Why Does Industry Need MBSE and Digital Twins?

Enabling Pharma 4.0/5.0, Advanced Manufacturing and Digital Transformation through Cross-Collaborative Partnerships

Doug Kiehl

Sr. Director

Disruptive/Transformative Technologies Team (DT3)

Spectroscopy, Extractables & Leachables

Eli Lilly and Company, Indianapolis, IN, USA

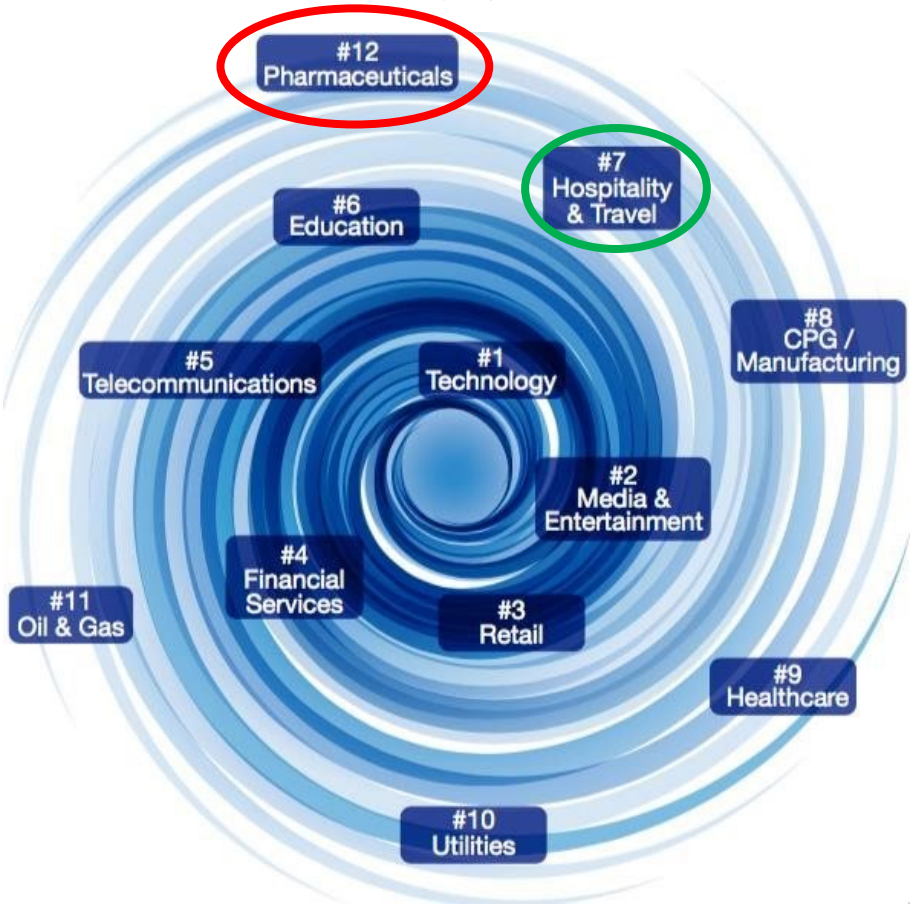
What is Driving "Smart MedTech," Disruptive Innovation and Transformation for Healthcare and Pharma?

Disruptive/Transformative Technologies Team

The Digital Vortex and Digital Disruption

2017

2019



Wade, M. R., Shan, J., & Noronha, A. (2017, June). Life in the Digital Vortex: The State of Digital Disruption in 2017.

Wade, M., Yokoi, T., Shan, J., & Macaulay, J. (2019). Digital Vortex 2019. Global Center for Digital Business Transformation.

What is Driving "Smart MedTech," Disruptive Innovation and Transformation for Healthcare and Pharma?

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Drivers for Disruptive Innovation in Pharma

- Precision medicine and patient-centric and tailored therapeutics in digital/collaborative healthcare ecosystem
- Next-gen cell/gene therapies and advanced therapy medicinal products (ATMPs)
- **AI mitigated development, advanced manufacturing and digital twins**
- R&D – "Pharma 4.0" extrapolation of "Industry 4.0" to Pharma space (ISPE 2017)
- Smart drug delivery (3D printed and smart oral dosage forms)
- Wearable monitoring/sensing, smart diagnostics, integrated drug delivery
- Rapid decision making with "big data" (e.g., leveraging large blinded clinical trial datasets with clinically relevant endpoints for predictive capability)
- VR/XR/AR/MR: Remote Interactive Evaluations (RIE) for limiting human interaction with onsite regulatory inspections and ops (e.g., FDA priority)
- As an event, COVID-19 represents an inflection point, accelerating a significant change in both industry and regulatory perception of risk and expediting innovative approaches to addressing unmet needs.
  It is possible to abbreviate a traditional 10-year process to 10 months!

What is Driving "Smart MedTech," Disruptive Innovation and Transformation for Healthcare and Pharma?

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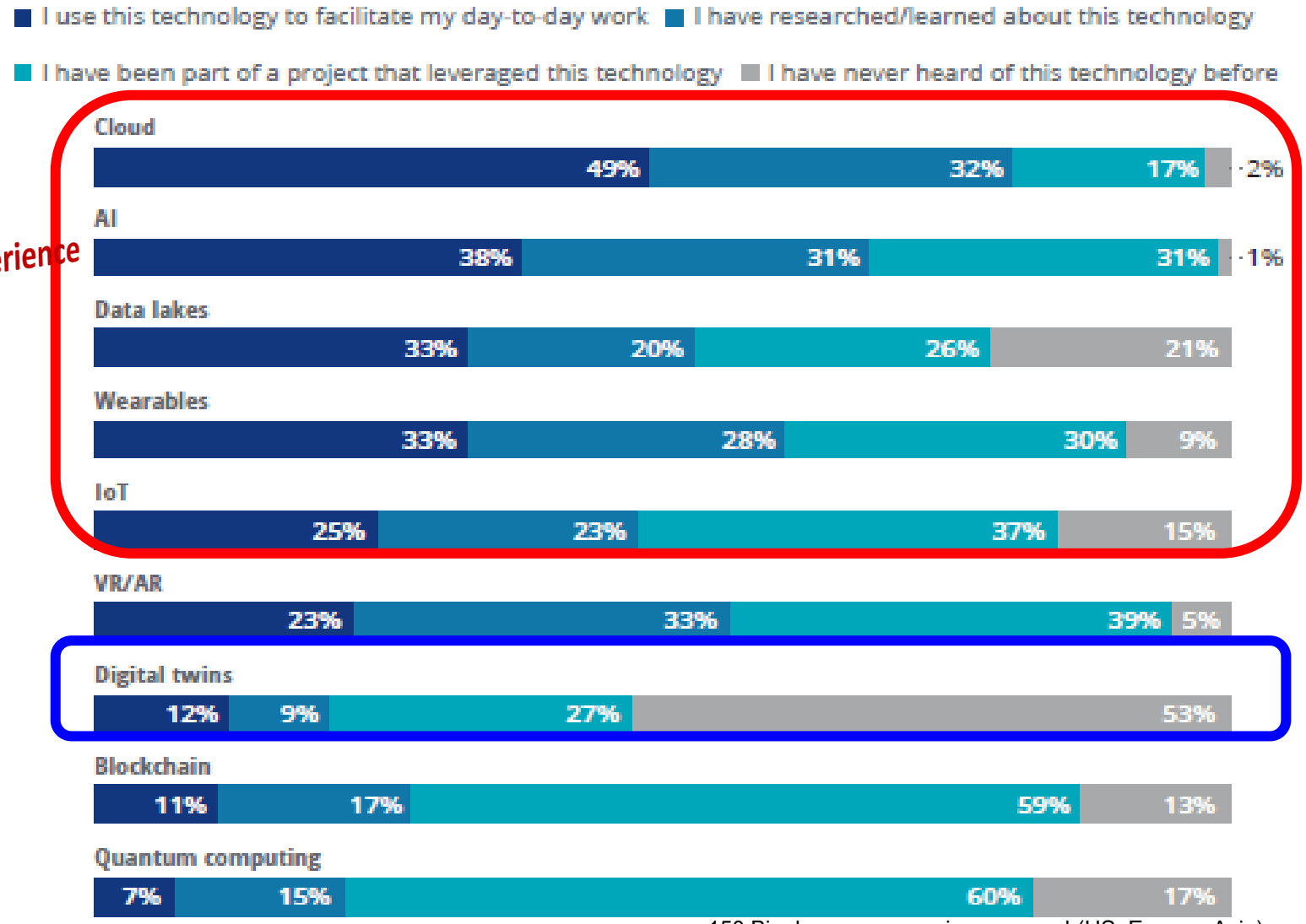
Primary Biopharma experience with digital technologies



150 Biopharma companies surveyed (US, Europe, Asia)

Source: Deloitte's Biopharma Digital Innovation Survey 2021.

gital innovation, Deloitte Insights, 2021

What is Driving "Smart MedTech," Disruptive Innovation and Transformation for Healthcare and Pharma?

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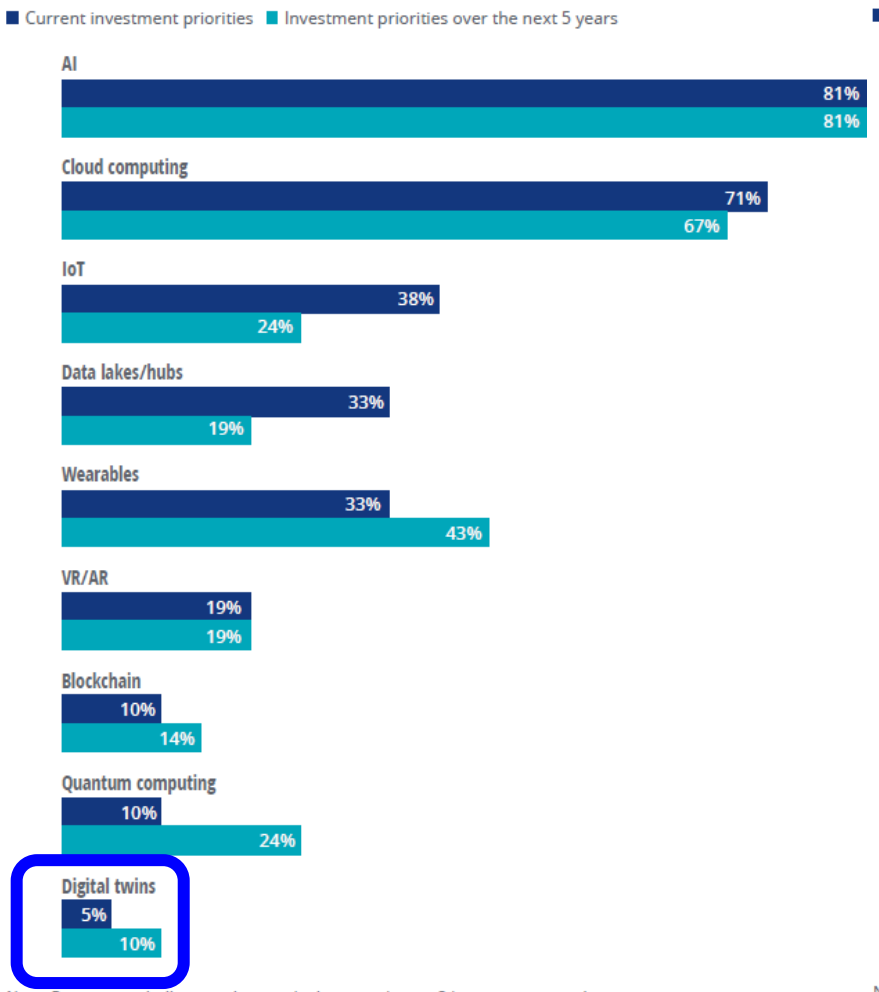
Drug discovery: Current and planned investments in digital technologies

Respondents were asked to rank the most innovative technologies in which their function is **currently investing and plans to invest in the next five years.**



Note: Percentages indicate options ranked among the top 3 by survey respondents.
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Drug development: Current and planned investments in digital technologies

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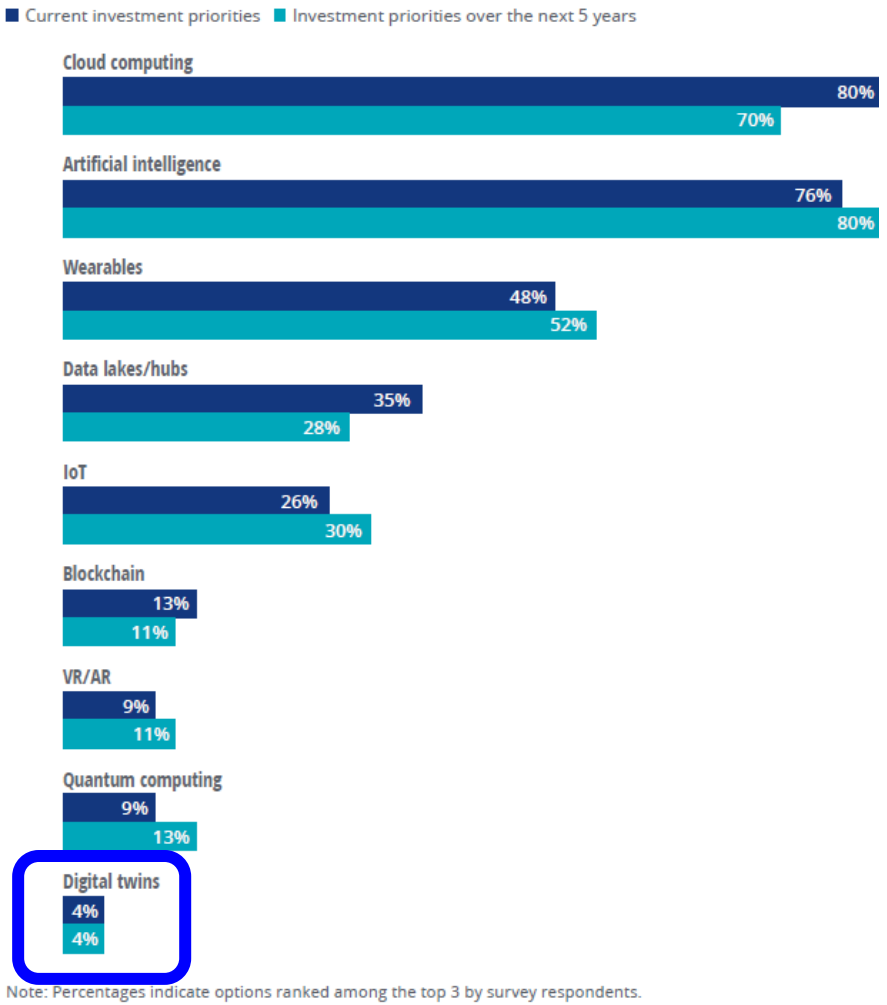

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Manufacturing: Current and planned investments in digital technologies

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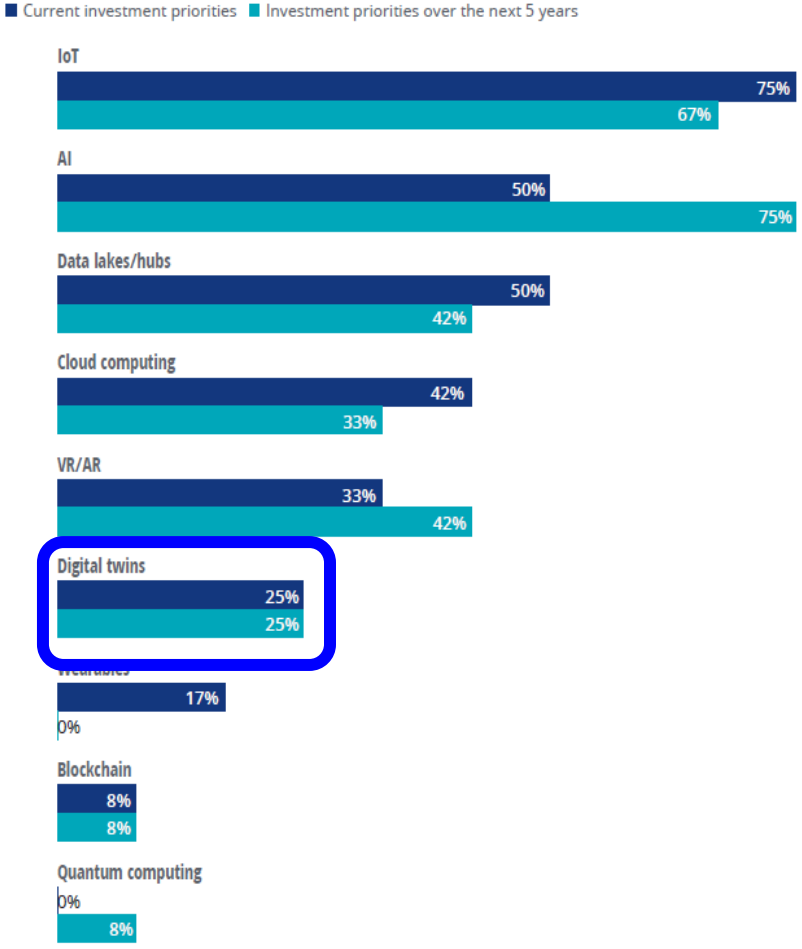

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Source: Deloitte's Biopharma Digital Innovation Survey 2021.

150 Biopharma companies surveyed (US, Europe, Asia)
Biopharma digital transformation: Gain an edge with leapfrog digital innovation, Deloitte Insights, 2021

Digital organization maturity roadmap

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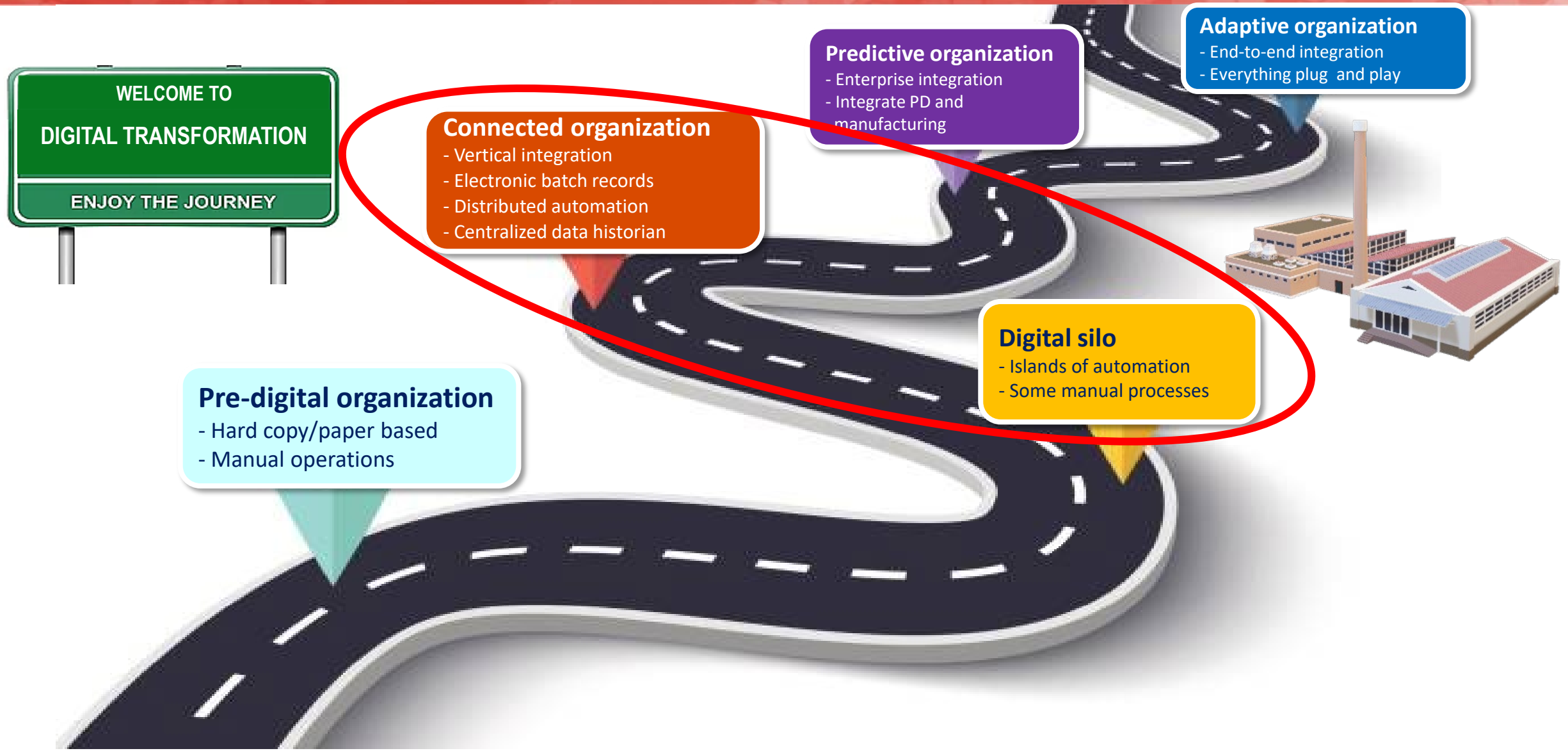

What is Digital Transformation?

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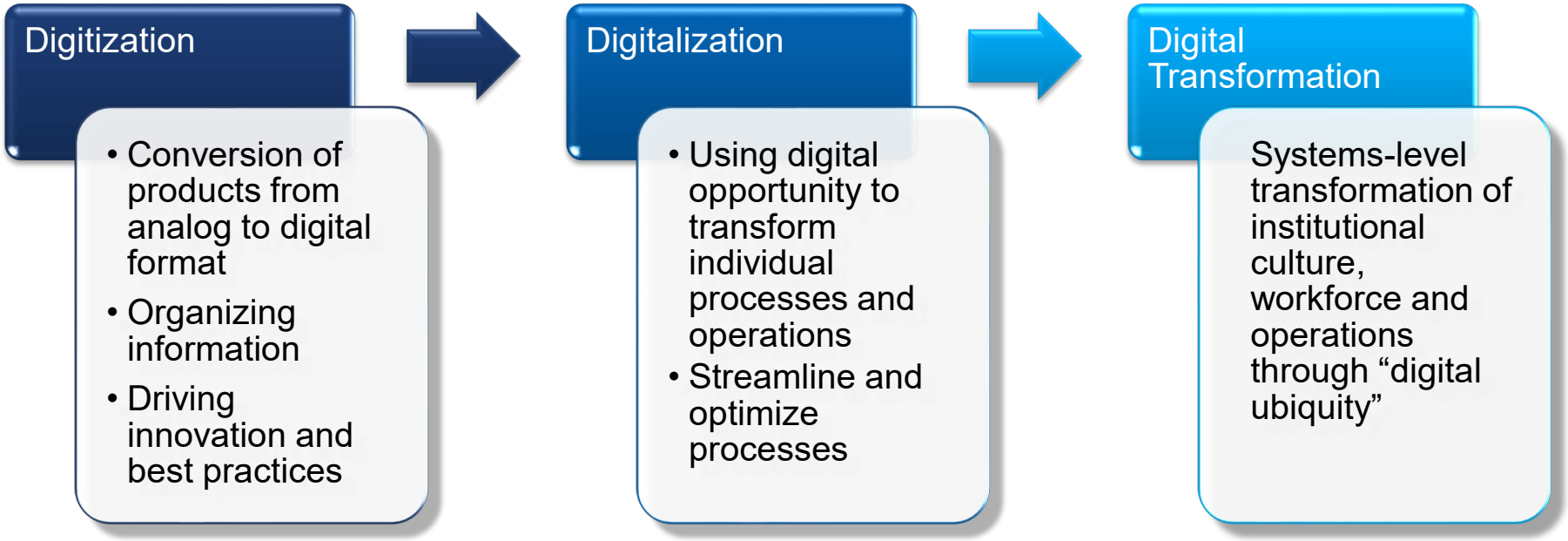
Digital Transformation is…

- The changes associated with the application of digital technology in all aspects of human society. Simply put, digital transformation includes going paperless and broad application of digital aspect.
- Successful digital transformation **will come not from implementing new technologies, but transforming an organization** to enable it to realize the advantages that new technologies provide.



DT3 Automation vision and future state (edge to end)

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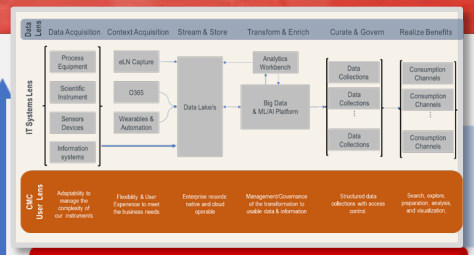

Fundamental Interface

- IT
- Data science/product
- Digital systems architecture
- Data capture
- Data curation
- Data storage
- Digital data quality/integrity
- Security/data governance and lifecycle management

Pharma Business Core

- IT
- Data analytics
- Digital systems architecture
- Smart/networked instrumentation
- Wearables
- Remote Interactive Evaluation (RIE), VR/AR/XR/MR

Lab and Manufacturing of the Future

- Smart manufacturing
- Digital twin
- Automation/robotics fully integrated
- Flexible/agile plant
- SUS/SUT

Growth, Maturity, Interconnectivity

Lights-out Laboratories → Lights-out Manufacturing

Integrated pre- & post-analytical systems

Automated Sampling
Automated Analysis
LIS/LES/LIMS
Consolidated Instruments

Safety
Data Quality
Modular Technology
Enablers
Standardization
Validation

Integrated manufacturing ops & control

MES
Inspection
Fill/Finish
Packaging
Assembly
Cleaning Disinfection

Cloud | IIoT | AI/ML/DL/RL | Vision Technology | 5G | Robot teaching

Hyperautomation and Convergent Technologies

Current State -> Autonomy -> Future State

D ties and enabling technologies

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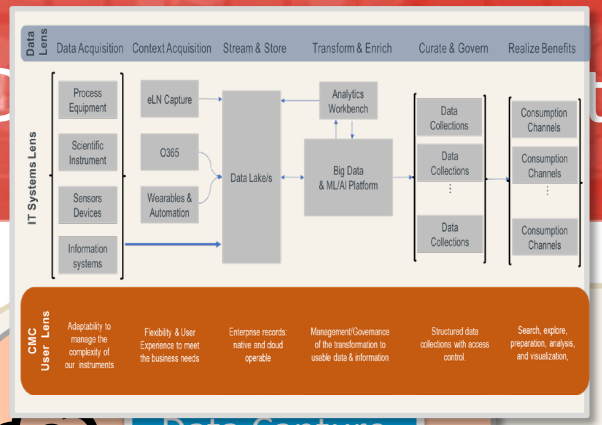


Data Capture

Data Storage

Data Curation

Digital Data Quality & Integrity

Networked Instruments, Sensors, Devices,Wearables

Enables

Big Data Data Lakes

ML / Adaptive Control

IIoT

LES

MES

WES

Digital Twins

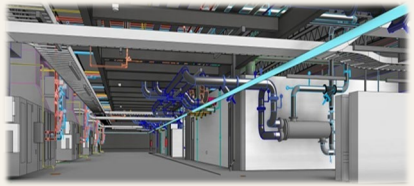
Enables

Autonomous Real-Time Collaborative Robotics and Automation

VR/AR/XR/MR

Vision Technology

Enables



Pharma 4.0/5.0 enabled Smart Manufacturing and Labs

Containerized deployment asset management

Enables

Cybersecurity and blockchain

Wireless communication, 5G and beyond

DT3 Core capabilities and enabling technologies

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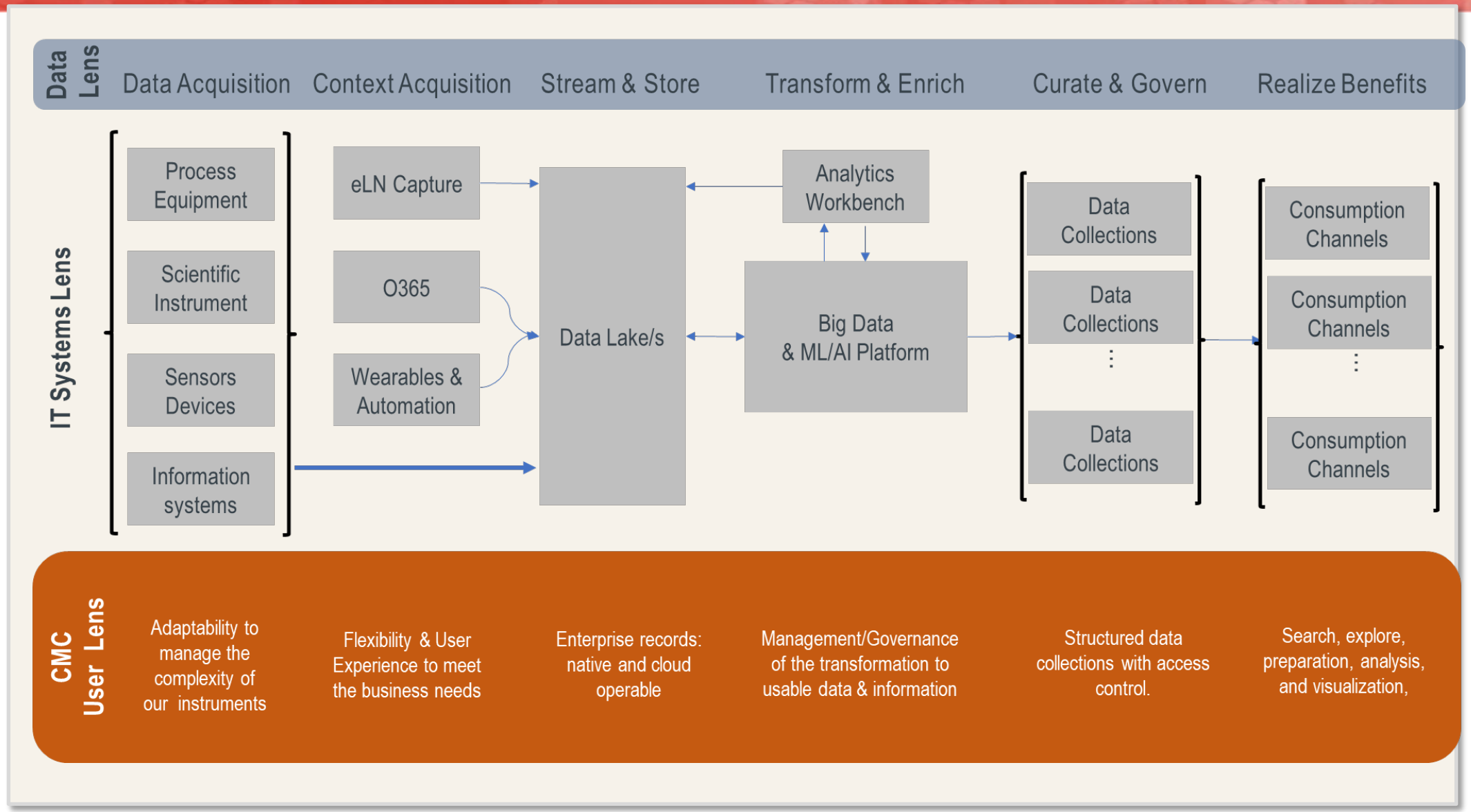

What is Driving "Smart MedTech" and Disruptive Innovation for Healthcare and Pharma?

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Digital Transformation: some focus areas for Pharma in regulatory science

Technology	Description
Pharma 4.0 to 5.0 Concepts	Framework for adapting digital strategies (e.g., IIOT) to achieve digital transformation with regard to unique contexts of pharmaceutical development and manufacturing. This is often described as "digital ubiquitization" introduced by ISPE in 2017 to develop a roadmap for digital transformation of Pharma manufacturing--extrapolation of Industry 4.0 to Pharma/Biopharma.
FDA FRAME initiative with AI mitigated manufacturing PQRI and FDA partnership established to advance industry practice and regulatory expectations	FDA strategic priority for developing a Framework for Advanced Manufacturing. FRAME is focused on four categories of manufacturing technology that are anticipated / encouraged to be developed and implemented by industry with application across multiple modalities within the next decade: • End-to-end continuous manufacturing • Distributed manufacturing (DM) • Point-of-care (POC) manufacturing • Agile manufacturing Application of artificial intelligence (AI) and machine learning (ML) across manufacturing processes
Digital and Virtual Twins	Process development and assembly in virtual space utilizing prior knowledge of materials, components, key parameters and tolerances to anticipate and mitigate issues prior to transfer to physical space with or without real-time interaction (virtual twin).
Remote Interactive Evaluation (RIE)	Remote interaction with advanced manufacturing (VR, XR, AR, MR) to minimize human intervention (e.g., HPAPIs)
Automation (smart)	Smart automation technologies to maintain operations with AI oversight and minimal human intervention
Regulatory expectations, standards	Regulatory guidance, regulations, industry and compendial standards (existing and/or anticipated)
Digital Data Quality Digital QBD	Development and implementation of activities that apply quality management expectations and best practices to data to ensure it is fit for consumption and meets the needs of data consumers.

What is Driving "Smart MedTech," Disruptive Innovation and Transformation for Healthcare and Pharma?

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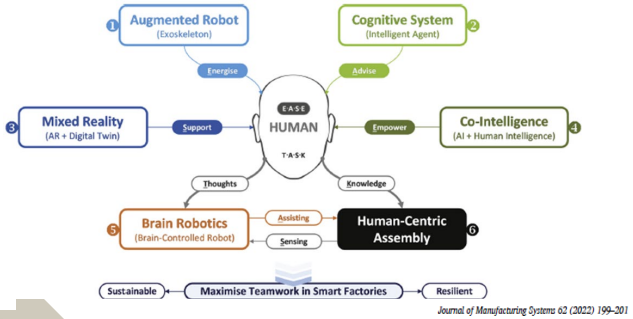


1.0

Mechanization
Steam / water power
Iron production
Textiles
Mining
Machine tools

1784

2.0

Electricity
Mass assembly
Telegraph broad use
Gas/water supply
Turbines
Engines

1870

3.0

Computers,
Microprocessors
Automation
Robotics
Digitization
Electronic notebooks,
Digital machines

1969

4.0

(I)IoT
Autonomous machines
Advanced robotics
Big data/analytics
Digital ubiquity
Cloud computing
Smart factories
AI/machine learning
Digital twins

2011

Present

5.0

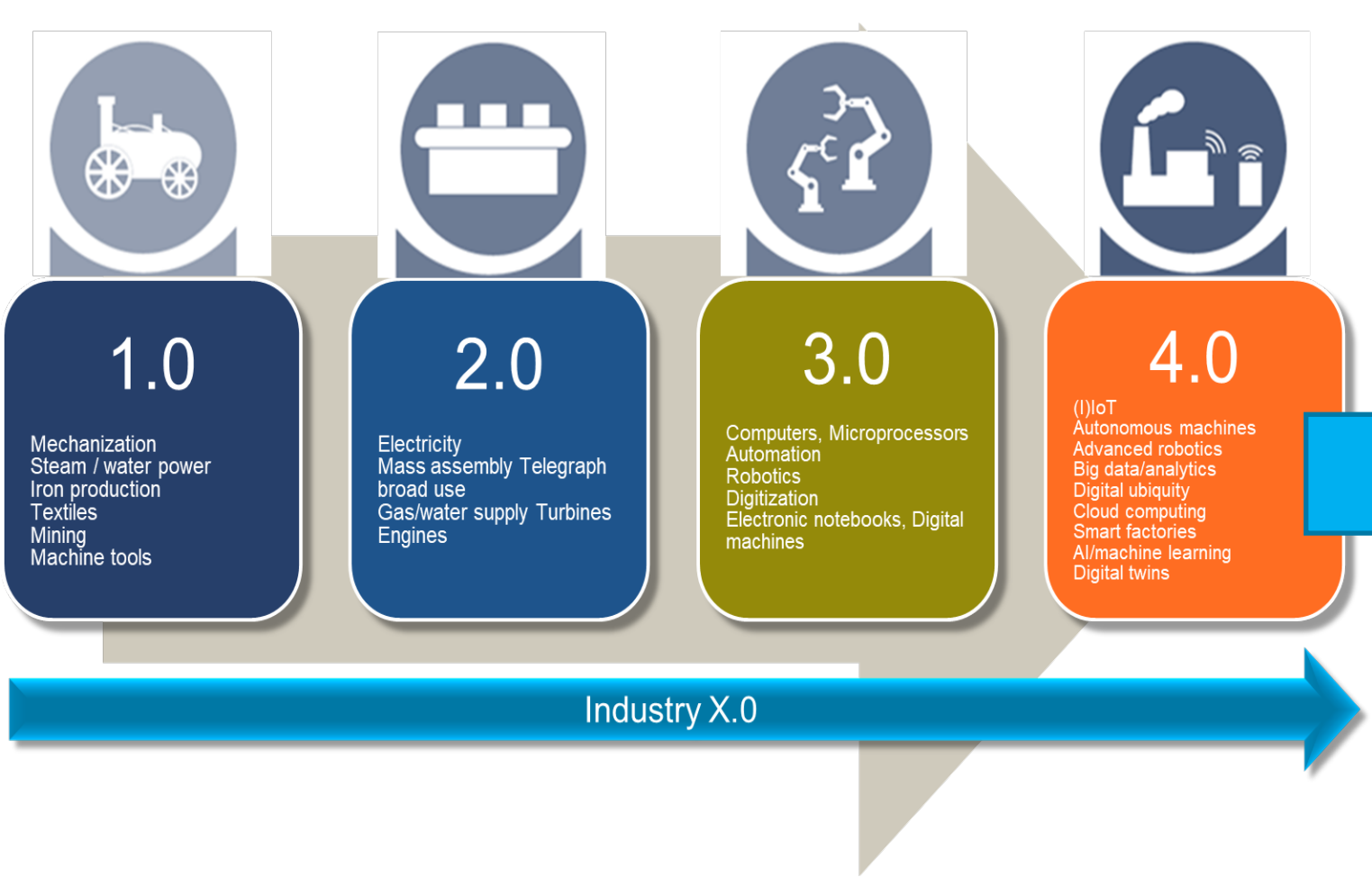
Cyberphysical systems
Mass personalization
Collaborative robots
Intelligent healthcare
Cloud manufacturing
Edge computing
Virtual twins
6G beyond networks
XaaS (anything as a service)

Future

Industry X.0

Pharma 4.0 Framework: Digital Transformation/Disruptive Technologies

Industry 4.0 (fourth industrial revolution) describes a roadmap for digital transformation of manufacturing - extrapolation to Pharma = Pharma 4.0.



Pharma 4.0: What Is it?

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- **Concept of "Digital ubiquitization" introduced by ISPE in 2017 to develop a roadmap for digital transformation of Pharma manufacturing**
- **Based on an extrapolation of Industry 4.0 to Pharma via disruptive / transformative technologies**
- **Data-driven business model; optimize the development process and leverage/enable process understanding**

1. Holistic Digital Enablement (Holistic Control Strategy)

2. Process Maps and Critical Thinking

- Developing process and data mapping/logging to virtual models
- **Digital and Virtual Twin as primary enablers**

3. Plug and Produce

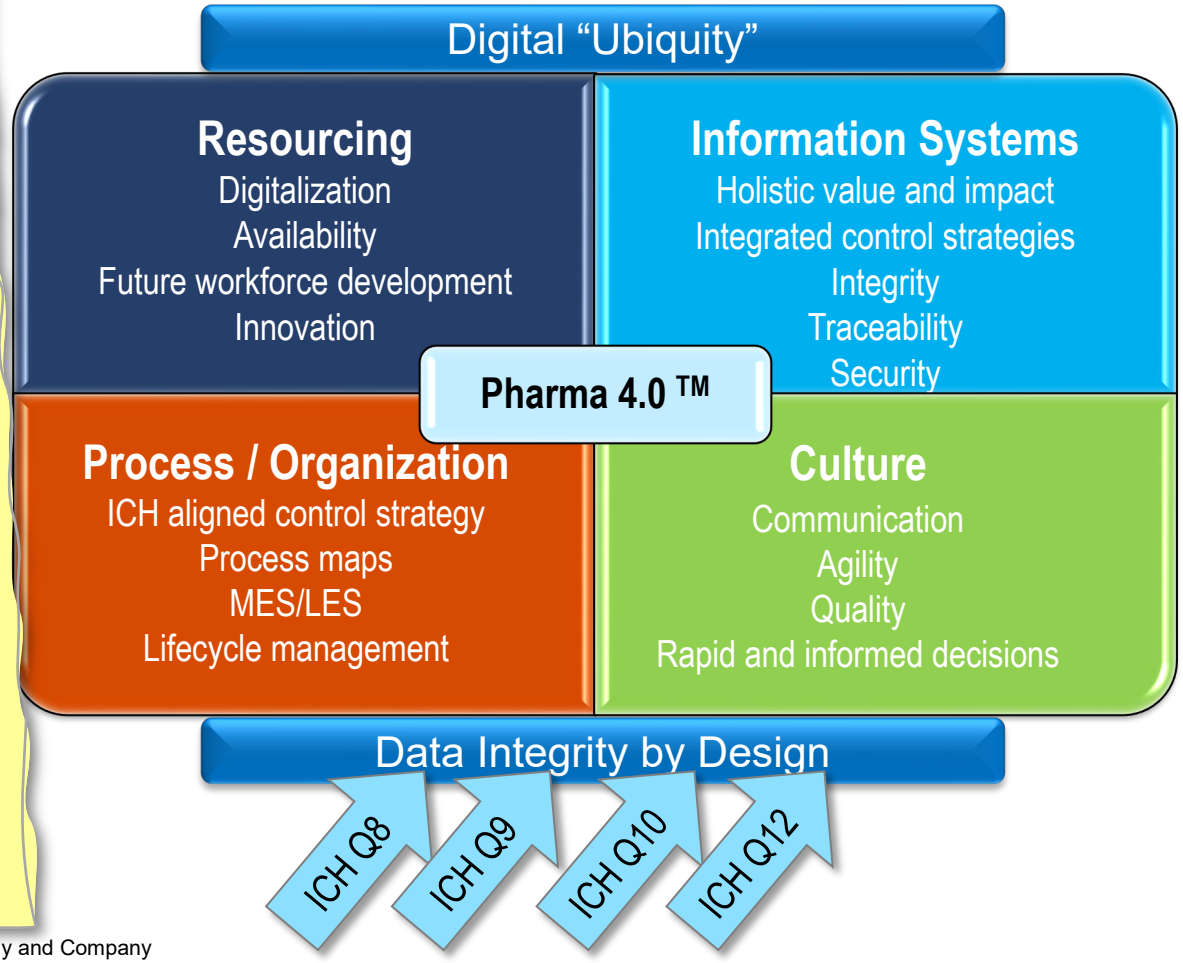
- Developing AI, machine learning in smart automation

4. Validation 4.0

- Develop a new paradigm of a less complex validation model

5. Continuous Process Verification & Process Automation

- Developing parametric release



Pharma 4.0: What Is it?

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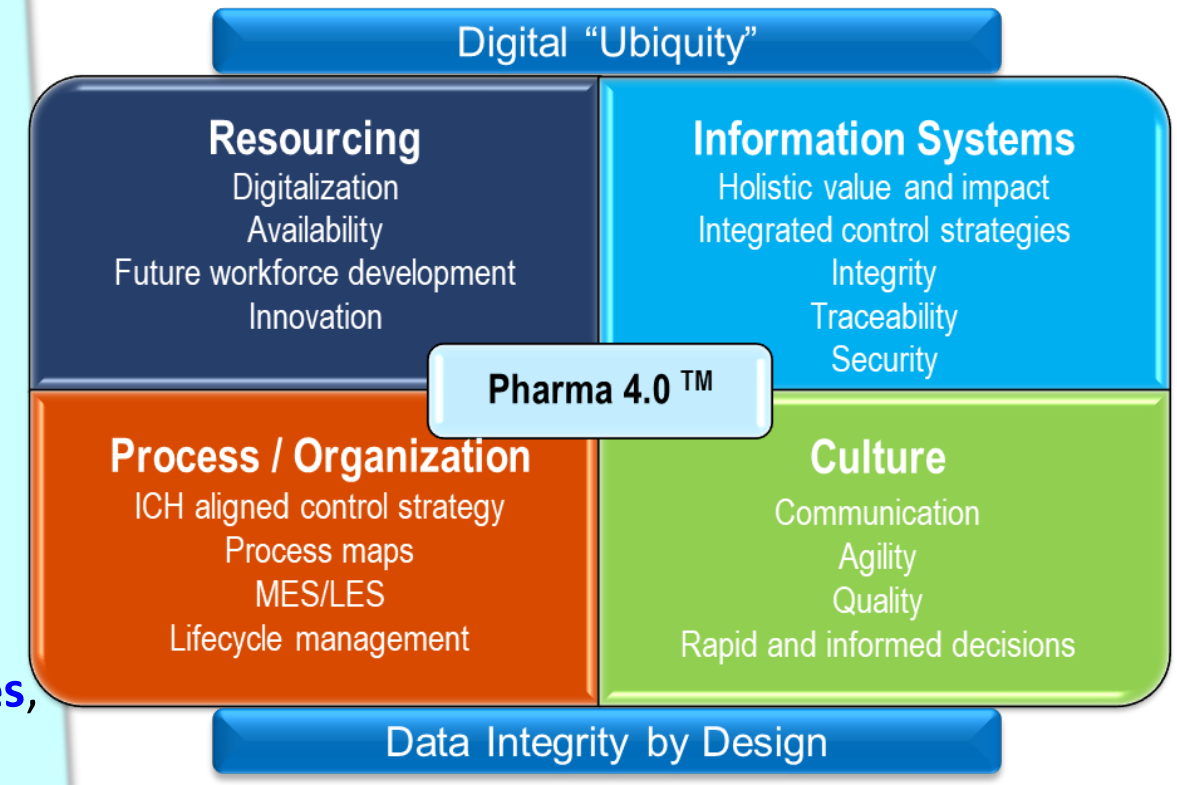
Pharma 4.0 drivers for digital transformation in development and process

- **Pharma 4.0 is NOT an IT Project!!**
- Extends the Industry 4.0 operating model for **medicinal products**.
- Embodies **health regulations and best practices**.
- Pharma 4.0 is **THE enabler** and business case for **next Generation Medicinal Products** and **new modalities**.
- Pharma 4.0 is not a must, but a competitive advantage. ***Missing Pharma 4.0 may represent a business risk.***
- When moving from **blockbusters to personalized medicines**, Pharma 4.0 is a new way evaluate business cases.



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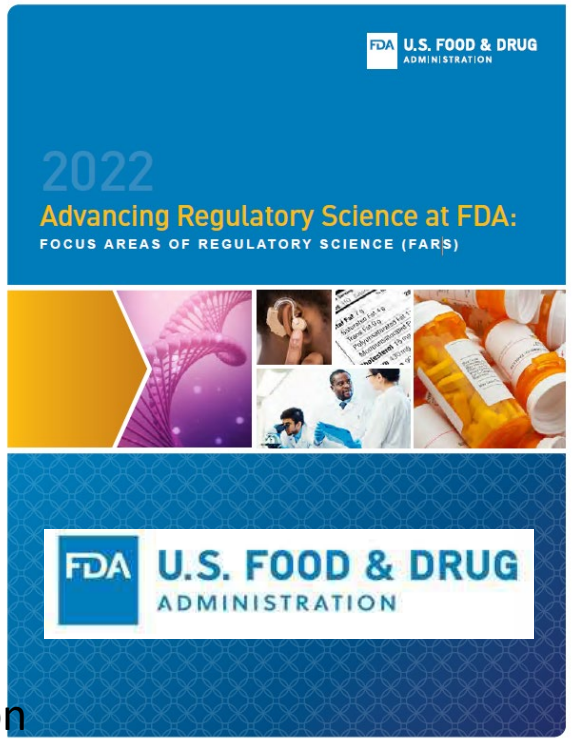
Digital process and smart manufacturing

- **FDA strategic priority: Framework for Advanced Manufacturing Evaluation (FRAME):**
  - End-to-end continuous manufacturing
  - Distributed manufacturing
    - Agile manufacturing
  - Point-of-care manufacturing (on-demand pharmaceuticals)
  - AI/ML application across manufacturing processes
- Quality control
- Supply chain integrity and security
- Clean room technologies
- Analytical technologies
- Automation
- Data visualization, pattern recognition, anomaly detection
- Image analysis
- Predictive modeling/simulation
- Additive manufacturing



PQRI
Product Quality Research Institute

FDA Strategic Initiative	Focus Area of Regulatory Science	Regulated Product Lifecycle: Product Characterization, Manufacturing, and Quality	Non-Clinical Pre-market Evaluation	Clinical Pre-market Evaluation	Post-market Activities
Public Health Preparedness and Response	Medical Countermeasures and Preparedness for Emerging Infectious Diseases	✓	✓	✓	✓
	Technologies to Reduce Pathogen Contamination	✓	✓	✓	✓
	Substance Use Disorders	✓	✓	✓	✓
	Antimicrobial Resistance	✓	✓	✓	✓
	Food Safety	✓	✓		✓
	Quality of Compounded Drugs				✓
Increasing Choice and Competition through Innovation	Individualized Therapies and Precision Medicine	✓	✓	✓	✓
	Complex Innovative Trial Design			✓	
	Microbiome Research	✓	✓	✓	✓
	Novel Foods and Food Ingredients	✓	✓	✓	✓
	Regenerative Medicine	✓	✓	✓	✓
	Advanced Manufacturing	✓			✓
	Increasing Access to Complex Generic Drug Products	✓	✓	✓	✓
	Biomarkers	✓	✓	✓	✓
	Novel Technologies to Improve Predictivity of Non-Clinical Studies and Replace, Reduce, and Refine Reliance on Animal Testing	✓	✓		
	Model-Informed Product Development	✓	✓	✓	
Unleashing the Power of Data	Product Safety Surveillance				✓
	Artificial Intelligence	✓	✓	✓	✓
	Digital Health	✓	✓	✓	✓
	Use of Real-World Evidence to Support Medical Product Development and Regulatory Decision-Making			✓	✓
Empowering Patients and Consumers	Patient and Consumer Preferences and Perspectives	✓	✓	✓	✓
	Patient-Reported Outcomes and other Clinical Outcome Assessments			✓	✓
	Empowering Patients and Consumers to Make Better-Informed Decisions				✓

16 Food and Drug Administration

Digital process and smart manufa

Digital process and smart manufacturing

- **FDA strategic priority: Framework for Advanced Manuf**
  - End-to-end continuous manufacturing
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PQRI Product Quality Research Institute

DTC/FDA Strategic Priorities 2023

Disruptive/Transformative

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	Quality of Compounded Drugs				✓
Increasing Choice and Competition through Innovation	Individualized Therapies and Precision Medicine	✓		✓	✓
	Complex Innovative Trial Design			✓	
	Microbiome Research	✓			✓
	Novel Foods and Food Ingredients	✓			✓
	Regenerative Medicine	✓			✓
	Advanced Manufacturing	✓			✓
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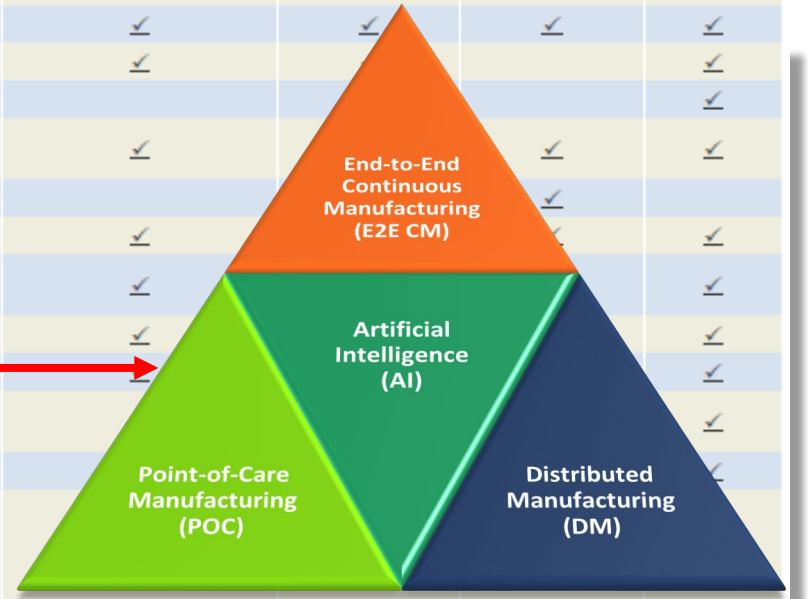

FDA FRAME Technology Focus

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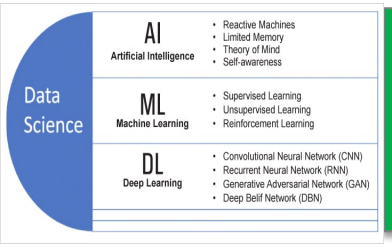
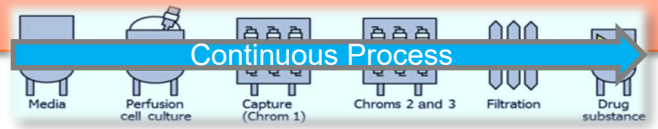
FDA FRAME Priorities



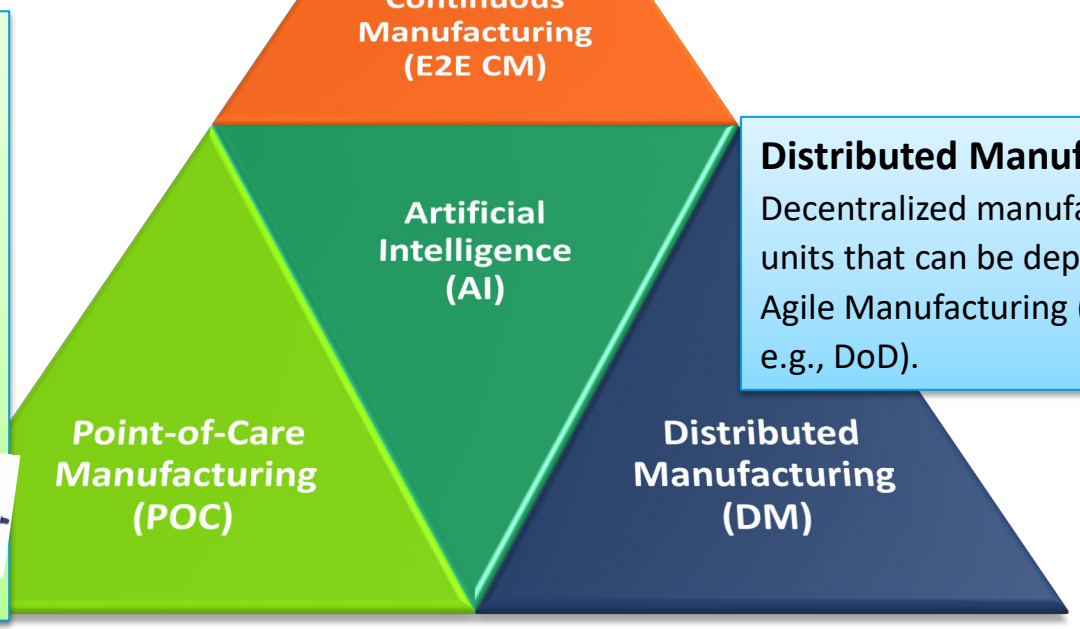
Artificial Intelligence (AI)
Software and hardware systems that can perceive the environment, interpret data, and decide actions.

End-to-End Continuous Manufacturing (E2E CM)
Fully integrated process into which raw materials are continuously fed and transformed and finished drug products are continuously removed.

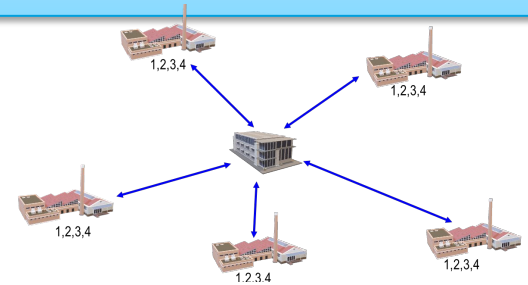


Point-of-Care Manufacturing (POC)
DM platform with manufacturing units in proximity to patient care; for example, at healthcare facilities.

Additive (3D printing) manufacturing
- Tablet
- Capsule
- Cell therapy
- Prosthesis
- Delivery device



Distributed Manufacturing (DM)
Decentralized manufacturing platform with manufacturing units that can be deployed to multiple locations. Includes Agile Manufacturing (rapidly reconfigurable/modular/mobile; e.g., DoD).



FDA FRAME Priorities

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Seek and Analyze Input

- Ensure thorough science- and risk-based understanding of AM
- Engage stakeholders, gather feedback via discussion papers and workshops

Address Risks

- Evaluate existing regulations and policy to ensure timely adoption of AM technologies

Clarify Expectations

- CDER may issue new or updated regulatory guidance
- Ensure global regulatory practice is clear to stakeholders implementing AM

Harmonize

- FRAME will align with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) to develop international guidelines (e.g., ICH Q13 for continuous manufacturing)

FDA U.S. FOOD & DRUG ADMINISTRATION

Digital Twin: Primary Enabling Technology

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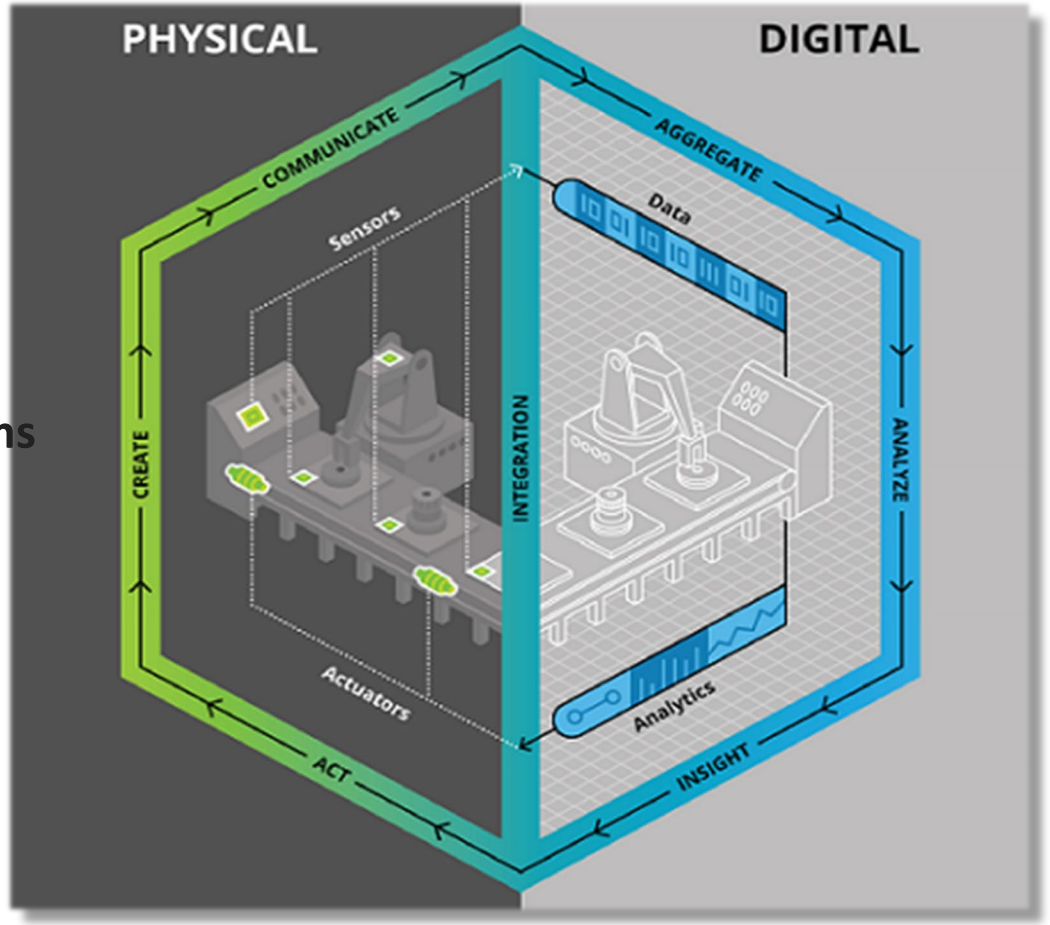
Digital Twin as a primary enabling technology

- **A current representation of a physical asset in operation**
  - Models the current asset condition
  - Includes relevant historical data
  - Predict future behavior, refine the control, or optimize operation
- **Models a component, system of components, or a system of systems** (e.g., pumps, filters, automation, manufacturing lines)
  - Include physics-based approaches or statistical approaches
  - Reflect the operating asset's current environment, configuration, tolerances, compatibility, material knowledge
  - Leverage operational data with predictive AI/ML for optimized productivity, asset reliability, and sustainability



Industry 4.0 and the digital twin, Manufacturing meets its match, Aaron Parrott, Lane Warshaw, Deloitte Insights, May 12, 2017

Digital Twin: Primary Enabling Technology

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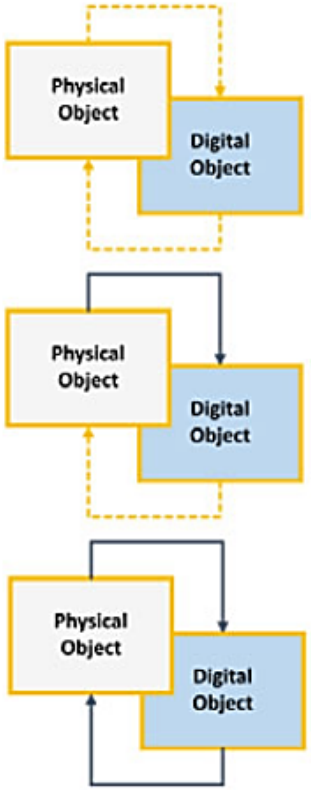
Digital Twin = Generally, a virtual digital representation of a process, product or service. Consists of physical part, virtual part and connections between them.

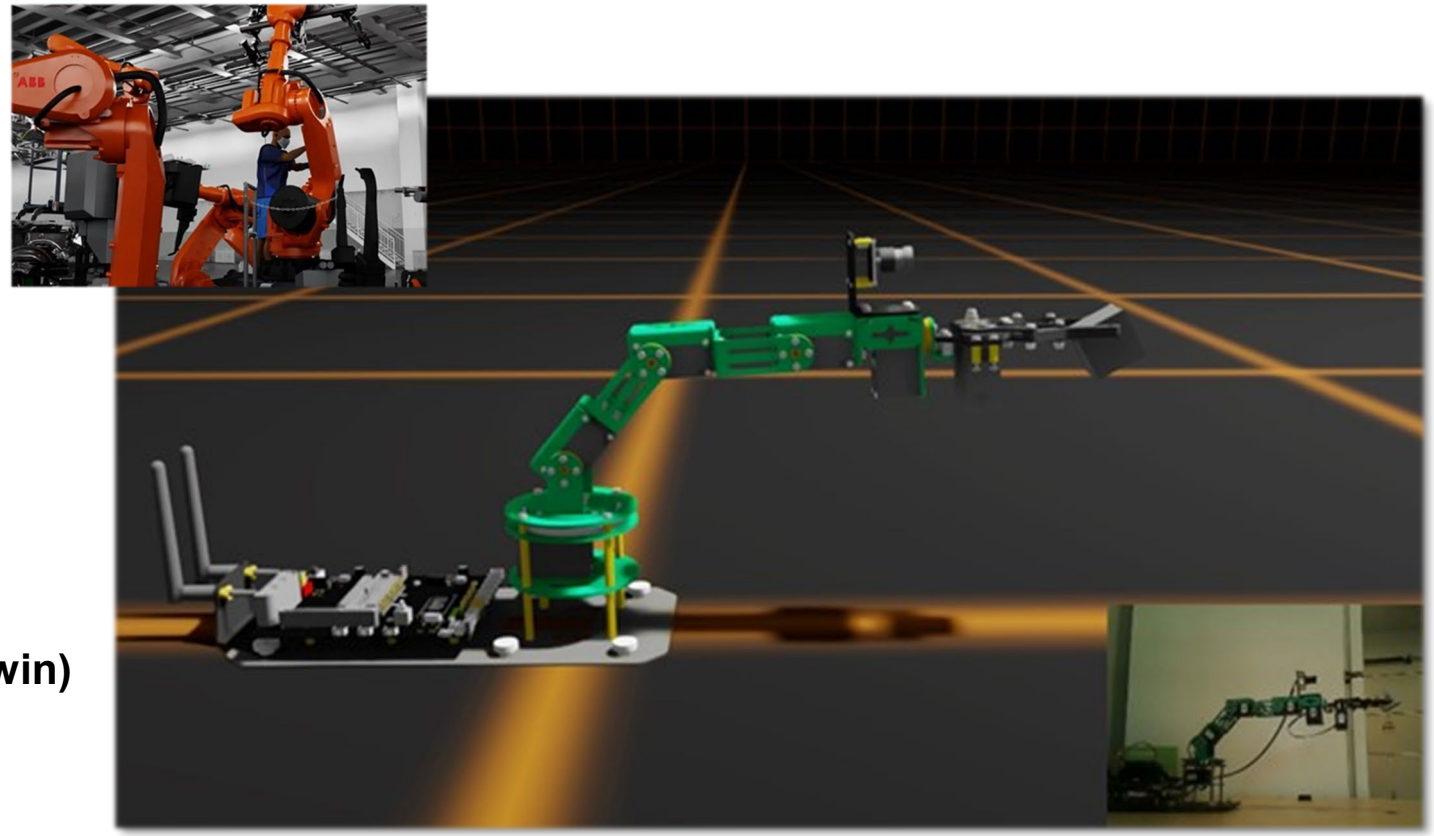


- **Level 1 - Digital Model**
  Process understanding with a virtual representation of the real-world. No connected data or control. Useful in Development
- **Level 2 - Digital Shadow**
  In-silico combination of models + PAT data to predict process control. Monitoring and predictive control with manual adjustments to process.
- **Level 3 - Digital Twin (Virtual Twin)**
  Automated process control through in-silico prediction and automated adjustments to real-world process

Disconnected Data Flow

Connected Data Flow

Digital Twins in The Development and Launch of Medicines and Vaccines
2022 PDA/FDA Joint Regulatory Conference, 12-14 September, Washington, DC



NVIDIA blog, Scott Martin, 14 Dec 2021

Digital Twin: Primary Enabling Technology

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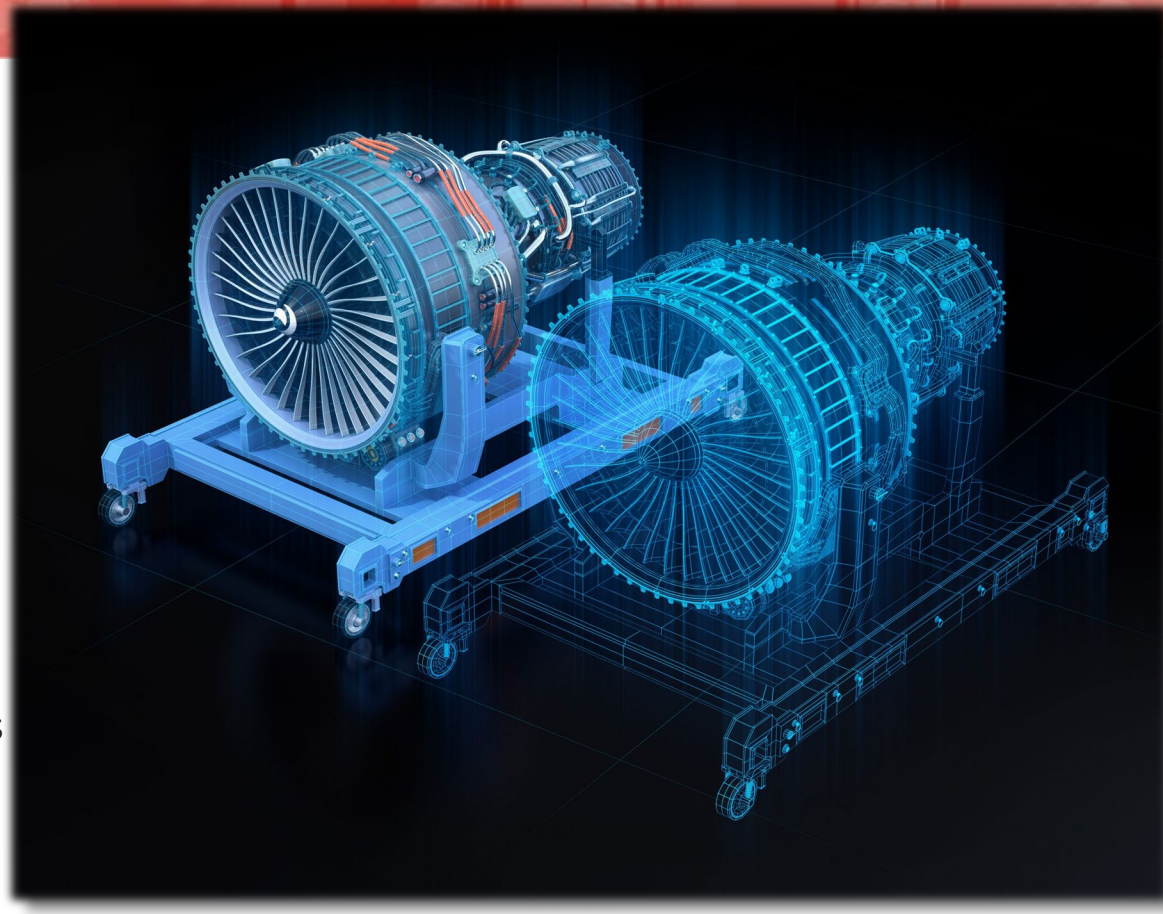
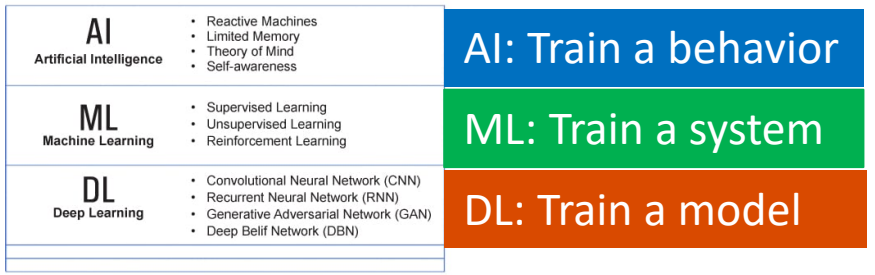
Digital Twin enabling attributes

- **Connectivity**
  - **Sensors:** capture operational/environmental data (e.g., MEMS)
  - **IoT:** technology facilitating integration of physical/digital space
  - **Big data:** sensor data is captured, aggregated and stored with multiple data feeds, design specs, enterprise systems
- **Digitalization**
  - **Simulation modeling:** physics/mathematics based modeling for physical world and processes (e.g., computational fluid dynamics (CFD))
  - **Data-driven modeling:** analyze the system data and discover relationships across inputs and outputs to enable decision making and course correction
- **Intelligence**
  - **Artificial Intelligence (AI)** and machine learning (ML)
  - **Analytics:** visualization and heuristic presentation, pattern recognition and anomaly detection
  - **Actuators:** AI mediated triggers initiating a physical process or action, with variable/minimal human intervention, comprising a dynamic control system



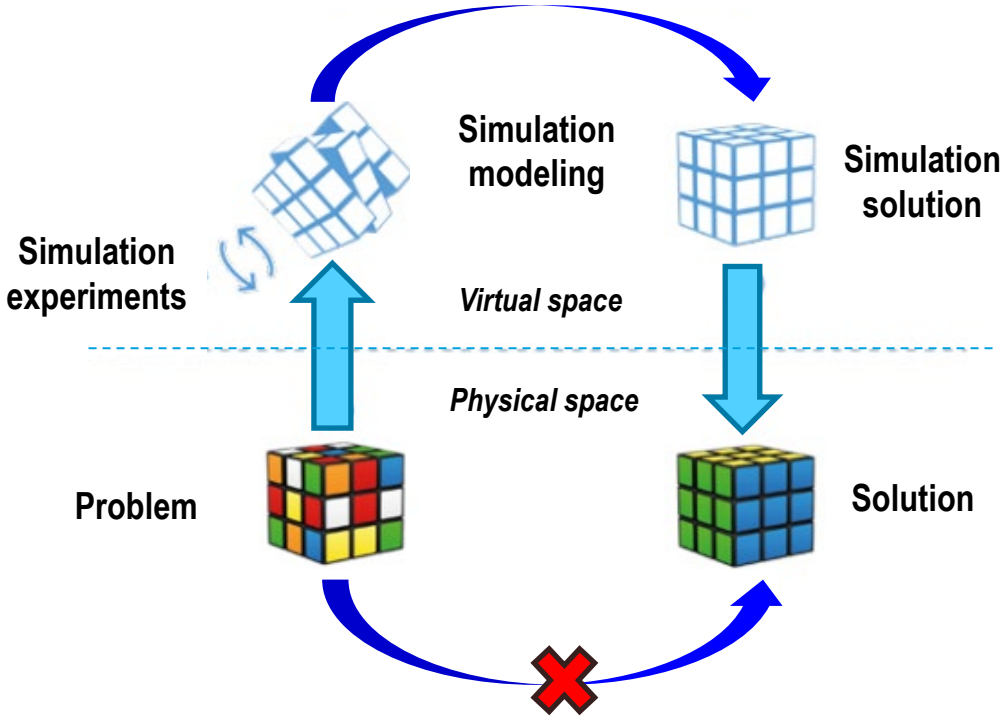
3 ways additive manufacturing and digital twins are transforming Air Force and Space Force supply chains, Gov Design Hub, David Presgraves, April 6, 2022

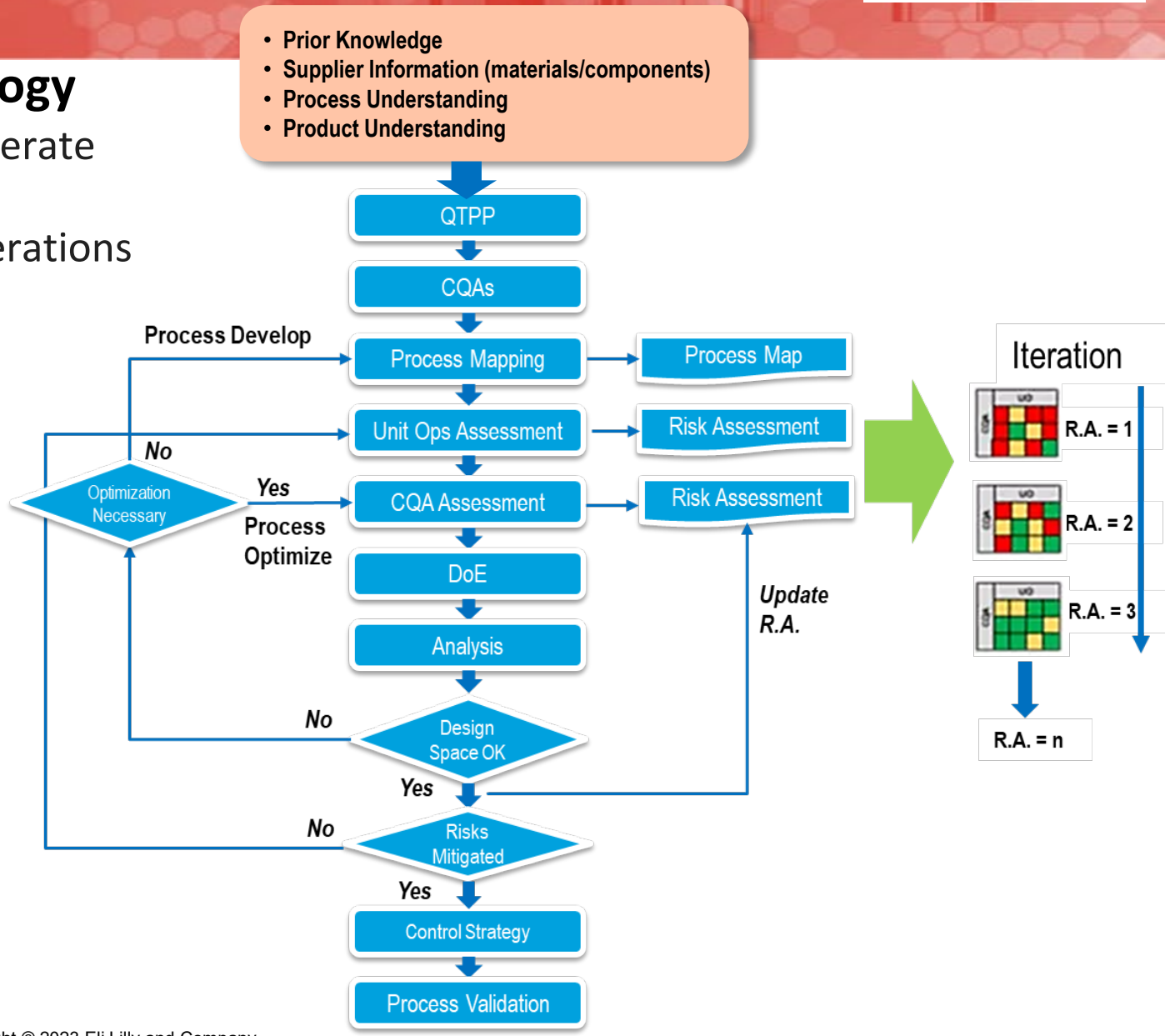


Digital Twin: Primary Enabling Technology

Digital Twin as a primary enabling technology

- **Operations optimization:** Variables used to generate models which can run hundreds/thousands of "what-if" simulations to adjust and optimize operations





Digital Twin: Primary Enabling Technology

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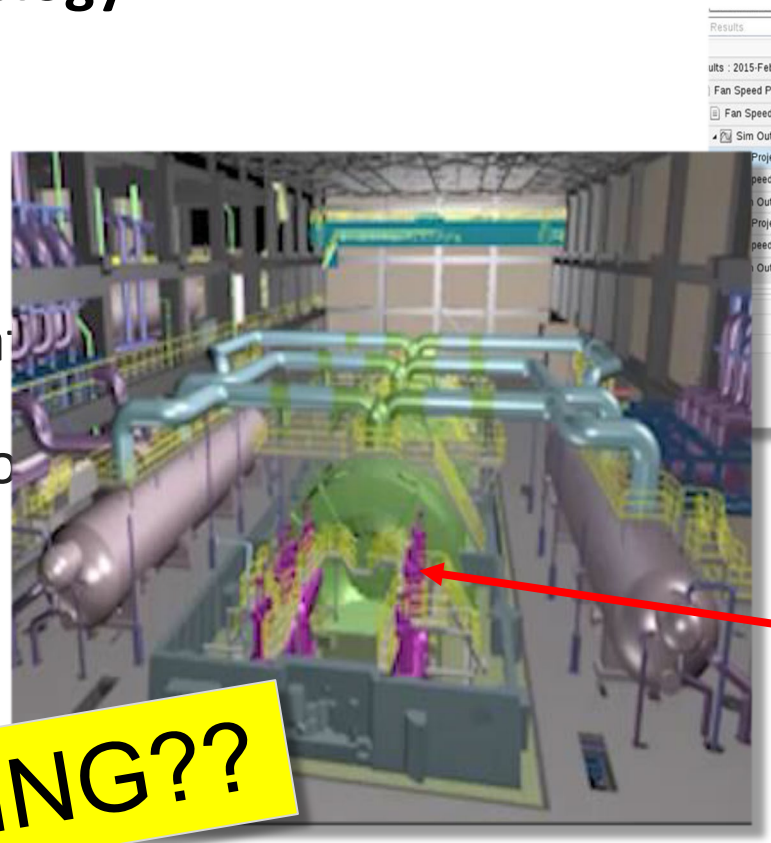
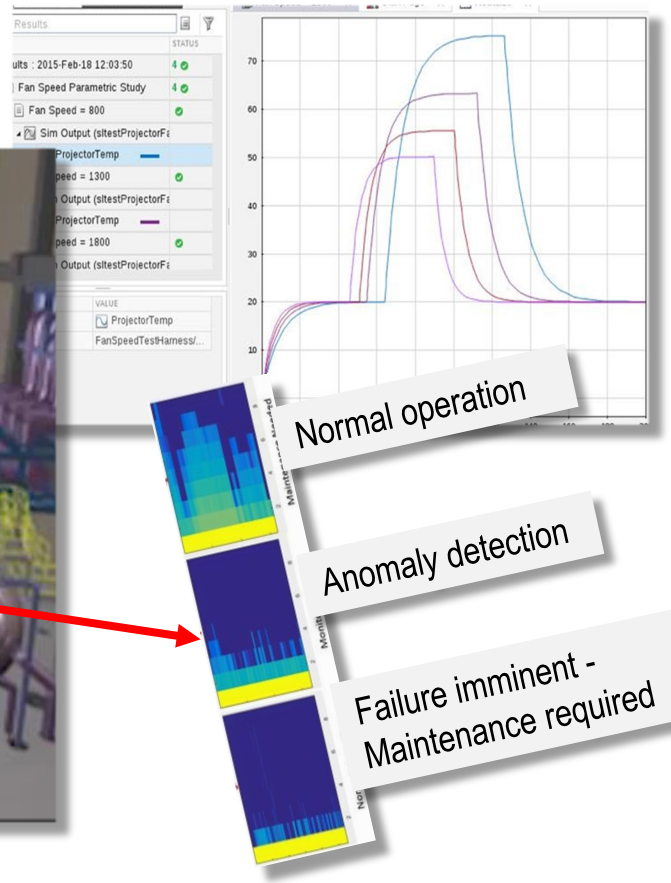
Digital Twin as a primary enabling technology

- **Predictive maintenance**
  - Lifecycle management
  - Failure mode analysis
- **Anomaly detection**
  - Deviation from ideal modeled/simula behavior
  - Avoid catastrophic failure and alert to error
- Constructing a digital twin prior to assembling in physical space avoids the question…



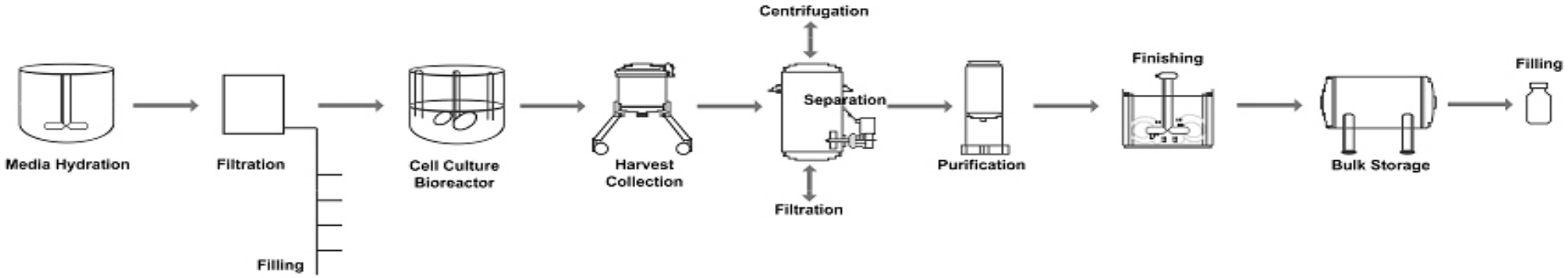


WHAT WERE WE THINKING??

Smart Digital Realities, Digital Twins @DNA-Level, Denise Miller, EAM Hexagon, IMC Conference 2022

Developing a Digital/Virtual Twin for Bioprocess

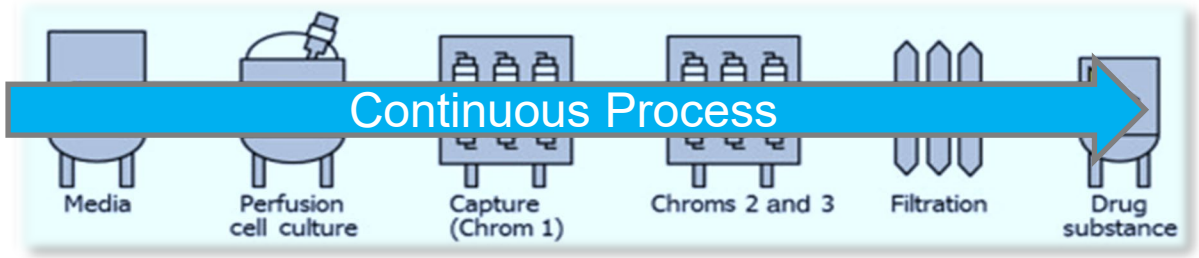
Disruptive/Transformative Technologies Team



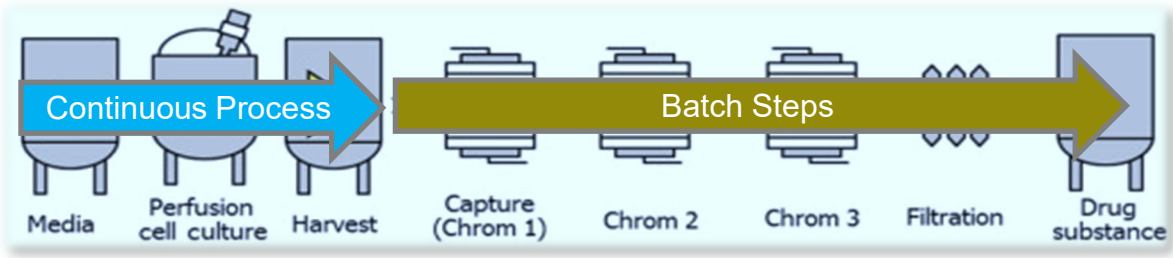
UPSTREAM	CELL CULTURE	DOWNSTREAM PROCESSING	FILL & FINISH
Media Prep Buffer Prep Reagents Prep	Cells Virus Media Broth	Biomass Unpurified Bulk Purified Bulk Formulated Bulk	Final Product Dose

Risk

Continuous (E2E) manufacturing



Semi-continuous manufacturing



Digital Twin for Bioprocess

Utilizes prior knowledge, material, component, process understanding

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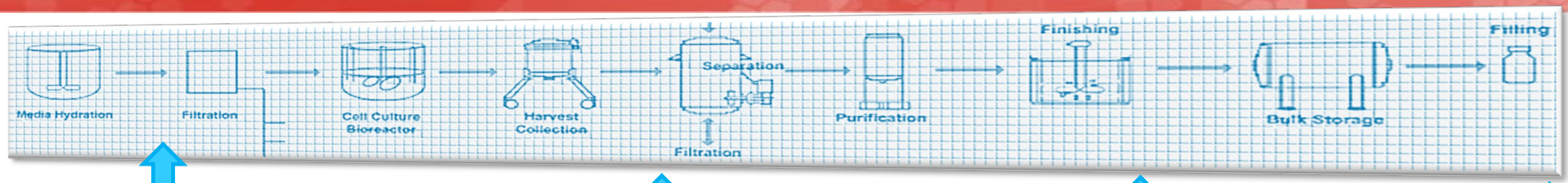
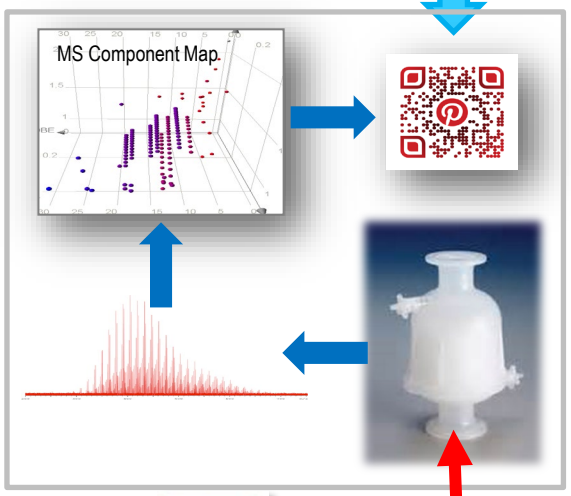
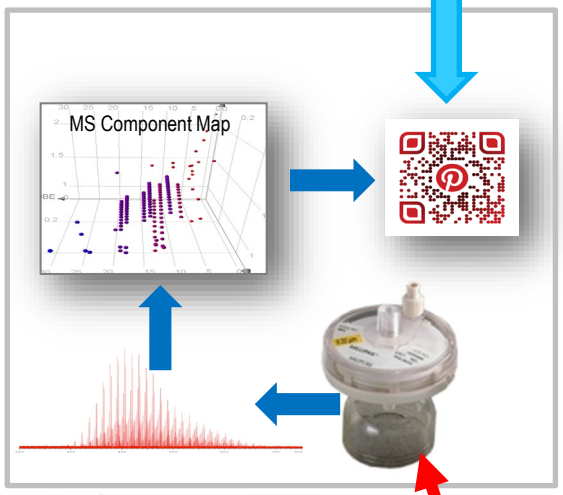
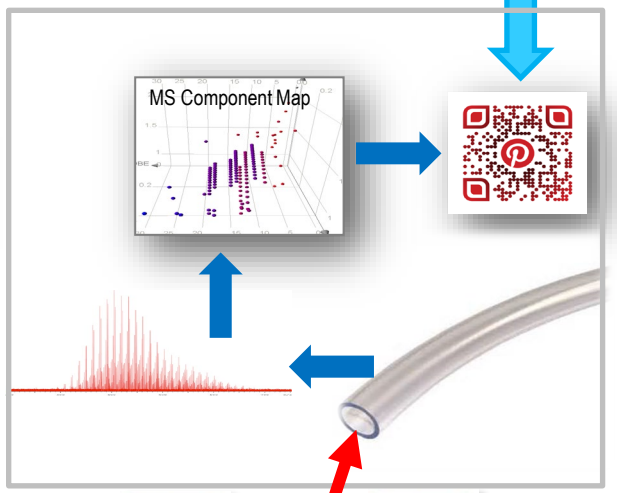
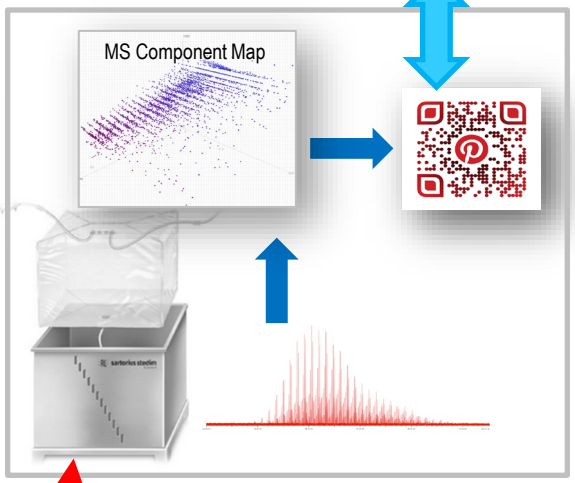
Digital Twin

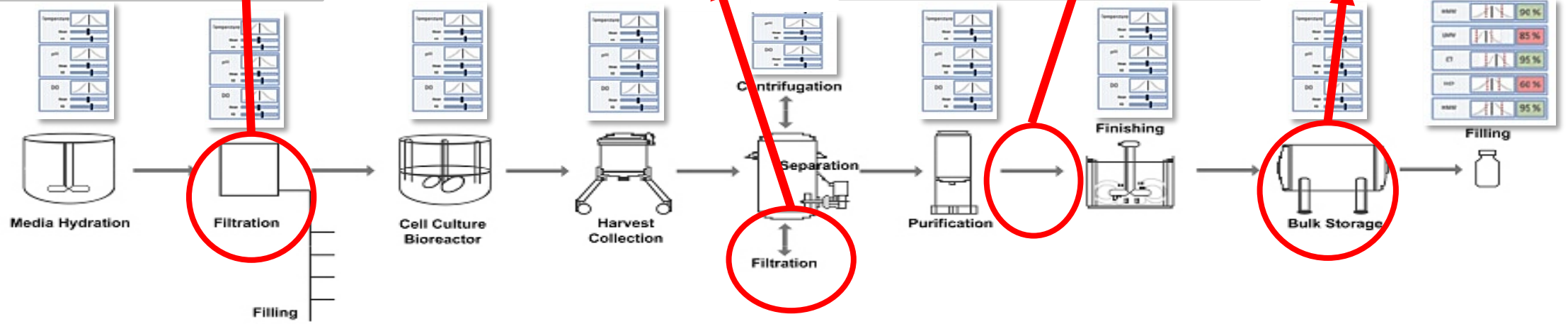












Sensing and control

Virtual Twin for Bioprocess – sensing and real time control

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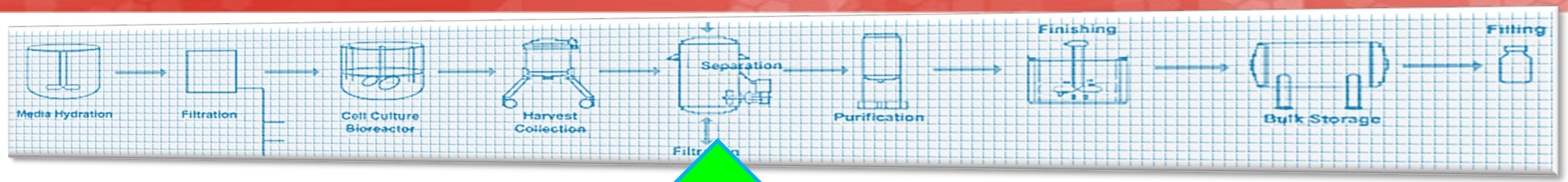
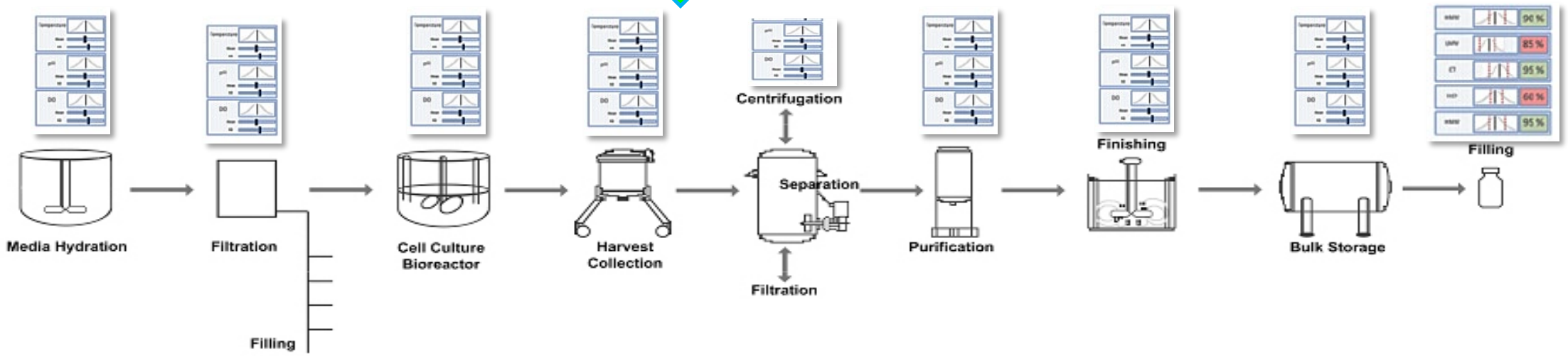
Digital Twin



Virtual Twin

Sensing and control



UPSTREAM	CELL CULTURE	DOWNSTREAM PROCESSING	FILL & FINISH
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Risk

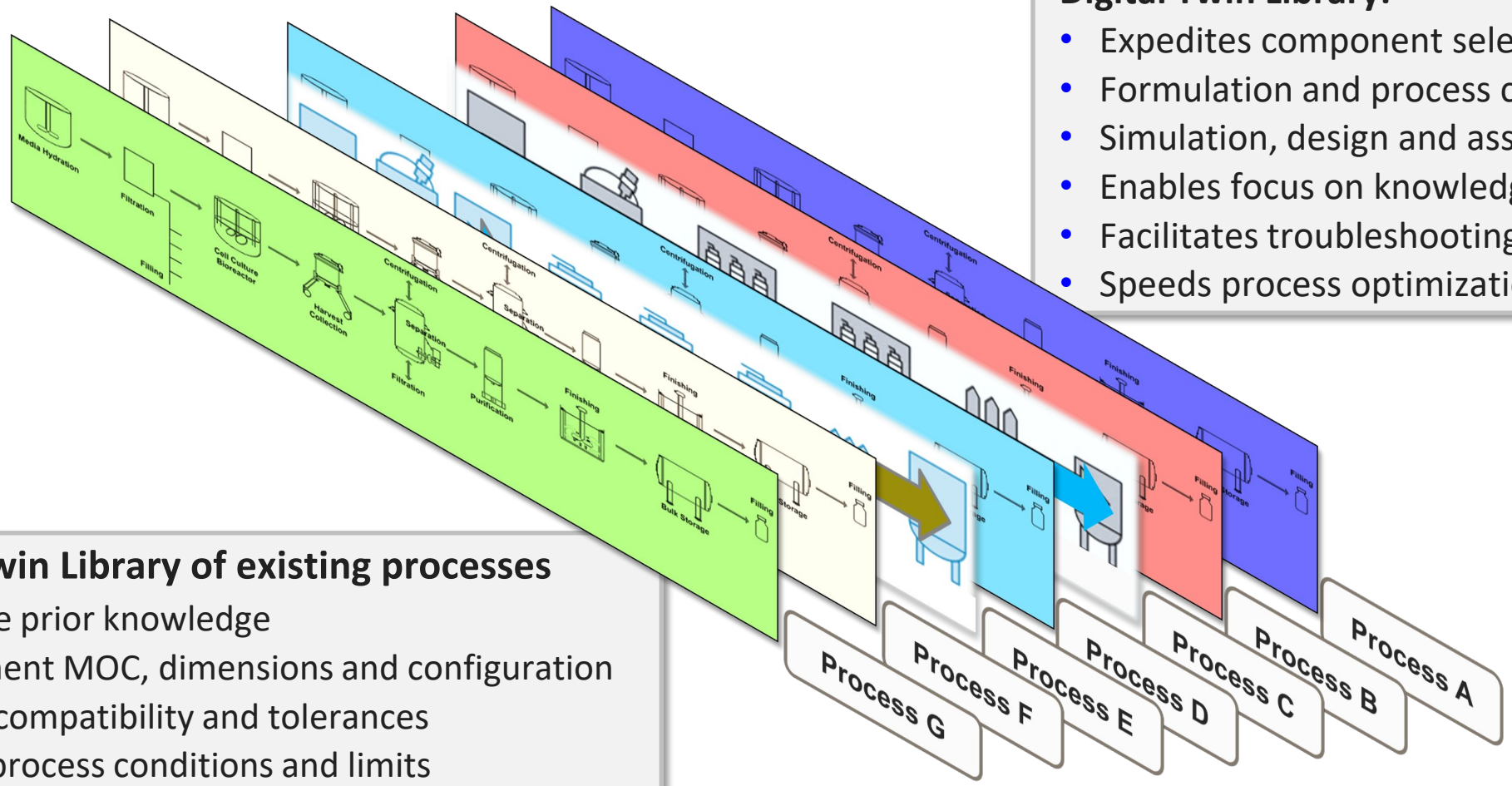
Developing a Digital/Virtual Twin for Bioprocess

Disruptive/Transformative Technologies Team

DT3

Digital Twin Library:

- Expedites component selection
- Formulation and process conditions
- Simulation, design and assembly of new processes
- Enables focus on knowledge poor unit operations
- Facilitates troubleshooting, FMEA
- Speeds process optimization and validation



Digital Twin Library of existing processes

- Leverage prior knowledge
- Component MOC, dimensions and configuration
- System compatibility and tolerances
- Known process conditions and limits
- Unit ops understanding
- Formulations understanding
- Extractables/Leachables profile

Industry (Pharma) 4.0 to 5.0: Where From Here?

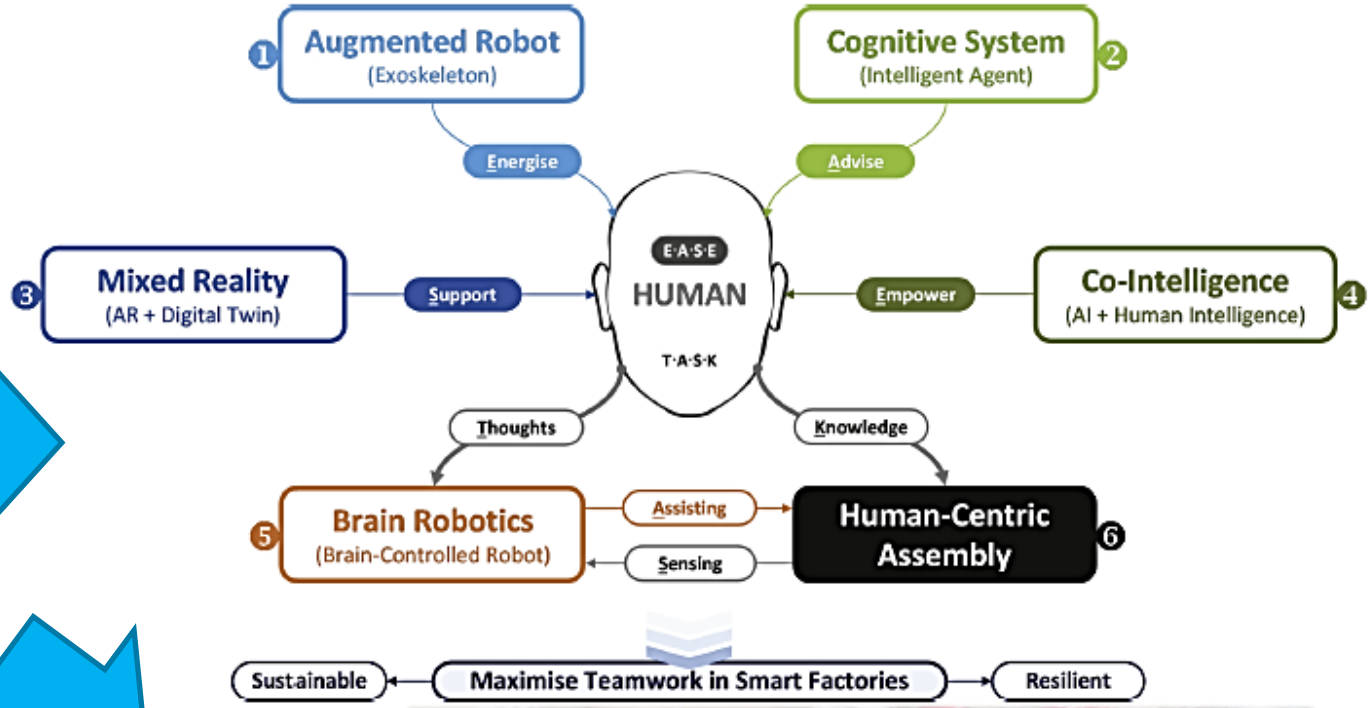
Disruptive/Transformative Technologies Team

Workforce development, talent, diversity, empowerment

… Agile, resilient, adaptable technologies

Leading, implementing sustainability focused strategies

Three pillars supporting core values of Industry 5.0



Smart city design

Journal of Manufacturing Systems 62 (2022) 199-201

Acknowledgments

Arup Roy
Jose Cintron
Ryan Darling
Mike DeFelippis

Disruptive/Transformative Technologies Team (DT3)

Digital Twin Center of Excellence

- Brian Good
- Li Liu
- Rachel Kaiser
- John Stafford
- Brie Barney
- Rohit Bhatia
- Kalyan Dey
- Inyoung Hur (intern)

Many thanks to the Purdue University faculty, staff!