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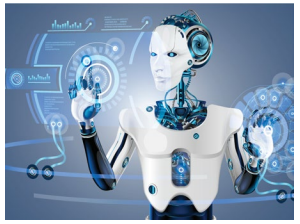
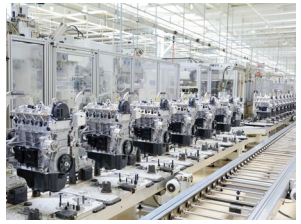
European Federation of Pharmaceutical Industries and Associations

Agile manufacturing - Transfer and Scale-up of Biologics *Aseptic* Manufacturing Processes through Control Site Concept


CASSS CMC Strategy Forum Europe, October 17 – 19, 2023

Karoline Bechtold-Peters, Sylvie Meillerais and Andrea Kurz

On behalf of MQEG/Biomanufacturing WG Subteam

WHAT TO EXPECT

Agenda of Presentation

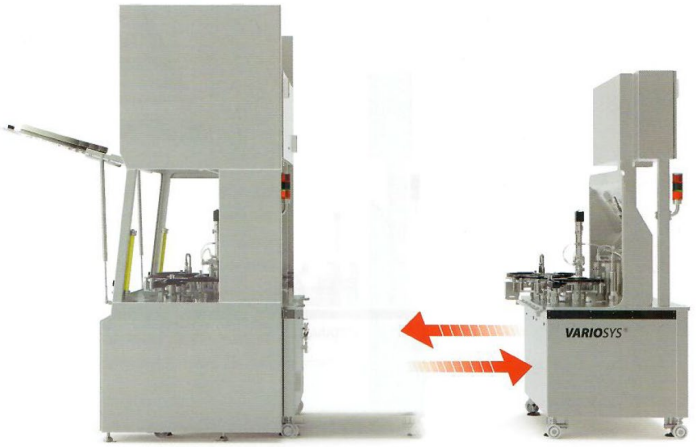
- **Innovative Aseptic Manufacturing (vials, syringes, cartridges) and Definition of "Agile Manufacturing" in General**
- **Basic components of a current aseptic filling line using Ready-to-Use (RTU) packaging material**
- **Examples of equipment answering the trend towards agile manufacturing machines and need for speed combined with increased aseptic assurance**
  - Gloveless fully automated & autonomous equipment in small footprint facilities
  - Novel environmental monitoring by biofluorescence
- **Opportunities of a new concept comprising machine fleets and a control site concept**
  - Connecting DS and DP (advancing continuous manufacturing to a new state)
  - Scaling out to speed up (eliminating) tech- transfer and production volumes ramp-up
  - Continuum from development to launch
- **How can such control site concept look like?**
  - Matrix concept for qualification, validation and change control
  - Examples

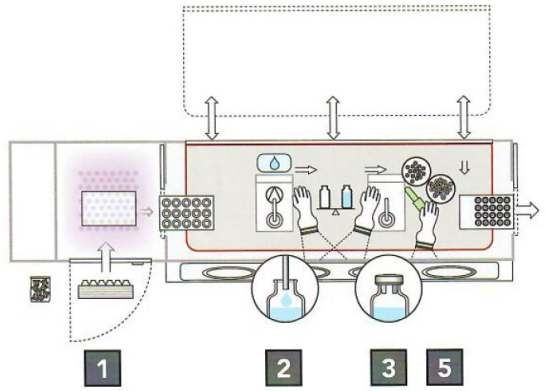
Innovations 2010 – 2022 in Parenterals Manufacture

(the pictures/machines given here are not exhaustive, only examples)

Innovation 1.0:

Highly Modular

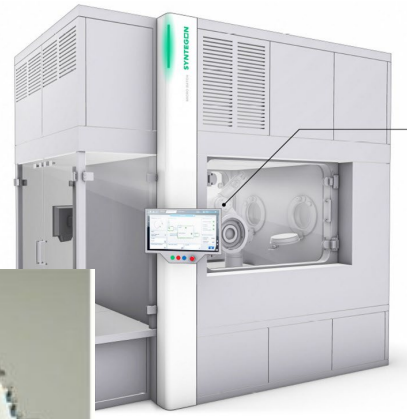




Innovation 2.0 NOW:

Gloveless, fully automated and autonomous

Just plug in!



What is needed: AGILITY & CONSISTENCY

CONSISTENCY

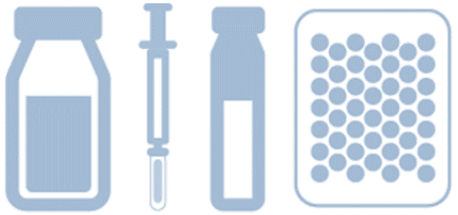
- Ensure reproducibility between sites and facility (same processes), identical equipment
- Ensure consistency throughout project lifetime and independent of product volumes
- Enhance sterility assurance, ready to meet

SPEED

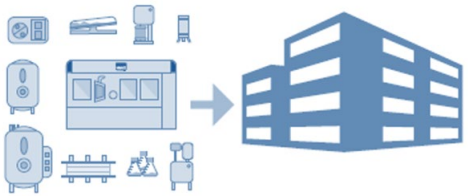
- Speed up the development of products that better meet customer needs
- Lower transfer risk
- Single-scale throughout lifecycle (identical technical-to-clinic-to-launch)
- Shorten unit delivery times

FLEXIBILITY

- Implement flexible facilities that can accommodate multiple molecule-types & formats
- Allow rapid change-over
- Minimize upfront investments at risk, when commercial volumes profile is still volatile



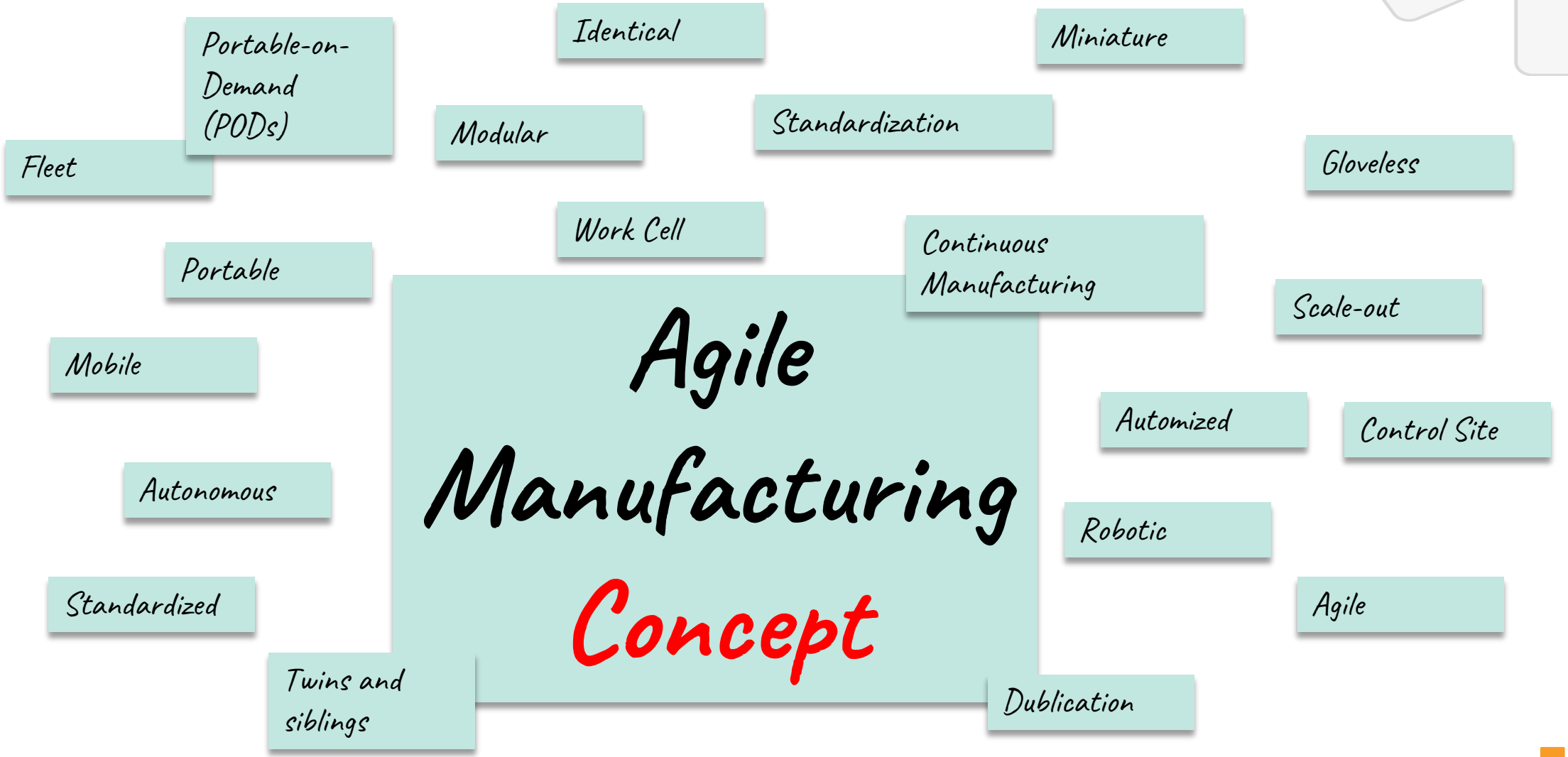
ADAPTABILITY



- Adapt to new modalities
- Implement small footprint facilities
- Allow for end to end and continuous processes
- Be responsive to demand changes (build to demand) ensuring reliable supply

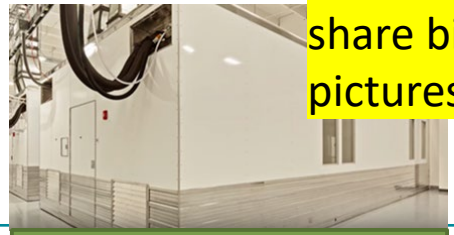
“Flexibility through standardization”

Word Cloud on “Agile Manufacturing”

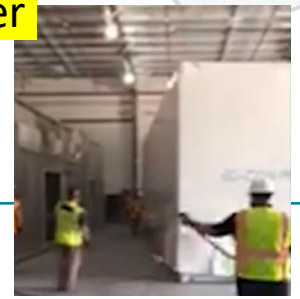


Autonomous & Portable manufacturing in General

Improve optically? Anne can share bigger pictures



Portable On Demand (POD) unit

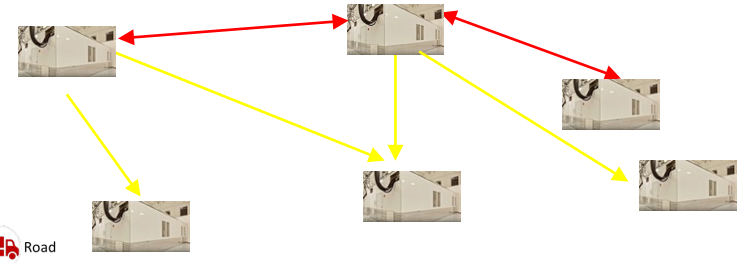


One or multiple units that

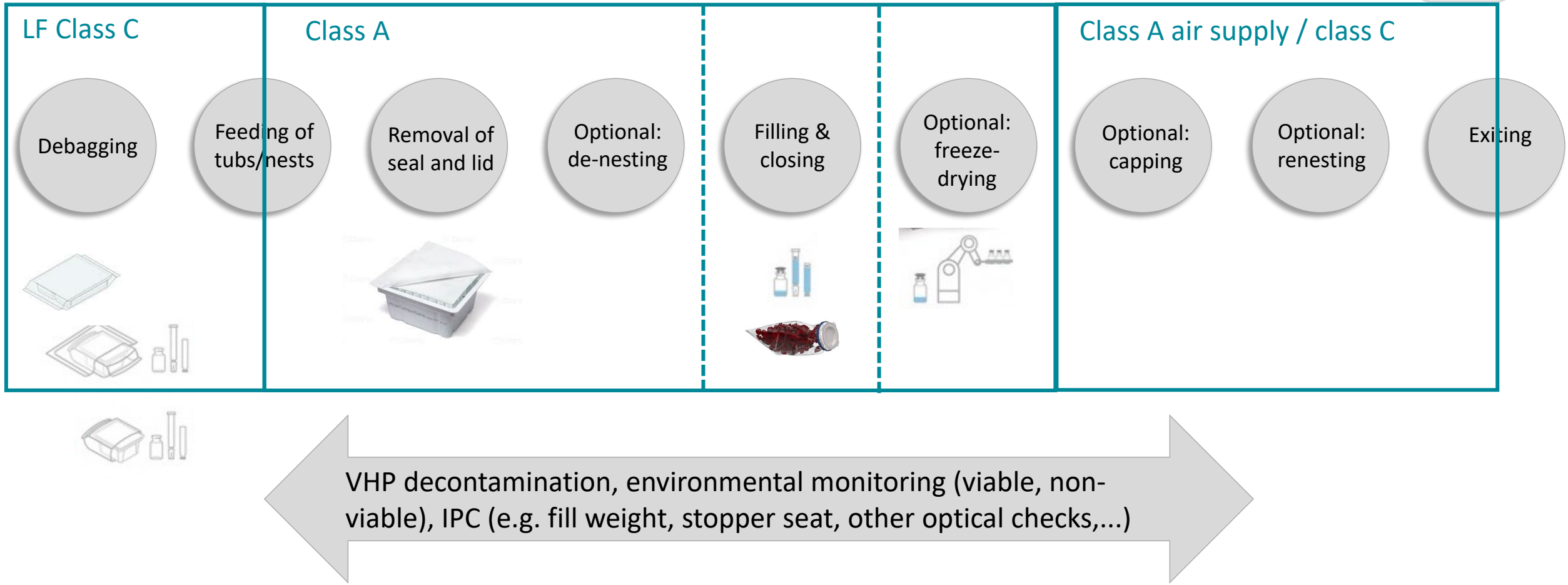
- House a defined set of pharmaceutical operations (formulation, packaging…)
- Can be placed within an *existing facility* or be *fully autonomous*

A same manufacturing unit that can be

- *Replicated* to rapidly increase volume, or *Relocated* to address specific needs



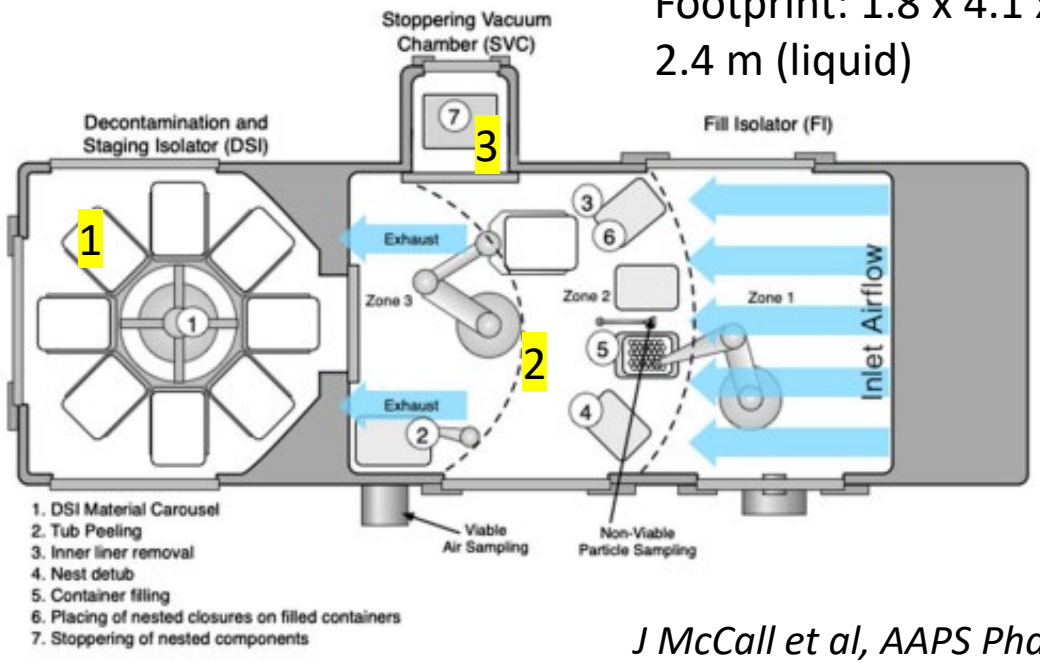
Functionality of such Agile Manufacturing Units in Aseptic Manufacture



EXAMPLES OF EQUIPMENT ANSWERING THE TREND TOWARDS AGILE MANUFACTURING MACHINES AND NEED FOR SPEED COMBINED WITH INCREASED ASEPTIC ASSURANCE

VanRx SA25

Footprint: 1.8 x 4.1 x 2.4 m (liquid)



J McCall et al, AAPS PharmSciTech 23, 2022

SA25 Aseptic Filling Workcell system layout

SA25 Aseptic Filling Workcell installed in a Grade C Cleanroom

- "SA25" = 25 units/min or 1500 units/hr output
- Semi-continuous process (needs decontamination cycle after each processing of carousel load)
- Nested vials, syringes, cartridges
- Nested snap-on caps or plungers
- Vial/syringe closure in vacuum chamber
- 1 (3) compartment

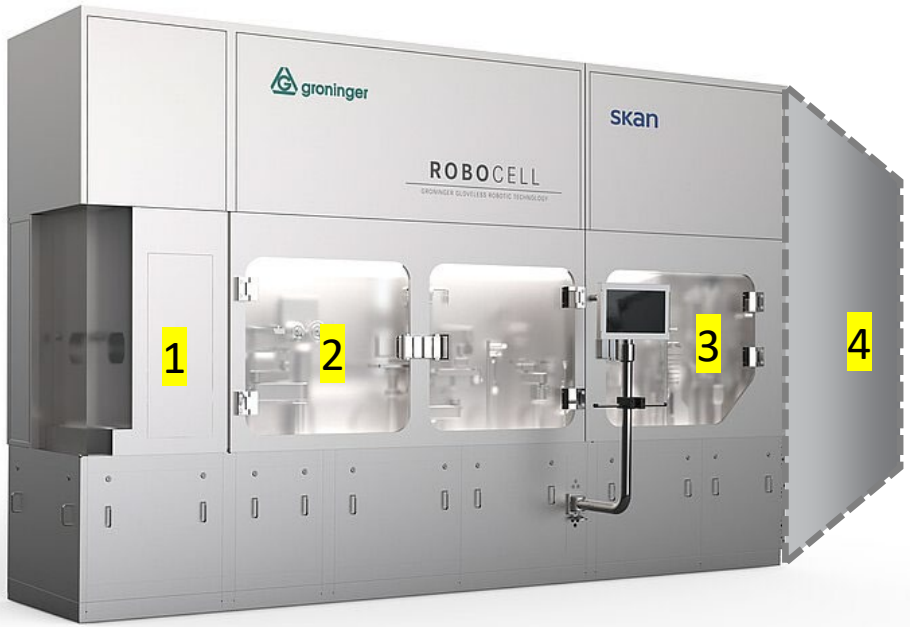
Equipment in brief

- Horizontal airflow
- IPC of fill weight up to 100%
- Ultra short change-over times
- Fully gloveless
- Continuous non-viable monitoring, viable monitoring periodically during a filling batch via RCS
- Robotic handling of fluid path

EXAMPLES OF EQUIPMENT ANSWERING THE TREND TOWARDS AGILE MANUFACTURING MACHINES AND NEED FOR SPEED COMBINED WITH INCREASED ASEPTIC ASSURANCE

Groninger Robocell

Footprint: 1.8 x 5 -7.3 x 2.8 m (liquid, wo/w crimping compartment)



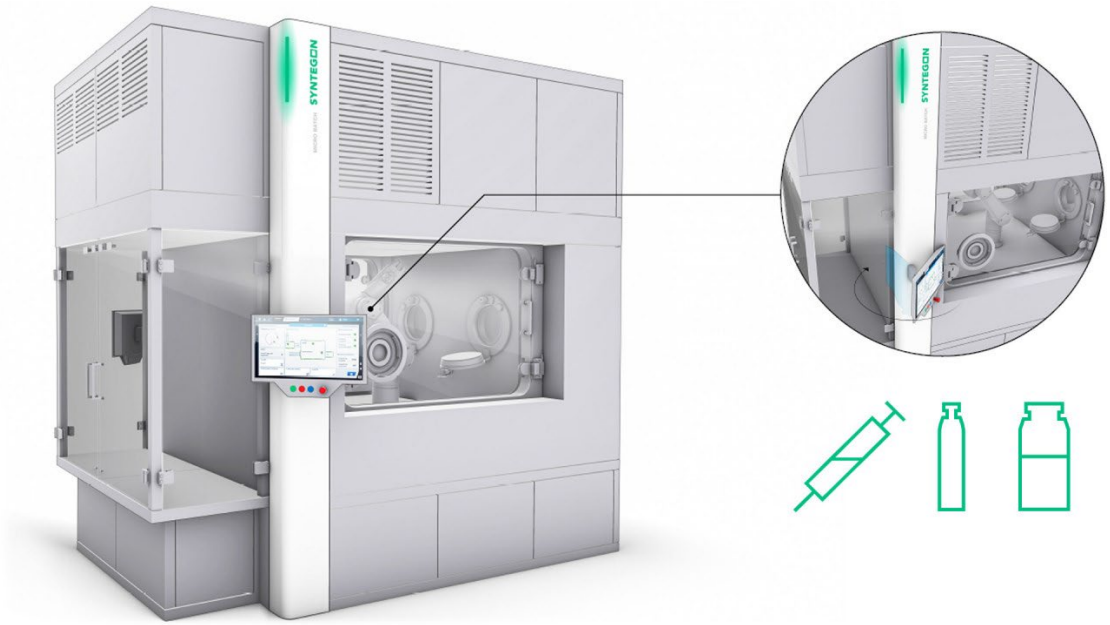
Equipment in brief

- Automated aseptic transfer of single bagged RTU container via log 6 outside decontamination → continuous process
- Individualisation / Separation / De-nesting of containers while maintaining no glass to glass contact → eliminates format parts and ensures inspection possiblities (100% IPC weighing and 100% verification of container closure especially for snap-on caps)
- Filling, closing and re-nesting with several inspection steps at 1500 units per hour
- Outfeed in nested (or individualized possible) configuration
- Snap-on caps or stoppers/crimp caps (bulk)
- Continuous viable and non-viable microbial monitoring, robotic handling of settling plates, real-time environmental monitoring integratable
- Vertical airflow with assurance first air principle by design
- Fully gloveless
- Ultra-short change-over times
- Robotic handling of fluid path
- 3 (4) compartments

EXAMPLES OF EQUIPMENT ANSWERING THE TREND TOWARDS AGILE MANUFACTURING MACHINES AND NEED FOR SPEED COMBINED WITH INCREASED ASEPTIC ASSURANCE

Synthegon microBatch FlexiCell

Footprint: 3 x 2 x 3 m (liquid)

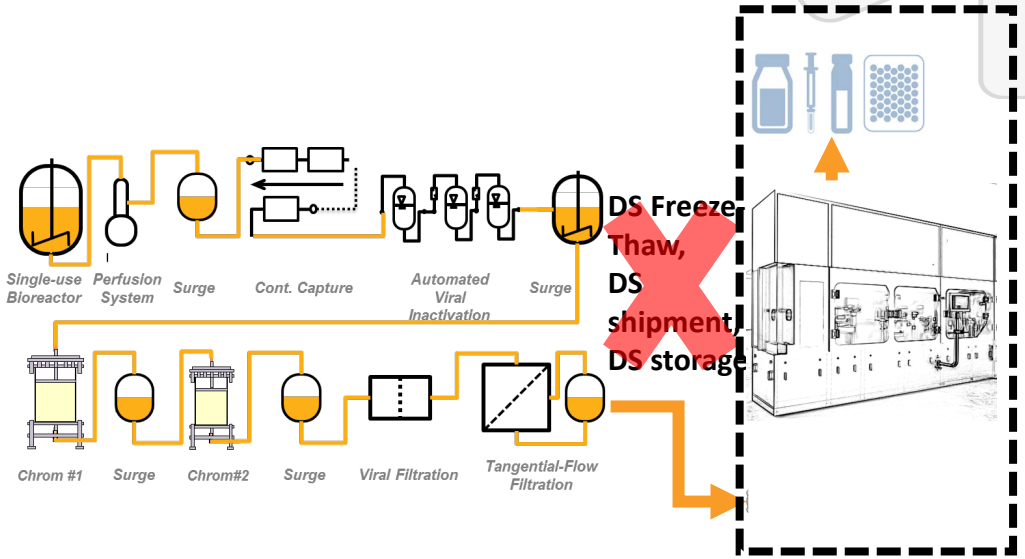


Equipment in brief

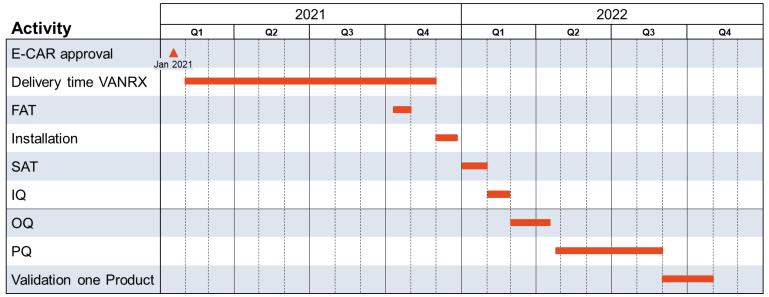
- Aseptic transfer of single bagged RTU container (tray or tub) including bag opening → continuous process
- No glass to glass contact
- Picking of stoppers/caps via camera system
- Up to 100% IPC weighing
- 500 units per hour in nest operation, 120 units/hour one-by-one filling
- Outfeed in nested configuration
- Snap-on caps or stoppers/crimp caps (bulk)
- Continuous viable and non-viable microbial monitoring, robotic handling of settling plates, real-time environmental monitoring integratable
- Vertical airflow
- Fully gloveless
- Ultra-short change-over times
- Robotic handling of fluid path
- 1 (2) compartment

Advantages of Autonomous & Portable Aseptic Units

Increasing the throughput by scaling out



Potential for Connectivity DS-DP

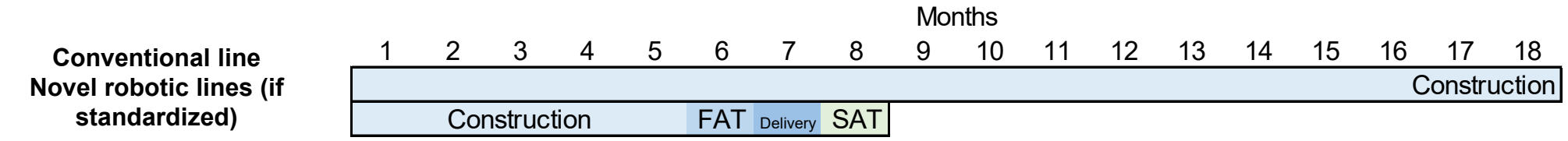


Agility in adding new lines

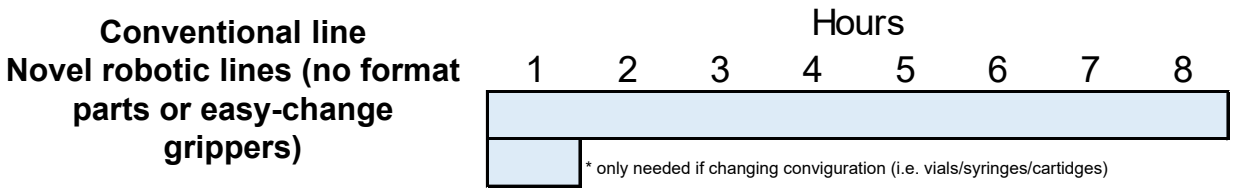
Flexibility in Dosage Forms and Fast Changeover (hours instead of days)

The time gain

Implementation



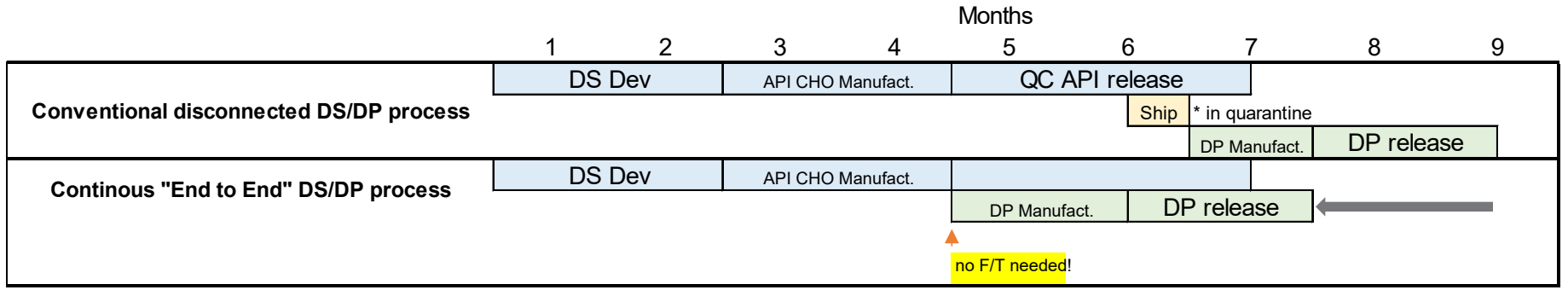
Change Over



- Could be 13 months time gain in setting up a new aseptic facility
- Could be 7 hours time gain regarding change over compared to conventional facilities

The time gain

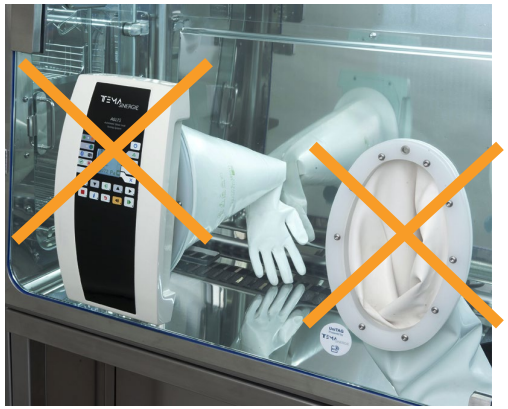
Std. Tox / Clinical supply lead time



- **Could be at least 1.5 months time gain in provision of Biologics Clinical Supplies by using the E2E DS-DP integrated concept (no intermediate release of DS)**

Taking out human interference

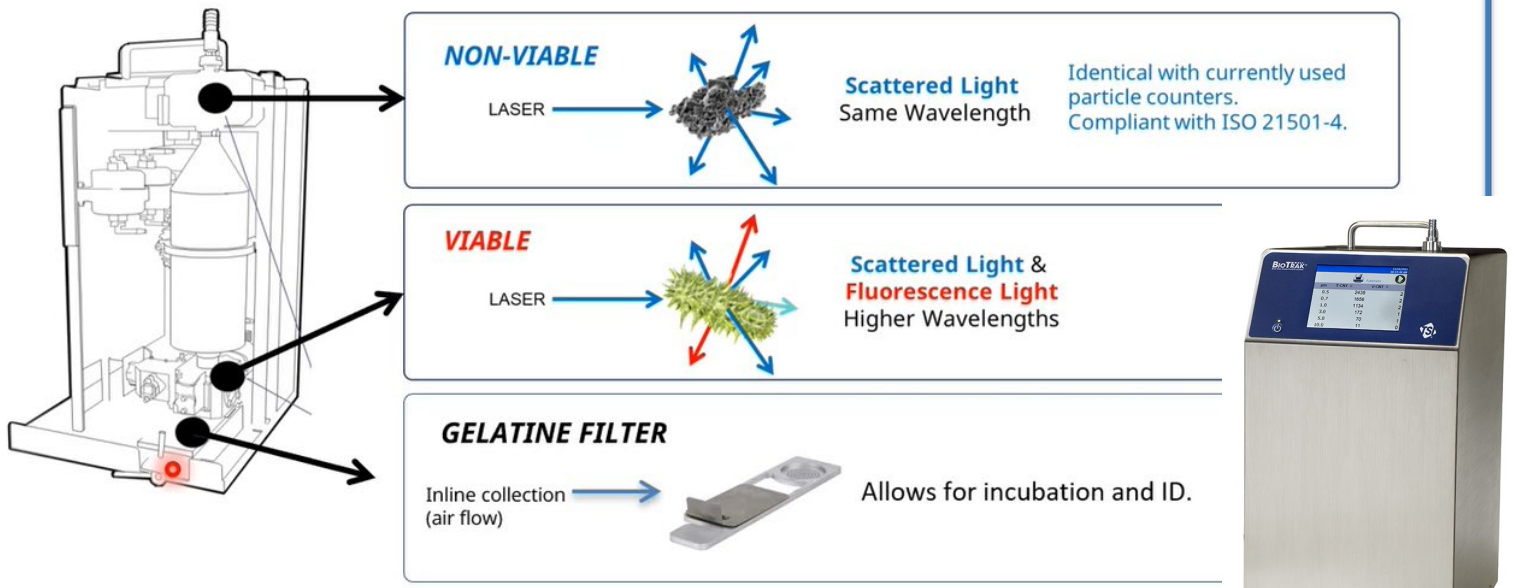
- By fully automating the process and waving gloves, a new level of aseptic security is gained
- With no human interference it gets increasingly impossible to microbially contaminate the product
- „Prospective microbial safety“ instead of safety secured whilst monitoring or testing for sterility afterwards



Rapid Environmental Monitoring ideal for use in the context with such autonomous & gloveless facilities

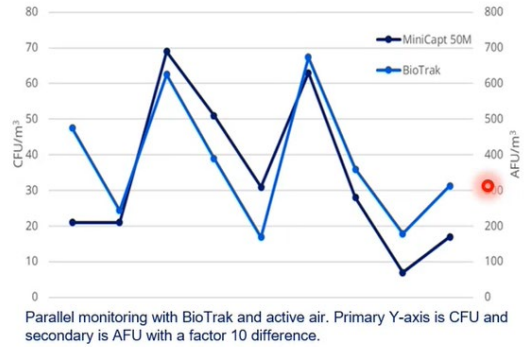
Courtesy Thais Vilgren, Novo Nordsik A/S
And 2021 PDA Pharmaceutical Microbiology Conference, 4 – 6 October

Technology Description



Preliminary tests

Comparison of viable counts in grade D



Parallel monitoring with BioTrak and active air. Primary Y-axis is CFU and secondary is AFU with a factor 10 difference.

Conclusion:

- ✓ BioTrak is more sensitive compared to traditional growth based methods

Challenges of Growth Based EM

Courtesy Jeffrey Weber, Zoetis

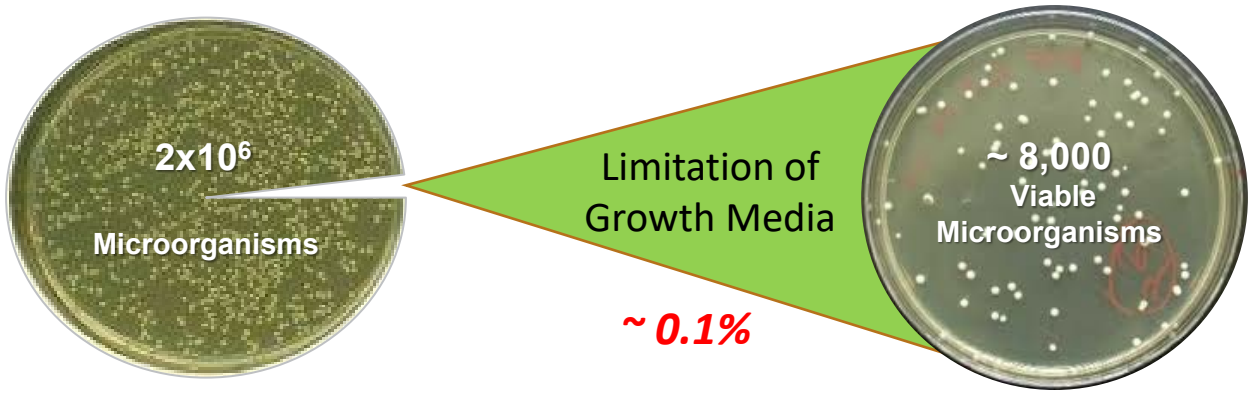
Settle Plates capture challenges

- Small portion of surface area / air flow challenges
- Introduction of media into aseptic area

Limited sample context

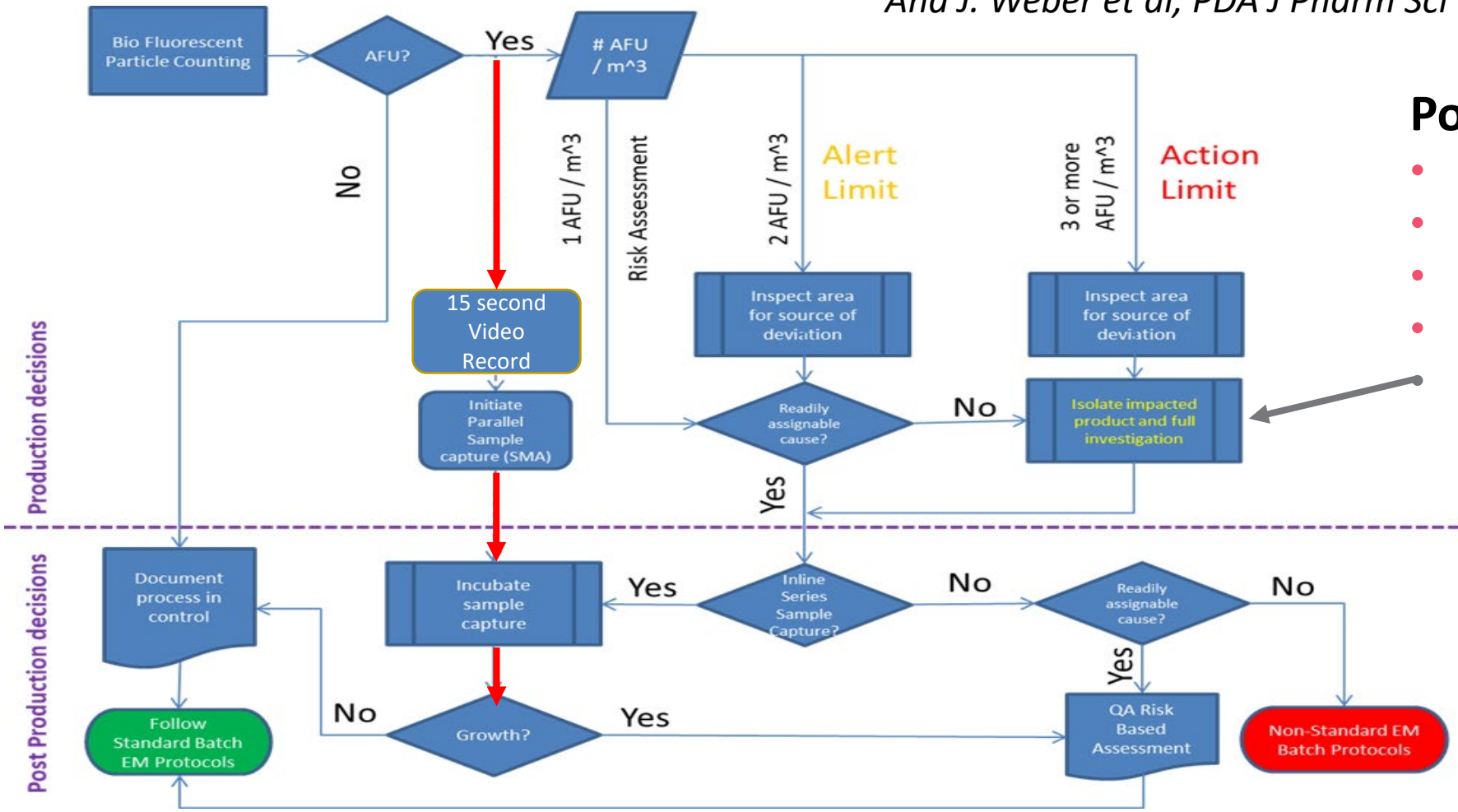
- When did the microorganism event occur?
- All or Nothing

"Viable But Not Culturable" (VBNC) microorganisms.



Real-Time EM Implementation

Courtesy Jeffrey Weber, Zoetis
And J. Weber et al, PDA J Pharm Sci Tech, 73, 2019



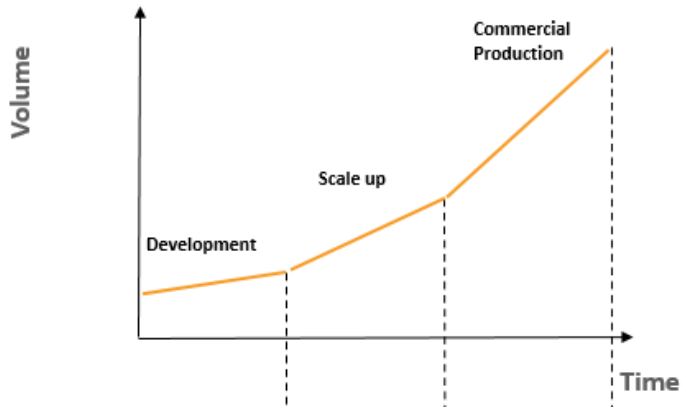
Points to consider:

- Sample capture
- Parallel systems
- Identification limitations
- VBNC
- *Vial Tracking*

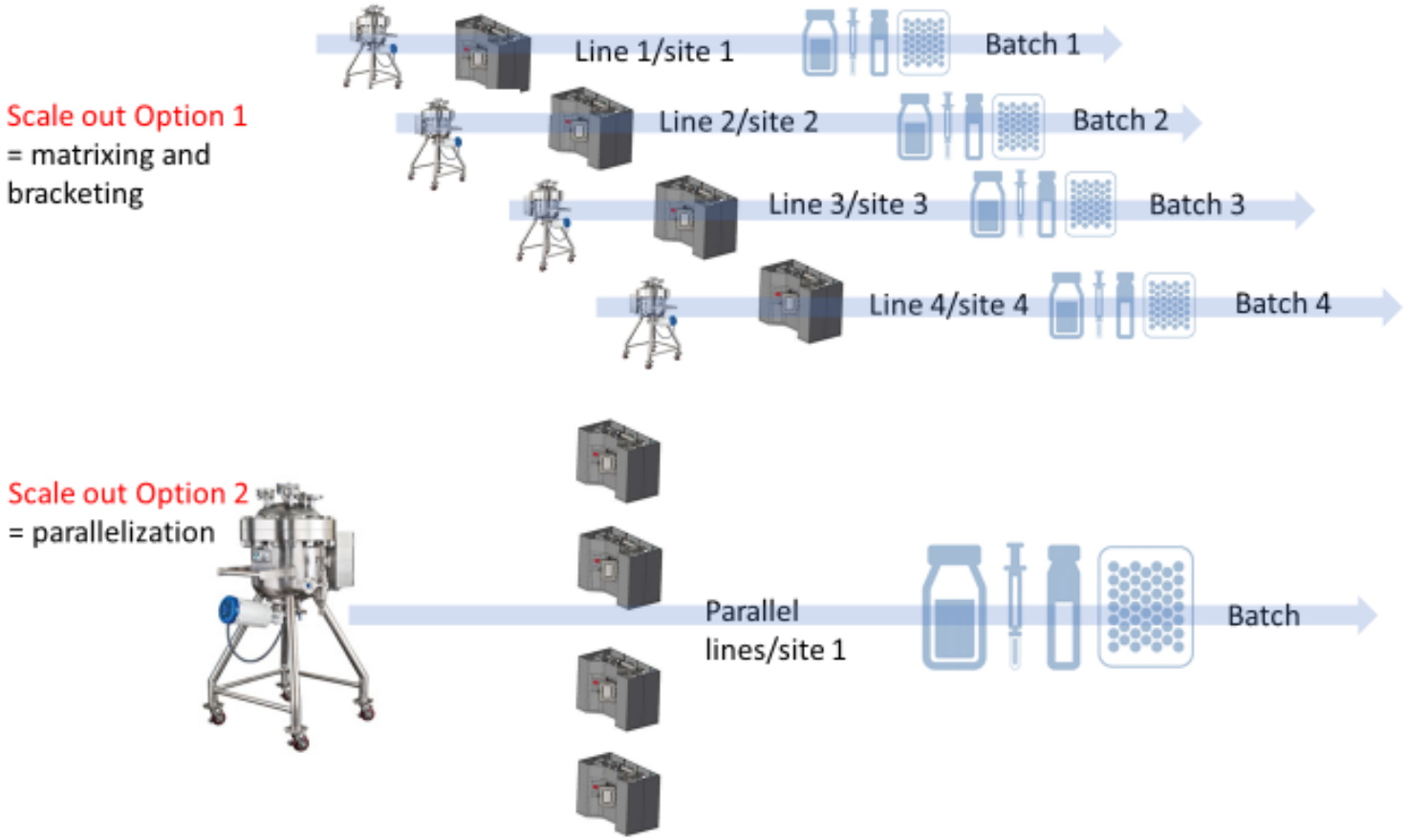
Flowchart for the response to AFU signals captured during manufacturing. The establishment of quality oversight response needs be developed prior to implementation.

Scale-out options leading to a “fleet of similar machines”

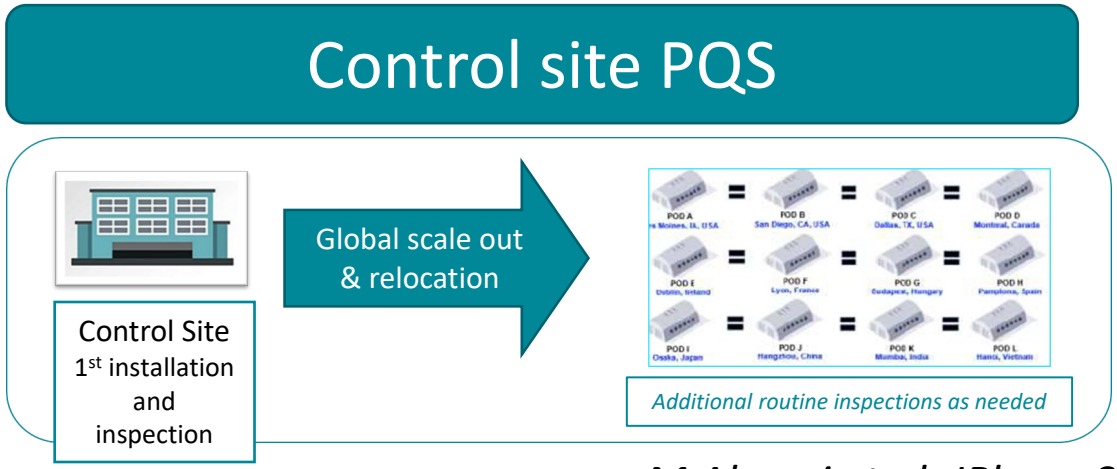
- Capacity “grows” with the volume
- Same fill technology over entire product life cycle = lean tech transfer
- Investment adjusted to demand needs
- Standardized module enables short lead-time and easy “like for like” installation & startup



Fast adjustment of production by adding further machines of same features



Controlling the additional capacity (i.e. the "fleet") under a Control Site concept?



M Algorri et al, JPharmSci, 2022

The control site PQS would describe the procedure to add a new location, via a notification mechanism, and would be responsible for monitoring any potential deviations at all locations

Initial Assessment revealing reduced risk of such concept

What remains the same?	What may change?
• Same unit with essentially same equipment from same supplier and same qualification/validation strategy • Same process (e.g. decontamination conditions, filling & sealing process) and Control Strategy (e.g. IPCs, alert/action limits) • Same environmental controls e. g. humidity, unit temperature, microbial/particle controls • All units operate under the company Pharmaceutical Quality System • Similar staff training under GMP • Materials released under same specifications	• Building, water, electrical power & other surrounding supplies • Equipment may evolve, but strict change control must implement improvements in all fleet components • Individual Operators (like any other setting) • Maintenance dates • ….

SCENARIO

Current Framework

Change example	Conditions
A.5 Change in address of a manufacturer of the finished product Requires formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name and/or address is mentioned, amendment of relevant section(s) of the dossier	Type IA linked to fixed site address
B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	Type II for biological/immunological medicinal products (condition c)
B.II.b.4 f) The scale for a biological/immunological active medicinal product is increased / decreased without process change (e.g. duplication of line). The results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least one pilot or industrial scale batch, covering a minimum period of 3 months.	Type IB

To benefit from these concepts, need ability to qualify and register such units in an accelerated and predictable manner while maintaining high Quality standards

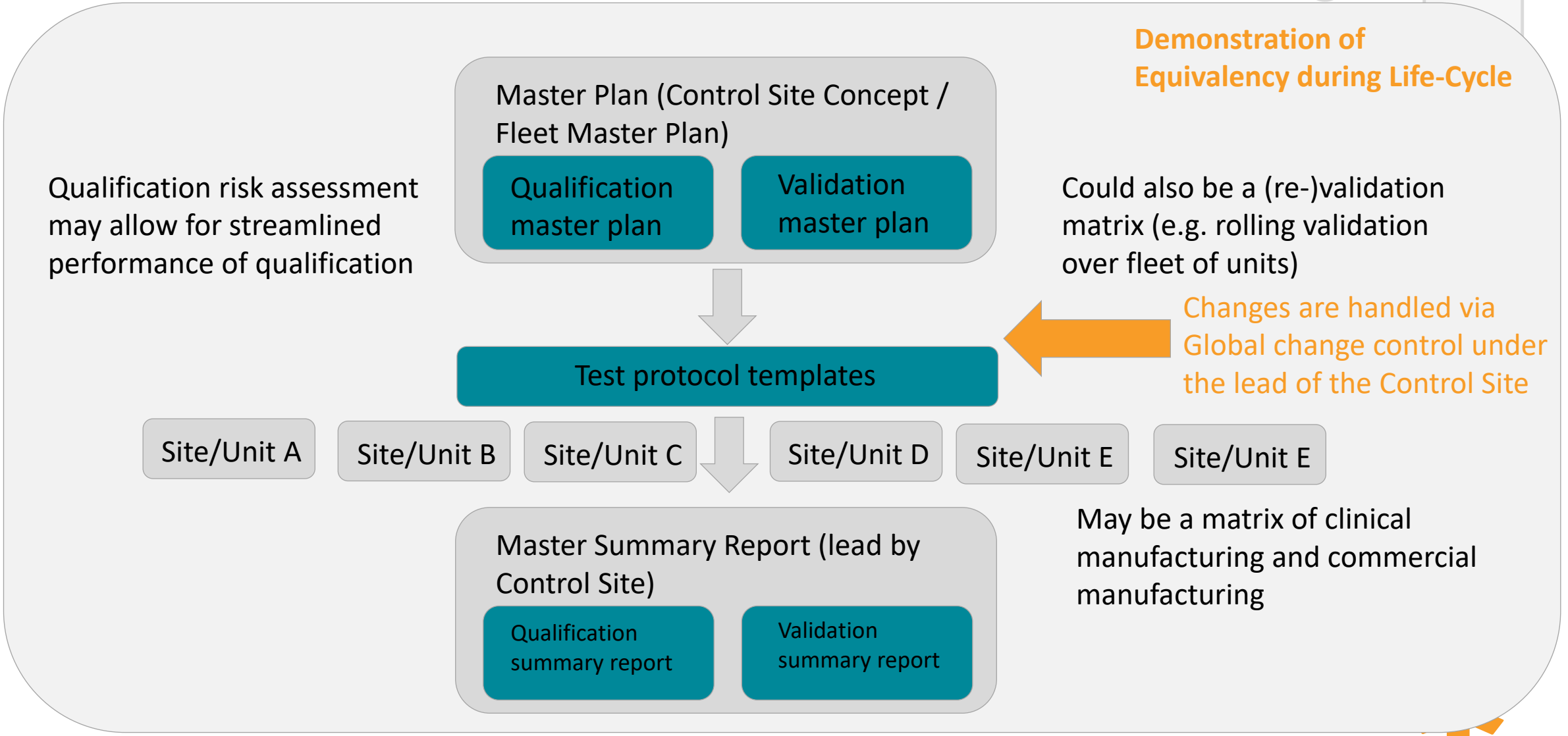
E.g.

=> Could the GMP compliance status of an autonomous unit to be kept when moved?

=> Could elements of the qualification and products validation efforts at first installation be transferred?

SKETCH OF A CONTROL SITE CONCEPT

Control site concept managing a “fleet of machines”



Takeaways & Next Steps

- **We are introducing these gloveless & portable units to enhance consistency and speed to better serve the patients on a global level**
- **EU regulatory frameworks should evolve to reflect the lower risks associated with**
  - Replicating units in relation to qualification, maintenance activities… and the higher degree of automation
  - Relocating units, i.e. changing the physical location only, while other elements remain the same
- **Importance of a globally aligned approach to these concepts**
- **Openness for „rethinking“ of some classical elements of aseptic manufacturing, as e.g. outline in Annex I changing**
  - Need for settling plates / frequent active microbial monitoring if operators are kept out?
  - Risk due to surface monitoring in closed units?
  - Vertical laminar flow or horizontal flow? Can data convince?
  - Positioning of machine in clean room class D?

Acknowledgements: Sub-Team on *Agile manufacturing with specific focus on Aseptic Modular Chamber*

Aseptic agile manuf. Subgroup:

Andrea Kurz, Roche (co-chair)

Karoline Bechtold-Peters, Novartis (co-chair)

Michel Eppink, Byondis

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Lawrence Starke and Karoline Bechtold-Peters (Novartis)

Andrea Kurz (Roche)

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Celeste Frankenfeld (MSD)

Doug Schrader (Lilly)

Jan Kildegaard Hansen (NovoN)

Alan Tully & Ryan Griffin (Abbvie)

Ben Stevens & Myrna Monck (GSK)

Backup

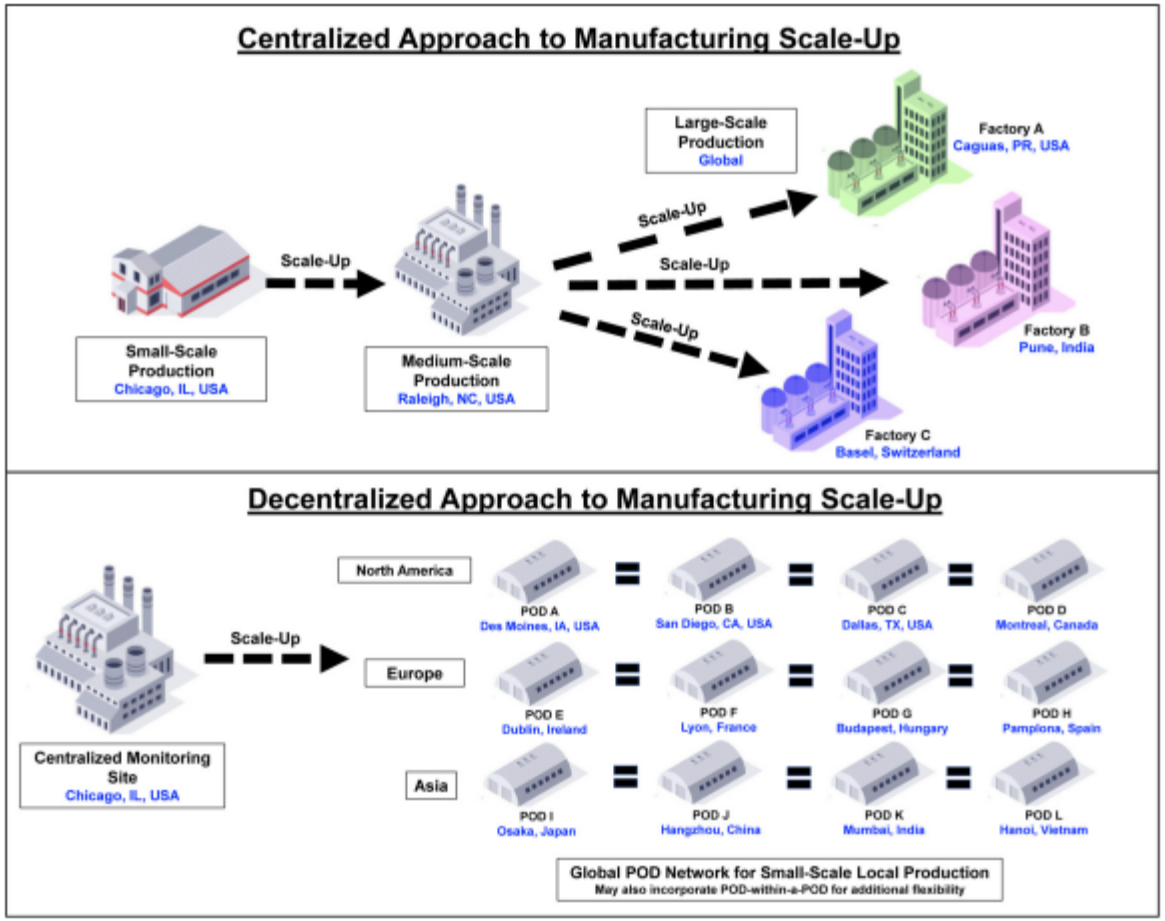


Figure 1. Centralized and Decentralized Manufacturing Paradigms.**Figure 1.** Centralized manufacturing approaches typically require gradual scale-up from small and medium scale production facilities to multiple, similarly-designed, but not identical, factories in different regions for large scale global production. Conversely, using a decentralized approach may enable local production at several identical small-scale manufacturing sites. Each Portable on Demand (POD) facility is monitored by a centralized facility that ensures process control and product quality.

Reflection Paper

Autonomous & Portable Manufacturing

Author: EFPIA ✱ Date: 23 March 2021 ✱ Version: 1

Reflection Paper

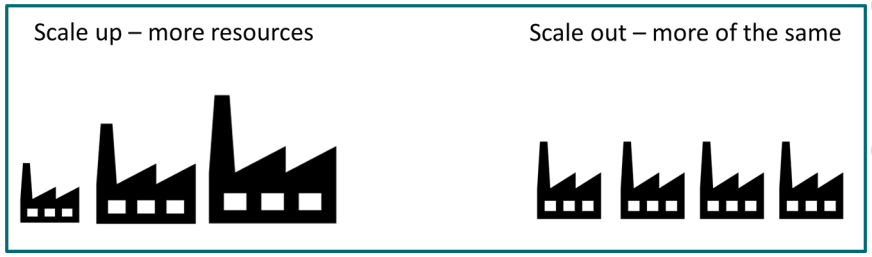
Executive Summary

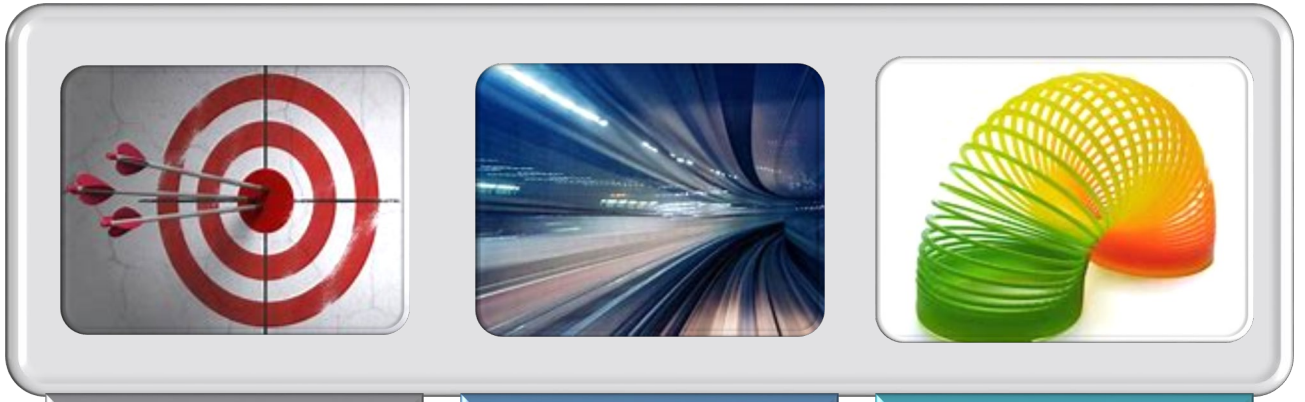
- Technologies are evolving at a rapid pace, and innovative pharmaceutical companies invest significantly in the modernisation of their manufacturing and supply operations towards more agile processes and methods that includes 'Autonomous & Portable' solutions.
- These provide unique opportunities to enhance consistency, in relation to traditional scale up, especially when moving from clinical to initial commercial supply or subsequent transfer/addition of manufacturing sites due to the consistency of equipment, procedures and Quality systems. Higher production volumes can more easily be reached through scale-out, in comparison to a traditional scale-up approach, and can overall enable more rapid response to patients' demands.
- This reflection paper will serve to initiate a dialogue with Regulators to introduce the concept in a way that ensures regulatory standards continue to be met, and products' Quality preserved, as these remain the innovative industry driving manufacturing principles. In Europe, such considerations are especially timely to address the EU Pharmaceuticals Strategy that will consider the "*impact of emerging new manufacturing methods such as decentralised or continuous manufacturing. These methods create new manufacturing models, with a shift from industrial to 'bedside' manufacturing. While speeding up production times, they create new challenges in terms of appropriate quality, inspection and oversight*", and building on the EFPIA initiated dialogue with the EMA Quality office to engage in discussions on emerging technologies.

Concept referred to in EU Structured Dialogue (Innovation workstream) and in response to EMA Quality Innovation Group survey

EFPIA Reflection Paper, March 2021

Benefits





Consistency

- Same equipment
- Same procedures
- Same environmental controls e.g. humidity

=> Reduced risk vs traditional scale up

Speed

- To reach higher production volumes
- When moving from small to large scale production, including from clinical to commercial supply

Flexibility

- Adapt to patients' demand