GLOBAL SUPPLY

Value-focused Analytics and Digital Technology Roadmap for Advancing Biomanufacturing

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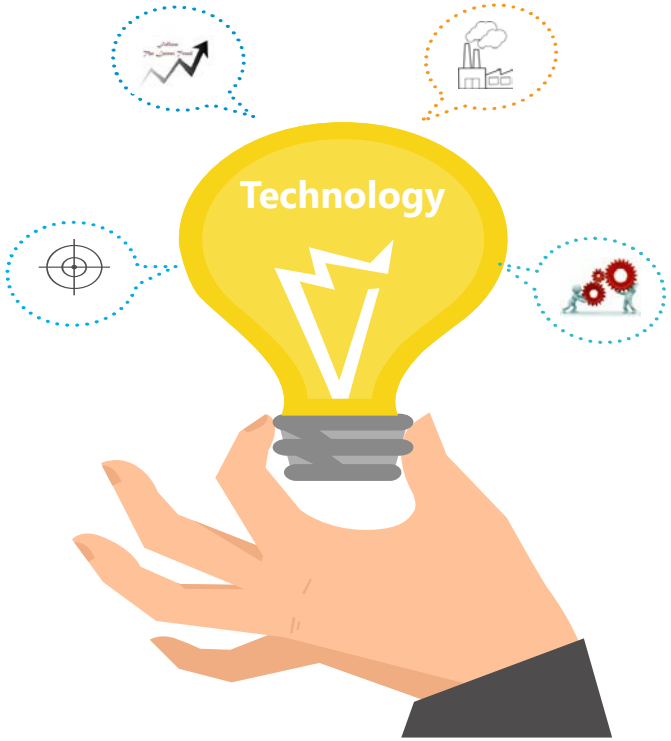
Agenda

Strategy & Roadmap

Operationalization & Implementation

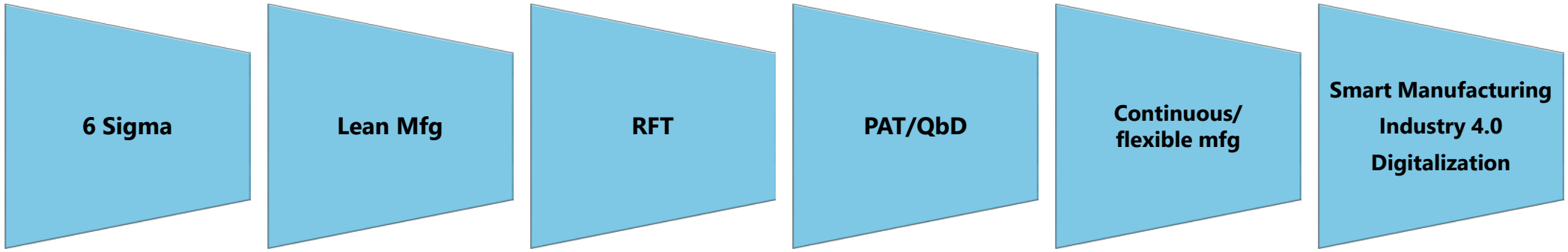


Vision & Value Proposition

Use Cases & Recommendations

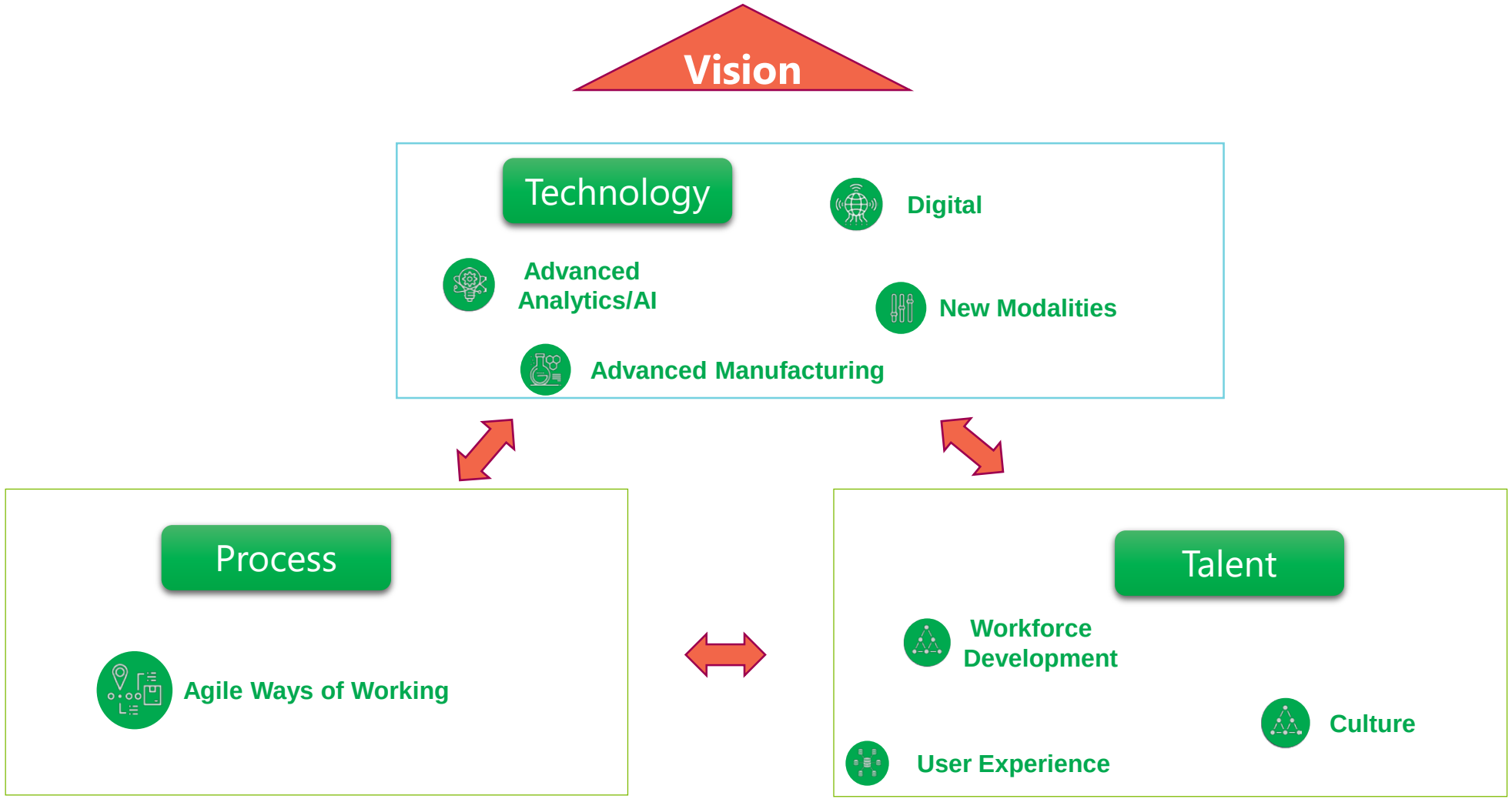
Define the right vision, strategy and roadmap to make a difference

Pharmaceutical Manufacturing Initiatives



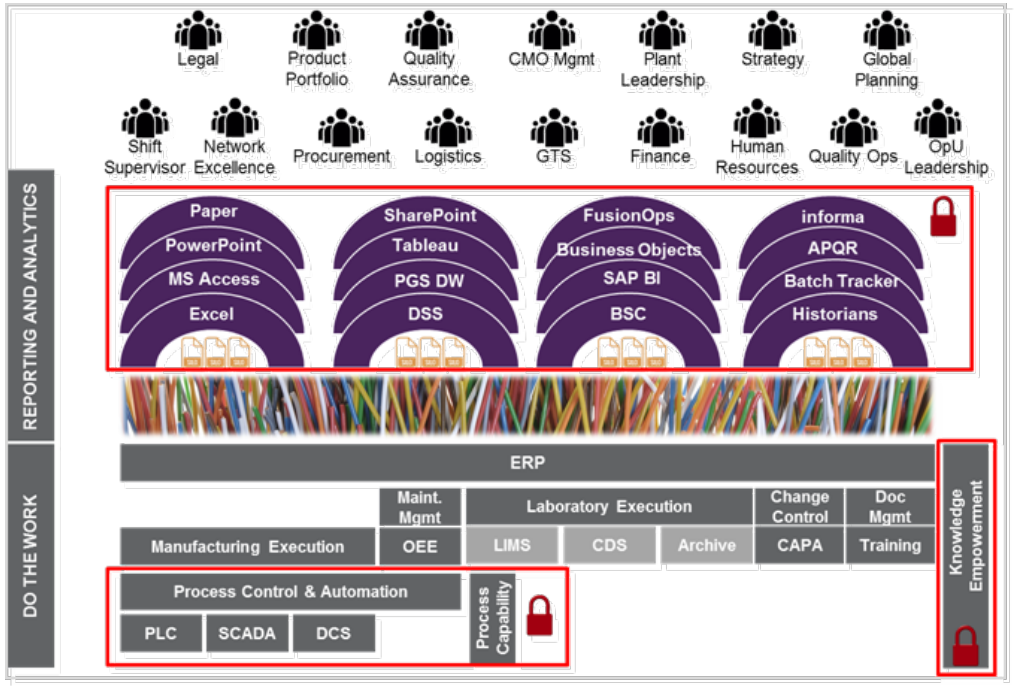
Analytics has always been a key enabling technology…

Pharmaceutical Manufacturing Innovations



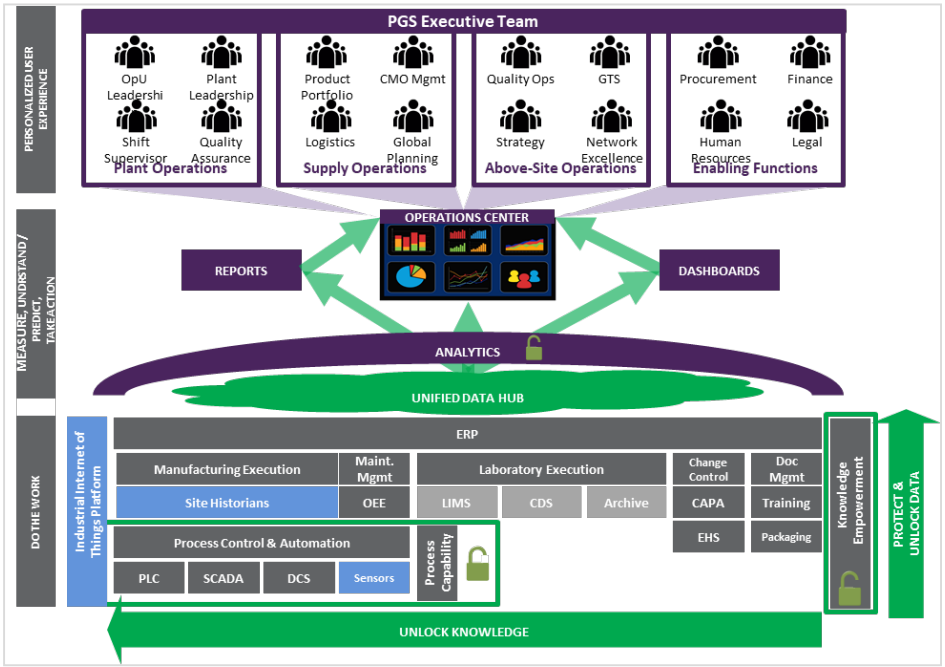
Digital Vision: CURRENT STATE VS. FUTURE STATE

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



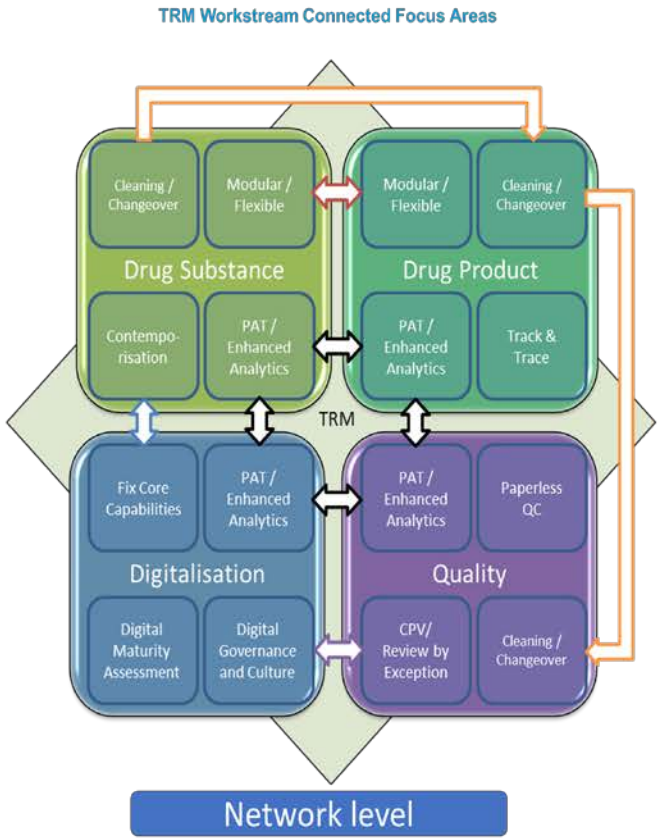
- One central data repository
- Knowledge sources unlocked
- Increased visibility & predictive capabilities

DPMM and Roles of Analytics

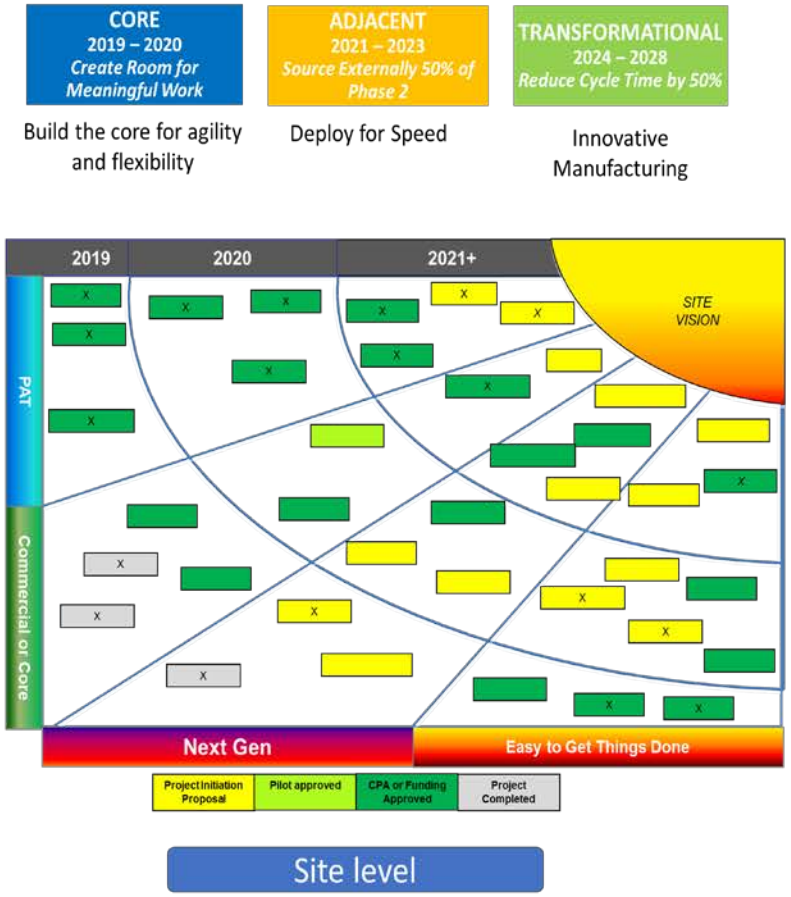
Level 1 Pre-digital Plant	Level 2 Digital Silos	Level 3 Connected Plant	Level 4 Predictive Plant	Level 5 Adaptive Plant
Primarily Paper-based processes Predominately manual processing. Low level of automation. Basic PLC controls. Applications are stand-alone with minimal or no integration.	"Islands of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

Source: BPOG

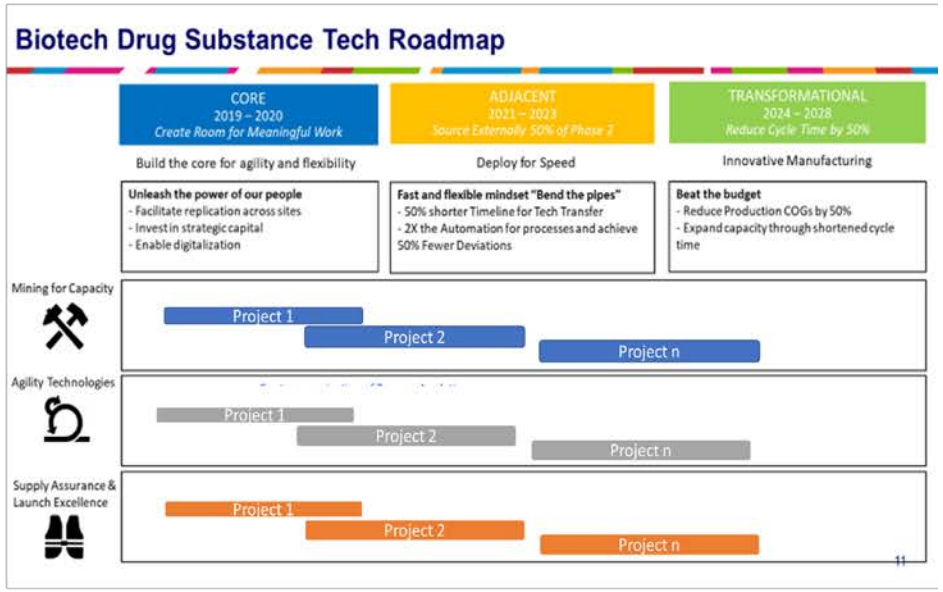
Biotech Operations Technology Roadmap



Network level

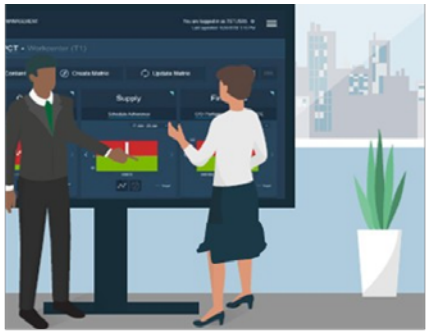


Site level



Department level

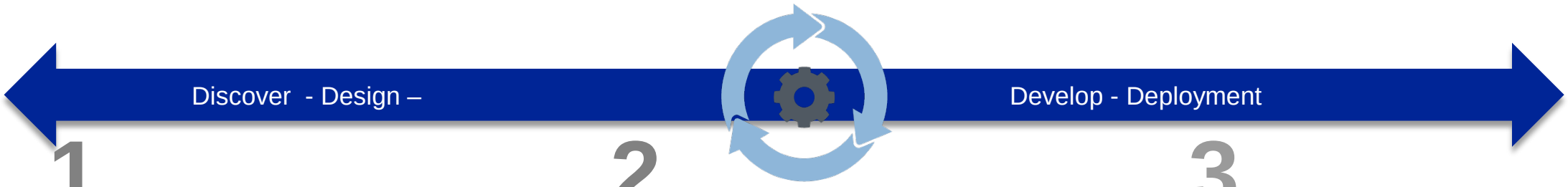
Technology Must Impact Metrics



KPI	
Process Capability	↑
Changeover	↓
OEE	↑
Repeat Deviations	↓
QC Lab Productivity	↑
Production Lead Time	↓

Build a scalable approach for the enterprise, Think Big, Start Small and Scale Fast

IIoT/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

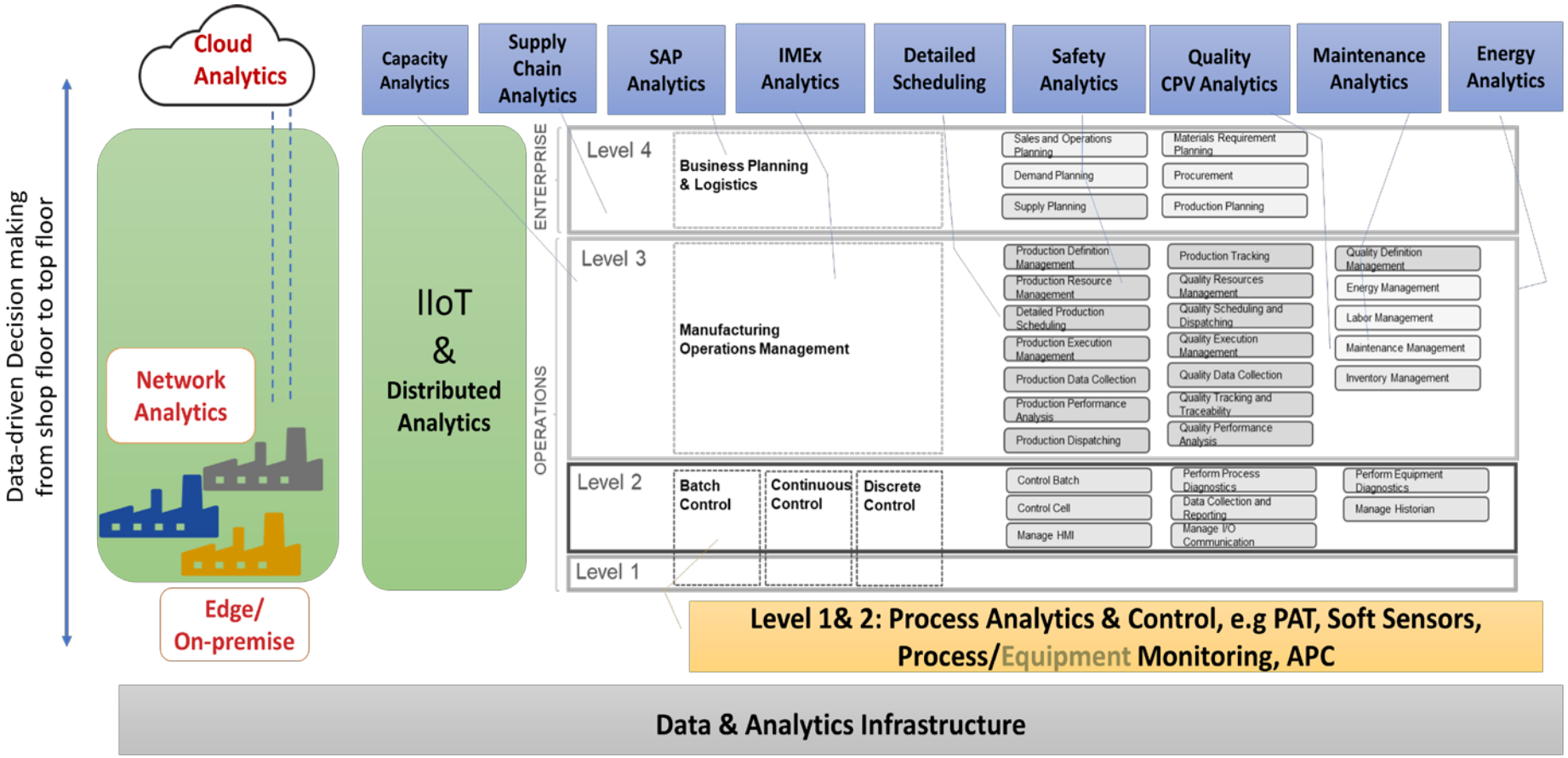
3

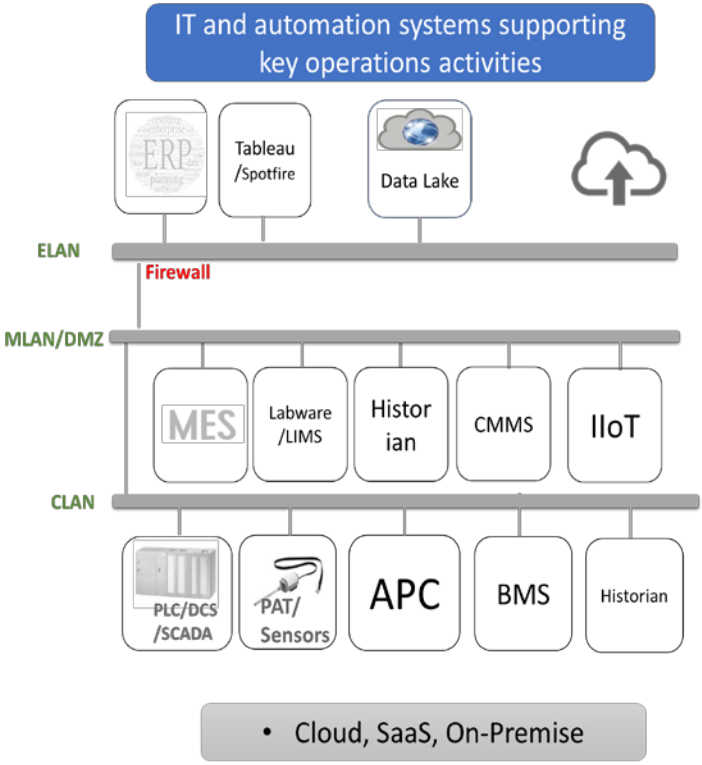
Benefit Realization

- 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

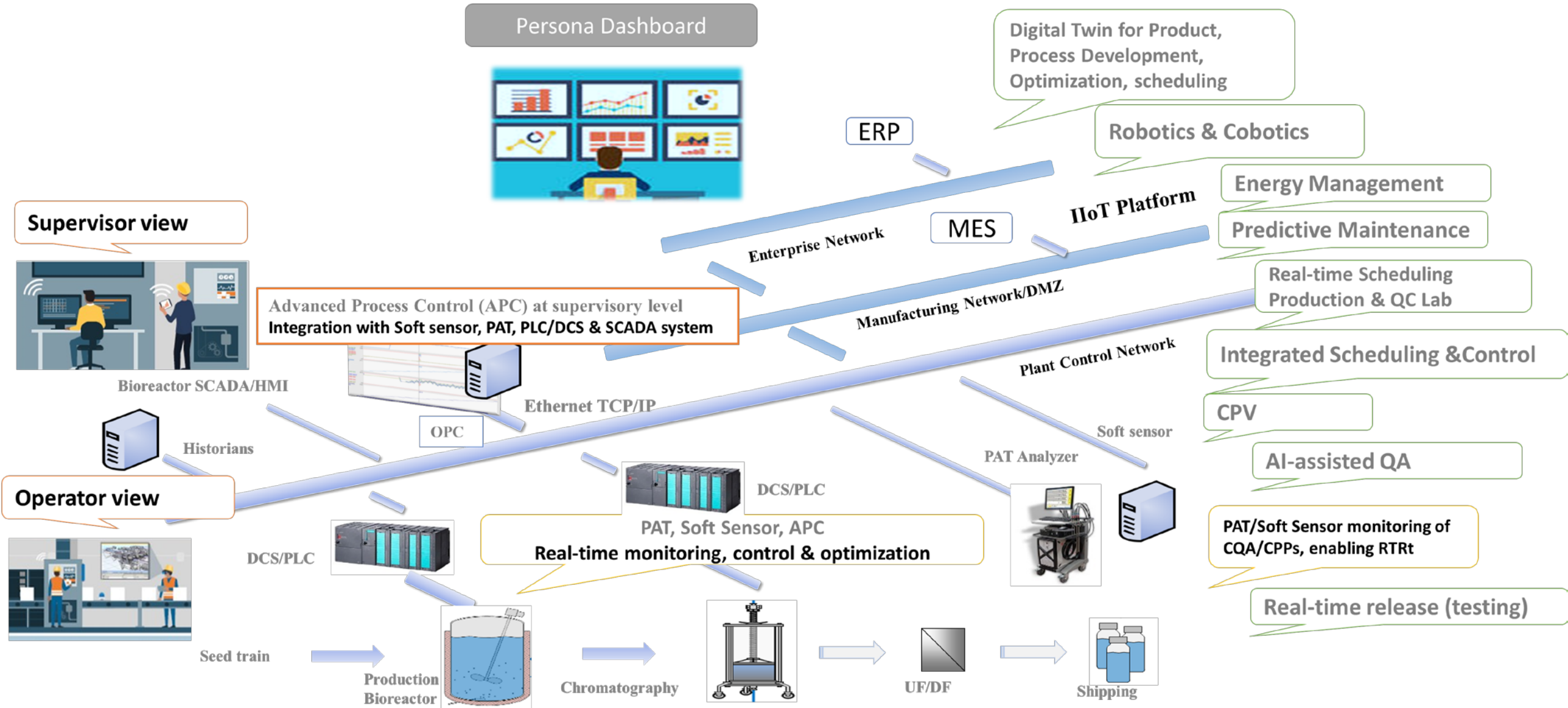
Distributed Analytics Opportunities Across Manufacturing Operations





- Cloud, SaaS, On-Premise

Collaborative Manufacturing and Quality Operations through Digitalization

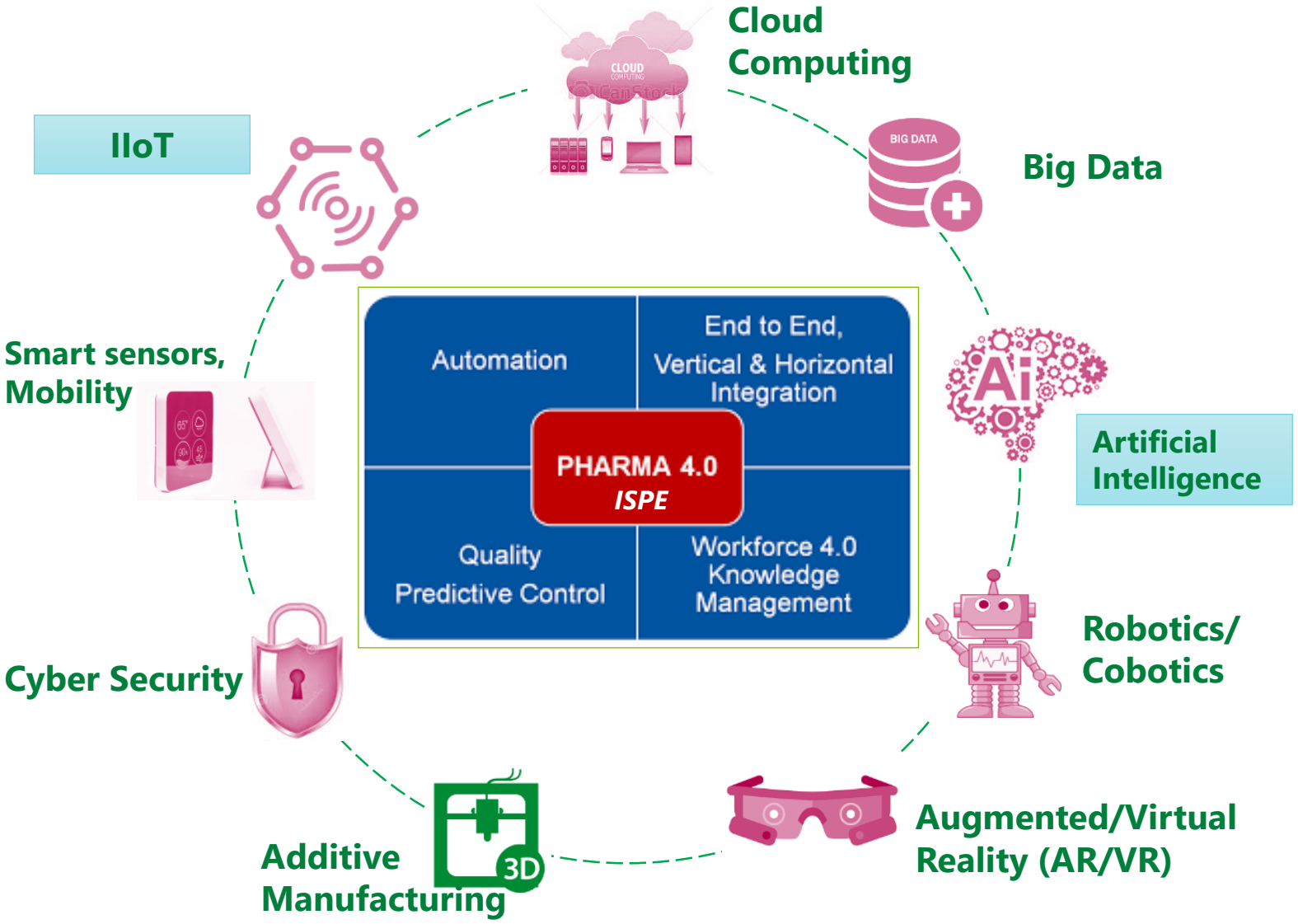


Address immediate needs and build future capabilities

Regulatory impact of these technologies and innovations

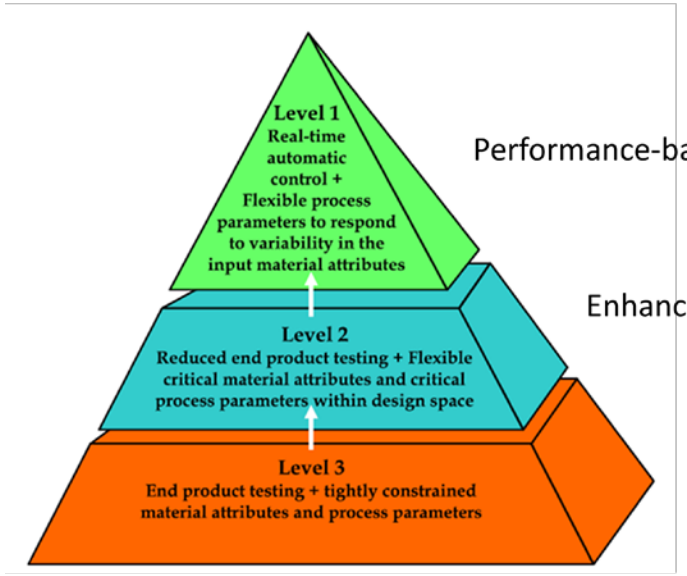
Recommendations for FDA on what technologies to focus on and associated workforce preparation in 5-10 years

Key Driving Forces for Industry 4.0/Pharma 4.0



Integrated Analytics and Control for Process Robustness and Productivity

Control Strategy Implementation Options

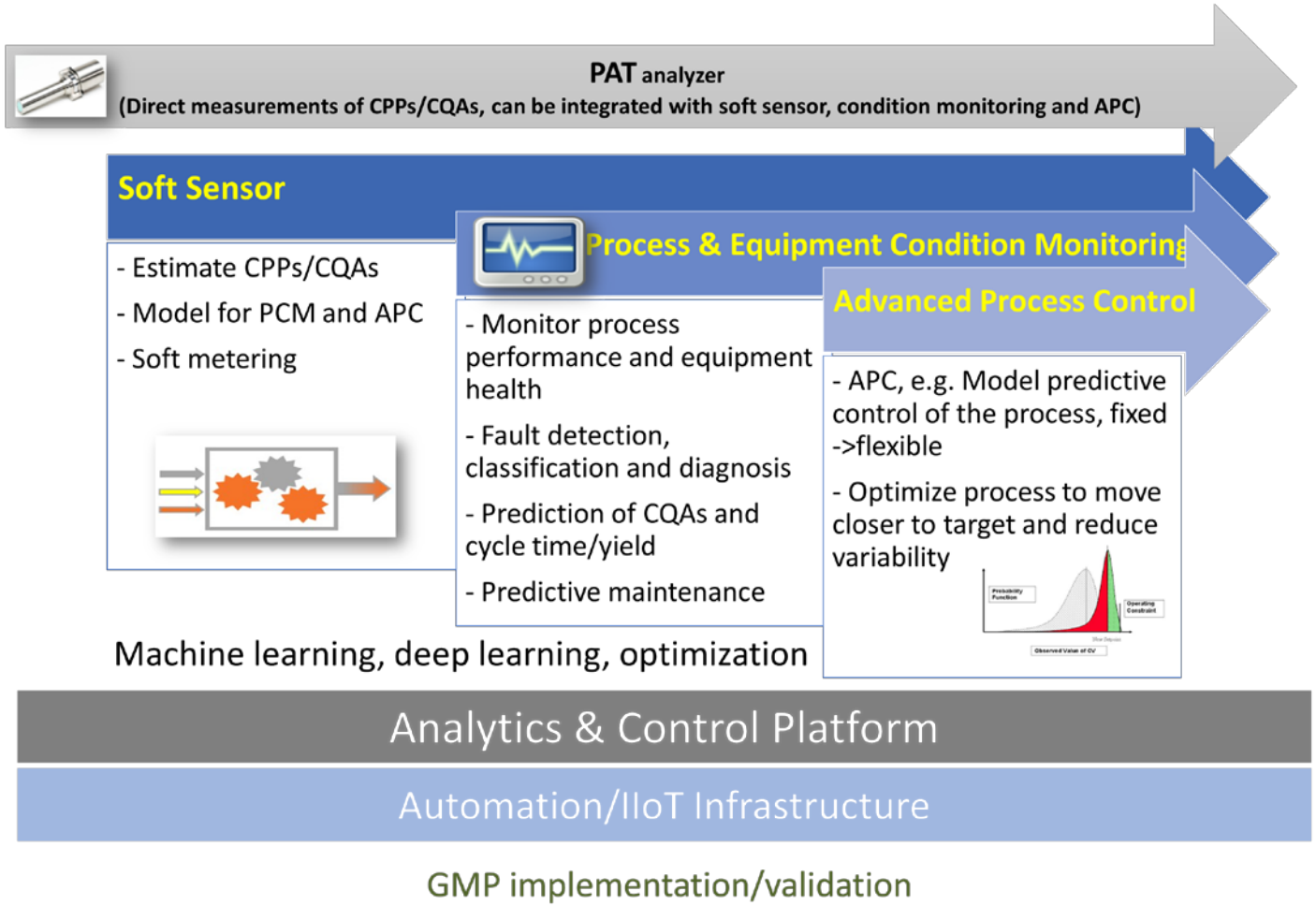


Performance-based approach

Enhanced approach

Parameter based approach

Yu LX, *et. al.* The AAPS Journal. 2014;16;771-783.



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:

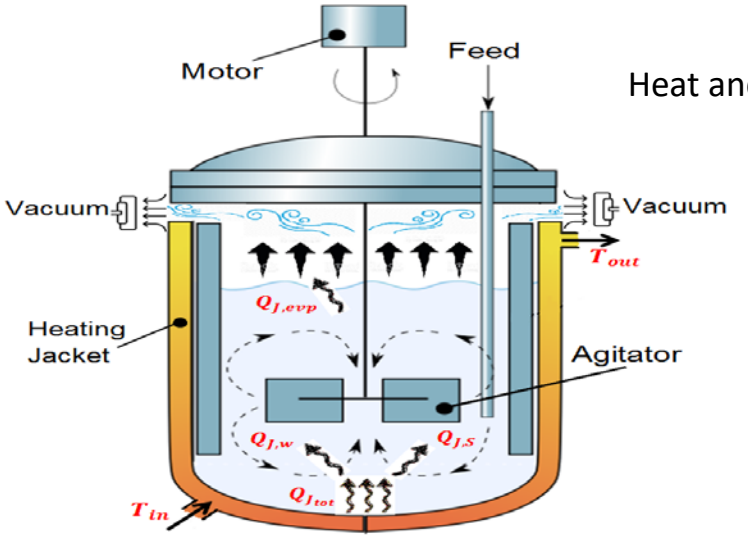
Hybrid Model-based Soft Sensor implemented in DeltaV

- 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.**

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

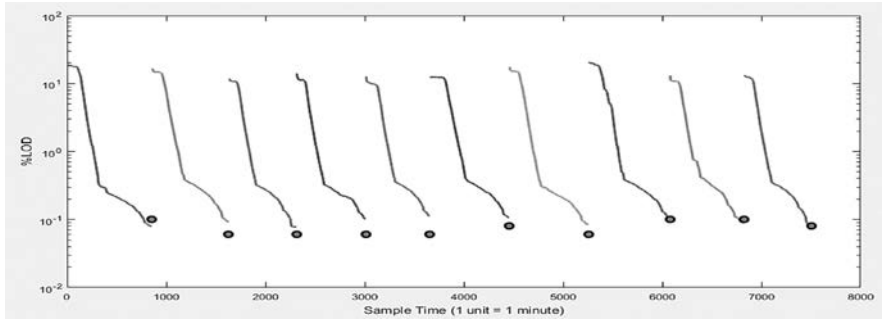


Heat and mass balance

$$\frac{\partial \vartheta_L}{\partial t} = \nabla.(D_L \nabla \vartheta_L) - \frac{\dot{m}_{LG}}{\rho_L}$$

$$\langle \rho C_p \rangle \frac{\partial T}{\partial t} = \nabla.(\lambda_{eff} \nabla T) - \dot{m}_{LG} \Delta H_{vap}$$

$$-\lambda_{eff} \frac{\partial T}{\partial z} = -h_q (T_h - T)$$



RMSEP < 0.027 (%LOD) based on 20 batches

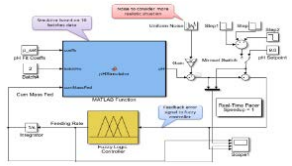
DeltaV
kepware
pharmaMV
python

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

Business Challenge

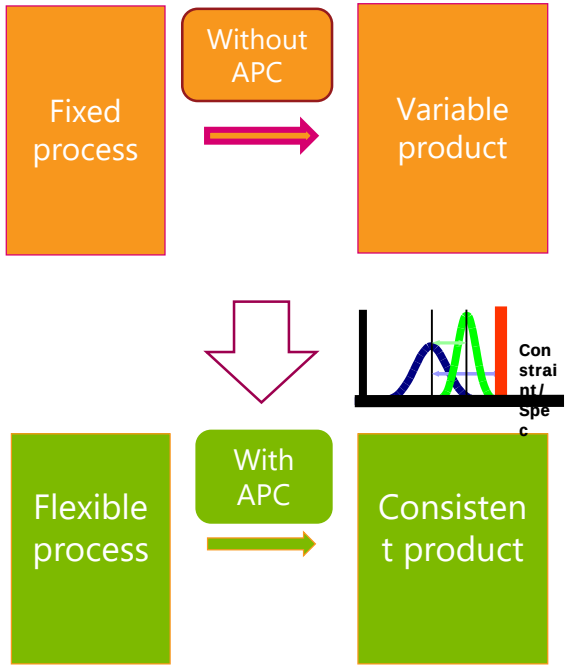
- CQA tests out of spec (0.10% max)
- pH control: risks of overshooting by manual operations

Fuzzy-logic based APC controller

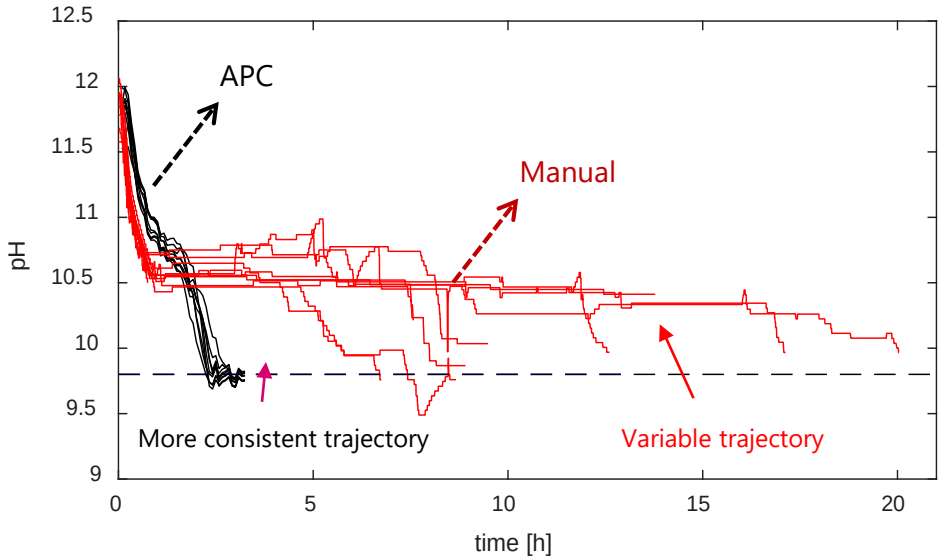


Business benefits

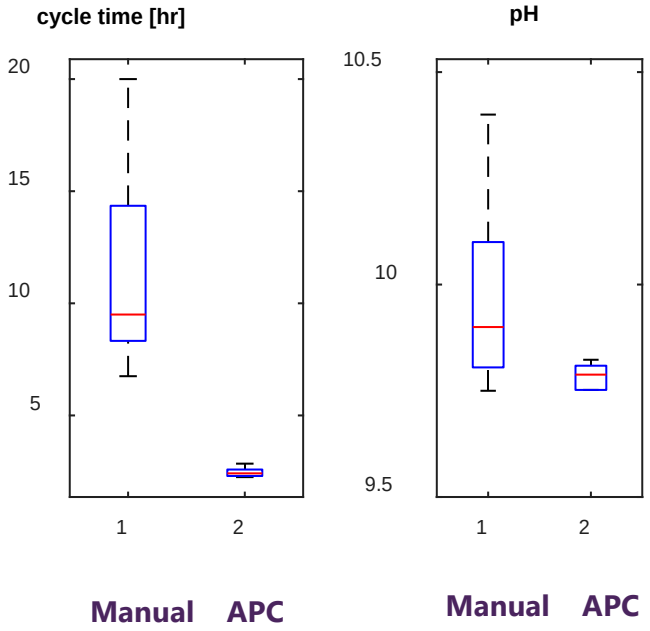
- Fully automatic & accurate pH control
- > 50% reduction in process time
- Significant reduction in variabilities
- Confirmed: Cycle time reduction of 9 hrs per lot for Product C



APC v.s. Manual control



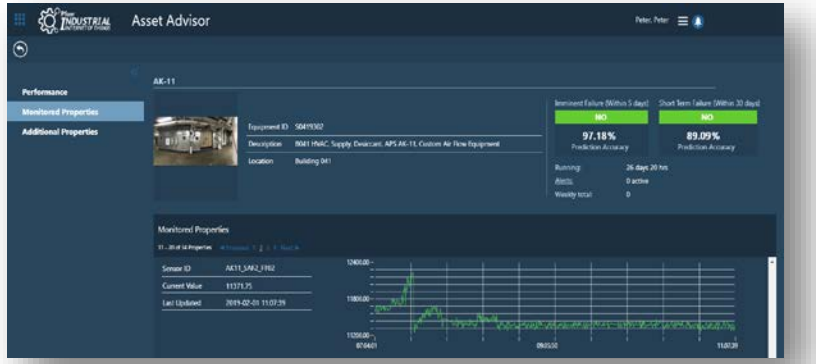
Closer to target while reducing variability



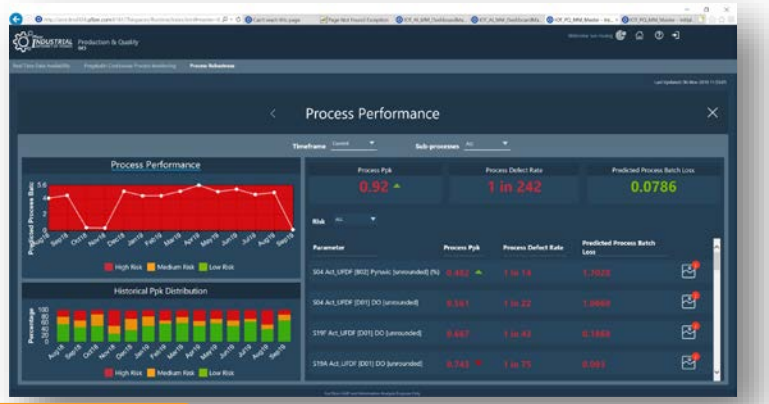
IIoT and AI-enabled Digital Manufacturing Capabilities

OEE Monitoring

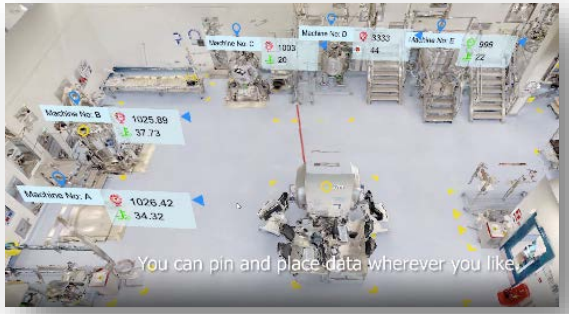
Equipment health monitoring & Predictive Maintenance



Process Robustness Monitoring



Augmented Reality for Visualization of Production Line



IIoT Platform

Soft Sensors for Continuous Process Monitoring

Energy Monitoring

Equipment/Proces → 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.

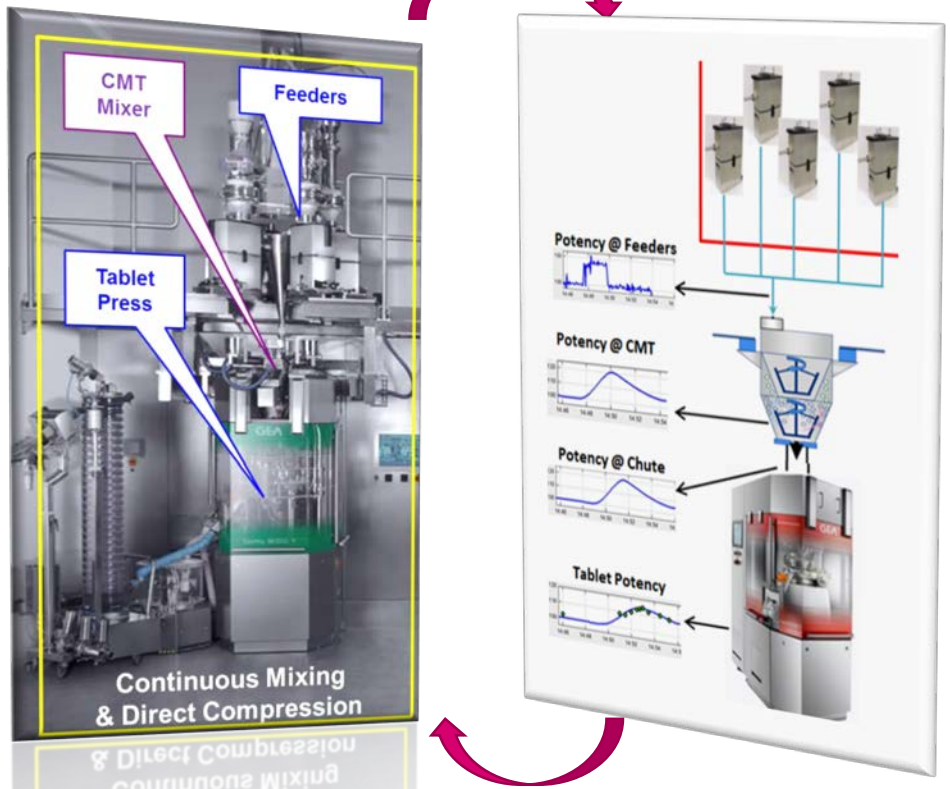
C.J. Parris. *Minds + Machines: Meet A Digital Twin*. Youtube. GE Digital. Wikipedia

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

Data from a physical process/system



Action from a virtual copy of the process/system

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

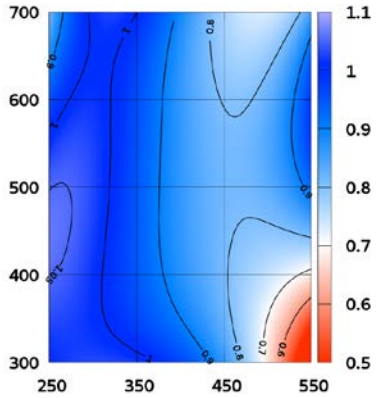
Digital Twin Core Technologies

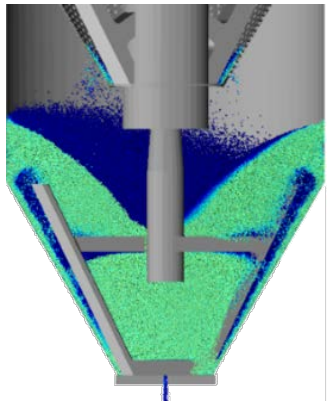
From simulation, facility/process/equipment design, development to real-time monitoring, control &optimization in manufacturing

Discrete Element Method

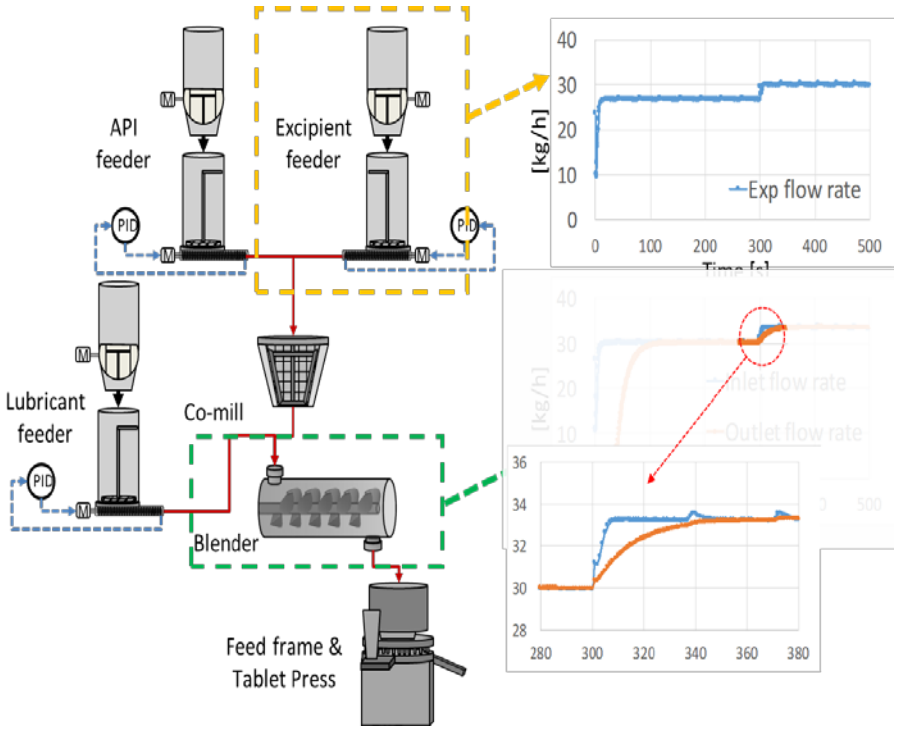
Flowsheet Modeling

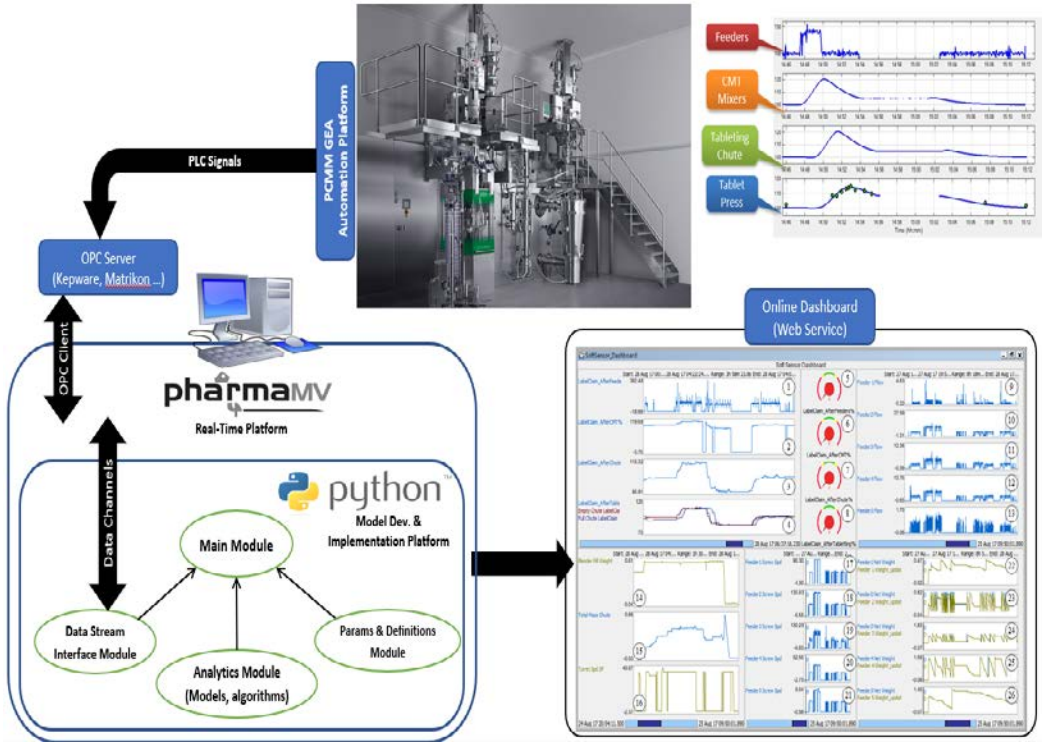
Modeling for real-time monitoring, control and optimization





Picture Courtesy of R&D





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

Data Lake/Hub

Process Development

Clinical Supply

ICH Stability

Commercial Registration

Commercial Production

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

OEE

- Monitor OEE
- Performance, speed and quality

Material/Batch Tracking

- End-to-end visibility of products/batches
- Batch geneology

Modular | Miniature | Flexible | Continuous | Disposable | Portable

Predictive Maintenance

- Condition monitoring
- Smart Sensors
- Machine learning

Persona Dashboard

- Integrated dashboard
- End to end visibility

Environmental Sustainability

- Process/Utility energy monitoring
- Energy optimization

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