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Whitepaper

The Future of Cell and Gene Therapy Production

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There is an increasing demand for innovative Advanced Therapy Medicinal Products (ATMPs) against various diseases in which conventional drugs, New Chemical Entities (i.e. small molecules) or New Biological Entities (i.e. therapeutic antibodies) lack therapeutic benefits for the patient. Among the ATMP family, Cell Therapy Medicinal Products (CTMPs), Gene Therapy Medicinal Products (GTMPs) and Tissue Engineered Products (TEPs) could have potential to shift the medical paradigm from symptomatic to curative treatment.

While only 15 ATMPs are approved for the EU market, a double digit number of ATMPs (in the US designated as Regenerative Medicine Advanced Therapies, RMATs) are expected to enter the US market per year and if successful, may be then also submitted for market application at the European Medicines Agency (EMA).
Most importantly, a strong pipeline of approx. 1000 ATMPs are worldwide in clinical development and most promising targets will move forward into clinical trials, either in the US, EU or Asia (1).

ATMPs originate from human-derived DNA, or human cells are applied as “drug” or “drug vehicle”. ATMPs can be processed from patient's own tissue as autologous products for personalized therapy. For example, Chimeric Antigen Representing T-cell (CAR-T) are cell-based GTMPs, genetically modified human T-cells from leukapheresis as starting material, shipped to the pharmaceutical manufacturer and there cultivated, genetically modified, expanded, harvested and cryopreserved. Following a sequence of quality control testing and final product release, CAR-T are transported back to bedside for patient treatment.
Focussing on EU region, the CAR-T marketed product Kymriah® is a designated medicinal product for the treatment of pediatric patients and young adults with refractory or relapse (R/R) B cell precursor acute lymphoblastic leukemia.
Another CAR-T marketed product, Yescarta® is prescribed for the treatment of adult patients with R/R large B cell lymphoma and manufactured in a similar manufacturing process but with other cell surface antigen-representing targets and viral vectors used. More CAR-T products are currently in preclinical and clinical development and will follow Kymriah and Yescarta.
Another class of autologous CTMPs/TEPs prominently exert their beneficial regenerative properties on various lesioned tissues and have been successfully applied for diverse cartilage defects in clinical practice (Novocart®, Chrondroselect® and co.don chondrosphere®) (2).

In contrast, allogeneic ATMPs derive from human cells as starting material derive from healthy voluntary donors.
For example, CTMPs and TEPs originate from diverse tissue sources of donors such as cell apheresis from blood, bone marrow, adipose tissue, umbilical cord blood. From these tissues, multipotent Mesenchymal Stromal Cells (MSCs) can be isolated (stimulated), and differentiated into a variety of cell types such as osteoblasts (bone cells), chondrocytes (cartilage cells), myocytes (muscle cells) and skin cells (keratinocytes).
Furthermore, MSCs can be limited expanded and

cryopreserved for later applications, predominantly infusion or implantation.
MSC based TEPs such as the marketed product ObnitixTM has been successfully introduced for the treatment of Graft versus Host disease (GvHD) to positively regulate patient's immune response.

Another example is Alofisel®, which is accepted in the EU for treatment of complex perianal Fistulas in Crohn's Disease. Further promising allogeneic MSC candidates are currently in late stage clinical trials, especially for their regenerative properties in larger indications such as ischemic stroke and neurodegenerative diseases (3).

Independent from the variety of alternative ATMP products in development for different applications and (derived from dendritic cells, natural killer cells..) innovative stem cell- derived products include induced Pluripotent Stem Cell (iPSC) and human embryonic stem cell (ESC) lines, genetically engineered with innovative viral vectors and CRISPR/CAS technology.
Such product are at preclinical to early clinical stage, despite under ethical debate.
Compared to adult tissues, Human cell lines derived from iPSC/ESC allow to combine pluripotency with advantages in cultivation performance and differentiation control. If no severe adverse events will abruptly stop further development, this new generation of ATMPs, especially if combined with advanced biopharmaceutical manufacturing technologies are capable to scale up for larger indications and new applications (4).

For academia and industry Cell and Gene Therapy product development and manufacturing are facing several challenges:

(Fig. 1 – page 5)

1. Product complexity impacts production costs

Most ATMPs are currently not produced off the shelf- they require product-specific development, coexistent with a regulatory and marketing strategy. ATMPs are refined across various biomanufacturing steps with a logistic chain from tissue procurement before manufacturing and back to the clinic for patient treatment.
Especially, autologous, genetically engineered ATMPs, individually produced for a designated patient are among the most expensive therapies. Consequently, patient treatments require innovative reimbursement strategies with measurable clinical outcomes in a long follow-up phase. Only those ATMPs will finally be accepted by patients, doctors, authorities, and payers, that show remarkable and sustainable benefits such as prolonged survival or even healing versus the standard of care.
Every ATMP undergoes not only a critical medical and quality review, but also a cost-value analysis from preclinical to market stage. At the same time, productions of ATMPs should be lean in their manufacturing process, economic in the costs of goods (CoGs) per each production, and de-risk in production failures (5).

2. The production process determines product quality and quantity

Production of a cell-based therapy relies on availability of patients and in case of allogeneic therapies, availability of a voluntary, qualified, matched donor. However, patient's tissue itself entails biological variability for downstream processing to the final product. Furthermore, each raw material used in the manufacturing process (i.e. cell culture media/supplements, viral vectors, RNA probes used for the manufacturing process) needs to be qualified, tested and proven compliant to Good Manufacturing Practice (GMP), available upon demand and also with representative quality.

Operator-dependent, open process steps are also at risk for potential environmental contamination and as a sonsequece, “failed” batches. On the

other hand, process optimization and scale up at late-stage clinical development require quality, technological and regulatory justification with a risk-based approach (6).

3. Seamless track and trace of materials, resources, and products

ATMP development programs that step across different clinical stages require dedicated and flexible resources guided by material and resource management. This includes detailed planning of material supply and warehousing, routine maintenance of equipment, and clean room reservations, especially if parallel productions collide for the same resource and ranking is required. Moreover, if products are manufactured at a Contract Development Manufacturing Organization (CDMO), the cell product needs interim stored and transported as stable and cryopreserved formulation with a safe cold chain logistics from the starting material to the patient treatment. Long-term planning of a successful ATMP may require a product specific facility design.
Only precise and continuously planning of changing production scenarios under certain prerequisites and assumptions can risk mitigation a lack of therapy available for a patient urgently waiting for treatment. While continuous productions for clinical supply of ATMPs are ongoing, parallel process optimization such as automation may be implemented to ramp up productions mandatory to fulfill future market demands in agreement with the ATMP guideline (7).

4. ATMP production requires qualified resources in place

For each ATMP, a Pharmaceutical Manufacturer is authorized to produce under a manufacturing license obtained from local regulatory bodies. Each manufacturing process step and all associated analytical methods needs to be validated before clinical production. Translation and optimization of a manual manufacturing process from lab scale into a scalable, automated production platform requires experienced and qualified operators, scientist, engineers, data analysts, IT experts, quality managers, each providing their core expertise into a multifunctional project /production team.

Furthermore, infrastructure such as soft- and hardware, biomanufacturing technologies, supply chains and data storage need to be qualified according to regulations and quality requirement. Process data are collected on various servers and administrators of the different organizations are involved to permit restricted access to a changing roles and responsibility scheme. The interplay between human and technology resources allocated to a project team force a structural, organizational, communication architecture from material and technology suppliers, external labs, production to clinical sites and clinical trial sponsors (i.e. Clinical Centers, Biotech and Pharma companies) (8).

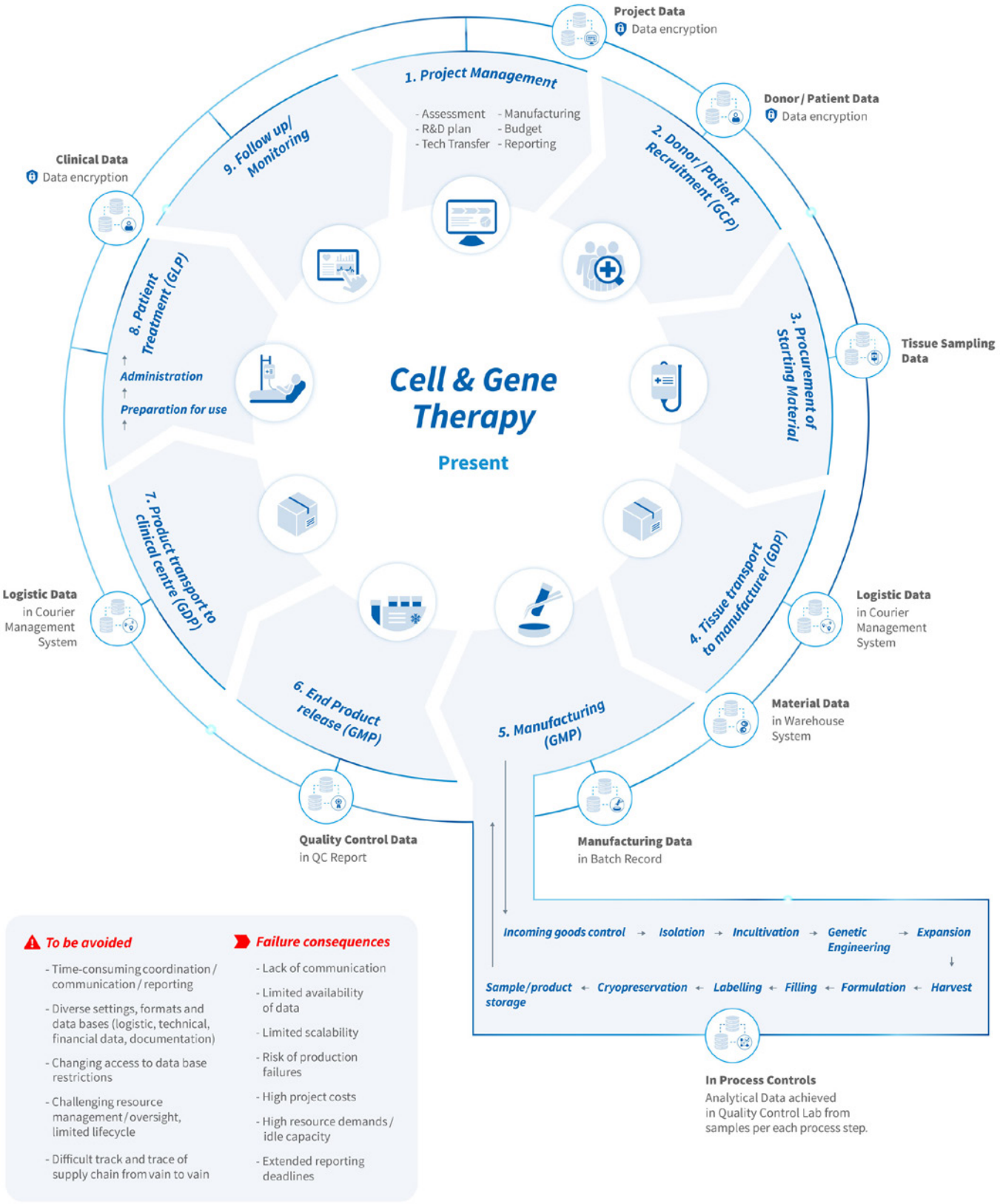

Fig.1: Current challenges in Cell and Gene Therapy development and production.

The future of Cell and Gene Therapy

In the competitive environment of Pharma and Biotech, first in class ATMPs not only contribute to an unmet medical need, enable treatment of the first patient, but also position product and license holder in the market. In turn, successfully marketed ATMPs help to enter into other related indications or to guide related products as fast follower.

Established product platform will improve the network of essential partners, material and technology suppliers and outsourcing opportunities to CDMOs.
In terms of production scenarios, more productions could be executed and delivered within a shorter time window (increase turnover while avoiding idle capacity).
Under these conditions, the real value of ATMP production could only be achieved through a synergistic combination of scientific, technological, operational and digital solutions, in which the most competitive enterprise has full control over material supply, resourcing, technology, process, quality and budget. Any technological, processual, organizational changes need to be implemented stepwise to set the bar for a new industry standard in ATMP production.

Independent from underlying science and technology of the products, four steps can position players against competitors in the field:
(Fig. 2 – page 8)

1. Standard sourcing of materials

At present, cells from a donor need to be matched for compatibility with the patient to avoid severe immune response such as the “cytokine storm”.
To avoid the dependence of availability of a suitable donor, advanced genetic engineering will be introduced to generate (immortalized or genetically controlled) human cell lines fully compatible and Human Leukocyte Antigens (HLA) matching may then be obsolete. Furthermore, cell vials from a cell line can be better characterized as starting material compared to primary cells, thawed under a standard operation protocol, and reproducible further processed. Finally, chemically defined cell culture media, compatible for thawing, expansion, cryopreservation will further help to obtain control over cell growth in suspended and adherent cultures on microspheres, biodegradable matrices and organoids.

2. Integrated production platform

If production is carried out in a specialized ATMP Center, ideally as an integrated production facility nearby a certified clinic for patient treatment, the risk of transportation from / to patient will be avoided. The production facility will not need to have highest biosafety level clean room capacities because productions can be executed in a platform using closed, automated, eventually later autonomous working units for scale out (autologous) or for scale up (allogeneic) productions.
The final product will be cryopreserved and stored in dedicated cryo-tank depots, while validated, fast and reliable analytical methods are executed, which then significantly reduce product release timelines. The platform approach enables assessment of data at critical process steps, comparison of data sets over productions, which can be subjected for Process Analytical Technology (PAT) to analyze data online and wireless for process control inside and outside the clean room. Massive data points generated from In Process Controls can directly feed into combinatory analytics, machine learning and artificial intelligence.

3. Predictive ERP – Predictive Enterprise Resource Planning

For detailed planning, a set of representative models for the diversity of ATMPs will be defined and implemented into a Predictive ERP software. In the software, the models are adjusted to each

product for simulation of virtual productions ranging from material supply chains, production processes to product release and patient treatment in the clinic.
Thereby, manufacturing and quality control can be reviewed in silico and in case of new products, a customized design of the process and eventually of the facility can be chosen based on most appropriate production scenarios.

Manufacturing campaigns will optimize scheduling, critical path analysis will lead to precision in deliverable deadlines.
Moreover, resource constraints or idle capacity will be avoided and indefinite cost estimations will be replaced by extrapolated cost calculations per each scenario. At the time of the first production, resourcing can be allocated based on automated production scheduling using verified and continuously improved algorithms, material supply will be controlled by autonomous ordering of raw materials and consumables. Documents can be linked with each process step and all data can be collected in the cloud.
For all operations, an integrated project management will enable systematic communications transparently across interfaces and between humans and machines.

4. Analysis of production data

Integration of different sources and formats of data in one tank will open the possibility to compare key performance indices (KPIs) as critical performance and quality data from in process controls to the final product. Operational KPIs will balance human and machine resources through algorithms and continuously control budget providing lean management decisions. Data integration can be used as part of Digital Transformation and will open new business fields for Big Data analysts driven by IT experts, engineers and scientists included.
The overall benefit of this development is to run every production safer and faster, being more effective through transparent and streamline communications in predefined settings. This should make ATMP production more reliable across batches and could significantly reduce the Costs of Goods per product, production, dose, and patient.

The new standard of data driven productions should be compliant to global regulations and importantly, follow cyber security to protect personal data. Again, this transition of data streams into products will economically generate an even more attractive business field for the players involved in development, production, supply and application of the ATMP.

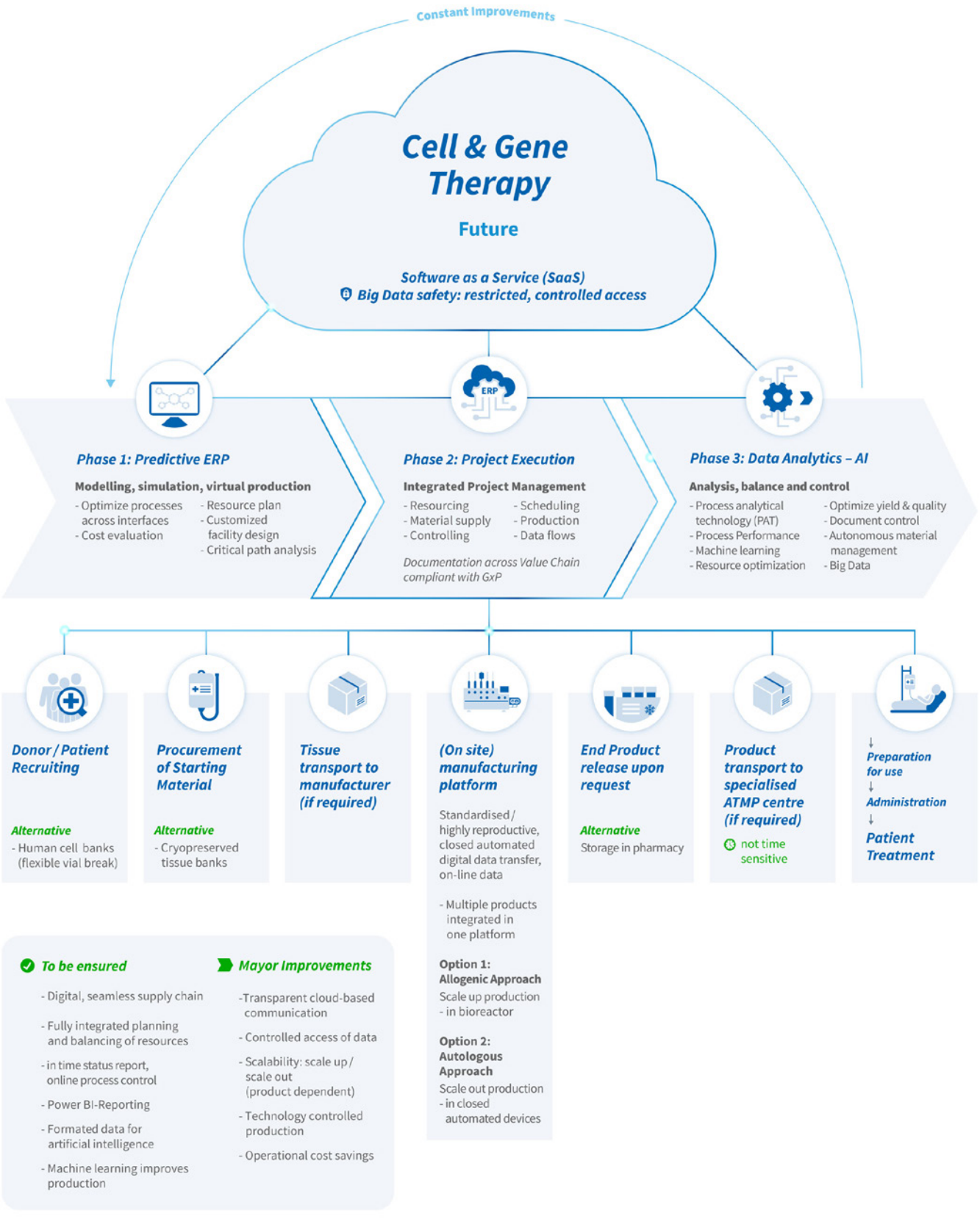

Fig. 2: Visualization of a potential future of Cell and Gene Therapy.

For the current production planning, availability of donors, patients, clinical trial centers, in house and contracted productions will first be assembled in product-specific models that run under certain production scenarios. Under such conditions, prerequisites and assumptions, a worst case, realistic case, and best-case scenario is necessary for contingency planning.
Such models are re-evaluated over time at different levels (technical, operational) from changing processes to quality parameters as a moving target. The model is iteratively adjusted for further decision making (access to patient/ donors at different clinical site, availability of product in time and in place). Simulations of production scenarios can only be done with a versatile, flexible tool, in which product, process, resource data are integrated across the vain-to-vain supply chain.

The power of Predictive ERP is to model planning, allocate resources upon availability and qualification, to provide risk mitigation and to guarantee lean value streams by avoiding waste of resources. Most importantly, model simulations can be carried out virtually before major investments are taken and before the first production starts and thus, can uncover production planning failures.

The Predictive ERP for use in ATMP production could systemically delineate the following questions:

1. What is required to deliver the drug to the patient in time?

- What are the current lead times for provision of starting material and raw materials – and impact of absence of such materials on already reserved productions?
- What is the anticipated product yield per production given biological and process variability and what is the impact of failed productions?
- Which requirements are needed by when to deliver the ATMP across the planned clinical stages?

2. Can the Pharmaceutical Manufacturer / Product License Holder supply the expected number of batches with reasonable resources?

- Which resources limit ramp-up of production, especially if a process is optimized in parallel to ongoing productions?
- How can yet identified capacity constraints during scale-up be avoided by an appropriate outsourcing strategy?
- How should the ideal, product-specific facility be designed to assure a defined production load per month?

3. What will be the return of investment for the stakeholders involved in ATMP delivery?

- Which resources are required exactly to reflect different production scenarios?
- How can costs of goods and production costs be reduced over a sequence of productions?
- How do costs per unit (cost per dose) develop across scales?

Modules of the Predictive ERP App - Suite

ATMP producing companies including CDMOs are confronted with challenges of product diversity, shorter delivery deadlines, production flexibility and consistent 100% product quality per each ordered production request. We introduce, apply, and further develop highly flexible and safe online solutions for biopharmaceutical manufacturing, and explicitly for ATMP development and production.

With the deployment of Predictive ERP, our clients (Pharma, Biotech, Academic Institutes, Clinical Centers, CDMOs, Technology providers) can better predict events of scenarios by today, as well as take planned measures and, in the process, adapt

production and business processes in the future. PREDICTIVE analytics forecast models enable future-oriented decisions. By simulating scenarios in which even complex influences are taken into consideration, future developments can be better forecasted and illustrated.

Integrated Manufacturing Solution (IMS)

makes existing and anticipated digital production data usable profitably. Starting from a well-defined project plan in advance, accurate forecasts can be accomplished to execute the necessary actions automatically.
The results of these real-time decisions are integrated by the system automatically and independently in intelligent, operative processes for continuous process optimization.
By proactive identification and resolution of unexpected faults or disruptions, the business processes are optimized and as a result, designed significantly more efficiently, for example, for demand planning, maintenance, supervision, or pricing.

Integrated Manufacturing Designer (IMD)

offers fast methodical support in the various stages of planning such as, for example, in the product analysis, resource planning and simulation, as well as manufacturing documentation. Processes can be design including all process steps from donor to patient (allogeneic) or from patient back to patient (autologous) as a seamless vain to vain chain. Set up a detailed and digital factory model for the production planning quickly and easily. Production plans can be prepared and designed as complex as desired: shorter sub-processes, products with more variants generated from a Process A to an optimized Process A` or an automated Process B. Both, manufacturing facilities with dedicated clean rooms for production of early stage clinical trials can be modelled and several facilities for multicenter studies engaged in clinical Phase III or market supply can be mapped.

Digital Value Stream Modeler VSM 4.0

a tool developed specially for tablet applications, value streams are acquired quickly and easily in the production directly with the help of mobile touch-screen devices. Process-related information from operators (and later facility and equipment) can read off the automatically calculated key figures immediately. Processes and material flow as well as defects and weak points identified are documented and could be integrated into the Quality Management System. Target value streams

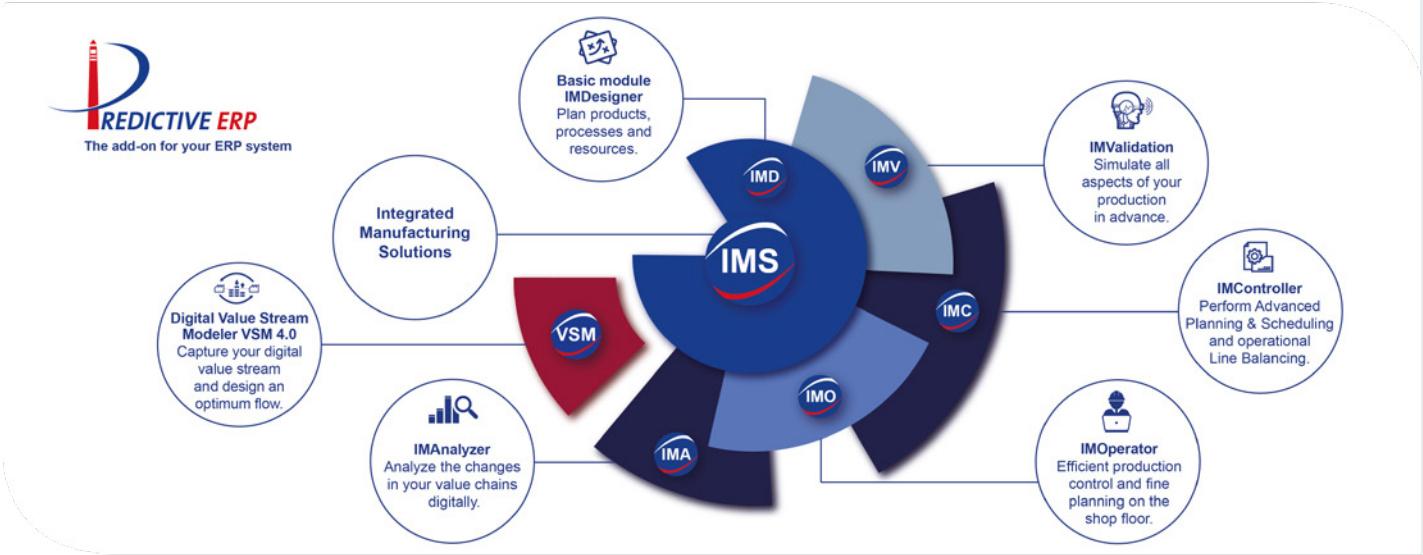

Fig.3: Illustration of all modules within the Predictive ERP App-Suite.

are created directly on the touch-screen devices to monitor critical process steps and to separate value-added from non-value-added process steps. The tool enables direct comparison and simulation of different value streams and can be used to integrate the existing planning data with the actual production data.

Integrative Manufacturing Controller (IMC)

module can perform Advanced Planning & Scheduling and operational Line Balancing in day-to-day planning. Detailed planning is optimized by short-term simulations based on current order information and thus, the production team can react in a flexible manner to fluctuations as well as enhance resources. This is especially important, if quantity/quality of the starting material is in the lower range of the specification the patient or the donor tissue as incoming starting material is delayed or postponed or by production shifts changes.

Integrative Manufacturing Operator (IMO)

module can provide the production team with the process data, workplans and documentation via tablet. This is especially important if the production schedules require continuous and flexible availability of clean rooms, manufacturing and analytical equipment. Employees can provide status information and report malfunctions directly. The organization itself can increase the performance of productions by precise scheduling of the processes involved, permanent transparency, and optimal capacity utilization in the clean room and in the Quality Control laboratories.

Integrated Manufacturing Validator (IMV)

provides dynamic simulation to analyze and improve production processes even prior to commencing production. You can check operative strategies for efficiency and compare various planning alternatives. The virtually safeguarded results permit well-founded and economically meaningful investment decisions to be made. Achieve transparency, increase productivity, and lowering of costs impacts a predictive and comprehensive view of planned and ongoing processes. With the help of material flow and resource models combined with statistically obtained demand and throughput parameters, the organization has a tool to predict both recurrent and basic changes and implement anticipatory measures. New production technologies as well as shorter innovation cycles require faster planning results and systems, which can adapt themselves in a flexible manner to the new product and production environments. In order that you continue to remain competitive despite the increasingly faster changing of market conditions, we support with our models on medium-term simulation of optimization scenarios.

Resource simulation models identify plan deviations in advance and undertake plan adjustments automatically. Line balancing in day-to-day and long-term planning utilizes your production lines optimally and respond to fluctuations at short notice as well as enhance the resource utilization. In the process, “waste” is avoided and share of value addition and response capability is enhanced to a leaner organization. The software platform can be used as Software as a Service (SaaS) and web-based. This avoids server related costs at the user, workload and time for installation, introduction and servicing compared to server solutions. Depending on the size of program, number of administrators and users, the software licenses are provided in line with your needs with great flexibility.
Multiple project partners can access the data online and collaborate at the same time. Data is stored on national servers in line with the most up-to-date data security standards and can be accessed any time and from anywhere.

The Future of ATMP production: Cell therapy 4.0

The future of the biopharmaceutical manufacturing is on the way of getting smarter: sensors are integrated into devices and equipment, wireless technologies and intelligent algorithms are used to process data.

ATMPs will also profit from process standardization combined with process analytical technology (PAT) as key enabler to improve production processes and generate big data for use of Artificial Intelligence (AI) algorithms.

This systemic approach has been shown to be successful in standardized and high- throughput branches such as automotive, aerospace, medical technology. ATMP production is on the way to fit industrial standards as well. Automation will be prominent for scale out autologous products and scale up allogeneic products. This development will corroborate with operational excellence, improved production efficiency, costs reduction and attractive price mark up of ATMPs.

Predictive ERP intelligently transforms operations management at all the levels of the company and across organizations working under the context of the Industry 4.0 (I4.0).

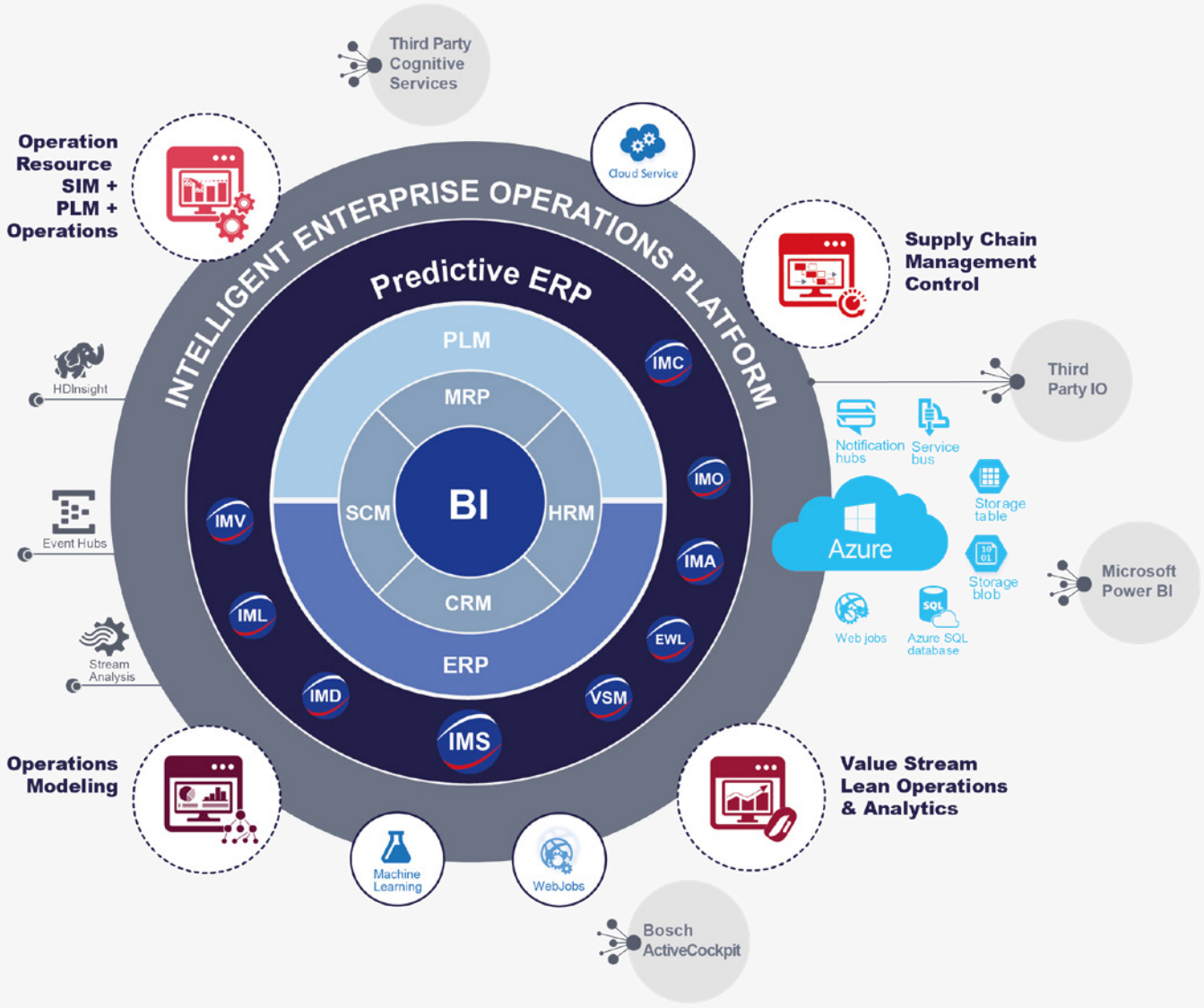

Fig. 4: Illustration of iFAKT‘s Software as a Service Platform.

Furthermore, its objective is to fill the previously mentioned gaps to fully benefit from advanced technologies data and I4.0. There were no constructive relationships between these backbone systems. Nonetheless, trends in the I4.0 paradigm propose to take advantage of data to manage the company's operations as an unique system. Such unique system would be brain and heart of the company's operations to have in-time delivery, product quality at the best possible cost structure.

In the future, biopharmaceutical manufacturing will also profit from I4.0 on the three major information layers: The Smart Factory, the Digital Thread, and the Value Chain Management. These layers themselves have sub layers enabling their functioning:

1. The Smart Factory optimizes the flow of products through production processes and orchestrates the allocation of resources. This layer encompasses another five sub layers: Business Intelligence, connected Enterprise system, Operations Management (smart Apps, controllers), OT-IT Bridges and Smart Machines (sensors, tooling, workforce).

2. The Digital Thread: It encompasses the creation of work instructions for the automated production and the verification of the processes: cell cultivation, genetic engineering, cell expansion, harvest. There are again three sub layers: Specifications management, Operations Management, and Service Management.

3. The Value Chain Management: It delivers real-time data from production processes to other business management functions and merges activities into the supply chain. This makes sure that materials, intermediate products are further processed to the final product at the right place, time and resources (skill sets). It encompasses the five sub layers: Customer Management, Compliance Management, Operations Management, Resource Management and Supplier Management.

Predictive ERP can be the driver to assist biopharmaceutical production of ATMPs from development and production to the clinical application. To our clients, we provide services in the field of ATMP production using our Predictive ERP App-Suite:

- Digital lean management including value stream analysis, mapping, and design
- Evaluation before production start using simulation of various scenarios
- Sustainable efficiency increases in production due to optimized resource utilization
- Supply chain optimization through integrated planning of the value creation networks
- Increasing the production rate by analyzing and avoiding bottlenecks in the material flow
- Patient-centric, dynamic resource planning of seamless end-to-end business processes
- Line balancing and production planning through intelligent performance optimization algorithms
- Integrated shop-floor feedback taking operational production improvement into account

Selected Literature for further reading:

1. VALUE HEALTH. 2019; 22(6):621–626
2. https://doi.org/10.1016/j.imlet.2019.10.014
3. https://doi.org/10.1155/2018/8031718
4. https://doi.org/10.1186/s13287-019-1455-y
5. https://doi.org/10.1016/j.omtm.2018.10.003
6. Cell Gene Therapy Insights 2016; 2(4), 425-452
7. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf
8. BioPharm International, Volume 31, Issue 11, pg 30–34