DIGITAL TRANSFORMATION TO SUPPORT INDUSTRIALIZATION IN THE BIOPHARMACEUTICAL INDUSTRY

In this document, we'll focus on the means allowing pharmaceutical companies to respond to these challenges, particularly on the production aspects to answer market demands with the required level of quality.

This will be discussed through the means available at the technological level with industry 4.0 concepts, notably with the establishment of connected flexible factories (Factory Of the Future).

CONTENT

GLOBAL BIOPHARMACEUTICAL CHALLENGES

Healthcare systems are putting more and more pressure on pharmaceutical companies to lower prices for new therapeutic antibodies and vaccines.

Biopharmaceutical Production Challenges

The production and availability of innovative therapies is highly dependent on improvements in production technologies. New disruptive technologies (new smart sensors, nano-electronics, microfluidics, robotics, **digital twins**, etc.) allow us to consider innovative approaches for intelligent bioproduction and at a level of productivity necessary to meet the needs (precision medicine, **short series, flexibility of production**, etc.).

Five levers will have to be used:

- Improving bioproduction processes, to increase the yields of cell expression of molecules and purification
- Reduce the variability of production stages through real-time and predictive production control, by combining sensors and digital technologies
- Mastering production in terms of Quality and market availability
- **Develop simulation and artificial intelligence tools to design the product and its manufacturing process**
- **Create real training courses, to guarantee the transformation of trades in the field of production.**

All these factors have led to pharmaceutical companies to review and adapt their production strategies to introduce the concept of **Factories of the Future** (Factory 4.0) and transform their **Supply Chain**.

Today we have two approaches:

- Manufacturing of biotherapeutics in large quantities in large, inflexible production facilities
- or setting-up more flexible and modular factories to manage a wide range of new product candidates defined during research and development. The goal would be to achieve industrial agility and cost optimization.

Supply Chain Process challenges

To answer market demands, the FoF is bringing the key solutions involving internal and external stakeholders from the Research & Development phase until the Commercialization phase to provide the right product to customers in a short time by considering all constraints.

Due to expensive development costs, it is expected that only the first three companies that enter the market for a field of application with a new biopharmaceutical product will be commercially successful.

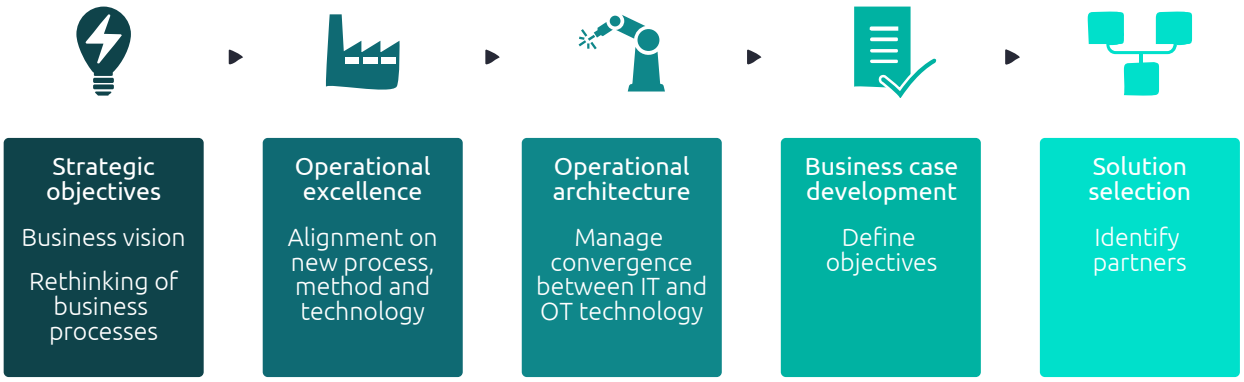
The typical Supply Chain consists of the following components:

PRODUCT DEVELOPMENT	MANUFACTURING AND SUPPLY CHAIN	COMMERCIALIZATION
• R&D, Engineering • Manufacturing Process • Sourcing : In House or Partners	• Serialisation • Labelling,.. • Distribution	• Delivery network (hospital, pharmacy, clinics)

Digital Transformation challenges

The Digital Transformation journey requires a strong organization relying on a phased process involving key stakeholders through different steps to answer the challenges.

To achieve this Digital Transformation, it is necessary to drive a strategy based on Business needs.



FACTORY OF THE FUTURE CONCEPT

In the Biopharmaceutical industry, the notion of Factory of the Future (FoF) means introducing modular and flexible production based on configurable product lines.

Single – Use Systems refers to biopharmaceutical manufacturing equipment designed to be used once (or for a single manufacturing campaign) and then discarded.

Generally, it is composed primarily of plastic components that have been sealed and sterilized using gamma irradiation.

These allow manufacturers to turn over from one drug product more easily and quickly to another or from one batch to another.

Single Use Systems reduce the time to perform cleaning and validation of this activity thus enabling reduction of operating costs.

To enable FoF, it is necessary for the Biopharmaceutical companies to embrace a **Digital Transformation** to meet the objectives and get the expected benefits.

Objectives	Benefits	Enablers
Reduce factory commissioning time	Acceleration of industrialization through re-use of in-context data for Tech Transfer Industrial set-up change-over execution optimization (simulation, …)	Test, train and prepare validation on digital twin Virtual Commissioning, 3D simulations, AR/VR training
Accelerate ramp-up and new product introduction	Reduce time to reconfigure line and introduce changes Reduce time to perform root cause analysis Facilitated Manufacturing/ Operations interactions for process industrialization	Simulate and optimize process in different operational conditions
Reduce cost of large projects	Equipment & building design re-use within & across facilities Equipment standardization & re-use across manufacturing processes (catalog approach) Optimized activities by enabling data sharing & collaborative work in configuration	Collaborate around common reference (requirements, specifications, design, …) PLM, Systems engineering
Increase operational efficiency	Reduced overall quality assurance efforts to track & trace critical parameters approval Smoother overall quality product & processes thanks to clear & unique dataset	Predict rather than react (maintenance, re-configuration, process deviation) Shopfloor connectivity and ontology

DIGITAL MANUFACTURING TRANSFORMATION FOR PRODUCTION SITES

Targeted Industrialization & Manufacturing Business Processes

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The typical Supply Chain consists of the following components:

MANAGE NEW BUILDING DESIGN

The objective is to structure & master revisions of plant layout data and support maintenance operations (plan/ prepare/execute) of Equipments and utilities.

By creating a referential of a plant this will:

- Establish a Single Source of Truth for the plant design and layout
- Ensure a detailed management of plant design and related changes using the Single Source of Truth as the baseline for comparing and managing changes across multidisciplinary teams
- Enable the optimization of the design through appropriate use of simulation for:
  - *Constructions project teams to make knowledgeable construction means and methods, decisions, and help produce an optimized work breakdown for construction.*
  - *Building Information Managers to perform P&ID Walkdown to do functional design verification (Design Qualification/Installation Qualification) and validate functional behaviors to support Commissioning and Qualification.*
  - *Facility managers can benefit from having a virtual building for streamlining maintenance and operations.*
  - *Manufacturing engineers to perform Factory flow simulation to analyze and optimize, including integrating Cobots for accessibility operations and confirm ergonomics of operation using Augment Reality (for existing facilities)/VR solutions (for new facilities). Also, Virtual Maintenance Training could be addressed.*
- Ensure a collaborative management of engineering design and manufacturing process evolution:
- Set-up the foundation to enable Virtual Commissioning simulations for automation and controls V&V, and Digital Twin creation.
- Ensure synchronization with facility management systems to create a living data set with a history

Business values for project team:

- Manage 4D construction sequence in a configured context in a seamless way
- Have a single referential of all data with change management (catalogs could be defined to facilitate re-use) and documentation needed to provide to the Facility Management System
- Significantly reduce the overall commissioning time, costs, and risks.
- Use simulation tools in Virtual environment to validate the integration of human and Cobots/ AGVs (collaborative robots) and confirm these technologies in a production line. Also, the benefit of the virtual environment is to improve through simulation the productivity, safety, and traceability.
- Simulate manufacturing operationsby using VR/ AR tools.

MANAGE EQUIPMENTS

The main objectives would be to manage module and equipment lifecycle for a given biopharmaceutical product from the requirements phase until the design validation phase then position them in the factory 3D layout. This will enable to the define industrial set-up to implement for a specific production campaign.

Business values for project team:

- Ensure the compliance of new data against the requirements through a change process and configured context
- Have an Equipment Digital twin that will allow to pull environment data such as: pressure, temperature, flow, and equipment vendor data... Then to run simulation to capture issues and bugs that may cause slowdowns, performance issues, safety concerns or other results that would compromise the functioning of the physical system.

MANAGE TECHNOLOGY TRANSFERS

The objective is to support Manufacturing process definition through digital continuity in knowledge transfer and requirements flowdown from R&D to Industrialized manufacturing

Business values for project team:

- Manage a Digital Twin and its manufacturing processes as the FoF will include connected and intelligent equipment, with sensors capable of measuring several thousand information throughout the production process and generating billions of data used to monitor, deeply analyze, and control the manufacturing of drugs.
- Accelerate introduction of new Manufacturing Processes through support of gap analysis, and early generation of Technology Transfer documentation.

DIGITAL FACTORY 4.0 ENABLED BY BLM

To be able to achieve a digital factory 4.0 approach, it is necessary to rely on BIM concepts for the management of building information data, on the concept of PLM for the lifecycle of assets and drugs, and on the ERP concept for the management of production data and supply chain.

Combining BIM data with a PLM system creates a Building Lifecycle Management (BLM) system, which enables Digital Factory 4.0.

Digital continuity can be further extended by the integration of the ERP concept for the management of production data and supply chain.

BIM/PLM/ERP CONCEPTS

PLM

Product Lifecycle Management is destined to industrials and has the objective to optimize a product during its lifecycle from the requirements phase until the phase out.

BIM

Building Information Modeling is a virtual clone of the real construction that enables to planify, quantify, analyze, simulate and detect errors... before implementing the project.

The BIM is the Digital Mock-Up of the project, composed of business objects and organized around exchange formats.

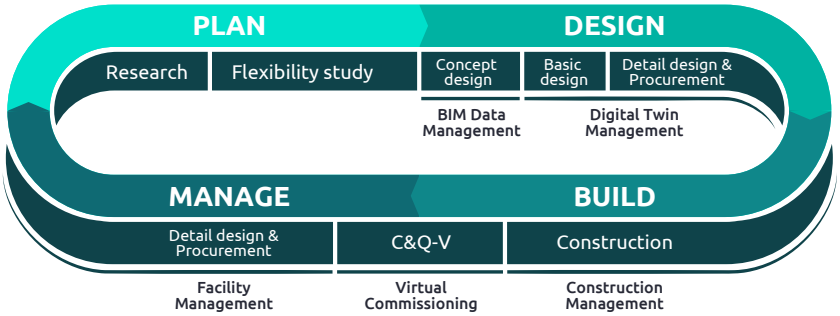
ERP

The Enterprise Resource Planning enables to manage the fabrication processes and the supply chain in terms of physical assets.

The objective is to increase productivity, efficiency and reduce delays.

BUILDING LIFECYCLE MANAGEMENT

A Building Lifecycle Management System, using BIM data within a PLM system manages information and formalizes Extended Collaboration with built-in governance, traceability, electronic approvals, and version control involving all stakeholders...



Moving from a traditional Siloed Model to an Extended Collaboration model enables the synchronization of productive interactions between stakeholders across the enterprise, including designers, suppliers, and builders:

BIM Data Management

The Digital Mock-Up (DMU) creation process takes a data-rich, model-based approach and produces a representation of all systems within a building.

The DMU sets the stage for a clear manufacturing context in which the team can make better design decisions based on the overall project.

Construction Management

During this phase, the DMU containing the source BIM data is tied to resources, tasks, issues, and documentation (including requirements) needed to complete the project.

The current, as-built data model used to deliver the facility is shared with the Operations team once the Design is complete.

Facility Management

During the production and maintenance phase, Facility managers and owners benefit from having a virtual building for streamlining operations.

Digital Twin Management

During the Basic Design Phase, Facility Design Review is done by BIM coordinators by using the DMU to compare detailed, coordinated BIM data on a single platform. It is an iterative process and establishes a Single Source of Truth as the baseline for comparing and managing changes across multidisciplinary teams.

Leveraging the DMU, Facility Process Simulation can be done by project teams to make knowledgeable construction means, methods, decisions and produce an optimized work breakdown for construction.

A Digital Twin can be created with the DMU as the foundation, regularly updated and enriched by equipment and process data.

Further Simulations can reveal integration errors and identify processes that are the most cost and time-effective.

BLM Benefits

The core benefits of employing BLM are improved productivity, sustainability, and quality, and reduced waste, risk, and cost. These advantages are achieved through BLM's ability to eliminate rework, reduce RFIs, centralize data, contextualize information, and more accurately predict outcomes.

CONCLUSION

We can conclude that the Biopharmaceutical production challenges can be addressed through Digital Transformation enabled by a BLM approach.

Indeed, the strategy to meet the challenges of the Biopharma manufacturing industry has to involve not only the organizational changes and the business processes re-engineering, but also the technology enabling the implementation of Digital Platforms.

According to studies, executives say the top benefits of Digital Transformation are:

- **40% Improved operational efficiency**
- **36% Time to market**
- **35% Customer Experience**

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