Value-focused Analytics and Digital Technology Roadmap for Advancing Biomanufacturing

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Agenda

- Strategy & Roadmap
- Operationalization & Implementation
- Vision & Value Proposition
- Use Cases & Recommendations
Define the right vision, strategy and roadmap to make a difference
Pharmaceutical Manufacturing Initiatives

- Quality & Compliance
- Supply & Productivity
- Cost & Value

Fundamental Value Propositions

- 6 Sigma
- Lean Mfg
- RFT
- PAT/QbD
- Continuous/flexible mfg
- Smart Manufacturing Industry 4.0 Digitalization

Analytics has always been a key enabling technology...
Pharmaceutical Manufacturing Innovations

Vision

Technology
- Advanced Analytics/AI
- New Modalities
- Advanced Manufacturing

Process
- Agile Ways of Working

Talent
- Workforce Development
- User Experience
- Culture
Digital Vision: CURRENT STATE VS. FUTURE STATE

**Current State:**
Digital Silos & Limited Operation Visibility

- Various reporting tools → unsustainable
- Knowledge trapped within systems
- Limited accessibility to equipment & process data

**Future State:**
Connected Plant and Supply Chain

- One central data repository
- Knowledge sources unlocked
- Increased visibility & predictive capabilities
## DPMM and Roles of Analytics

<table>
<thead>
<tr>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
<th>Level 4</th>
<th>Level 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-digital Plant</td>
<td>Digital Silos</td>
<td>Connected Plant</td>
<td>Predictive Plant</td>
<td>Adaptive Plant</td>
</tr>
<tr>
<td>Primarily Paper-based processes</td>
<td>&quot;Islands of automation&quot;</td>
<td>Vertical Integration</td>
<td>Enterprise Integration - internal integration of plant to value chain</td>
<td>Full end-to-end value-chain integration from suppliers to patients</td>
</tr>
<tr>
<td>Predominately manual processing.</td>
<td>Some manual processes.</td>
<td>ERP, LES, MES and Automation layer are fully integrated to support digitized business processes.</td>
<td>Integration of Product Development and Manufacturing (PLM with Recipe Management)</td>
<td>IT supports multiple manufacturing modes: Modular, mobile, continuous...</td>
</tr>
<tr>
<td>Low level of automation.</td>
<td>Batch records may be semi-electronic or “paper on glass”</td>
<td>Full Electronic Batch record with review by exception.</td>
<td>End-to-end supply chain visibility with limited external collaborations (suppliers / CMOs).</td>
<td>&quot;Plug-n-play everything&quot; from an instrument to a production scale or a CMO</td>
</tr>
<tr>
<td>Basic PLC controls.</td>
<td>Local batch-recipe system interfaced to PLCs</td>
<td>Standard application platform adopted across plant network</td>
<td>Online/At-line quality testing with Real Time Release.</td>
<td>Zero system down-time (including upgrades) – continuous evolution.</td>
</tr>
<tr>
<td>Applications are stand-alone with minimal or no integration.</td>
<td>Site-specific systems; limited integration across functional silos</td>
<td>Islands of real-time Process analytics</td>
<td>Simulation used for process modeling and improvements</td>
<td>In-line, real-time, continuous, closed loop, process verification and control with automated real-time quality release</td>
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<tr>
<td></td>
<td>Analytics on demand, &quot;why did it happen?&quot; high manual effort</td>
<td>Analytics semi-automated; &quot;where else can it happen?&quot;</td>
<td>Integrated Real-time Process analytics and simulation</td>
<td>Self-aware, continuously adaptive, &quot;Autonomous&quot; plant; exception conditions handled by remote experts</td>
</tr>
<tr>
<td></td>
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<td>Proactive analytics across plant and internal value chain; “what can happen and when?”</td>
<td>Pervasive use of adaptive analytics and Self/Machine learning across value chain.</td>
</tr>
</tbody>
</table>

Source: BPOG
Biotech Operations Technology Roadmap

CORE 2019 – 2020
Create Room for Meaningful Work
Build the core for agility and flexibility

ADJACENT 2021 – 2023
Source Internally 50% of Phase 2
Deploy for Speed

TRANSFORMATIONAL 2024 – 2028
Reduce Cycle Time by 50%
Innovative Manufacturing

Biotech Drug Substance Tech Roadmap

2019
2020
2021+
SITE VISION

Network level

Site level

Department level

Breakthroughs that change patients’ lives
## Technology Must Impact Metrics

<table>
<thead>
<tr>
<th>KPI</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>Process Capability</td>
<td>Up</td>
</tr>
<tr>
<td>Changeover</td>
<td>Down</td>
</tr>
<tr>
<td>OEE</td>
<td>Up</td>
</tr>
<tr>
<td>Repeat Deviations</td>
<td>Down</td>
</tr>
<tr>
<td>QC Lab Productivity</td>
<td>Up</td>
</tr>
<tr>
<td>Production Lead Time</td>
<td>Down</td>
</tr>
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</table>
Build a scalable approach for the enterprise, Think Big, Start Small and Scale Fast
IloT/AI Implementation and Roadmap

1. Business Opportunities
   - Assess compelling business needs and pain points
   - Alignment with corporate strategies, priorities and fundamental value propositions

2. Use Case Development
   - Identify key focus areas
   - Use case identification and prioritization
   - Scaled Agile Framework for delivery
   - Establish lighthouses

3. Benefit Realization
   - Scale-out, Implementation, Deployment and Optimization
   - sAFe
   - Performance evaluation
   - Measure successes with predefined metrics
   - Replicate across network
Connect disparate IT and OT systems together into a unified whole
Distributed Analytics Opportunities Across Manufacturing Operations

Level 1 & 2: Process Analytics & Control, e.g. PAT, Soft Sensors, Process/Equipment Monitoring, APC

Data & Analytics Infrastructure
Address immediate needs and build future capabilities

Regulatory impact of these technologies and innovations

Recommendations for FDA on what technologies to focus on and associated workforce preparation in 5-10 years
Key Driving Forces for Industry 4.0/Pharma 4.0

- **Digital Plant** engrained with Industry 4.0 technologies
- **Cloud Computing**
- **Big Data**
- **Artificial Intelligence**
- **Robotics/CoBiotics**
- **Augmented/Virtual Reality (AR/VR)**
- **3D Additive Manufacturing**
- **Cyber Security**
- **Smart sensors, Mobility**
- **IIoT**
- **ISPE**

End to End, Vertical & Horizontal Integration

Workforce 4.0 Knowledge Management

Quality Predictive Control
Integrated Analytics and Control for Process Robustness and Productivity

Control Strategy Implementation Options

- Level 1: Real-time automatic control + Flexible process parameters to respond to variability in the input material attributes
- Level 2: Reduced end product testing + Flexible critical material attributes and critical process parameters within design space
- Level 3: End product testing + Tightly constrained material attributes and process parameters

Performance-based approach
Enhanced approach
Parameter based approach

Soft Sensor
- Estimate CPPs/CQAs
- Model for PCM and APC
- Soft metering

Process & Equipment Condition Monitoring
- Monitor process performance and equipment health
- Fault detection, classification, and diagnosis
- Prediction of CQAs and cycle time/yield
- Predictive maintenance

Advanced Process Control
- APC, e.g., Model predictive control of the process, fixed -> flexible
- Optimize process to move closer to target and reduce variability

Machine learning, deep learning, optimization

Analytics & Control Platform
Automation/IIoT Infrastructure
GMP implementation/validation

Key enablers for RTRt, CPV and flexible process

Soft Sensor Replacing IPC or End product Testing in Commercial Manufacturing

Moving towards RTR(t)

**Business Challenge**
- 1500 drying operations per year in the network
- Risk of over-drying and long cycle time
- QC lab testing delays dryer offload
- Inconsistent endpoint

**Solution:**
Hybrid Model-based Soft Sensor implemented in DeltaV
- Combined power of first-principles (model structure) & data-driven modelling (model parameters) methodologies, minimal DOE, and more robust model

**Business Value (Validated)**
- Cycle time reduction of 10 hrs per lot allowing 14 extra lots for Product A. ROI $1M/yr based on EAV
- Cycle time reduction of 400 hrs QC testing time for Product B.
- RMSEP < 0.027 (%LOD) based on 20 batches

- Low cost
- Reduced cycle time
- Eliminate QC lab testing via RTRt
- Leverage real-time connectivity and data

Heat and mass balance

Heat and mass balance diagram

DeltaV diagram

Kepware diagram

PharmaMV diagram

Python diagram
APC for pH Control to Improve Process Robustness and Reduce Cycle Time in Manufacturing

**Business Challenge**
- CQA tests out of spec (0.10% max)
- pH control: risks of overshooting by manual operations

**Business benefits**
- Fully automatic & accurate pH control
- > 50% reduction in process time
- Significant reduction in variabilities
- Confirmed: Cycle time reduction of 9 hrs per lot for Product C

**APC v.s. Manual control**

- APC: Closer to target while reducing variability
- Manual: More consistent trajectory

**Fuzzy-logic based APC controller**
IloT and AI-enabled Digital Manufacturing Capabilities

- **OEE Monitoring**
- **Equipment health monitoring & Predictive Maintenance**
- **Process Robustness Monitoring**
- **Augmented Reality for Visualization of Production Line**
- **Soft Sensors for Continuous Process Monitoring**
- **Energy Monitoring**

**IIoT Platform**

- Equipment/Process
- Sensors
- Data Historian
- Predictive Analytics

Courtesy of Pfizer Digital Manufacturing
Digital Twin to Accelerate Process Development, Tech Transfer and CI

**Definition**

Digital twin refers to a digital replica of potential and actual physical assets, processes, people, places, systems and devices that can be used for various purposes.


A digital replica to simulate, design, monitor, control and optimize a manufacturing process/system or multiple steps from end to end, leveraging advanced analytics and IIoT.

**Technologies/Solutions**

- Flowsheet modeling, e.g. gProms
- Discrete Element Method (DEM) and Computational Fluid Dynamics (CFD), e.g. Fluent
- Process modeling for real-time monitoring, control and optimization, e.g. PharmaMV

**Business Value/Impact**

- Reduce physical experiments
- Identify CPPs and CQAs and study the effects of input on output
- Global System/Sensitivity Analysis
- Define design space and control strategy
- Training tool for the process
- Accelerated process development and tech transfer

Data from a physical process/system

Action from a virtual copy of the process/system
Digital Twin Core Technologies

From simulation, facility/process/equipment design, development to real-time monitoring, control & optimization in manufacturing

Discrete Element Method  Flowsheet Modeling  Modeling for real-time monitoring, control and optimization

Production planning & scheduling, PdM etc
Accelerate Process Development through Digital-Enabled Flexible Manufacturing Platform Technology

- The same platform technology is used, with no scale-up
- The same data accessible by the users, and analytics, control & digital solutions
- Reduced efforts on process development, tech transfer, validation
- Improved end-to-end visibility, process robustness and productivity...

Deliver visibility, quality and productivity through Analytics & Control Solutions
Summary - Digital Manufacturing Capabilities from Hype to Reality

**Analytics & Control**
- Digital Twin, PAT, soft sensor, Process Condition Monitoring, RTRt, CPV
- Advanced Process Control

**Smart QC/QA**
- AI-assisted QC testing and QA investigation and reporting

**Scheduling & control**
- Integrated real-time scheduling & control
- Real-time and optimal

**Material/Batch Tracking**
- End-to-end visibility of products/batches
- Batch genealogy

**OEE**
- Monitor OEE
- Performance, speed and quality

**Predictive Maintenance**
- Condition monitoring
- Smart Sensors
- Machine learning

**Persona Dashboard**
- Integrated dashboard
- End to end visibility

**Environmental Sustainability**
- Process/Utility energy monitoring
- Energy optimization

**Modular**

**Miniature**

**Flexible**

**Continuous**

**Disposable**

**Portable**

**Automation/Robotics**
- Plant floor robotics
- Automation
Acknowledgement

Global Technology & Engineering

- Roberto G Silveira
- Jim Brinkman
- Seamus O’Neill
- Mark Smith
- Reza Kamyar
- Hamid Mehdizadeh
- David Lauri Pla
- Zilong Wang

Pfizer Digital

- Mike Tomasco
- Shawn Mullins
- Kieran O’Sullivan
- Venkadesan Alagarsamy
- Dan Glenn
- Jason Ren
- John Allyne
- Rina Lulka