iFAKT

Illustration Medical staff by Vicky Peucker

White Paper

PREDICTIVE ERP

DIGITAL TRANSFORMATION OF A CLINICAL-STAGE COVID-19 THERAPY

Modeling and simulation of a convalescent plasma therapy using in silico simulation, measure and execution of a reconvalescent plasma therapy using iFAKT`s Predictive ERP software.

THE ORGANIZATION

Over a decade, iFAKT GmbH established its proprietary Predictive ERP software solution to optimize productivity, line balancing and capacity utilization in the field of automotive and aerospace production (1). Cellerata GmbH partners with iFAKT GmbH to apply, model, simulate and analyze manufacturing projects of biopharmaceutical production of innovative therapies, in which time-to-patient is critical and conflicts of resources are evident. Specifically, cell and gene therapy projects entail additional project risks regarding biological variability of starting material, single batch productions and flexible capacities (2). Here, excellence in digital project management provides a helicopter view to the project team on the supply chain, process operations, and resource allocation with control of budget, milestones, and decision points to the project leadership.

In the present outline, we introduce iFAKT´s Integrated Manufacturing Solution Predictive ERP for a clinical project to potentially fight COVID-19 disease. We use convalescent plasma therapy as a recommended, safe, immediate and potentially effective intervention for COVID-19, which shows comparable project requirements with an allogeneic cell therapy project. Our case study provides insights on how Predictive ERP can support drug developers, pharmaceutical manufacturers and clinical centers in planning a safe, time-critical and optimized clinical supply. Finally, we evaluate the current limitations of critical capacities in the software and recommend optimization strategies based on our first process analysis.

THE PROJECT

The SARS-CoV-2 virus is causative to COVID-19 and currently puts strong pressure on healthcare systems. High prevalence of severe COVID-19 cases with ventilation support in intensive care units (ICUs) already required a resource, where demands exceed capacity. Thus, patient turnover in ICUs limits rescue for as many patients as possible within their critical therapeutic window. While no SARS-CoV-2 specific pharmacological therapy is available on the market for COVID-19, convalescent plasma therapy has been shown to increase survival rates and reduces ICU stay in related virus infectious diseases. Immune, convalescent COVID-19 donors with a detectable virus-specific antibody serum titer against SARS-CoV-2 could be recruited for plasmapheresis. Convalescent plasma can be transfused in matched COVID-19 patients in ICUs as supportive therapy to rescue COVID-19 patients (3). We exactly want to model the process flow from donor plasmapheresis to patient treatment and simulate which bottlenecks impact patient treatment.

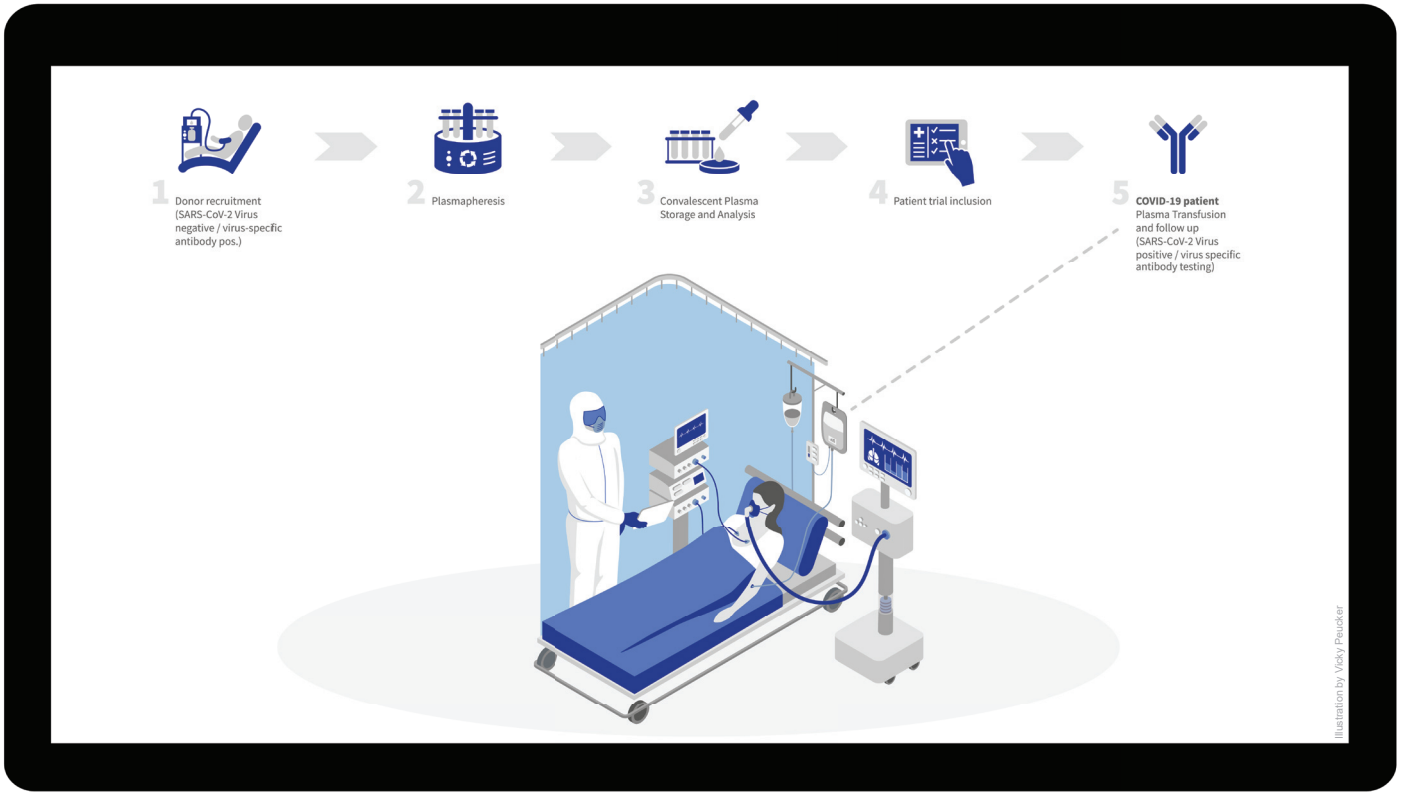
GENERAL PROJECT REQUIREMENTS

Several project requirements need to be managed by project management before production start.

First, legal, regulatory and organizational requirements need to be tackled by an interdisciplinary team of scientists and medical doctors from the transfusion center, plasma manufacturer and clinical center. This includes the submission of the clinical trial and the set-up of regulatory compliance in the Quality Management System.

Second, the number of severe COVID-19 cases, available and matched donors, access to non-infected personnel and limited ICU capacity need to be continuously evaluated with short reaction time. All relevant information needs to be collected in the Predictive ERP software to enable simulation of plasmapheresis, plasma manufacturing, and patient treatment.

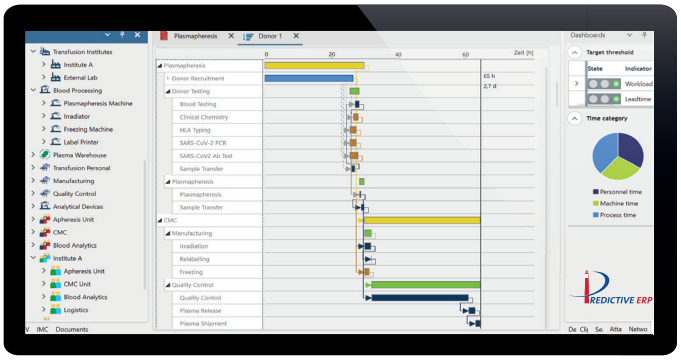
Third, it is extremely important to orchestrate the supply chain from plasmapheresis to convalescent plasma supply at transfusion units to patient treatment at clinical centers. This needs to be managed under restricted communication roles with limited direct contact of team players involved.

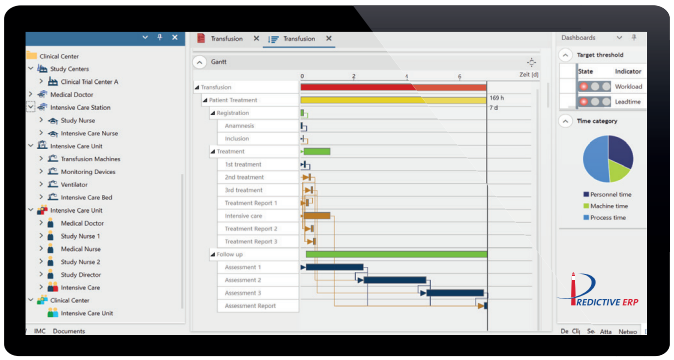


THE SOFTWARE APPLICATION Predictive ERP

We consider Predictive ERP as a digital platform for convalescent plasma production, logistics processes and patient treatment at the time of project evolution.

1. **Plan products, processes and resources**
   We feed the module IMDesigner (IMD) with simple, but realistic data sets to methodically support various stages of planning including donor recruitment, plasmapheresis, manufacturing and patient selection, treatment and follow-up. We link processes with resources for simulation in a digital factory model across the interfaces from donor to patient. Pharmaceutical production, logistics processes, and clinical site management are modeled to allow streamlining of resources and capacities.



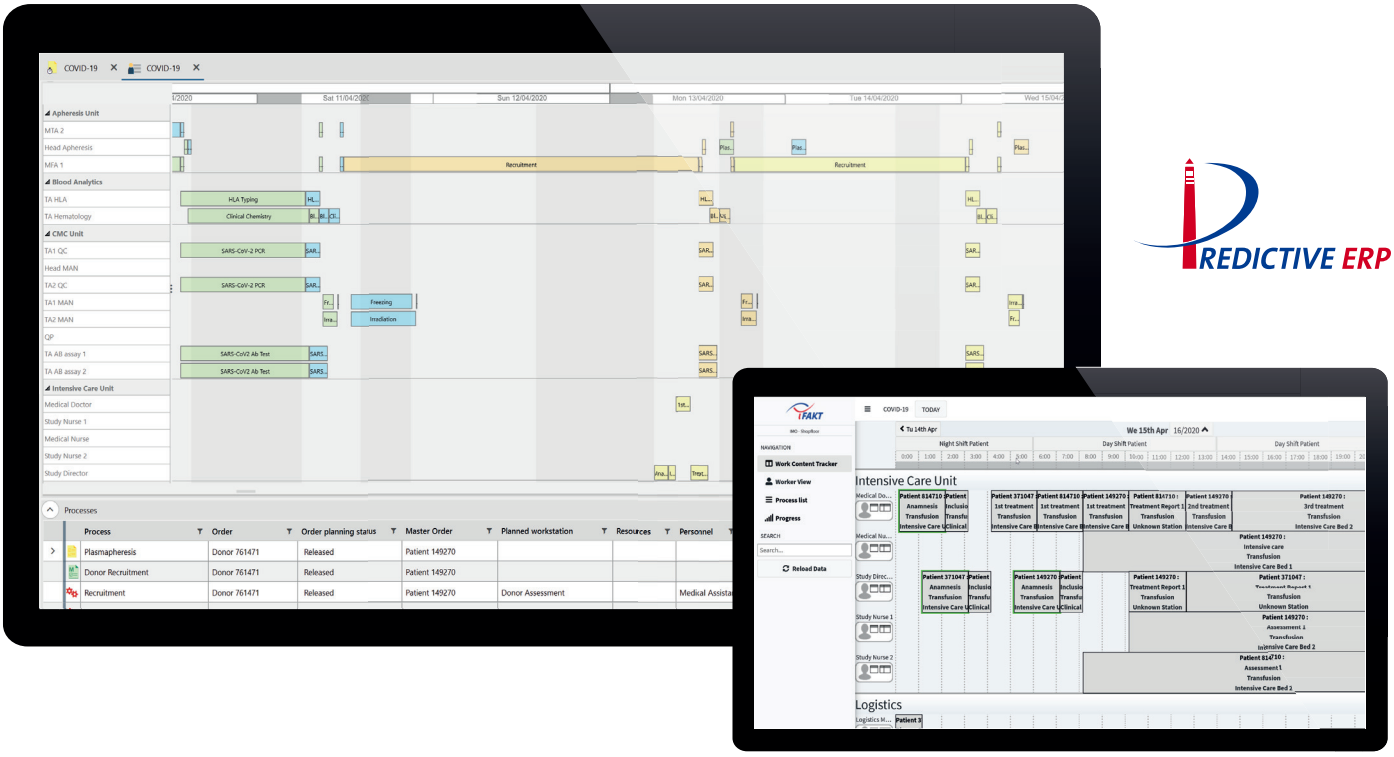


Projection of convalescent plasma therapy.
From a voluntary donor tested positive for SARS-CoV-2 antibody titer plasmapheresis is taken. The transfusion center processes, releases and provides 3 convalescent plasma units to the hospital. The intensive care unit transfuses plasma units per patient. Clinical outcomes are measured at 3 clinical assessment points. The Gantt charts show plasmapheresis and patient treatment (IMD module).

Furthermore, the interplay between raw materials, intermediate products and project activities with the supply chain is shown in comprehensive process charts with dependencies across the process. This results in network plans in which the minimum throughput time, the critical path and the demand for resources are calculated with a static line balancing algorithm.

2. **Simulation and scale up from an operational model to multicenter study**
   In the IMValidation (IMV) module, we simulate, visualize and validate various aspects of plasma supply and patient treatment with accessible information at the time of planning. We check, analyze and optimize plasma production and logistics processes before commencing a first plasma production at the transfusion unit. Due to complex interplay and dependencies, planning errors and capacity bottlenecks are modeled and thus identified in an one donor - one patient relationship. We compare different production scenarios based on bottlenecks in material flow, manufacturing resources, and personnel capacities to identify the best-case scenario covering the seamless value chain from needle to needle. The simulation model is the basis to scale up within multiple plasma productions from different transfusion centers and multiple ICUs treating patients in several clinical centers.

3. **Perform Advanced Planning & Scheduling and operational Line Balancing**
   In the IMController (IMC) module, we perform Advanced Planning & Scheduling, operational Line Balancing and day-to-day planning for plasmapheresis and patient treatment. We optimize planning in detail by short-term simulations based on requests for convalescent plasma to have the possibility to react in a flexible manner to the availability of plasma. We optimize resource utilization by automated process allocation and establish in-time reporting, similar to a “shop floor” at plasmapheresis center, pharmaceutical manufacturer and clinical site. Later on, this could provide real-time data and enables response to disruptions, setting up a building block system for responding to recurrent disruptions and faults in order to learn across clinical trial centers. Due to the high number of severe cases, we expect to include not only one but several centers for plasmapheresis and plasma transfusion, which increases complexity to another stage.



CONCLUSIONS

The Predictive ERP software modules allow the presentation of a simplified, scaled 3D-layout of a product-to-clinic COVID-19 project across teams and sites. Using the iFAKT software modules, we generate a blueprint of material flow and resource allocations from pharmaceutical production to the medical treatment and we can analyze performance indices at different scenarios. We provide an identification of work overload under various conditions at the transfusion site, the production site and in the clinical center. Information flow charts and graphs are systematically compiled in Predictive ERP with insights into process- and resource-related limitations. The most realistic scenario can be used for right-in-time resource planning, cost calculations, and communication of planned timelines under the prerequisites and assumptions given.

FROM VIRTUAL TO REALITY

Emerging R&D projects for the treatment of COVID-19 from product development, CMC manufacturing, and clinical development need digital project management solutions for a systematic assessment of products, processes, and resources. We now anticipate a COVID-19 project with an initiation phase of days using this project as a blueprint in which we adjust parameters to new conditions for an initial stress test. Virtual planning, production, and treatment, as well as simulations, can be directly implemented in an actual operational mode. Furthermore, the Predictive ERP shop-floor module IMOperator (IMO) can be used as a real-time feedback loop from operators at transfusion sites/ production sites and clinical centers to process data, work plans, and documentation. Project team members can provide their status information and report malfunctions. Data on the availability of donors and plasma are systematically saved for precise scheduling and adjustments of production processes. This provides permanent transparency in the workflow and optimal capacity utilization. Microsoft Teams interactively connects multidisciplinary teams to share the project status in the cloud as a digital solution (4).

Our approach is essential for an immediate availability of innovative therapies and patient treatments, such as convalescent plasma for severe COVID-19 patients. The present showcase underlines the need for a digital transformation to streamline supply chain across key players such as academia, manufacturer and their suppliers and clinical sites (5).

REFERENCES

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- https://www.nature.com/articles/d41586-020-00895-8 **(3)**
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- https://www.ifakt.de **(5)**
- Illustrations: Medical staff & conv. plasma therapy process I Vicky Peucker I https://www.vickypeucker.com

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CELLERATA GMBH

Cellerata is a dynamic start-up company, boasting extensive project management experience and expertise in biopharmaceutical development and manufacturing of Advanced Therapy Medicinal Products (“ATMPs”). We interactively manage projects in a multi-organizational environment to cover the diversity and complexity of innovative cell derived therapy of human origin along the value chain - from the cell to the patient.

We work with clients that are developers and manufacturers. This includes academic institutes, clinical sites, biotech and pharmaceutical companies and contract development and manufacturing organization (CDMO) ensuring leverage of their know-how, technology and capacity.

Cellerata`s digital transformation strategy reduces process complexity, improves coordination and communication in the project team - and accelerates product development. We guide the project proactively while considering the opinion of the stakeholders, connect at interfaces, provide solutions at decision points and especially cover time, quality, costs through capacity. And finally, we keep a watchful eye on data confidentiality and data integrity.

OUR SUPPORT. YOUR PRODUCTS.

- Considerations of legal, regulatory and Quality Management frameworks
- Biopharmaceutical process evaluation (e.g. value stream analysis, mapping, and design, optimization)
- Identification of idle capacity and resource constraints (personnel, clean room, equipment, materials)
- Dynamic resource planning under consideration of the “biological flexibility”
- Validation of production scenarios (e.g. number of patients, number of doses, number of clinical sites, timeline)
- Reduce production risks by analyzing and avoiding bottlenecks such as availability of starting raw materials
- Supply chain optimization of raw material supplies, CMC activities, and therapy at clinical sites
- Evaluation of dependencies, restrictions, and synergies in a multi-project – multi-product environment

iFAKT GMBH

As an independent, internationally operating consulting company and software specialist in the Industry 4.0 environment, we support you in the planning of production and logistics processes, the optimization of resource utilization in the company and the improvement of your business processes.

Our many years of experience, innovative technology and methods expertise, supported by our software, are our decisive success factors. Our customers include well-known companies from the aerospace and automobile industries, fields of mechanical engineering and medical technology.

We advise large OEMs as well as small and medium-sized companies on the implementation of their digital business transformation. Our head office is in Stuttgart - in the center of the manufacturing industry in Baden-Wuerttemberg.

OUR SERVICES - YOUR ADVANTAGES. WE OFFER COMPREHENSIVE SOLUTIONS.

- Digital lean management (e.g. value stream analysis, mapping and design)
- Dynamic resource planning of end-to-end business processes
- Line Balancing and production planning through intelligent performance optimization algorithms
- Integrated shop floor feedback taking operational production changes into account
- Sustainable efficiency increases in production due to optimized resource utilization
- Validation of production startups using the simulation of various scenarios
- Increasing the production rate by analyzing and avoiding bottlenecks in the material flow
- Supply chain optimization through integrated planning of the value creation networks