European Federation of Pharmaceutical Industries and Associations

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



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On behalf of MQEG/Biomanufacturing WG Subteam

FOCUS OF THE SUBGROUP "AGILE ASEPTIC MANUFACTURING"

2022 – 2023 achievements

- **Cross-Industry Exchange on Innovative Autonomous Aseptic Manufacturing (vials, syringes, cartridges) in "Work Cells", regulatory acceptance and Annex 1 compliance**
  - Gloveless fully automated & autonomous equipment in small footprint facilities
- **Cross-Industry Exchange on novel Environmental Monitoring technologies and paths to get regulatory acceptance**
  - Novel environmental monitoring by biofluorescence
- **Design and opportunities of a "fleet concept" of such "work cells" enabling fast doublication and control site concept comprising a matrix approach for qualification, validation and change control**
  - 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

Goal for 2023 end of the year

- **Write up an Annex on the above topics to the existing 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.

Annex to Reflection Paper specific to Aseptic Manufacturing

White paper to function as Annex (Concrete/Case Studies) to 2021 Concept Paper of larger group

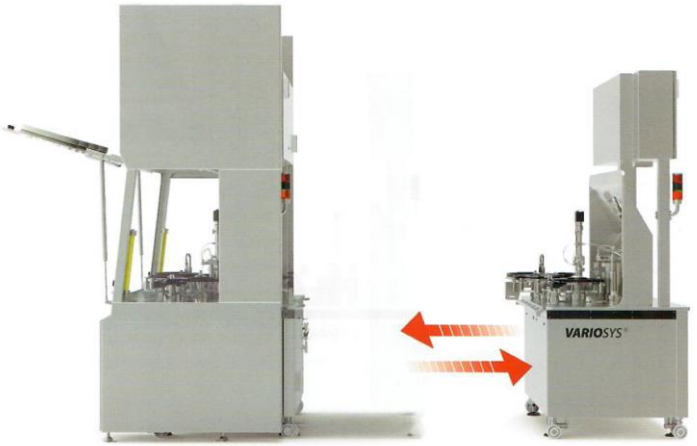
- Advances in the technology of aseptic, standardizable and autonomous work cells
    - Describe some general principles of machinery/technical solutions that qualify for this (e.g. Robocell, Microbatch, SA25, Variosys,...), degree of automation, gloveless or not,...
- Advances in environmental monitoring
    - Real-Time Viable Particle Counter by biofluorescent particle detection – principle
    - Case study how to qualify as only EM method
    - Outlook in the context of automated aseptic work cells
- Fleet concept using the example of multipliable aseptic work cells in implementation of the revised European Pharma Legislation
    - Control site concept as applied to biologics
    - Role of the qualified person
    - Change management
    - Inspection and audit

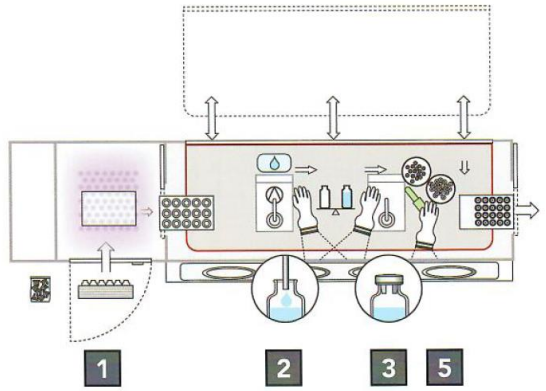
Innovations 2010 – 2022 in Parenterals Manufacture

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

Innovation 1.0:

Highly Modular

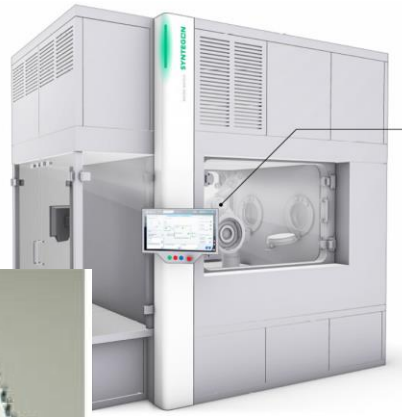




Innovation 2.0 NOW:

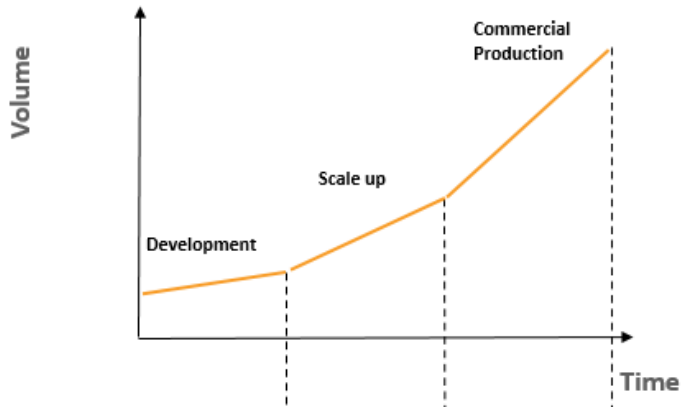
Gloveless, fully automated and autonomous

Just plug in!

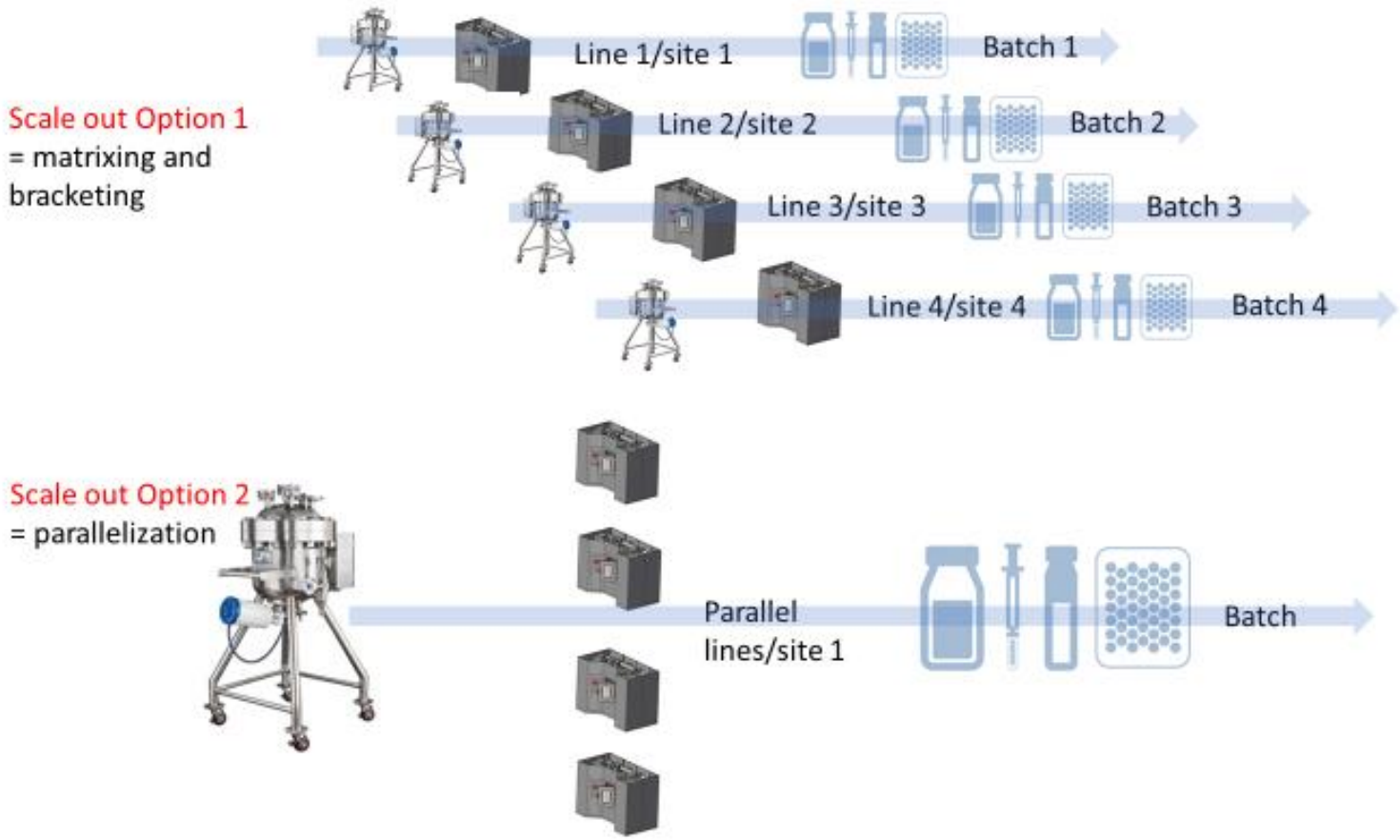


Scale-out options leading to a “fleet of similar machines”

- 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

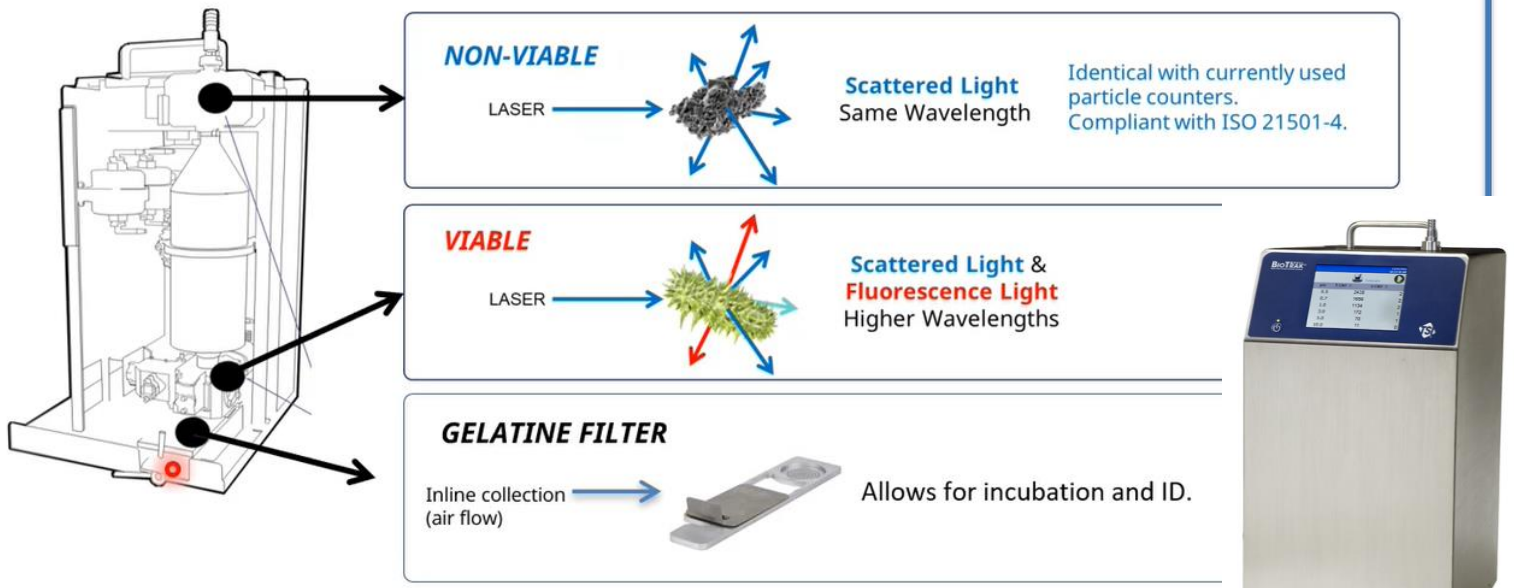


Rapid Environmental Monitoring ideal for use in the context with such autonomous & gloveless facilities

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

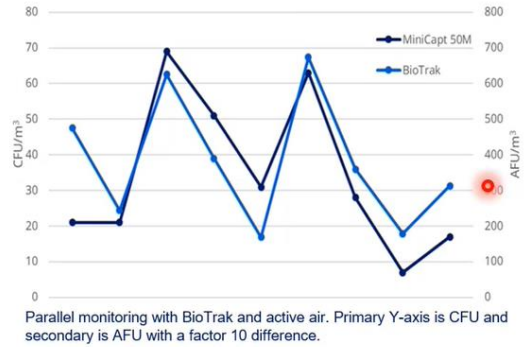
Technology Description

CFU/Colony Forming Unit ≠
AFU/Active Fluorescent Unit



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

Over time acceptance of alternative method as the only method by default without having to proof over hundreds of hours non-inferiority

Validation Strategy

Non-inferiority in Grade A isolator

Purpose

- To verify that BioTrak® is non-inferior to the current method regarding detection of viable particles in the grade A Isolator

Method

- Comparison of BioTrak® and conventional air sampling in Grade A Isolator by monitoring in parallel. This is supported with a parallel study in grade D where more hits are expected

Test Duration

- > 1000 hours covering the Assembly and Filling processes including batches intended for the market

Ongoing tests (Reviewed by FDA ETT)

1. Parallel in grade A during assembly with open doors and during assembly and fill with closed doors
2. Test if gelatine filter can be used

Current status:

- >300 hours of filling with parallel monitoring including 3 APS runs
- 1 hit with 1 AFU (0,5 µm particle) and no hits on agar

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

5.1.6 and Ph. Eur. General Notices

5.1.6. ALTERNATIVE METHODS FOR CONTROL OF MICROBIOLOGICAL QUALITY

The following chapter is published for information.

1. GENERAL INTRODUCTION

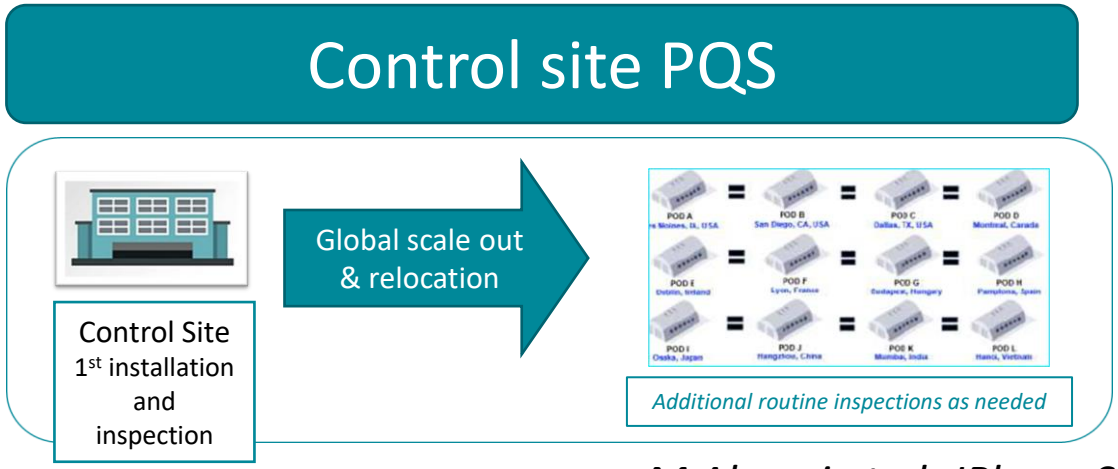
The objective of this chapter is to facilitate the implementation and use of alternative microbiological methods where this can lead to efficient microbiological control and improved assurance for the quality of pharmaceutical products.

Alternative methods. *"The tests and assays described are the official methods upon which the standards of the Pharmacopoeia are based. With the agreement of the competent authority, alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. In the event of doubt or dispute, the methods of analysis of the Pharmacopoeia are alone authoritative."*

How often must the comparability of the conventional EM method with BioFluorescent Particle Counting (BFPC) be demonstrated?
When can this equivalence considered accepted?

HOW SUCH CONTROL SITE CONCEPT CAN LOOK LIKE

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

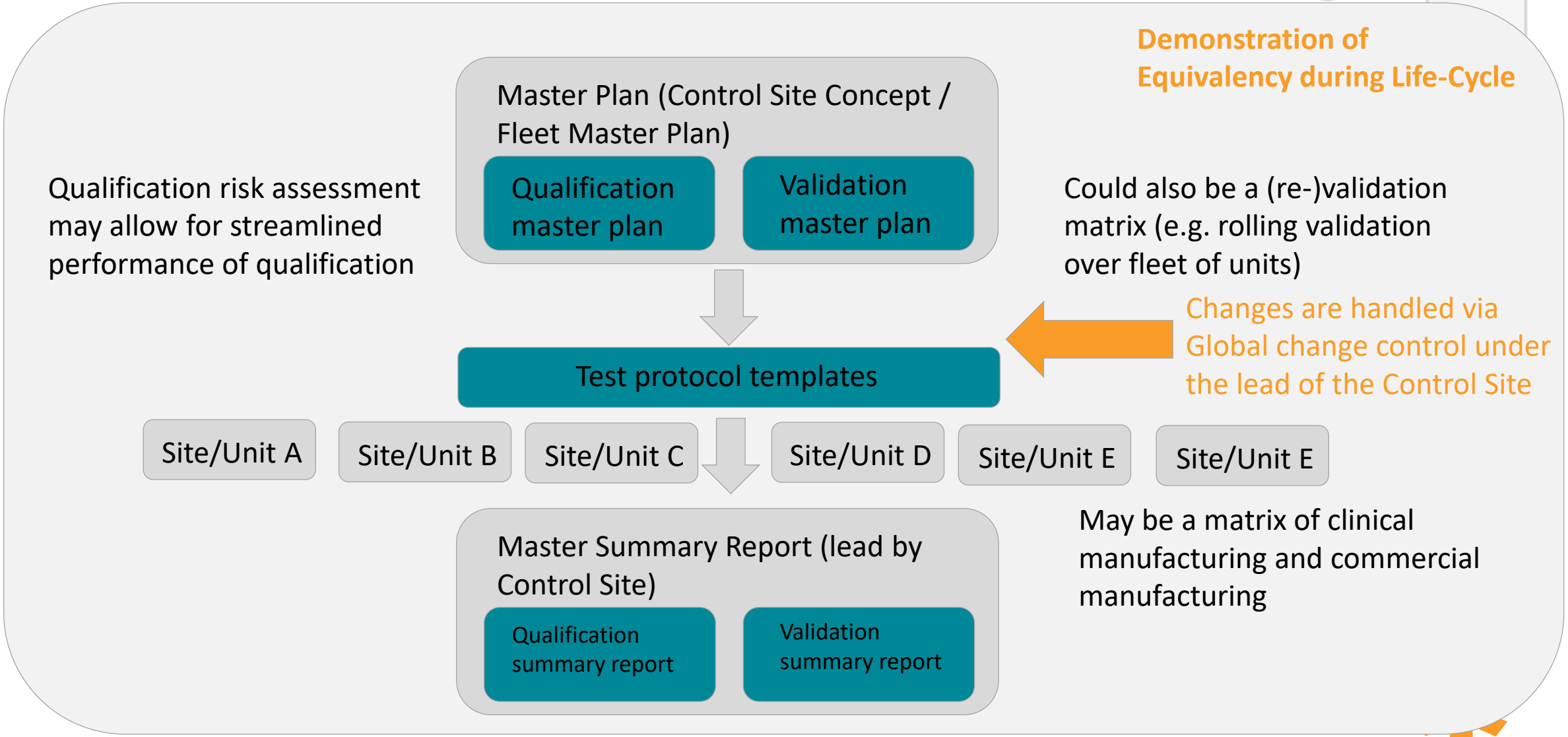


M Algorri et al, JPharmSci, 2022

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

SKETCH OF A CONTROL SITE CONCEPT

Control site concept managing a “fleet of machines”



BRUSSELS, 26.4.2023 COM(2023) 192 FIN

Proposal for a DIRECTIVE OF THE EUROPE… AND OF THE COUNCIL

The new draft Pharma Legislation supports such a fleet (of distributed units) concept under a central control site

- What does the directive say on decentralized manufacturing?

The directive includes provisions on decentralized manufacturing. Specifically, it states that in cases where manufacturing or testing steps of medicinal products need to take place in sites close to patients, such as advanced therapy medicinal products with short shelf-life, these steps may need to be decentralized to multiple sites to reach patients across the Union. When the manufacturing or testing steps are decentralized, they should be carried out **under the responsibility of the qualified person** of an authorized central site. The decentralised sites should not require a separate manufacturing authorization from the one granted to the relevant central site but should be registered by the competent authority of the Member State in which the decentralised site is established. *Page 38, (109)*

- How are decentralised sites controlled?

Decentralized sites are controlled through registration and supervision by the competent authority of the Member State in which the decentralised site is established. The manufacturing authorization holder of the central site must register all of its decentralized sites in accordance with the provisions of the Directive, and request the competent authority of the Member State in which the decentralized site is established to register the decentralized site. The marketing authorization holder may commence the activity in the decentralized site in connection with the central site only when the decentralized site is registered in the Union database referred to in Article 188(15) and the link is made in the database with the authorization of the corresponding central site by the competent authority of the Member state where the decentralized site is located. The competent authority of the Member State supervising the decentralized site may decide to carry out an inspection as referred to in Article 188(1), first subparagraph, point (a), and shall cooperate with the competent authority of the Member State responsible for the supervision of the central site. *Chapter XI Manufacturing and import, Articles 142 - 153*

Takeaways & Next Steps – comparison to situation at time of presentation at last CASSS Meeting

- **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?

Due to the pressure of the pharma industry many more machine manufacturers have embarked, convergence of Biologics/ATMPs solutions ✓

New EU Pharma Legislation describes decentralized manufacturing under central site surveillance ✓

Can the decentralized site be also <u>outside</u> of Europe? ?

Annex I quite conservative, risk reduction due to construction not really appreciated ?

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

Aseptic agile manuf. Subgroup:

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