

Driving Digital Transformation in the Pharma Industry: The Industry 4.0 Journey

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A short introduction.....







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Entire city in gridlock



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Labor concerns Where we **L'ÉOUIP**

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B. BORLARD AN INVESTIG

Ingenuity for life



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Living in France No Kids (yet!) Not at Siemens (yet!) Chelski win their first title!



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The New York Times

Succumbs to Illness Suffered

at Length and in Public













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Megatrends that are changing our world Digitalization

By 2025, the global volume of data will soar to 163 zettabytes.

By 2020, 30 billion devices will be connected.

Source: EY report on IDC, Internet of Things: Human-machine interactions that unlock possibilities, 2016; Cave, Ande, What Will We Do When The World's Data Hits 163 Zettabytes In 2025?, April 2017; (both studies based on MacGillivray, Carrie, Worldwide Internet of Things Forecast Update, 2015-2019, International Data Corporation (IDC), February 2016.)



The Digital (r)Evolution





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Industrie 4.0 for manufacturing means





Making more customized products at an affordable cost



Gaining insight to reduce cost of quality



Experiencing less costly downtime, reducing waste and improving yield



Requiring fewer raw materials, resources and energy

Winning the Race Against Time





It is the beginning of the era of digitalization

of respondents are either engaged in or planning an IIoT project in the next year.

Technology and Innovation for the Future of Production: Accelerating Value Creation World Economic Forum, Mar 2017

Early adopters receive the biggest gains

More than half the market is investing in the IIoT

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... these factors are also bringing change and disruption to the pharmaceutical industry



Customized coffee can be ordered to go.

Why not medicine?

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Scientific Advances are Fuelling Innovation in Healthcare





Current exponential growth of innovation in healthcare is similar to the growth of computing power observed by Moore's Law "Right now is the "transistor moment" for the human body. In the coming decades, health care will begin to improve at the same radical pace we've seen in computing."

Bill Maris, Founder & CEO, Google Ventures

"Right now is the Transistor Moment"

Healthcare's Transistor moment

Highlighted by four major healthcare trends

Digital Health

Breakthrough Therapies

Miniaturization

Microbiome



Digital biomarkers & digiceuticals, Artificial Intelligence ATMP, gene & cell therapies, organ regeneration, Precision Medicine Cell on chip, diagnostics, Microproduction at Point of Care

Understanding human bacteria

Digital health is the convergence of digital technologies with health, healthcare and society that enhance the efficiency of healthcare delivery, making care and medicines more personalized and precise.

Three new trends will bring change to pharma manufacturing

Changing Pipelines

Personalized Medicine

In-silico approaches



favoring cell/gene therapy, and demanding alternative manufacturing systems



product quality linked to pharmacological performance and patient outcomes



using modelling tools for simulation & testing, reducing time-tomarket

Changing and Growing Pipelines: The shift to orphan drugs & cell/gene therapies



- Gene Therapy pipeline growth is at an all-time high
- New Orphan drugs represent 40% of recent FDA approvals
- 64% of gene therapy pipeline is based on oncology

Requiring new versatile manufacturing concepts

- Simultaneous product and manufacturing development
- Requiring closed automated systems with highly integrated quality control
- Single patient bioreactors, closer to point-of-care, integrating product, process and patient data





Source: PharmaProjects 2018; pharmaintelligence

892 cell, gene and regenerative development companies workdwide



Source: PharmaProjects 2018; pharmaintelligence

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Personalized Medicine:

Product quality linked to performance and outcomes

Integrated data along the product life cycle:

- Linking to the patient, for patient-centric development
- Linking to manufacturing and quality systems
- Leading to precision & value/outcomes medicine
- Combining data through the lifecycle, from clinical development to manufacturing





Pharmacological performance to manage biological gates Evidence to manage market access gates Precision medicine to manage clinical excellence gates Experience to manage prescriber and patient gates Outcomes to manage value gates

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Solving the Challenges of Individualized Production – Linking the Patient to integrated MES, Scheduling & Robotics

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Source: Siemens DI PL MOM Template Library Concept for Individualized Therapy, A. Lassalle (2018)

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In-silico approaches to reduce time-to-market

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Replacing large-scale confirmatory trials with "conditional" approvals and "real-life" trials

Support in-silico and on-chip testing to reduce time and make real-world predictions:

- Increasing understanding of how the human body works at molecular level
- Developing an in-silico model of the molecular and cellular components of the human body
- Enabling **preliminary testing and simulation** in order to get later in-human

Current Process



- The current process is long, between 10-15 years, linear and expensive,
- By 2025 the likely R&D process, will see significant efficiencies and time savings
- In the future world, much more of the process could be conducted in silico

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Where is today's focus for innovation in pharma?



Industrial & Digital Transformation: Must translate business drivers into tangible projects

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From idea to production

- PAT & Continuous
- Smart Modular Standards

Quality / Regulations



- Right first time production
- Data integrity (lab to patient)
- Data consistency

Flexibility



Personalized medicine

- Production at point-of-care
- Patient Outcome Focus

Efficiency

- Operational excellence
 - Resource management
 - International collaboration

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Manufacturing Transformation: Highly influenced by digital technology



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Manufacturing Transformation translates to key initiatives

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Manufacturing Transformation



Smart Biopharma



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Integrated Engineering

Integrated OEM Secondary Lines

Paperless

Manufacturing



Personalized Medicine

MindSphe

Digitalization and



Continuous Mfg



Machine Simulation



Digital Supply Chain, e.g. AGV,* ..



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Manufacturing Transformation translates to key initiatives

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Smart Biopharma



Paperless Manufacturing .



Digitalization and Pharma Apps



Personalized Medicine



Machine Simulation



Digital Supply Chain, e.g. AGV,* ..







Integrated

Engineering

Continuous Mfg



Integrated OEM

Digital Twin & Simulation

Digital Twin: A real asset with a connected replica



A digital twin is a virtual & connected replica of a process or product

Capturing real-time data, the digital twin understands current state, simulates future state & optimizes performance. It enables in-silico testing, improved control, problem detection and asset management



Digital Twin: A real asset with a connected replica





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Systems-based Pharmaceutics – Digital Twins – Digital Design of Drug Products and their Manufacturing Processes









With Siemens' integrated technologies, Bausch and Ströbel realized digitalization across the entire machine lifecycle



30% shorter engineering time

Increased flexibility

Consistent, end-to-end digitalization with the **Digital Twin**

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With Siemens' integrated technologies, Bausch and Ströbel realized digitalization across the entire machine lifecycle





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Examples of Digital Design Inhaler Design

Understand the flow behavior in the mouth cavity

Simulate the actual dosage required to reach the lung branches

Simulate how to vary spray angles, particle sizes and distributions





Individual Vaccine Production

Production of Individualized Vaccines against Cancer (IVAC) – Creating a digital and automated plant



Make the medicine more affordable

Enable Fast Scale Up

Access data centrally

Release by Exception

Be paperless

Intelligent guidance and scheduling

Integrate with Robotics

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Smart Bio Production

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Smart Biopharma Initiative: Bioprocess Platform using Plug & Produce Identification







Customer Benefits as stated by Sartorius:

- Cost reduction up to 50%
- Increased flexibility
- Floor space reduction up to 40%
- Faster & improved quality up to 75%



1 RFID: Radio Frequency Identification || 2 RTLS: Real-time Locating System

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Smart Modularization of Single-Use Equipment – Integrated Platform using plug and play identification



Strategies for Operating Single-Use Equipment

- Flexible manufacturing
- Faster changeover (reduced cleaning)
- Cost savings thanks to compact design
- Improved process understanding and optimization
- Plug and Play Equipment Identification



Paperless Production

SIMATIC

FT.

F3

F5

Specific challenges for Pharmaceutical manufacturing





What do I need to produce? How will I document? How will I produce it? How will I review it? How will I test it?

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It is easy to manufacture pharmaceutical products. The hard part is proving it. Production Manager, GSK

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Integrated Operations through Paperless Manufacturing – Integrating Manual and Automated Operations





- Save time in engineering and design thanks to the native integration between the control system and MES
- Improve guidance and control for both manual and automated operations
- Drastically reduce review and approval efforts thanks to "Review by Exception"



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Different Concepts between Primary and Secondary



Drug Substance Manufacture

- Integrated Recipe
- Integrated Workflow

SIMATIC IT MES Workflow	Recipe Phases in PCS 7	
Manual Instruction	Recipe Step	

Integration MES and Automated Recipe

Drug Product Manufacture

- Centralization of Data
- Centralization of Equipment



Centralization MES and SCADA

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eBR Innovation Program Improving operator experience and data collection



eBR Review App

Native cloud App for Batch review and release by exception from anywhere



eBR Equipment Logbook App

Native cloud App for production equipment logbook, easily from everywhere in the plant



eBR Execution App

Native cloud App for executing eBR missions / instructions sequenced and dispatched by the eBR Engine.



Use of New Tech Devices

Biometric Bracelet (Nymi), easy and secure login and sign on, with double authentication

AR Glasses (HoloLens), hands free process execution and guidance









eBR Innovation Program towards cloud-based a digital enterprise solution





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Continuous Production

SIPAT as enable for Continuous Manufacturing – First FDA approved change1 from traditional batch to continuous





FDA – Food Drug Administration; NIR – Near Infrared; PAT – Process Analytical Technology;
1 Yu, Lawrence, Ph.D. "Continuous Manufacturing Has a Strong Impact on Drug Quality." FDA Voice.12 Apr. 2016.

Innovative partnerships to transform manufacturing operations

- Transforming assembled unit operations to continuous
- PAT Enabled central control system
 - Continuous quality verification
 - Real-time release testing
 - Smaller footprint and reduced waste
 - Improved yield and labor cost savings



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ConsiGma™

GEA Continuous Tabletting Line developed in cooperation with Siemens

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Cloud & Pharma Apps

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MindSphere – the Cloud-based, open IoT Operating System from Siemens



Applications Powerful industry solutions Apps developed by Siemens, end-with advanced analytics customers, OEMs, partners ... Open PaaS Application Framework **Develop robust industrial** IoT solutions faster MindSphere with global scalability Connectivity \bigcap_{\bigcirc} n \bigcirc \square Connect products, plants, 01 01 01 systems, machines and enterprise applications

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Al and Analytics will bring the next level of productivity



Semantic Knowledge Graphs

- Knowledge graphs and artificial memories as core module
- Google like search

Application Engineering Model



Engineering Model

Complex Event Stream Analytics

- Control system health monitoring
- Alarm analytics
- Root cause analytics
- Security analytics

Application

Digital Lifecycle Portal



Advanced Analytics for Biological Processing

Advanced Process Optimization

- Real time monitoring
- Analytics

Application

Improved yield/output



Disruptive process control for pharma

Learning historical conditions for Pre-Alarm of Equipment Anomaly

- Machine learning for whole lifecycle
- Multi-variate analytics within process context

Application

Predictive maintenance i.e. compressors failures



Predictive analytics for process industries

Automated Digitalization of Domain Know How

Knowledge engineering

Application

Predictive maintenance i.e. prediction of valve failures



DCS Lifecycle Portal

Application

Optimization of water works operation

Reinforcement learning

Constrained nonlinear optimization



SIWA Optim

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Using Cloud Based Data Analytics for Improved Process Understanding





Using data analytics to improve yield and consistency of output of biopharmaceutical processes

This graphic is the online monitoring page for the process.

- Interactively customize any plot while the process is running.
- Easily read data in from any source: Excel spreadsheets, CSV files, SQL databases, and more.
- Investigate and filter data and export in a variety of formats.
- Directly enter code to define new visualisations and immediately visualize graphically





Proof of Concept for the Pharmaceutical Factory of the Future

GSK IIM, UK

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Cleaning Od 19b 26min

Customer benefits

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- Optimize operations and visibility
- Showcase future manufacturing concepts

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Demonstrating the "art of the possible"

- Consider current and future operator requirements
- Provide an innovative and immersive operator experience
- Use real automation and equipment for a real industrial context
- Seek, incubate and deploy advanced technology

Virtual Reality and Dashboarding







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Leveraging Technology to Drive Innovation





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Thank You!





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