CMC Strategy Forum Japan 2025
Session IV - Innovative Approaches in Biopharmaceutical Manufacturing: Advanced Manufacturing, Dx, and AI/ML

# Continuous Manufacturing and Portable On-Demand (POD) for Biologics: Development Challenges and Regulatory Considerations

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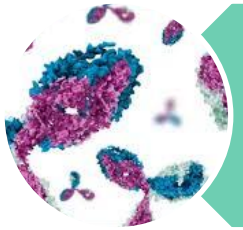
MSD

# Drivers for Innovation in Pharm Manufacturing



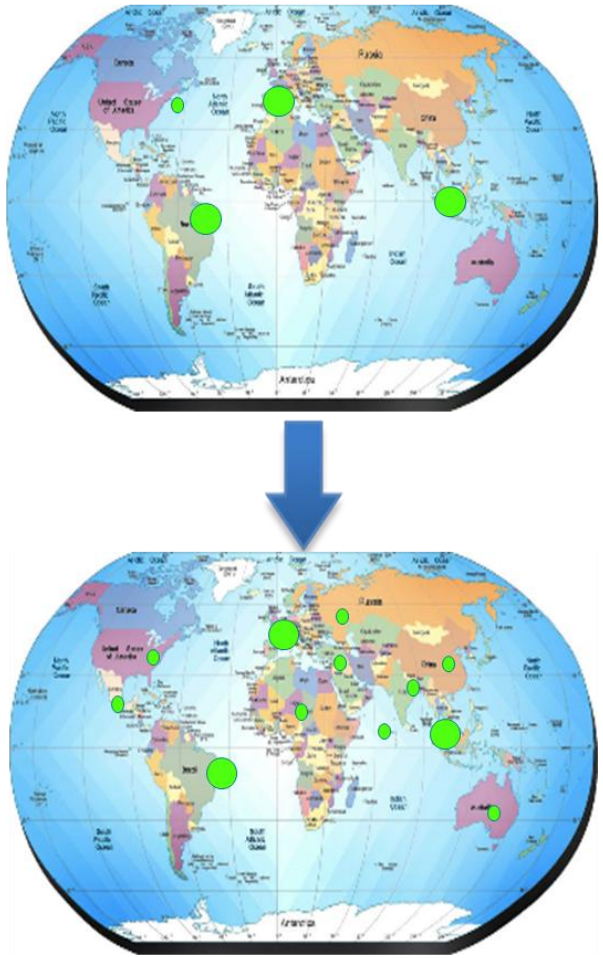
Increasing Pipeline with New Modalities
and Complex Products

Greater Range of Product Demands
with increasing Demand Uncertainty

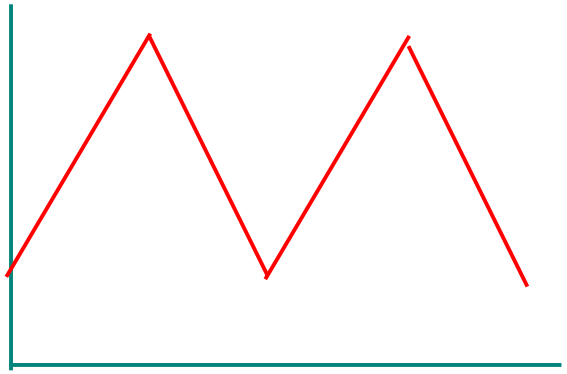

Evolving Reimbursement
Global Competition & Lost Drug Exclusivity
Development Cost and Short Timeline


Need for Global Presence
Everchanging Geopolitical Environment

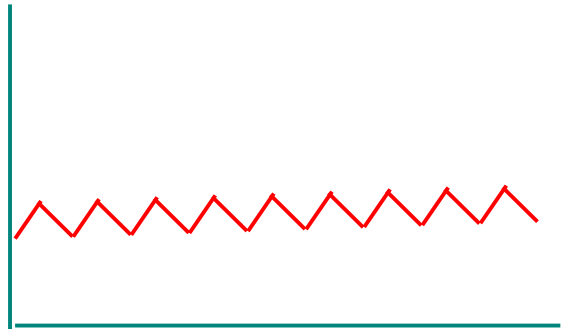
# Pharmaceutical Industry Shift



- Large, centralized facilities
- Few campaigns of large batches

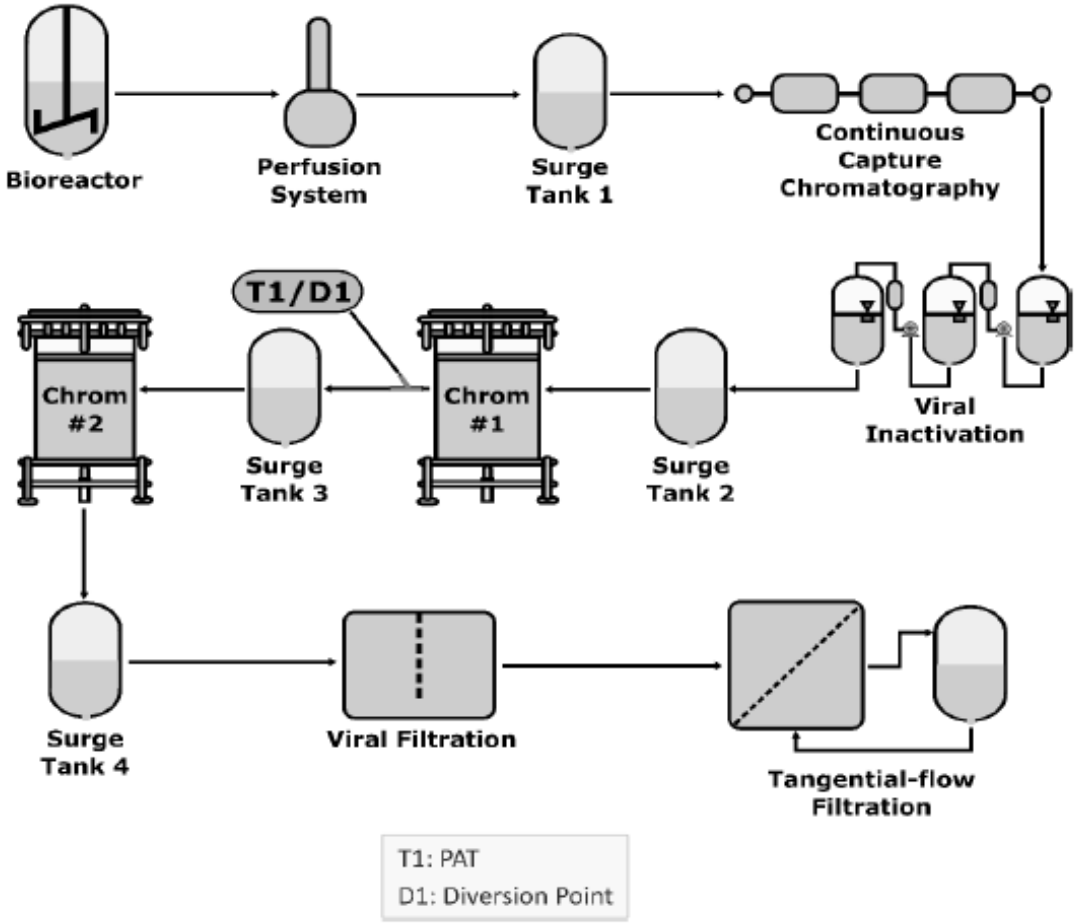


- Smaller volume products
- Small and agile local plants
- Many campaigns, quick turnaround



# Emerging Technologies

- Continuous Manufacturing (CM)




- Portable On-Demand (POD)

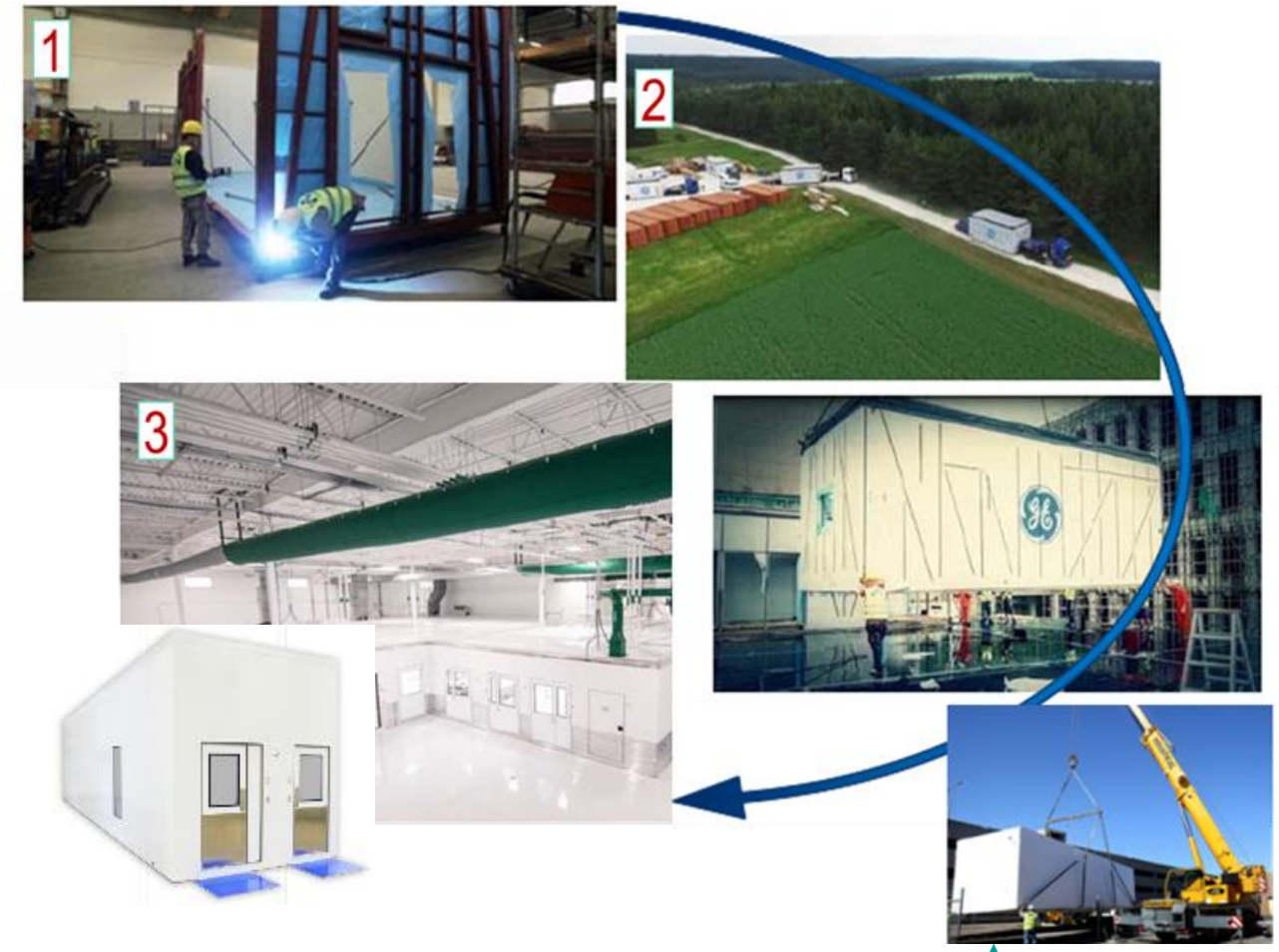



Image from ICH_Q13_Step4_Guideline_2022_1116.pdf

# Portable, Plug & Play

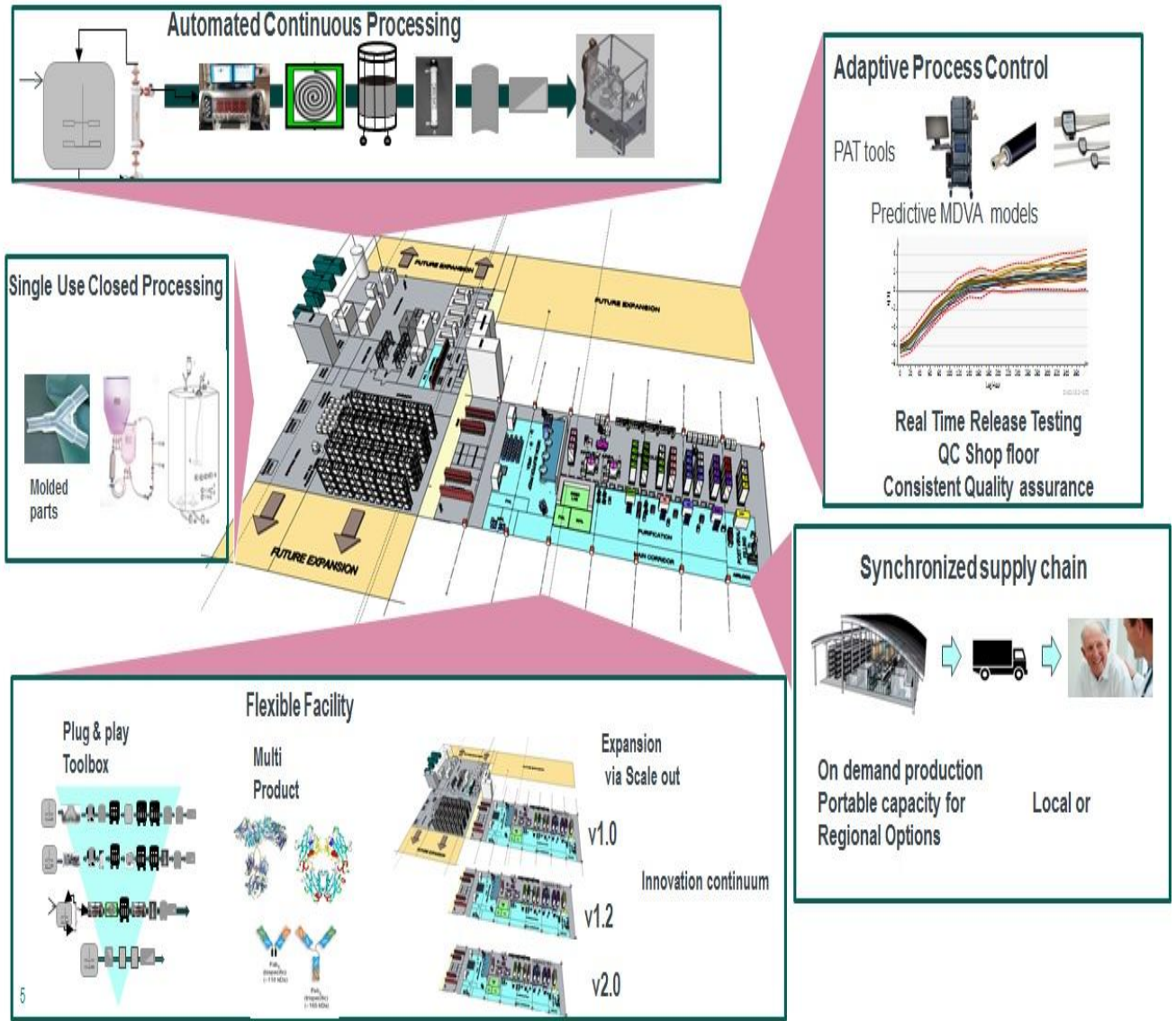

Image from ICH_Q13_Step4_Guideline_2022_1116.pdf

# Vision for the Future State of Biologics Manufacturing and Supply

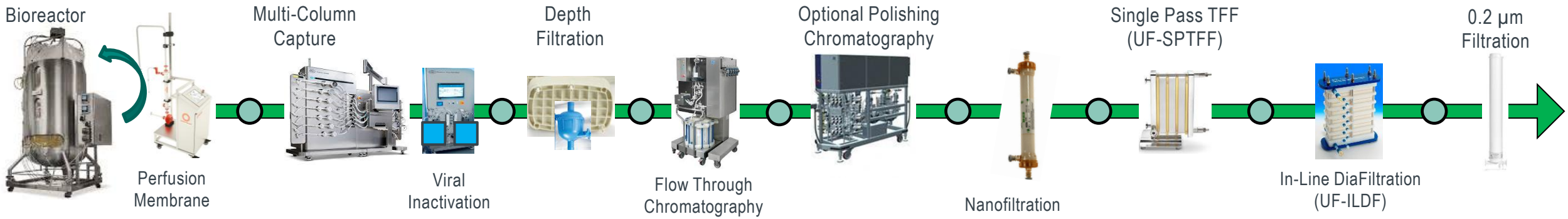
## Historical State

- Stainless steel batch processing
- Rigid Batch Size
- Separate API & drug product
- Conventional laboratory QC
- Long lead time supply chain
- Fixed costs focus

## Future State



# MSD BIOLOGICS CM PROCESS OVERVIEW



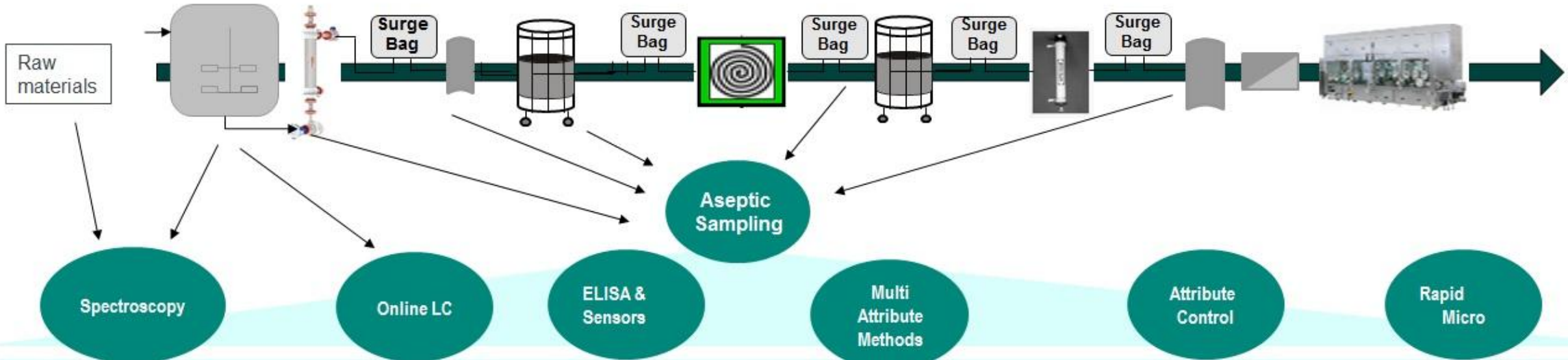

**Legend:** Cell culture broth stream | Smart Surge Vessel | Cell-free product rich stream

**Overall DSP time cycle is dictated by the longest step**
**Other steps are lengthened to compensate**

- Smart Surge Vessel (SU Vessel)

pH/Conductivity Control
Speed Compensation

# Batching: linked to *the control strategy* that is designed to ensure the process under a *state of control*




Raw materials

Titer
Biomass
Analytes

w/ PDA

w/ QDa

w/ Fraction Collector

2D-LC

Aggregates
Impurities
Concentration



Activity
Impurities
Biomass


Identity
Glycans
Oxidation
Process Impurities
Charge variants


MVDA
Product Attribute Control
Adaptive Control

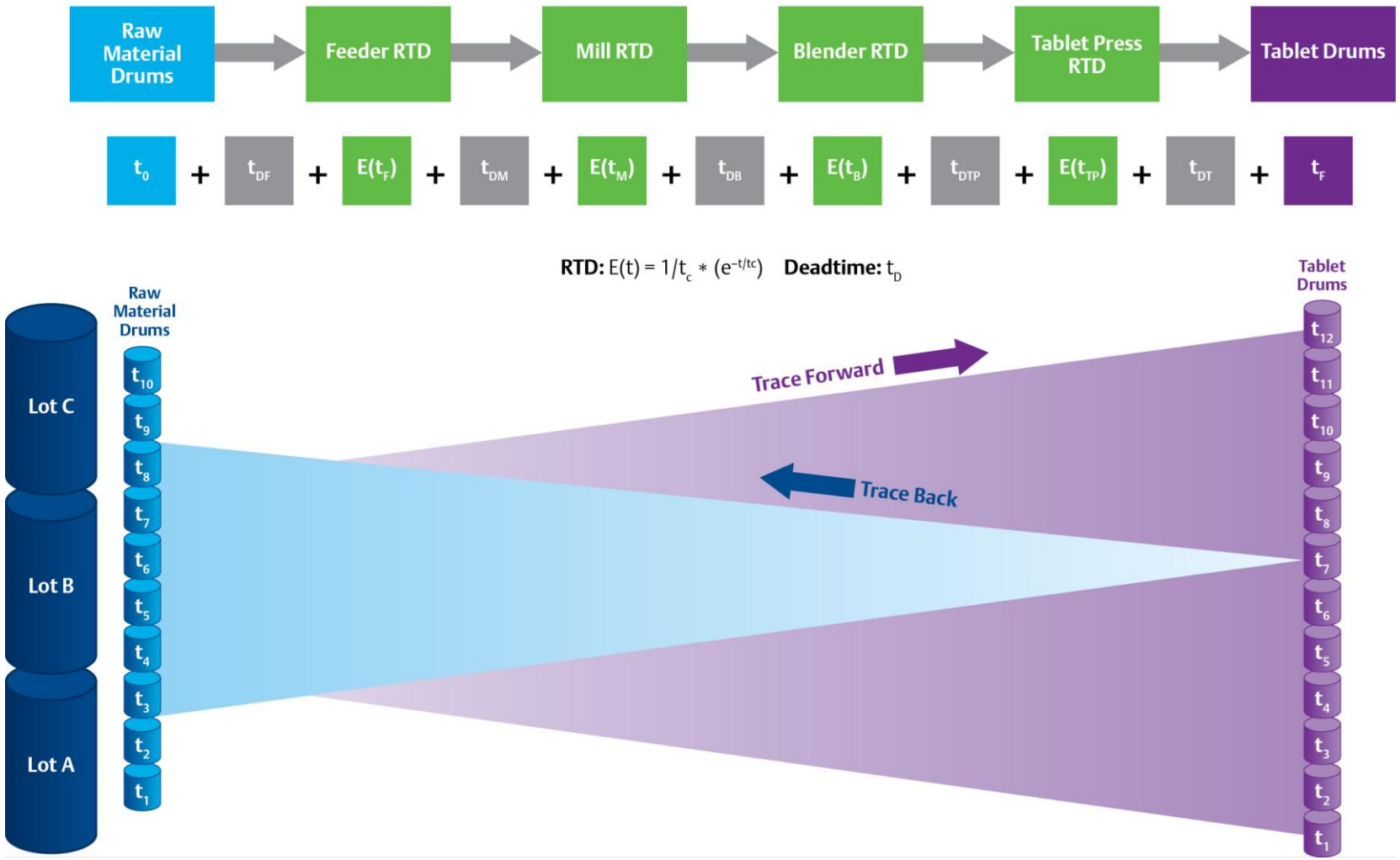
Sterility
Bioburden control
Air Monitoring

**Developed for integration into continuous processing**
**Deployable into current batch processes**

MSD

Proprietary

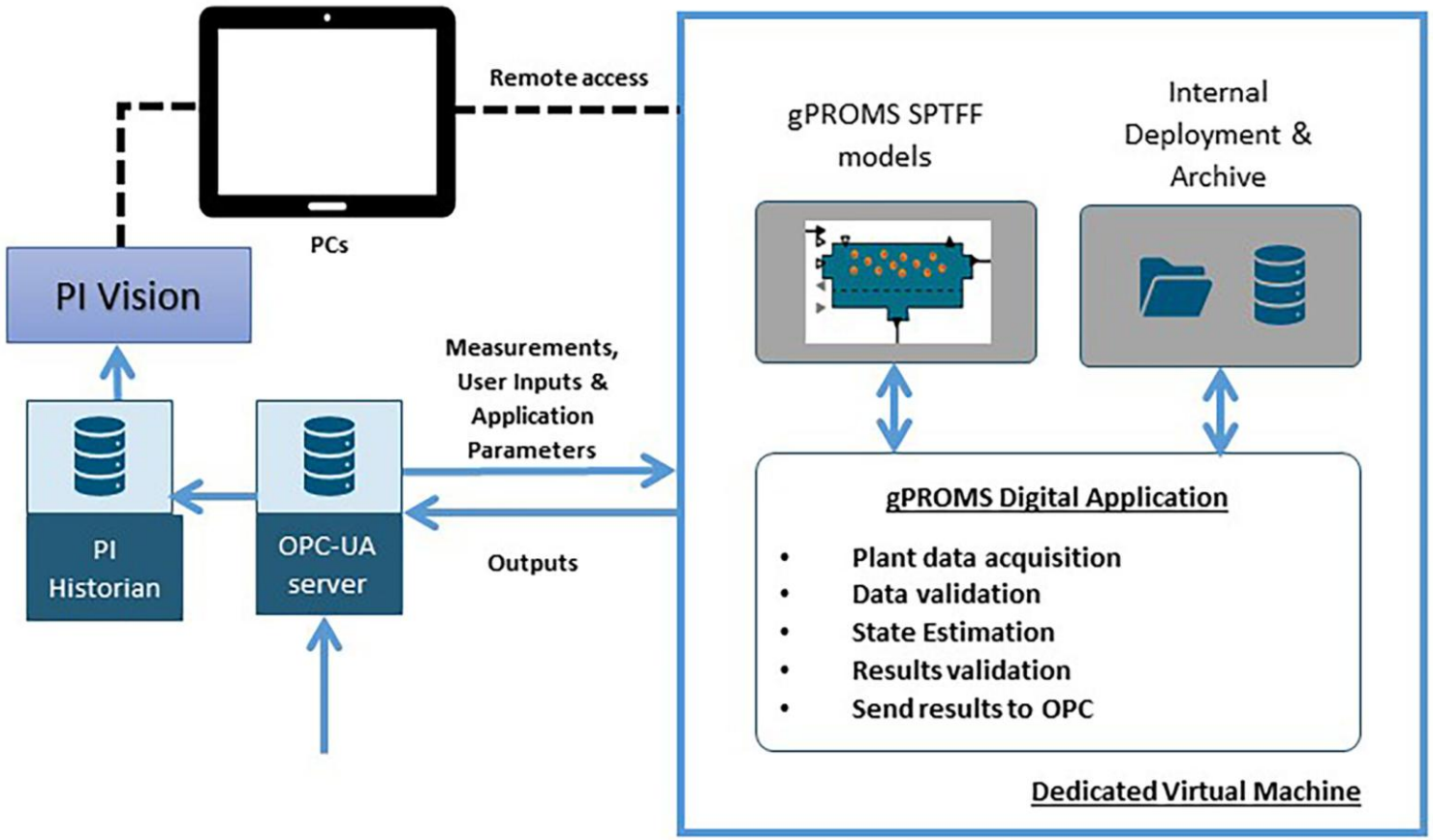
# Batching: linked to *the control strategy* that is designed to ensure the process under a *state of control*

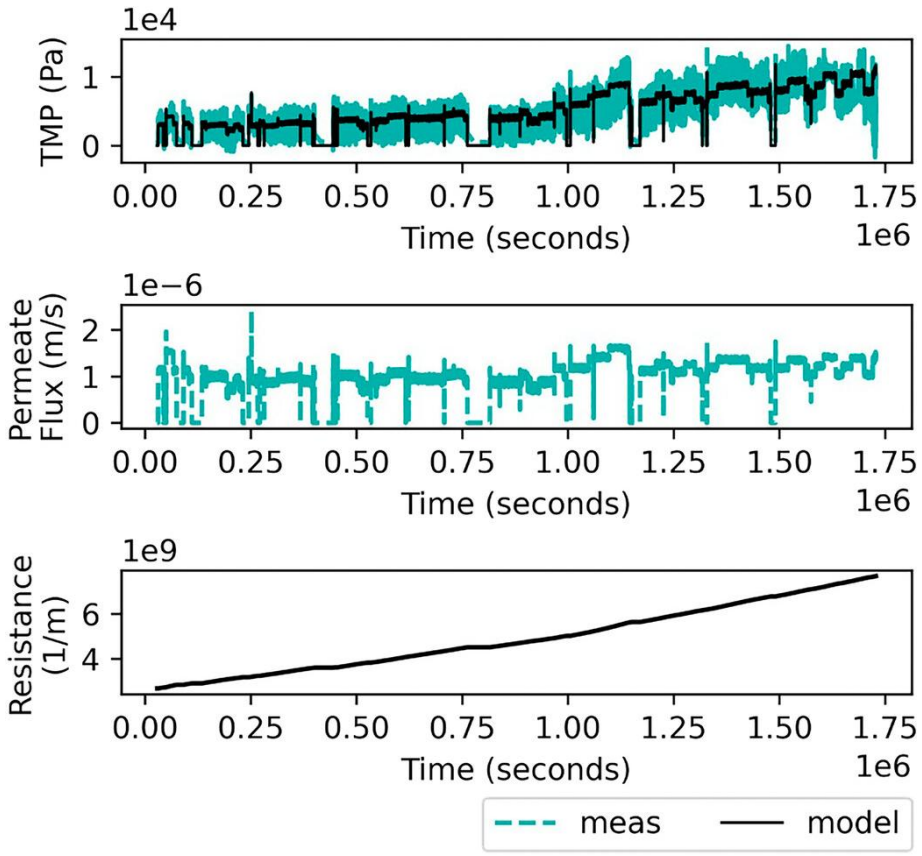



By learning the minimum and maximum residence time of a component traveling through the system, a prediction can be made as to when a change in component will reach the outlet and when the previous lot will be fully cleared.
https://www.pharmaceuticalprocessingworld.com/continuing-progress-in-continuous-manufacturing/

# Digital Twins

Use of live digital twin (shadow) soft sensor to monitor membrane degradation in continuous manufacturing single pass tangential flow filtration



# Advantages of CM

## Productivity & Efficiency

- Eliminate unit operations
- Eliminating the need for batch-to-batch setup & cleaning
- Optimal use of equipment & resources

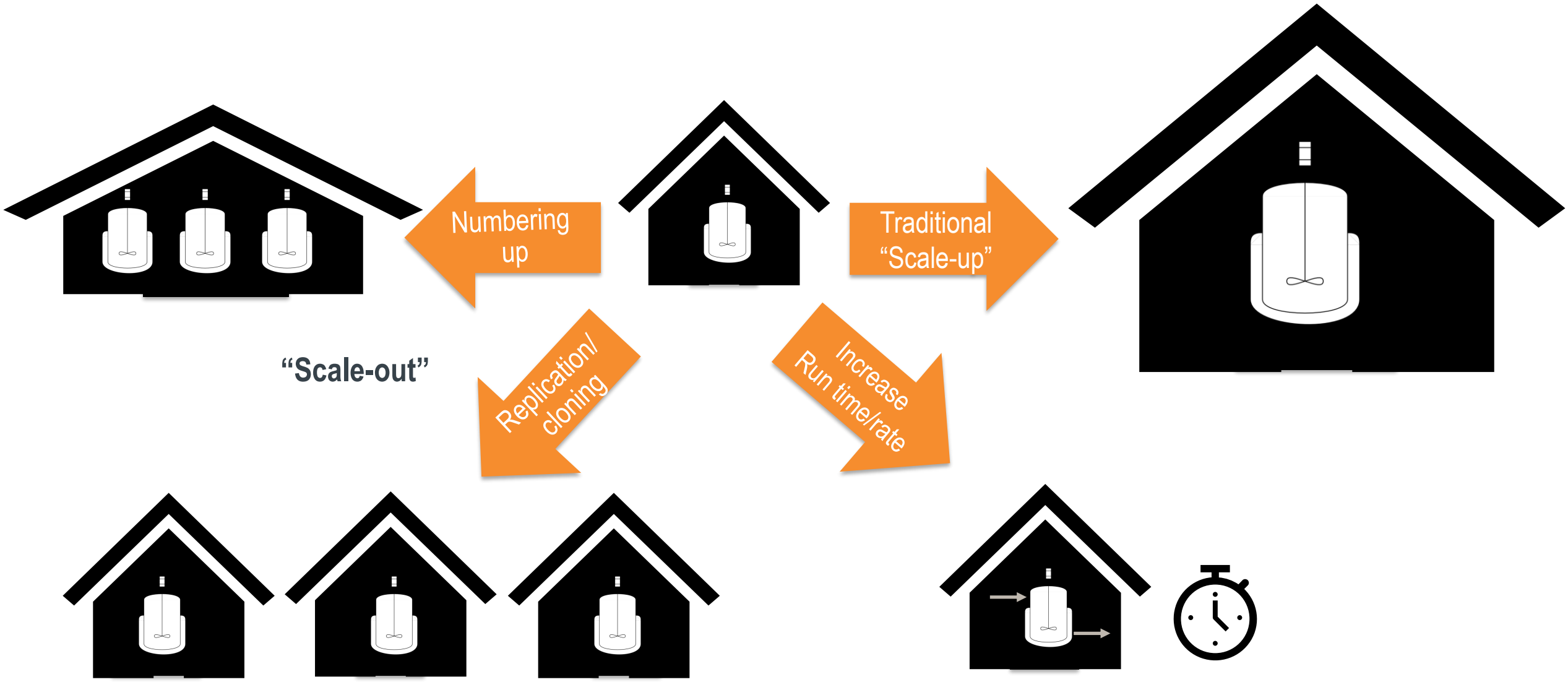
## Quality & Consistency

- Enhance process control – real time monitoring and testing
- Automated handling
- Operate in a steady state without any break in time

## Supply Chain Robustness

- Flexible production
- Shorter lead time
- Lower inventory
- Reduces discards

# Scaling Up and Scaling Out



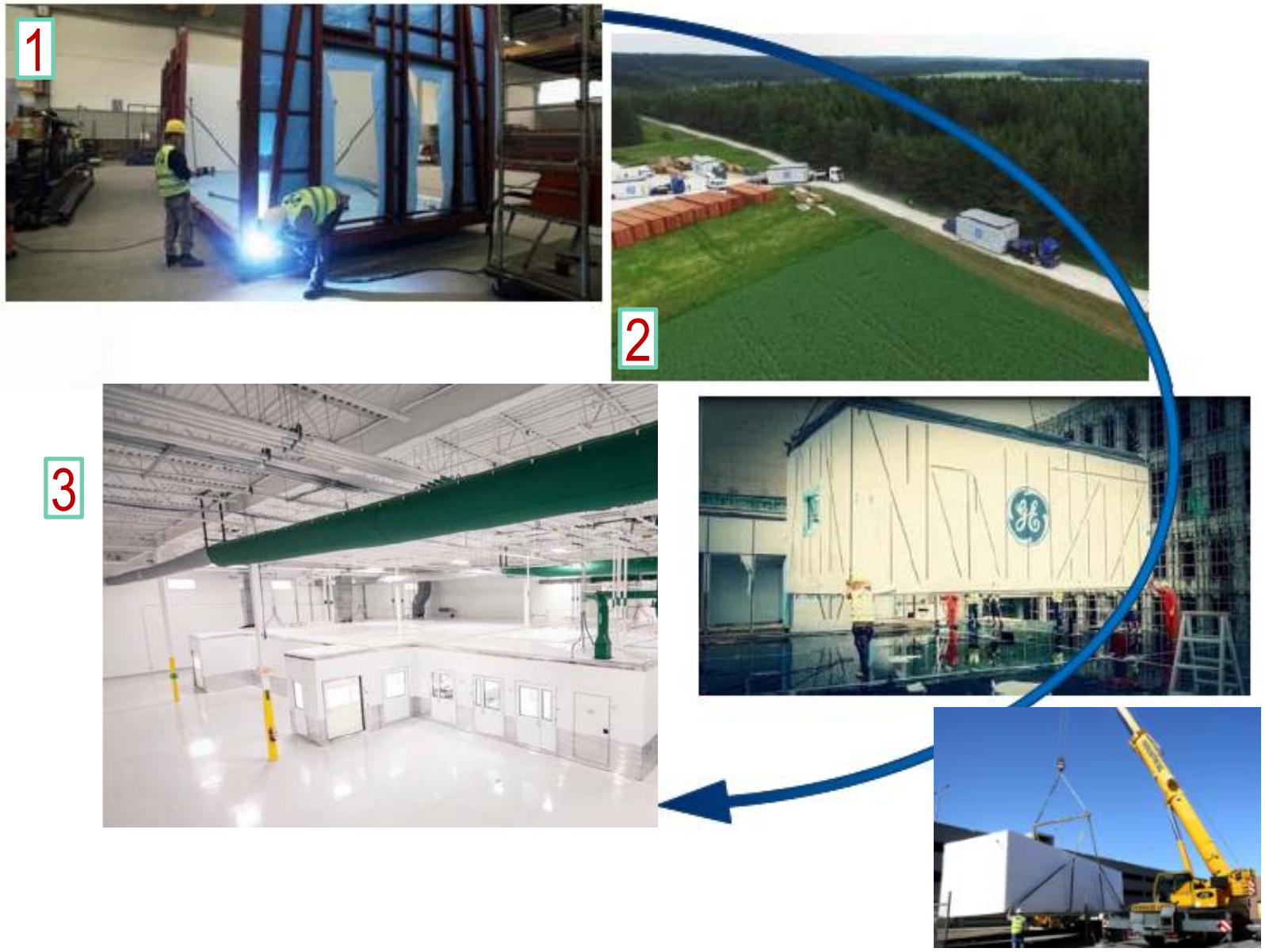

*Minimizes equipment and process design changes as volume is increased*

# What are PODs?

1. Built off-site

2. Road-based transport to site

3. Assembled on-site in a host structure

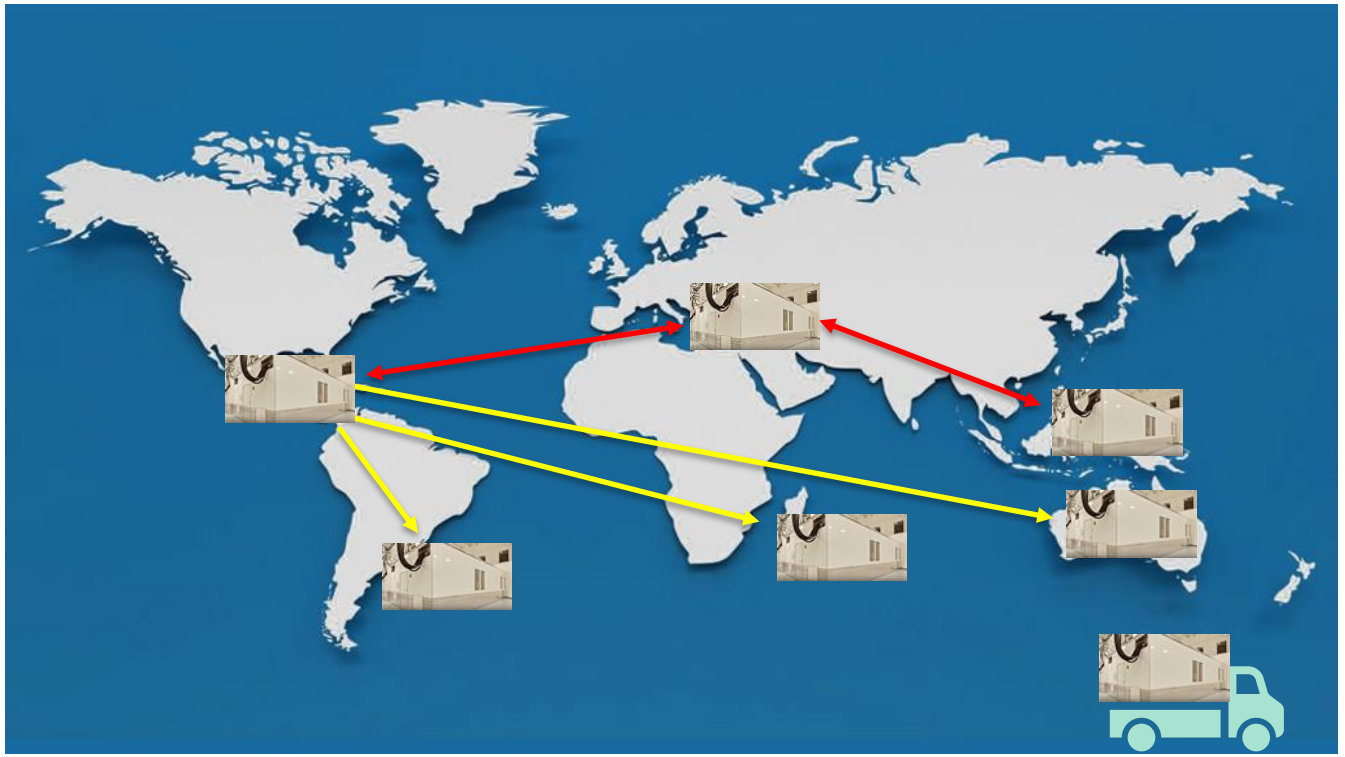



*Other POD options:*

- *Stand alone structure*

# Agile Manufacturing Scenarios

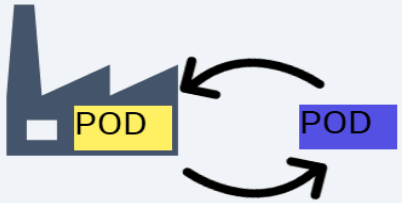
- A unit (POD) could be ***replicated*** in another location (scale out)?
- A unit could be ***relocated*** to another region/market?
- A unit could be ***moved to the point of administration***? Point of care manufacturing



Scale-out (vs scale-up)

# Covering Broad Scope

## Modular




Attach to host facility/ standalone unit

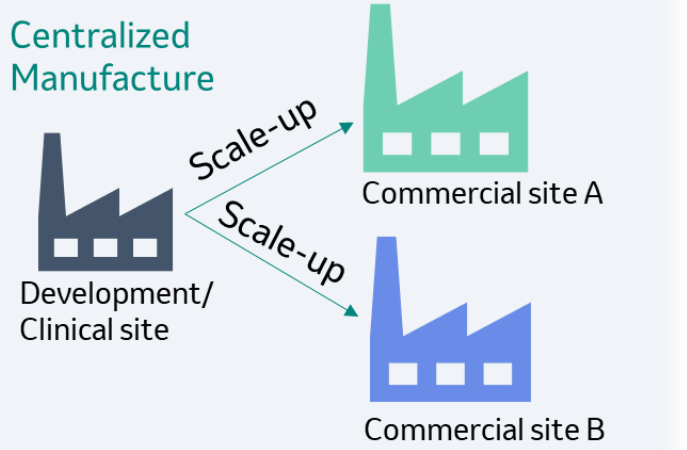
## Portable

Relocation to another region/ market



Moved to the point of administration - Point of care manufacturing

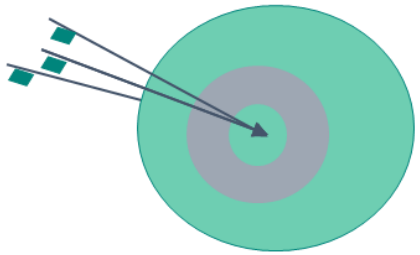
## Distributed



# Advantages of PODs

## Consistency

- Same structure
- Same equipment
- Same environmental controls
- Reduces risk compared to a traditional manufacturing site change



## Speed

- Swifter response to changing volume demand
- Rapid commercialization
- Closer to patients

## Flexibility

- Location
  - Enable point of care manufacturing
  - Meeting logistical needs
- Networks
- Specialization
  - Novel equipment
  - Unique environmental needs

# Agile Manufacturing is Outside Scope of Current Regulations

Manufacturing Site - Static, Physical Location

Inspectional Authority - Tied to Physical Location

Additional regulatory expectations, e.g. stability studies, bioequivalence studies, process validation, prior approval

Do not consider **reduced risk** when there is consistency of equipment, processes, environment, quality documentation etc.

# How Regulators are Supporting Advanced Manufacturing

## PMDA

**Pharmaceutical Innovative Manufacturing Technology Consultation**

- When introducing new, innovative manufacturing technologies or equipment for the future commercial production of pharmaceuticals, guidance and advice are provided at the stage of considering such introductions regarding
  - (1) development strategies aimed at future commercial production
  - (2) formulation of product quality management strategies and their verification methods, etc.

## FDA

Framework for Regulatory Advanced Manufacturing Evaluation (FRAME)

Focus Upon:

- **End to End Continuous Manufacturing**
- **Distributed Manufacturing**
- **Point of Care Manufacturing**
- **Artificial Intelligence**

## EMA

Formation of Quality Innovation Group (QIG)

- Goal of a predictable regulatory framework that incentivizes innovation
- Listen & Learn session – **Decentralised manufacturing**

## MHRA

**Point of Care** Proposal for Public Consultation

- Hub and spoke model, managed via a control site
- Oversight of :
  - Training
  - Pharmaceutical Quality System
  - Manufacturing Equipment
  - Control strategies
  - Supply of raw/input materials
  - System to capture and report incidents

# Conclusions

## Flexible Manufacturing holds great promise

- Benefits patients and public health by bringing uninterrupted and robust supply of medicines to meet changing demands.
- Can increase efficiency, productivity, speed to market with consistent quality.

## There is a need for supportive regulatory framework & globally aligned regulatory approaches

- Regulators are already examining where there are gaps/barriers in regulation, and to inject opportunities to support innovation.
- Industries to share experience and collaborate with regulators to drive globally aligned solutions.

# Acknowledgements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