases or are still in clinical trials and therefore need to ultimately prove their potential and their GMP manufacturing suitability as commercially viable drugs[7].

In addition, the current ATMP products bear considerable costs (initial price tags: Kymriah $475,000, YESCARTA $373,000) which hamper an extensive, European-wide first- to second-line ATMP **access** by patients for the treatment of cancer and other devastating diseases. At this time point labour costs during GMP manufacturing but also at a variety of other supply chain touch points are a major share of the overall product cost. Kymriah as well as YESCARTA are ATMPs which demand a lot of hands-on time during GMP production and therefore innovative approaches to reduce hands-on time will help to cut costs. Another key issue is the lack of experience when it comes to massive upscaling of ATMP production. For example it is completely unknown if linear up-/out-scaling of current workflows for autologous ATMP treatments will also correlate with linear cost development or allogeneic treatment can really improve scalability on the overall cost side[8,9].

Finally, there is only very limited knowledge about the **acceptance** of these novel kinds of medical treatments among the European public. Due to the increasing digitalization and democratization of (medical) knowledge, patients will become more and more active parts of the ATMP treatment regimens and the entire value chain. There is a clear trend that, for example, ethical and sustainability concerns become increasingly important for European citizens when they take personal decisions including the acceptance of medical interventions. It will thus be key to pro-actively and appropriately educate the European public about the nature of ATMP treatments including the GMP manufacturing process and to take reasonable doubts and questions seriously. Last but not least we will also need an exceptional number of highly skilled workers who are able and willing to contribute their expertise within the GMP manufacturing process. Primary and secondary educational institutions will have to understand the novel demands of ATMP GMP manufacturing technologies and identify, attract and develop suitable talents to drive innovation in this new industrial sector.

3. Putative solutions

The RESTORE consortium believes that it will be very difficult to predict just one blueprint solution to address the very high volatility, uncertainty, complexity and ambiguity (VUCA) of the current ATMP GMP manufacturing landscape. We see it as much more helpful to define **generic strategies** to constantly

improve knowledge, quality and innovation in the ATMP manufacturing process instead of focussing on a certain way of manufacturing or by comparing different models for ATMP GMP manufacturing with each other. Thereby we can exploit the full spectrum of the partners` know-how, scientific and technical excellence as well as former experiences towards real co-creation and value chain building.

GMP manufacturing strategies to improve ATMP treatment safety

The manufacturing and administration of ATMPs introduced a list of novel risks for the patients which needs to be addressed on several different levels starting from the ATMP development process over tech transfer and setup of GMP manufacturing to the management of the entire (cell) product supply chain including the administration of the ATMP to the patient. Here, we will focus on GMP manufacturing strategies to improve ATMP treatment safety. The three major topics to address ATMP treatment safety are:

- process control
- process/data integrity
- education/training

Similar to classical pharmaceutical drugs or most of the biologicals, stringent **process control** is a key aspect to guarantee comparable product quality and biosafety as well as to avoid unwanted side-effects, especially when the starting material is patient-specific (autologous approach) but also when only batch-to-batch variabilities need to be controlled (allogeneic approach). **Automated and closed manufacturing platforms** have been successfully used in the past to increase the overall process control and it will be important to further innovate and improve in this direction[10,11]. Beyond the increased variability of the starting material, the need to define surrogate **critical quality attributes (CQAs)** is very important. Due to the impossibility of measuring definite parameters when analysing a super complex and "living" biological drug and the often long list of difficult to control raw materials, some of them are biologicals themselves, the selection of valid CQAs will be a major prerequisite to enable this level of process control.

In order to address **starting material variability**, sensitive and highly effective selection of target cells from complex mixtures has been established as a gold standard in ATMP GMP manufacturing. For now most of the selection processes have relied on one or two selection markers and some kind of permanent cell labelling but it is expected that novel and innovative ways of GMP conforming cell sorting will help to further refine and improve this essential process. The RESTORE consortium has therefore compiled a dedicated strategy paper on GMP conforming cell sorting methods which will be delivered alongside with this dissemination activity.

Next, the usage of highly defined and comparable **raw materials** is a must to reduce the number of process variables to an absolute minimum. This is especially true when biological raw material such as (human) serum, cytokines or growth factors are used in the cell culture medium. Firstly, ATMP GMP manufacturers should seek to secure (production of) sufficient amounts of critical raw materials and to make sure that different production sources will become available. In addition, it will be important to exactly titrate biologicals depending on their intrinsic activity thus demanding excellent and precise analytical information of the utilized raw materials. As this will become more and more challenging in light of the emerging ATMP market and increasing competitions between ATMP manufacturer, GMP facilities should push process developers to reduce and/or replace biologicals with chemically defined substances wherever possible.

Finally, **in-process controls (IPCs)** and **quality control (QC)** of the final drug product are perhaps the most difficult issue to tackle when trying to improve ATMP treatment safety. Due to the fact that increasing the amount, complexity and technical variety of testing assays will inevitably increase the ATMP cost of goods

(COGs) and thus decrease patients overall accessibility it seems straightforward to reduce analytical testing to an absolute minimum especially in a GMP controlled environment. However, we at RESTORE think differently and propose to rather simplify complex analytical procedures by improving design and automation of IPC/QC testing and analysis, increasing the amount of real-time (inline) measurements using closed systems and introduce automatic sampling and robotics to minimize the need for costly human interaction. As a result, ATMP manufacturers will have the possibility to include even more complex tests and readouts like functional/potency testing of ATMPs in 3D organoid or human-on-a-chip systems to control the GMP manufacturing process and the safety of the ATMP for release to the patient.

The complexity and novelty of ATMP GMP manufacturing and analytics subsequently increases the need to further improve process/data integrity of the ATMP manufacturing process. The individuality of the patient material quality makes it much more difficult to recognize potential mix-ups or confounding actions early on and without profound subject matter expert (SME) and/or qualified person (QP) investigation when compared to conventional pharmaceutical or biological manufacturing. High-class and continuous operator, SME and QP training is one way to avoid such pitfalls and will thus be discussed at the end of this section. Another way to improved process/data integrity is to increase the degree of automation when it comes to labelling of the patient batch and thereof derived analytical samples. In addition, analytical acquisition should be coupled to automated sample detection and measurement, followed by automated analysis of the raw data and ideally a legally non-binding ear marking if the measured results is within the expected range, close to the borderline specification or out of specification. Here, the usage of machine learning algorithms combined with image segmentation (in terms of more complex imaging analytics) are likely to be key measure to address this evolving need. At the end it would be desirable if the manufacturing and the analytical devices could "talk to each other" to further decrease the likelihood of process/date integrity breaches.

One of the most neglected but in our view very important aspects is the matter of adequately trained personnel in the ATMP GMP manufacturing sector but also along the entire supply chain. Despite of the fact that the technology which is used in ATMP manufacturing is becoming more and more automated, it will still be people for a long time, who setup the ATMP manufacturing process, train workers and take decisions in case of unexpected situations and deviations. Subsequently, guaranteeing safety for the patient should stay within the hands of people and not machines and this will have implications for the professional landscape of ATMP manufacturing.
Due to the exponential growth of the industrial sector the "war of talents" has already started and will soon become even more critical due to the increased ATMP manufacturing activities of large scale pharma companies which usually lack a long history of ATMP manufacturing experience. In order to close this gap, European academic institutions, biotech and industry have to work closely together to close this widening gap.
As a consequence of the novelty of the ATMP manufacturing processes, many of them also having highly automated and totally new non-compendial QC analytical assays, the gap is not only on the operator and subject matter expert (SME) side but also on the leadership positions. Especially in industry, many technical leads would have to teach and check compliance of working processes that they never worked out by themselves. Re-qualification of existing personnel might be a suitable way but depending on the ability of the employee to adapt to sudden and significant changes the outcome will be highly variable and very hard to project for the industrial sector. Therefore, we at RESTORE suggest to take the following measures to enable sufficient personnel capacities for the exponential needs of ATMP manufacturing:

- understand and listen carefully to the **professional needs** of European (bio-)pharma companies for GMP manufacturing to tailor specific education programs in schools, academia and research institutes
- identify and further develop **talents and technical specialists** within the biotech sector to become "ambassadors" for ATMP GMP manufacturing in other sectors including primary & secondary education, academia, clinics/hospitals and pharmaceutical industry but also regulatory bodies, governmental and health care institutions.
- Public/governmental **investment** in excellent biotech companies to further improve the strength of this and related industrial sectors in Europe to secure and grow well-paid and sustainable working places
- Modernize **curricula** in all educational sectors to put innovative biotechnological manufacturing including ATMPs on the agenda of each and every student
- Join forces with experts and leaders from the humanities to find **novel ways of teaching and education**. Recent studies have shown that even operators have identified strong social skills as THE major asset to deal with the challenges of the VUCA world and to deliver highest quality work.

The last years have shown the enormous potential of ATMP treatment. However, only when safety will become the primary goal of every ATMP manufacturing step will there be a chance to make ATMP manufacturing a sustainable and thriving business to become a cornerstone of patient health. Therefore, quality has to become part of the ATMP manufacturing "DNA" which will be the blueprint for all different working fields among this industrial sector.

GMP manufacturing strategies to improve ATMP treatment efficacy

Many of the strategies to improve ATMP treatment safety will address the need to improve treatment efficacy using "quality by design" approaches. However, we see this more as a prerequisite and bystander effect than actual redundancy with the ATMP treatment safety discussion point. In order to take real leaps in ATMP treatment efficacy, operational excellence will not be sufficient. It is highly likely that the current ATMP design and manufacturing processes will not last for a long time because of the rapid advances in the field. While technical innovation is for sure part of the ATMP development and not of the ATMP manufacturing process, it will be key to use the current GMP-compliant ATMP manufacturing process and connected clinical trials including real-world data of ATMPs with a market authorization to thoroughly revisit the original promises and process (manufacturing) designs.
This feedback loop has to be bidirectional, otherwise ATMP process development and ATMP manufacturing will become decoupled and thus enhance the chance of failure of a promising new treatment paradigm.

In our opinion ATMP manufacturing can help to address the matter of improving ATMP treatment efficacy by the following actions:

- Continue to gain further **process knowledge** under GMP conditions
- Increase allowance for **flexibility** in the ATMP manufacturing process
- Shift the **focus** from the technological process to the patient and the treatment outcome

In theory, developing ATMP manufacturing processes means checking a lot of variables in a short time frame and to come up with an all-in-one solution that can be directly transferred to the manufacturing space. In reality, it is often the first "good-enough" solution. While we might be able to resist the temptation of prematurely selecting the "good-enough" solution by following rational **Quality by Design (QbD)/Design**

of Experiments (DoE) approaches it is rather hard to transfer conditions of a clean room to the R&D lab space. Again, automated and mostly closed manufacturing platforms can help to master this balancing act and accelerate the transfer of process knowledge from an unregulated R&D space to the GMP manufacturing space. Nevertheless, some of the potentially diverging GMP conditions can still not be adequately controlled and mirrored during process development. Therefore, it is key to continuously monitor the efficacy of the manufacturing process. This could be done, for example, by an adequate in-process control testing strategy, ideally by automated sampling methods or if possible by real-time in-line measurements. The sensor devices which are needed to do this have been already developed and used for the production of biologicals. Thus it will now be key to integrate them into the complex ATMP manufacturing devices, systems and platforms. From there the data have to flow to centralized or maybe even decentralized software tools to make them available for retrospective and at a later time point maybe even predictive analysis.
Regular data review meetings from manufacturing and QC shall allow to build on the process knowledge from the ATMP development phase and understand if additional development projects might be useful to specifically address findings from ATMP manufacturing within the GMP space. The very complex and multivariate biological interplay between cellular starting material, other cell product touching raw materials and manufacturing parameters (e.g. feeding strategies, shaking patterns, gas exchange, etc.) will most likely need dozens if not hundreds of runs to better understand which strategy is the best for the biggest share of patients. Starting from allogeneic starting material would be one way to reduce variability in one of these variates but even here, different cell bank passages and growth/differentiation kinetics can make consistent ATMP efficacy challenging.
Another way to gain more process knowledge could be the implementation of concomitant research activities that focus on additional analysis of non-release criteria under GMP conditions. Ideally, some of the analytics would make use of unbiased intra- and extracellular metabolic/proteomic/lipidomic profiles to find novel bio- and activity markers. As this kind of concomitant analysis is usually not very attractive for pharmaceutical industry and difficult to implement in GMP-compliant environments, collaborations with biotech or in some cases even academic and research institutions might be a feasible option for initial proof-of-concept studies[12].
Biobanking of ATMP intermediates and drug product provisions might be important as well, however for these and also for the previous measures to gain more data points from human cellular starting material, manufacturing intermediates as well as final ATMPs, ethical and regulatory aspects have to be taken into consideration and pro-actively addressed with the regulatory authorities.

As soon as enough process control and knowledge has been gathered in the GMP space, predictive algorithms could be used to increase the flexibility of the ATMP manufacturing process. One of the most straightforward approaches could consist of flexible end points depending, for example on the cell count, viability and functionality of the ATMP. Additionally, timing of feeds, intensity or modes of shaking and gassing could be directly adapted towards real-time biological feedback from IPC analytic of the manufactured cells. However, this needs to be translated into GMP compliant documentation and into the design of the preceding tech transfer and process qualification activities, which needs to be jointly determined by technological/manufacturing experts, regulatory bodies and clinical specialists.
There is a high likelihood that machine learning algorithms will be helpful to orchestrate and evaluate all the simultaneously occurring information from different sources. The FDA has already provided a regulatory framework for modifications to Artificial Intelligence (AI) /Machine Learning (ML) based software as a Medical Device[13] showing that this is going to be an evolving topic that need to be shaped by the biotechnology and biomedicine specialists. It will be interesting to see if self-learning algorithms will come up with unexpected strategies to improve ATMP quality and efficacy as it was already seen when Google´s conventional AI program AlphaGo first defeated the world´s best Go players and was then

beaten 100:0 by an even further developed self-learning KI program called Alpha Go Zero[14]. Ultimately, virtual interconnectors ("digital twins") between AI-algorithms and human decision takers like qualified persons could become the norm of the future even in ATMP GMP manufacturing[15].

Finally, ATMP GMP manufacturing should not only focus on the quality and efficacy of the cell product itself but also on the fit with the recipient. As ATMPs are living, human-interacting drugs with potentially very long half-lives in the immunological compartments, it will become key to understand the drug and the patient as one holistic unit. Maybe there is no such definition as a "superior" ATMP but it will be rather a "best-fit" ATMP that is the desired manufacturing product. Thus, in the future personalized medicine might not only mean personalized drug and treatment but also **personalized GMP manufacturing**. Pharmacovigilance will then become another challenge and as already laid out in the chapter about ATMP treatment safety, education and training of sufficient personnel to take care of this process will have to start sooner rather than later. Increasing flexibility and individualization of GMP ATMP manufacturing will not only be a challenge in terms of IPC/QC, batch recording and meeting regulatory requirements but also with respect to intellectual property rights. If the manufacturing process itself becomes an essential part of the efficacy of the ATMP who is then the owner of the product when ATMP license holder and ATMP manufacturer are not the same entity? New ways of thinking and maybe even economy/business models will be needed to address this question.

GMP manufacturing of ATMPs holds more innovative potential to take leaps in efficacy than every other type of (bio-)pharmaceutical manufacturing. Strong cross-disciplinary and cross-sectoral collaborations will be necessary to unlock this hidden treasure and to support innovation experts of the ATMP development process to discover the full potential of ATMP treatment.

GMP manufacturing strategies to improve patient access to ATMP treatment

In order to take a global leadership position for the setup, execution and continuous improvement of ATMP GMP manufacturing operations, Europe will have to provide a significant and targeted private as well as public investment by (bio-)pharma industry and governmental bodies. As outlined before, ATMP manufacturing is a relatively new industrial sector which is based on pioneering work from academic institutions and innovative biotechnology companies. Although the ground-breaking potential of ATMP manufacturing and administration to (leukemic) patients is beyond doubt, further commercialization in a typical industrial setting will need additional considerations which are summed up below:

- Cost of goods
- Sustainable and resilient supply chains
- Improve European-wide location factors to attract ATMP manufacturing personnel

High Cost of Goods (CoGs) are a hallmark of many innovative products with a defined market share and a limited competitive landscape. While this situation is highly desired to encourage private investments and risk taking of entrepreneurs, it will also limit the product accessibility for the customer or patient. Joint efforts from different industries and academic research institutions will be necessary to come up with technical solutions to reduce the CoGs without compromising safety and/or efficacy of the ATMP treatment. Further automation of all parts of the supply chain, including but not limited to manufacturing and analytics, will be a key element to address this issue. Another aspect will be in the **reduction of process time** and IPC/QC quantity or hands-on time in general. This could either happen due to intelligent process design, creative problem solving or by the incorporation of economy-of-scale models like sophisticated allogeneic ATMP manufacturing. However, all of the latter options will demand a significant

upfront investment in terms of personnel and time. Co-creational ATMP realization projects between (bio)pharma, biotechnology and IT corporations could help to tackle these challenges without having unbearable economic risks in case of failures. Depending on the ATMP manufacturing process, the raw materials could make the biggest portion of costs, so academia, biotech companies and the bio-pharmaceutical industry will also have to work together at this point to reduce batch prizes. Moreover, as for so many other industries, following of lean manufacturing and operational excellence principles will help to further cut costs for manufacturers, thereby reducing ATMP price tags and increasing accessibility for the patient. Finally, Europe should seek to encourage **competition** between ATMP manufacturers as well as between ATMP developers to have a strong grip on ATMP CoG development in the upcoming years. With the current price tag it will be highly unrealistic to evolve from an experimental, last resort treatment to an economic sustainable first-line treatment option supplying the highest standard of care to all European patients.

With the increasing complexity but also competitiveness of ATMP manufacturing, securing of **stable and resilient supply chains** tailored to ATMP manufacturers becomes more and more crucial. When the ATMP industry is not be able to prevent further bottle necks like the already existing lack of high-quality and GMP compliant (lentiviral) vector stocks it is highly likely that only a very few ATMP manufacturers will survive in the long run. This would in turn reduce competitiveness, innovation and by that increase or at least maintain the extraordinarily high price tag of ATMPs for the patient. How could ATMP manufacturing help with this point? We at RESTORE think that the time is now to **"industrialize" ATMP treatments**. As nearly all of the current ATMP products, including the manufacturing and analytics processes, have been developed by academia and small to medium scale biotech companies, paradigms like operational excellence/lean manufacturing or one-piece-flow/just-in time production have not been the primary focus when designing the manufacturing process. The following years should be used to understand and adapt the principles of other complex and on-the-spot **supply chains** like in the automotive industry. But as many of the raw materials are actually already processed intermediates with very short shelf lives (e.g. cytokines or growth factors) scheduling and one-piece flow production of hundreds of (maybe even personalized) ATMP products in one facility will certainly need additional innovations in the supply chain like AI-guided MES/ERP systems and a fully integrated commissioning, manufacturing and analytical ecosystem (IoT approach). Allogeneic cell platform approaches could be a good way to take a graded approach towards personalized ATMP manufacturing which certainly has much more inherent challenges to tackle, when implementing lean manufacturing systems.

Beside efficiency, **flexibility** of the production process but also the flexibility of the production line itself will be another key factor to further industrialize ATMP manufacturing and the entire ATMP supply chain. There is a high fluctuation and unpredictability in patient numbers and medical indications and it will be even more difficult to foresee the unmet medical needs for the future. A good way to address this issue could be highly flexible ballrooms that are equipped with adaptable manufacturing platform modules and analytical suites very close to them[16]. While the increasing need for flexibility in the ATMP supply chain to increase patient access is obvious, novel and more adaptable manufacturing strategies also pose a higher risk to comply with the highest standards of process safety and integrity. Biotech and (bio-)pharmaceutical industries will have to come up with very stringent risk mitigation plans and invite the regulatory authorities to learn about novel strategies to balance risks and flexibility in the ATMP manufacturing process and the supply chain as a whole.

A good way to start might be the building of **dedicated and decentralized hubs** for production and/or storage of raw materials and ATMP intermediates. In a next step, ATMP manufacturing could also move from a centralized plant to a few decentralized hubs to build networks with excellent clinical care centers and research institutions[17]. Bringing the suppliers closer to the manufacturer and the manufacturer closer to the patient would decrease the costs for logistics and transport but also for inventory and storage.

Finally, ATMP manufacturers should seek to find innovative ways to offer a wide range of **attractive and sustainable job opportunities**. While industrialization of the ATMP manufacturing process is an important way to go, "industrialization of job profiles" will inevitably lead to a brain drain of highly skilled and motivated workers over time. Automation of rote work but also implementation of some aspects of agility, mindfulness and "new work" will help to make ATMP manufacturing a safe and attractive job for the future. The ping pong act to switch between strictly following (GMP-) compliance and applying creative problem solving is a huge undertaking and will need experienced leaders and mentors, not only on the technological but maybe even more in the social/emotional arena. Europe has a long and great history of the Humanities including a high number of very skilled experts and this will be a good time to bring these very different sectors together to achieve the primary goal of improving patient health by increasing Safety, Efficacy, Access and Acceptance of ATMP treatment all over Europe.
ATMP manufacturing could therefore function as a ripple maker to build up entirely new economic ecosystems leading to quantum leaps in technology and production efficiency thus enabling companies to pay significantly less for ATMP manufacturing, increase their employees' salaries due to growing skill levels and finally offer the ATMP for a reduced price on the market.

Decreasing the Cost of Goods while increasing ATMP quality will be the only chance for ATMPs to become a sustainable and affordable treatment paradigm for all European citizens. Although automation of manual handling steps and synchronized refinement of operational excellence will help to achieve this, only the future-oriented attraction, education and empowerment of highly skilled workers could function as a real lever to achieve an exponential accessibility of European citizens towards ATMP treatment in the future.

GMP manufacturing strategies to increase patient acceptance of ATMP treatment

When thinking about all the technological, economic and organizational layers of ATMP manufacturing we often forget that is actually the human who will receive the administration of the living drug into their veins. And in case of autologous procedures the starting material will also be donated by the patient by themselves. While the level of **self-determination** of the patient has only slowly evolved from the beginning of professional medical until the early 1990s, the establishment of high-speed internet has enabled and democratized patient access to a wealth of scientific and medical data and thus lead to an exponential increase in a patient´s will to be an active part of the treatment process. Today it is possible to find comprehensive and easy-to-understand explanation of complex surgeries, treatments and even "translation of code" coming from doctor´s letters in the world wide web. While this development comes with a certain amount of risks (fake news, simplified explanations and unjustified hate speech on platforms to evaluate physicians and hospitals, etc.) it also holds a great potential to put humans back into the centre of all our efforts and thoughts. ATMP hold the potential to become a first-line treatment option against a multitude of devastating diseases but they are also very new therapies for all humans involved. Patients, nurses and physicians need a good and fair understanding about chances and risks of these kind of treatments.
Therefore, ATMP manufacturers should come up with up-to-date and customized dissemination activities to inform the specialists and the greater public a) how ATMPs are exactly produced b) which measures are taken to deliver a safe and effective product, especially when ATMPs will become more than the last resort treatment and c) should try to establish direct personal interfaces with patients, physicians and research scientists to further increase the acceptance and the transparency of this novel kind of treatments.

Finally, it seems to be totally undefined how ATMP manufacturers and ATMP license holders will use the huge amounts of process but also biological data that will come out of digitalized manufacturing processes. While the process data will either stay in the hands of the technology provider, the ATMP manufacturer or the license holder, the biological data are actually owned by the patient (even if there are national legislations in place which indicate differently). A broad panel of scientists, politicians and representatives from the public should determine this in open consultations and ATMP manufacturers need to be part of these discussions as they will be very close to data acquisition and analysis.

ATMP manufacturers should pro-actively engage in direct patient dialogues and customized dissemination and outreach activities to pave the way for high patient acceptance of the novel ATMP treatment option. Trust and transparency are the most important assets to make a broad public acceptance reality.

4. Summary and Challenges/Opportunities for RESTORE

SAFETY

The last years have shown the enormous potential of ATMP treatment but only when safety will become the primary goal of every ATMP manufacturing step there will be chance to make ATMP manufacturing a sustainable and thriving business to become a cornerstone of patient health. Therefore, quality has to become part of the ATMP manufacturing "DNA" which will be the blueprint for all different working fields among this industrial sector.

EFFICACY

GMP manufacturing of ATMPs holds more innovative potential to make leaps in efficacy than every other type of (bio-)pharmaceutical manufacturing. Strong cross-disciplinary and cross-sectoral collaborations will be necessary to unlock this potentially hidden treasure and to support innovation experts of the ATMP development process to discover the full potential of ATMP treatment.

ACCESS

Decreasing the Cost of Goods while increasing ATMP quality will be the only chance for ATMPs to become a sustainable and affordable treatment paradigm for all European citizens. Although automation of manual handling steps and synchronized refinement of operational excellence will help to achieve this, only the future-oriented attraction, education and empowerment of highly skilled workers can function as a real lever to achieve an exponential accessibility of European citizens towards ATMP treatment in the future.

ACCEPTANCE

ATMP manufacturers should pro-actively engage in direct patient dialogues and customized dissemination and outreach activities to pave the way for high patient acceptance of the novel ATMP treatment option. Trust and transparency are the most important assets to make a broad public acceptance reality.

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