



Why change is inevitable in aseptic manufacturing?

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INTRODUCTION

Aside from the usual challenges of traditional blockbuster drugs, on which patents provided a crucial period of exclusivity and protection, the new era of the pharmaceutical industry has been facing expiring patents and a consequent increase in R&D expenditure addressing also a rapidly growing demand for anti-cancer drugs. The largest number of ongoing clinical studies focus on cancer treatments and half of the newly developed anti-cancer drugs are injectable. Additionally, biopharma research is generating new higher value/lower volume drugs, many of which are highly active.

The key drivers for 2020 are related to high value niche therapies and personalized drugs that will require smaller batches, shorter runs, process flexibility and greater process complexity. Increasing quality expectations in this more volatile demand are expected to drive the market towards lower risks, shorter time to market and increased cost-effectiveness.

ASEPTIC MANUFACTURING

In the last 50 years, aseptic manufacturing has evolved slowly. In the mid-1950s, the high-efficiency particulate air (HEPA) filters started to be adopted to perform most of the aseptic processing activities. The use of isolators for sterile processing was firstly introduced in the 80s. Since then, a critical point in isolators has been the reliability of gloves as manual operations were still required (1).

Since the operator still plays an important role in aseptic manufacturing, glove boxes, isolators and RABS can be considered a simple solution to segregate the processing environment and improve Grade A continuity and SAL (sterility assurance level). However, the environment is presumed to have a greater chance of actually being sterile if the operator is not present.

BARRIER SYSTEM HISTORY

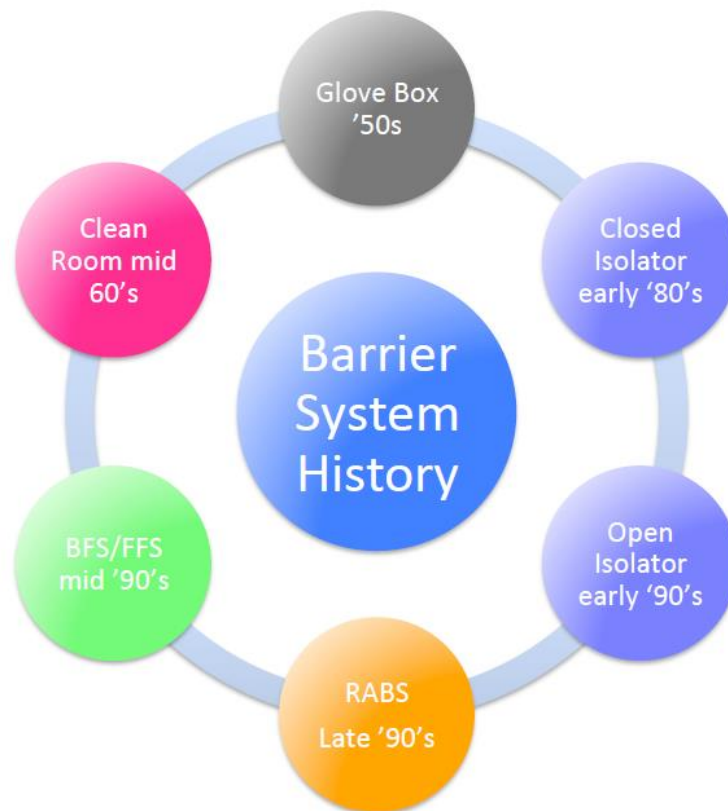


Fig.1 Barrier System History. (Source: Agalloco & Akers, 2007.)

GRADE A CONTINUITY

Although non-viable contamination can have machine or human origin, it cannot be directly related to microbial contamination. Since airborne contamination through the air handling system is very unlikely, microbial contamination in pharmaceutical clean rooms can be considered to be predominantly (>99%) of human origin. Therefore, the ideal for an aseptic process can be defined as Grade A continuity with ZERO human intervention.

How can we achieve this? By introducing a new generation of robotics, re-designing the aseptic process and applying a cluster tool concept we can develop an advanced aseptic processing. Furthermore, a higher level of flexibility in handling small batches is required to achieve cost effectiveness in sterile fill finish operations. Addressing this need, Fedegari Group has developed a gloveless sealed isolator hosting a GMP robotic arm that can be adapted for different small batch- es needs such as:

- High speed lines processing primary containers
- Semi-automatic production line for nested PFS (pre-filled syringes) and vials
- To replace laboratory manual fill/finish of the batch

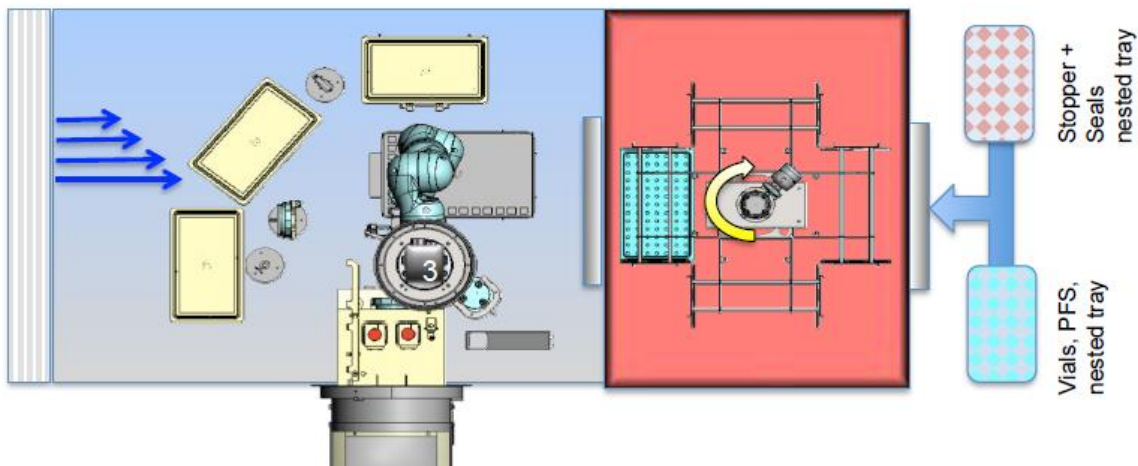


Fig.2 New concept of gloveless robotic isolator. (Source: Fedegari Group).

This new concept of gloveless robotic isolator is suitable for multi formats (e.g. handling – vials, PFS, cartridges, ready to use or bulk glasses, liquids and freeze-dried products). It can manage variable production outputs (100÷1,000 pcs) with a quick format change over and achieving 100% yield. The fill/finish isolator integrated with different processes and the robotic arms, dedicated to the logistic handling, together represent the **cluster tool concept**, see Figures 1 and 2. The cluster tool concept allows the combination of two different decontamination processes: decontamination with hydrogen peroxide inside the isolator chamber for the preparation of the aseptic environment and the use of saturated steam in the autoclave connected to the isolator to sterilize the Tyvek protected nested tubs before they enter the isolator chamber. This way it is possible to sterilize the Tyvek protected nested tubs with saturated steam rather than with hydrogen peroxide which causes oxidization.

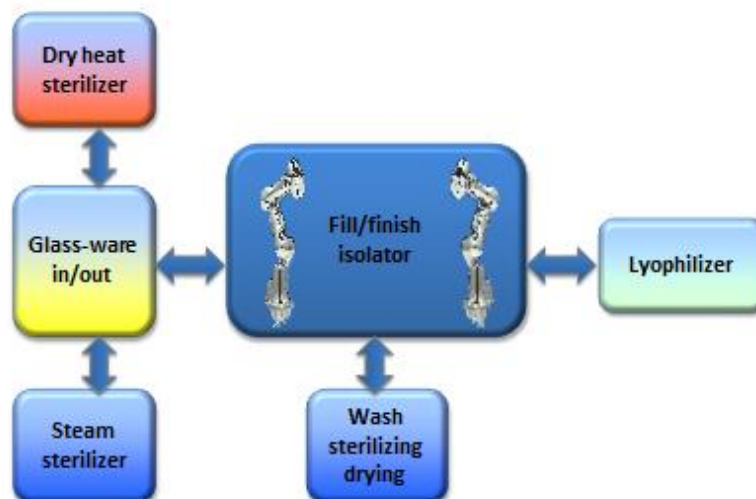


Fig.3 Cluster tool concept. (Source: Fedegari Group).

Advanced aseptic manufacturing through the application of the cluster tool concept provides several competitive advantages for pharmaceutical companies:

- Improved injectable drug SAL;
- Top operator safety in handling extremely toxic API;
- Reduced risk of highly cost product loss;
- Accelerated time to market;
- Lower operating cost vs. traditional solutions;
- Single & Ready to Use materials to increase reliability;
- Getting rid of glass breakage;
- More confidence in facing regulatory risks.

IMPROVED INJECTABLE DRUG SAL

Possible viable and non-viable contamination can be avoided by providing a fully sealed isolator solution without an uncontrolled inlet or outlet. The fill/finish process is completely automated and no human intervention is needed thus eliminating the need for validation of operator GMP aseptic techniques. In addition, the need for handling and testing of glove ports and gauntlets is eliminated.

OPERATOR SAFETY

The filling work-cell is a closed isolator working on a batch basis with WIP (wash in place) capability to inactivate and clean the contamination generated by the process before opening the doors. The system was developed according to HPAPI containment design to achieve an hourly leak rate $< 2.5 \times 10^{-3} \text{ [h}^{-1}\text{]}$, Class 2 ISO 14644-7:2004, Table E.1..

BEST OPERATOR SAFETY IN HANDLING EXTREMELY TOXIC APIs

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REDUCED RISK OF HIGH-COST PRODUCT LOSS

Product losses are mainly due to equipment set up, lack of sterility resulting from poor aseptic techniques, cross contamination generated by fill/finish equipment lacking integrity, operator errors and equipment breakdown. The gloveless fully closed robotic isolator concept is designed to avoid all the possible failures due to personnel and to achieve Quality by Design as established by FDA guidelines (1).

ACCELERATED TIME TO MARKET

Introducing the Quality by Design approach from the early development of a new drug, and streamlining vial and syringe filling operations in a single isolator can speed up the time to market of clinical trial batches. Furthermore, material-handling simplicity avoids the costs associated with the upstream process as primary containers and closures washing and sterilizing on site and a quick changeover between different primary container forms including vials, syringes and cartridges can support time to market acceleration.

LOWER OPERATING COST VS. TRADITIONAL SOLUTIONS

Table 1 shows a comparison between a gloveless robotic work-cell and traditional solutions applied to aseptic manufacturing. The robotic isolator represents the most cost-effective solution by increasing compliance and lowering risks and operating costs.

Table 1: Aseptic process comparison								
	Risk of trial failure	Product quality consistency	Primary container. format flexibility	Product loss ratio	Batch transit time	Cap Ex	Batch cost	GMP compliance
Semi-automatic line	Low	Very high	Partial	Significant	Low	Moderate	Fair/high	Good
Lab manual fill/finish	Very high	Very low	Good	Significant	High	Low	Low	Poor
Robotic work-cell	Very low	Very high	Good	Low	Low	Moderate	Fair	Excellent

Table 1 – Filling lines comparison. (Source: Fedegari Group).

Additional features that contribute to lowering the costs can be related to material integration such as:

- Ready to use nested primary containers and closures
- RTP system and beta bag for single use product pathway
- Minimal product holdup
- Environmental monitoring tools to the isolator chamber through a beta bag;
- Single Use items disposed in a waste beta bag.

ELIMINATION OF GLASS BREAKAGES

One of the most time consuming phases during in-line or star wheel fill/finish operations is removing the broken glass of the primary containers. This operation is critical because of relevant issues on sterility of the product related to isolator glove punctures and operator protection in case of high potent cytotoxic products handling. In case of robotic filling, the risk of glass breakage is close to zero.

MORE CONFIDENCE IN MEETING REGULATORY REQUIREMENTS

Regulatory bodies are more confident with sterile filling operations carried out in a closed isolator since no human intervention means a lower risk of viable contamination of the product and less scrutiny. Environment health and safety can be dramatically enhanced by the use of a completely sealed isolator chamber. Process automation with robotics means more GMP compliance and less risk of human errors as well as less issues with *OELs* (Occupational Exposure Limits).

THE GLOVELESS ROBOTIC SOLUTION

The vast majority of robots are made in aluminum and have not been designed to be air-tight and shed particles. Their surface coatings cannot be considered optimal for hydrogen peroxide decontamination since internal vacuum on arms usually limits its use.

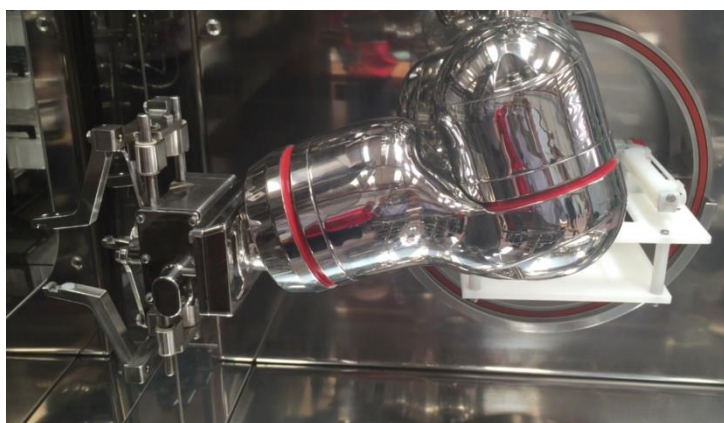


Figure 3: Preparing for handling nested tubs



Figure 4: Tyvek peeling



Figure 5: Filling

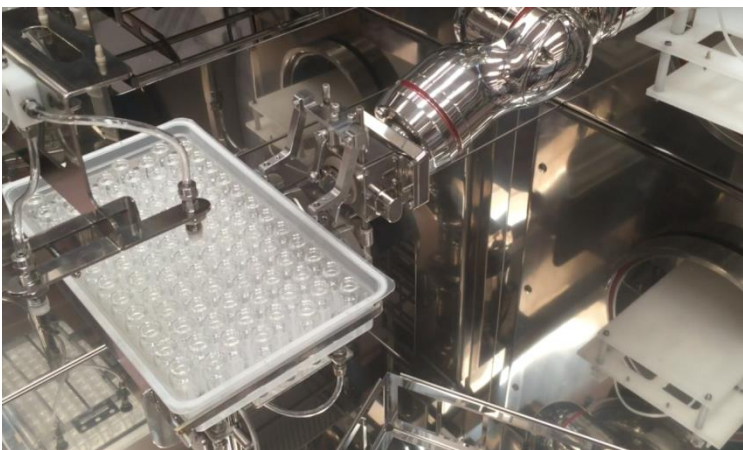


Figure 6: Capping

With its hollow wrist design and total airtight construction, the Fedegari seven-axis robot arm, shown in Figures 3 – 6, is made in AISI 316 L stainless steel and engineered to operate in Grade A environment with the lowest possible particle shedding. The IP67 rating of the GMP robot means that it is resistant to high pressure / high temperature wash-downs and is suitable for decontamination with vaporized hydrogen peroxide. It can operate in both positive and negative pressure environments. An electronic motor controls the strength of the grip of the arm. External parts and

tub surfaces are treated with steam sterilization in the autoclave connected to the isolator robot. The isolator is equipped with the built-in FHPV (Fedegari Hydrogen Peroxide vaporizer), totally engineered and manufactured in-house by Fedegari. With its PID based control loop controller, the FHPV system provides superior reliability and repeatability for easier validation (see Figure 7).

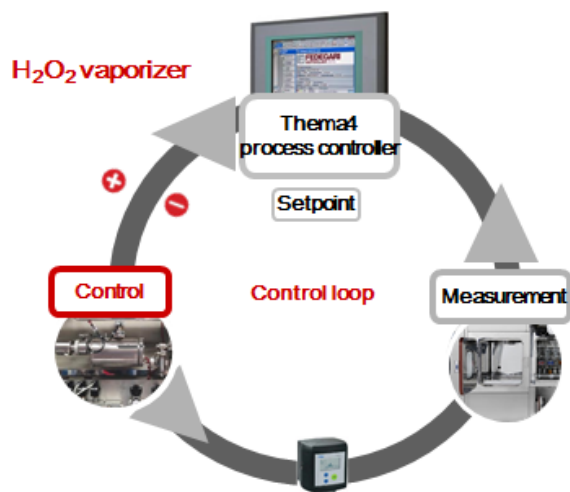


Figure 7: Revolutionary PID based H₂O₂ vaporizer. (Source: Fedegari Group).

DEVIL IS IN THE DETAILS

Future trends in pharma manufacturing have created a need to look outwards in search of new approaches. An aseptic process cannot be considered advanced while requiring human intervention. The cluster tool concept allows the redesign of aseptic manufacturing processes to lower or even eliminate the risk of personnel induced contamination. Since increasing complexity means reducing reliability, the existence of fewer moving parts leads to fewer problems and fewer particles. Considering these aspects, change seems to be inevitable to achieve cost-effective and flexible aseptic production that addresses the challenges of the post-blockbuster drugs industry.

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