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

**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

**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

**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
Word Cloud on “Agile Manufacturing”

- Agile Manufacturing
- Concept
- Identical
- Modular
- Work Cell
- Standardization
- Miniature
- Gloveless
- Portable-on-Demand (PODs)
- Fleet
- Portable
- Mobile
- Autonomous
- Standardized
- Twins and siblings
- Continuous Manufacturing
- Automized
- Robotic
- Agile
- Control Site
- Scale-out
- Dublication
- Dublication
- Avalon
DEFINITION OF “AGILE MANUFACTURING” AND WHAT IS NEW?

Autonomous & Portable manufacturing in General

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

Improve optically? Anne can share bigger pictures.
Functionality of such Agile Manufacturing Units in Aseptic Manufacture

<table>
<thead>
<tr>
<th>LF Class C</th>
<th>Class A</th>
<th>Class A air supply / class C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debagging</td>
<td>Feeding of tubs/nests</td>
<td>Optional: capping</td>
</tr>
<tr>
<td></td>
<td>Removal of seal and lid</td>
<td>Optional: renesting</td>
</tr>
<tr>
<td></td>
<td>Optional: de-nesting</td>
<td>Exiting</td>
</tr>
<tr>
<td></td>
<td>Filling &amp; closing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Optional: freeze-drying</td>
<td></td>
</tr>
</tbody>
</table>

VHP decontamination, environmental monitoring (viable, non-viable), IPC (e.g. fill weight, stopper seat, other optical checks,...)
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)

SA25 Aseptic Filling Workcell system layout

SA25 Aseptic Filling Workcell installed in a Grade C Cleanroom

J McCall et al, AAPS PharmSciTech 23, 2022

• “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 possibilities (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
Synthecon microBatch FlexiCell

Footprint: 3 x 2 x 3 m (liquid)

Examples of equipment answering the trend towards agile manufacturing machines and need for speed combined with increased aseptic assurance:

- 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)**

<table>
<thead>
<tr>
<th>Activity</th>
<th>2021</th>
<th>2022</th>
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</thead>
<tbody>
<tr>
<td>E-CRM approval</td>
<td>3Q3</td>
<td>3Q2</td>
</tr>
<tr>
<td>Delivery time VAREX</td>
<td>3Q2</td>
<td>3Q3</td>
</tr>
<tr>
<td>FAT</td>
<td>3Q2</td>
<td>3Q3</td>
</tr>
<tr>
<td>Installation</td>
<td>3Q3</td>
<td>3Q3</td>
</tr>
<tr>
<td>SAT</td>
<td>3Q2</td>
<td>3Q2</td>
</tr>
<tr>
<td>IQ</td>
<td>3Q3</td>
<td>3Q3</td>
</tr>
<tr>
<td>OQ</td>
<td>3Q3</td>
<td>3Q3</td>
</tr>
<tr>
<td>PQ</td>
<td>3Q3</td>
<td>3Q3</td>
</tr>
<tr>
<td>Validation one Product</td>
<td>3Q3</td>
<td>3Q3</td>
</tr>
</tbody>
</table>
## The time gain

### Implementation

<table>
<thead>
<tr>
<th>Months</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Construction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FAT</td>
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<td></td>
<td></td>
<td></td>
<td>SAT</td>
<td></td>
</tr>
</tbody>
</table>

- Conventional line
- Novel robotic lines (if standardized)

### Change Over

<table>
<thead>
<tr>
<th>Hours</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
</table>

- Conventional line
- Novel robotic lines (no format parts or easy-change grippers)

*only needed if changing configuration (i.e. vials/syringes/cartidges)*

- 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

<table>
<thead>
<tr>
<th>Conventional disconnected DS/DP process</th>
<th>Continuous &quot;End to End&quot; DS/DP process</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS Dev</td>
<td>DS Dev</td>
</tr>
<tr>
<td>API CHO Manufact.</td>
<td>API CHO Manufact.</td>
</tr>
<tr>
<td>QC API release</td>
<td>QC API release</td>
</tr>
<tr>
<td>Ship * in quarantine</td>
<td>Ship * in quarantine</td>
</tr>
<tr>
<td>DP Manufact.</td>
<td>DP Manufact.</td>
</tr>
<tr>
<td>DP release</td>
<td>DP release</td>
</tr>
</tbody>
</table>

• 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

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

Courtesy Thais Vilgren, Novo Nordsik A/S
And 2021 PDA Pharmaceutical Microbiology Conference, 4 – 6 October
Challenges of Growth Based EM

**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.**

![Image of petri dishes showing microorganisms](image.png)

2x10^6 Microorganisms

Limitation of Growth Media

~ 0.1%

8,000 Viable Microorganisms

Courtesy Jeffrey Weber, Zoetis
**Real-Time EM Implementation**

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

**Points to consider:**
- Sample capture
- Parallel systems
- Identification limitations
- VBNC
- Vial Tracking

**OPPORTUNITIES OF A NEW CONCEPT COMPRISING MACHINE FLEETS AND A CONTROL SITE CONCEPT**

Courtesy Jeffrey Weber, Zoetis
And J. Weber et al, PDA J Pharm Sci Tech, 73, 2019
OPPORTUNITIES OF A NEW CONCEPT COMPRISING MACHINE FLEETS AND A CONTROL SITE CONCEPT

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

Scale out Option 1 = matrixing and bracketing
Scale out Option 2 = parallelization
Controlling the additional capacity (i.e. the “fleet”) under a Control Site concept?

Control site PQS

1st installation and inspection

Global scale out & relocation

Additional routine inspections as needed

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.

M Algorri et al, JPharmSci, 2022
**Initial Assessment revealing reduced risk of such concept**

**What remains the same?**

- 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

**What may change?**

- 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
- ....
### Current Framework

<table>
<thead>
<tr>
<th>Change example</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A.5 Change in address of a manufacturer of the finished product</strong></td>
<td>Type IA linked to fixed site address</td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td><strong>B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product</strong></td>
<td>Type II for biological/immunological medicinal products (condition c)</td>
</tr>
<tr>
<td><strong>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).</strong></td>
<td>Type IB</td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

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”

Qualification risk assessment may allow for streamlined performance of qualification.

Master Plan (Control Site Concept / Fleet Master Plan)

- Qualification master plan
- Validation master plan

Test protocol templates

Demonstration of Equivalency during Life-Cycle

Could also be a (re-)validation matrix (e.g. rolling validation over fleet of units)

Changes are handled via Global change control under the lead of the Control Site

May be a matrix of clinical manufacturing and commercial manufacturing

Site/Unit A  Site/Unit B  Site/Unit C  Site/Unit D  Site/Unit E  Site/Unit E
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

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Ben Stevens & Myrna Monck (GSK)
Backup
Figure 1. Centralized and Decentralized Manufacturing Paradigms. 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

EFPIA Reflection Paper, March 2021

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