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

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A short introduction.....

Andrew Whytock
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Where were you in 2005?

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

Digitalization is still being defined ...

- Industrie 1.0
  - Steam power – Shift from manual to mechanical production
- Industrie 2.0
  - Founding of Siemens
- Industrie 3.0
  - Electrification & assembly lines
- Industrie 4.0
  - Digitalization & Cyberphysical systems
  
Automation of manufacturing
What is Digitalization?

Humans, devices and systems are connected along the entire value chain.

All relevant information are available in real-time – across suppliers, manufacturers and customers.

Parts of the value chain can constantly be optimized with respect to different criteria, e.g. cost, resource utilization, customer needs.

Characteristics

Industrie 1.0
Water and Steam

Industrie 2.0
Electrification

Industrie 3.0
Automation

Industrie 4.0
Digitalization

Enabling Technologies
- Big Data and Analytics
- Autonomous robots
- Augmented reality
- Simulation
- Additive manufacturing e.g. 3D printing
- Horizontal/vertical software integration
- Industrial Internet (network of hardware-integrated sensors)
- Cloud
- Cyber security

Industrie 1.0
Industrie 2.0
Industrie 3.0
Industrie 4.0
Industrie 4.0 for manufacturing means

- Making more customized products at an affordable cost
- Experiencing less costly downtime, reducing waste and improving yield
- Gaining insight to reduce cost of quality
- Requiring fewer raw materials, resources and energy
Winning the Race Against Time

85% of potential assets remain unconnected.
Technology and Innovation for the Future of Production: Accelerating Value Creation World Economic Forum, Mar 2017

64% 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

It is the beginning of the era of digitalization

Early adopters receive the biggest gains

More than half the market is investing in the IIoT
... these factors are also bringing change and disruption to the pharmaceutical industry
Customized coffee can be ordered to go.

Why not medicine?
Scientific Advances are Fuelling Innovation in Healthcare

“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

Current exponential growth of innovation in healthcare is similar to the growth of computing power observed by Moore’s Law.
Healthcare’s Transistor moment

Highlighted by four major healthcare trends

- **Digital Health**: Digital biomarkers & digiceuticals, Artificial Intelligence
- **Breakthrough Therapies**: ATMP, gene & cell therapies, organ regeneration, Precision Medicine
- **Miniaturization**: Cell on chip, diagnostics, Microproduction at Point of Care
- **Microbiome**: 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.

ATMP: Advanced Therapy Medical Product
Three new trends will bring change to pharma manufacturing

**Changing Pipelines**
favoring cell/gene therapy, and demanding alternative manufacturing systems

**Personalized Medicine**
product quality linked to pharmacological performance and patient outcomes

**In-silico approaches**
using modelling tools for simulation & testing, reducing time-to-market
Changing and Growing Pipelines: The shift to orphan drugs & cell/gene therapies

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

Gene therapy pipeline volume, preclinical through pre-registration phase, 1995 – 2018

Source: PharmaProjects 2018; pharmaintelligence

892 cell, gene and regenerative development companies worldwide

Source: PharmaProjects 2018; pharmaintelligence
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
Solving the Challenges of Individualized Production – Linking the Patient to integrated MES, Scheduling & Robotics

Source: Siemens DI PL MOM Template Library Concept for Individualized Therapy, A. Lassalle (2018)
In-silico approaches to reduce time-to-market

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

- Target ID
- Design of Molecule
- Synthesis of Molecule
- Screening of Molecule
- In-vivo Testing
- In-vitro Testing
- Human Pharmacology (Phase I)
- Explore Therapeutics (Phase II)
- Confirm Therapeutics (Phase III)
- Submission
- Therapeutic Use (Phase IV)

Likely 2025 Process

- Target ID
- Design & Test Treatment
- Synthesis of Treatment
- In-vitro Testing
- In-vivo Testing
- Human Testing
- Submission
- Clinical Use

R&D Process of the Future

- Target ID
- Design of Treatment
- Testing of Treatment
- Synthesis of Treatment
- Human Testing
- Submission
- Clinical Use

• 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
Where is today’s focus for innovation in pharma?
Industrial & Digital Transformation:
Must translate business drivers into tangible projects

**Time to market**
- 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
Manufacturing Transformation: Highly influenced by digital technology

Time to market

Quality / Regulations

Flexibility

Efficiency

Manufacturing Transformation

Classic Stainless Steel
- Single Use/Flexible/Modular
- Stainless Steel/Multi product
- Ballroom Concepts

Paper Record
- Electronic Batch Record
- Review by exception

Off-line Quality Check
- Inline/online integrated Quality
- Continuous Manufacturing
- Recipe/Model Transfer (CQA/CPP)
- Digital Twin, Simulation, In-silico
- Patient Outcome Focus (TPP/TOP)

Gap between R&D & Production & Patient
- Robotics
- VR/AR Guidance and Training
- Production at Point-of-care

Classical Plant Operations
- Industrial IoT and Connectivity
- Smart Data and Analytics
- Data from R&D → Mfg → Patient

Disconnected Data
Manufacturing Transformation translates to key initiatives

- **Time to market**
- **Quality / Regulations**
- **Flexibility**
- **Efficiency**

### Manufacturing Transformation

- **Smart Biopharma**
- **Paperless Manufacturing**
- **Digitalization and Pharma Apps**
- **Integrated Engineering**
- **Integrated OEM Secondary Lines**
- **Personalized Medicine**
- **Continuous Mfg**
- **Process, Plant and Machine Simulation**
- **Digital Supply Chain, e.g. AGV,**
Manufacturing Transformation translates to key initiatives:

- Smart Biopharma
- Paperless Manufacturing
- Digitalization and Pharma Apps
- Integrated Engineering
- Integrated OEM Secondary Lines
- Personalized Medicine
- Continuous Mfg
- Process, Plant and Machine Simulation
- Digital Supply Chain, e.g. AGV, ..
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

Drug Substance Manufacture
- Synthesis
- Crystallisation
- Milling
- Drying
- Distillation
- Filtration
- Granulation
- Compaction
- LL Extraction
- Washing
- Blending
- Coating

Drug Product Manufacture

Processes

Products

Performance

Mechanistic models calibrated against small number of targeted experiments

Product and Process Design (manufacturing robustness focus)

Product Performance (efficacy and safety focus)
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**
With Siemens’ integrated technologies, Bausch and Ströbel realized digitalization across the entire machine lifecycle
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
Smart Bio Production
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%**

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

It is easy to manufacture pharmaceutical products. The hard part is proving it.

Production Manager, GSK

- 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”
Different Concepts between Primary and Secondary

Drug Substance Manufacture
- Integrated Recipe
- Integrated Workflow

Drug Product Manufacture
- Centralization of Data
- Centralization of Equipment

Integration
MES and Automated Recipe

Centralization
MES and SCADA
eBR Innovation Program
Improving operator experience and data collection

<table>
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<tr>
<th>eBR Review App</th>
<th>eBR Equipment Logbook App</th>
<th>eBR Execution App</th>
<th>Use of New Tech Devices</th>
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<td>Native cloud App for Batch review and release by exception from anywhere</td>
<td>Native cloud App for production equipment logbook, easily from everywhere in the plant</td>
<td>Native cloud App for executing eBR missions / instructions sequenced and dispatched by the eBR Engine.</td>
<td>Biometric Bracelet (Nymi), easy and secure login and sign on, with double authentication</td>
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eBR Innovation Program
towards cloud-based a digital enterprise solution

- Applications & apps available on any device
- Build new apps with low-code

- Distributed services
- Leverage on platform native services

- Multi-database agnostics
- Multi-tenant ready

- Compliant with Pharma regulations
- Security embedded
Continuous Production
SIPAT as enable for Continuous Manufacturing – First FDA approved change1 from traditional batch to continuous

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

FDA – Food Drug Administration; NIR – Near Infrared; PAT – Process Analytical Technology;
ConsiGma™

GEA Continuous Tabletting Line developed in cooperation with Siemens
Cloud & Pharma Apps
MindSphere – the Cloud-based, open IoT Operating System from Siemens

Applications
Powerful industry solutions with advanced analytics

Open PaaS Application Framework
Develop robust industrial IoT solutions faster with global scalability

Connectivity
Connect products, plants, systems, machines and enterprise applications

Apps developed by Siemens, end-customers, OEMs, partners …
AI and Analytics will bring the next level of productivity

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

Complex Event Stream Analytics
- Control system health monitoring
- Alarm analytics
- Root cause analytics
- Security analytics

Advanced Analytics for Biological Processing
- Real time monitoring
- Analytics

Learning historical conditions for Pre-Alarm of Equipment Anomaly
- Machine learning for whole lifecycle
- Multi-variate analytics within process context

Automated Digitalization of Domain Know How
- Knowledge engineering

Advanced Process Optimization
- Reinforcement learning
- Constrained nonlinear optimization

Application
- Predictive maintenance i.e. compressors failures

Application
- Predictive maintenance i.e. prediction of valve failures

Application
- Predictive maintenance i.e. yield/output

Application
- Optimization of water works operation

Application
- Improved yield/output

Application
- Disruptive process control for pharma
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

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

Customer benefits

• Optimize operations and visibility
• Showcase future manufacturing concepts
Virtual Reality and Dashboarding
Leveraging Technology to Drive Innovation

Use **Big Data Analytics** to gain insight and drive continuous improvement

**Simulation** to achieve foresight in the Virtual World

Drive intra-company and supplier collaboration via data integration

- **Smart BioPharma**
- **Paperless Manufacturing**
- **Cloud & Pharma Apps**
- **Integrated Engineering**
- **Integrated Secondary Lines**
- **Personalized Medicine**
- **Continuous (PAT)**
- **Process, Plant and Machine Simulation**
- **Digital Supply Chain**
Thank You!

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