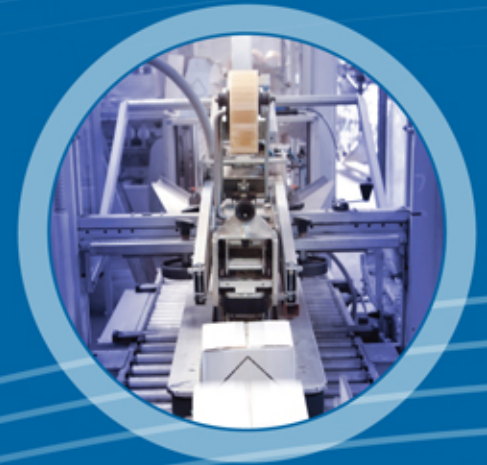




*Connecting People, Science and Regulation*

# Gloveless Robotic Technologies in Aseptic Manufacturing for Personalized Cytotoxic Drugs

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# Presentation outline

- Pharma outlook trends and the aseptic manufacturing challenges;
- Advanced aseptic manufacturing including GMP robotics;
- Quality by Design and process optimization;
- Containment, SAL, nested glassware and closures integration;
- Robotics, filling, weighing and HPV Generator Integrated Control.





# Pharma business outlook

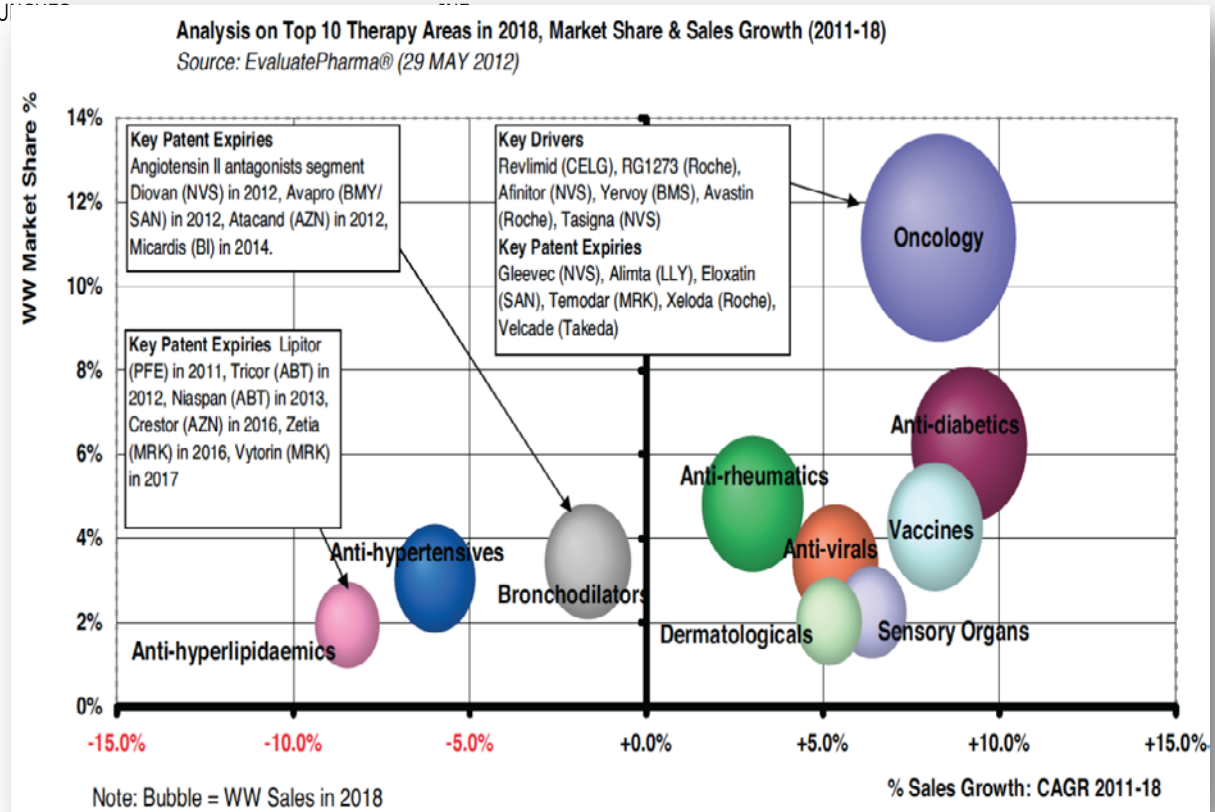
- Expiring patents are causing the increase in R&D expenditure;
- Demand of anti cancer drugs is growing fast;
- The largest number of on going clinical studies focus on cancer treatments;
- Bio-pharma research is a relevant source of new active principles;
- **Half of the newly developed anti cancer drugs are injectable.**





# Innovative therapeutic drug outlook spending

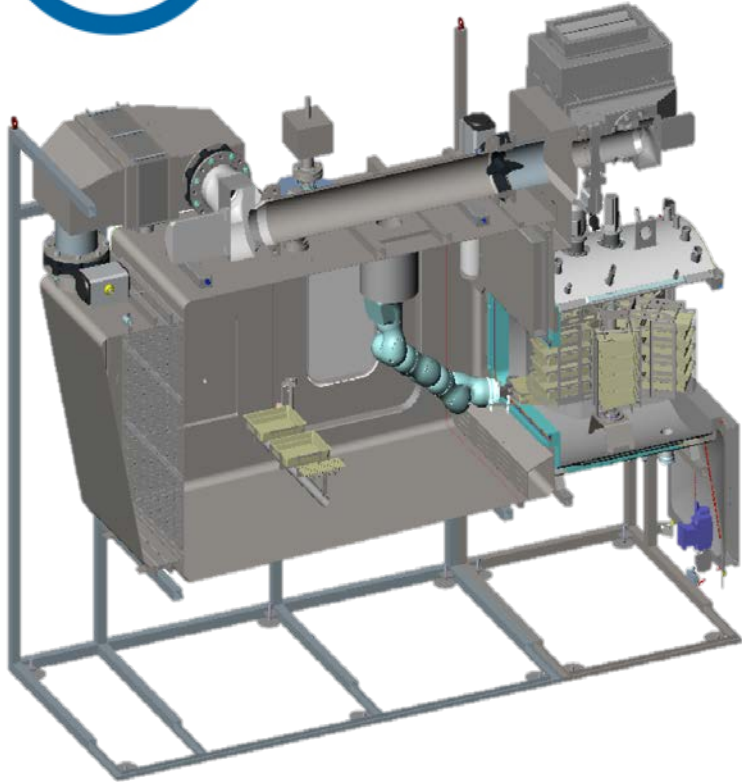
LAU







# The idea



There is a need of bespoke solutions addressed to companies who need flexible, efficient and cost-effective systems for their sterile fill/finish operations of clinical trials small batches.

**A gloveless totally sealed isolator hosting a GMP robotic arm is in an advanced development stage.**



# Who is it for?

## High value niche therapies and personalised drugs

- New generation oncology drugs;
- Monoclonal antibodies;
- Therapeutic vaccines;
- Gene therapeutics;
- Orphan drugs.
- Antigen specific immunotherapies;
- Adapted dosage forms;
- Recombinant proteins;
- Drugs combinations;
- Cell therapies.

*smaller  
batches*

*shorter  
runs*

*greater  
complexity*

*more  
volatile  
demand*

*higher quality  
expectations*



# Innovative sterile manufacturing:

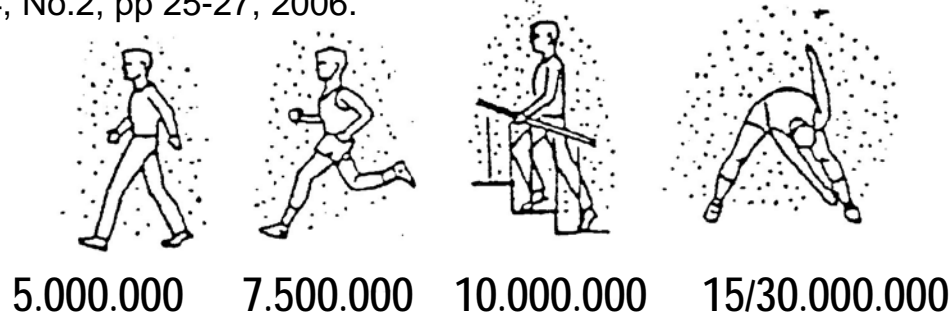
what is advanced?

The issue

"An advanced aseptic process is one in which direct intervention with open product containers or exposed product contact surfaces by operators wearing conventional clean room garments is not required and never permitted.



© Akers, J., Agalloco, J., Madsen, R., "What is Advanced Aseptic Processing?", Pharmaceutical Manufacturing, Vol.4, No.2, pp 25-27, 2006.



Particle shedding, equivalent diameter  $\geq 0,3 \mu\text{m}$



# Options for clinical trials batches

- High speed lines processing primary containers;
- Semi automatic production line for nested PFS, vials;
- Laboratory manually fill/finish of the batch;

The new concept

- **Gloveless robotic isolator**





# Why a Robotic Aseptic Filling?

- Flexible and modular solution for small scale manufacturing;
- Designed for multi-format, multi-product and multiple dosing capability;
- Safe handling of highly potent, high value and patient focused products;
- Rapid project technology transfer and scale up;
- Compact equipment footprint and can be operated in a ISO 8 cleanroom;

- FDA and EMA recognition as the future standard in aseptic manufacturing.



# Competitive advantages

- 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 drug SAL

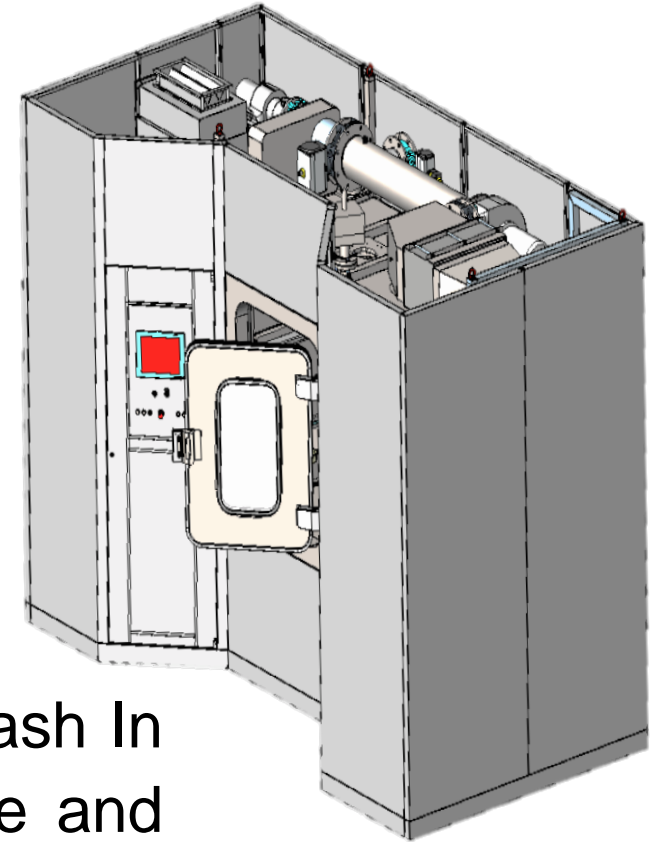
- Providing a fully sealed isolator solution without uncontrolled inlet and outlet avoiding any possible viable and non viable contamination;
- The fill/finish process is completely automated and no human intervention is needed thus avoiding operator certification of GMP aseptic techniques;
- Getting rid of glove ports and gauntlets handling and testing.





# Operator safety

- The filling workcell is a closed isolator working on a batch base;
- HPAPI containment design to achieve an hourly leak rate below  $< 2.5 \times 10^{-3} [\text{h}^{-1}]$ , class 2 ISO 10648-2:1994(E);
- The equipment is provided with Wash In Place (WIP) capability to inactivate and clean the contamination generated by the process before opening the doors.





# Reduced risk of product loss

Product loss is mainly due to:

- Lack of sterility generated by poor aseptic techniques;
- Cross contamination because of a lack of integrity of the fill/finish equipment;
- Operator's mistake;
- Equipment breakdown.

The gloveless fully closed and robotic isolator concept is to avoid “by design” all the possible failures due to personnel.





# Accelerated time to market

By streamlining vial and syringe filling operations in a single isolator, the time to market of the of the clinical trials batches is faster.

- Material handling simplicity avoiding the cost associated with the upstream process as primary container, closures washing and sterilizing on site;
- Quick changeover between different primary container forms including vials and syringes;
- Introducing Quality by Design attitude since the early development of a new drug.



# Trial operations comparison

	Risk of trial failure	Product quality consistency	PC format flexibility	Product loss ratio	Batch transit time	Cap Ex	Batch cost	GMP compliancy
Semi automatic line	Low	Very high	Some how	Significant	Low	Moderate	Fair/high	Good
Lab manual fill/finish	Very high	Very low	Good	Low	High	Low	Low	Poor
Robotic workcell	Very low	Very high	Good	Low	Low	Moderate	Fair	Excellent



# Single Use material integration

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





# Get rid of glass breakage

One of the most time consuming phase in “in-line” or “star wheel” fill/finish operation is removing the broken glass of the primary containers.

This operation is critical because of isolator gloves punctures with relevant issue on sterility of the product and operator protection in case of high potent cytotoxic products handling.

In case of “static pedestal” filling the risk of glass breakage is close to zero.





# Confidence vs. regulatory risks



- Regulatory bodies are more confident with sterile filling operation carried out in a closed isolator;
- No human intervention means lower risk of viable contamination to the product – less scrutiny;
- EH&S is dramatically enhanced because of the completely sealed isolator chamber – less issues with OEL;
- Process automation introduced with the robot means more GMP compliance and less risk of human errors.







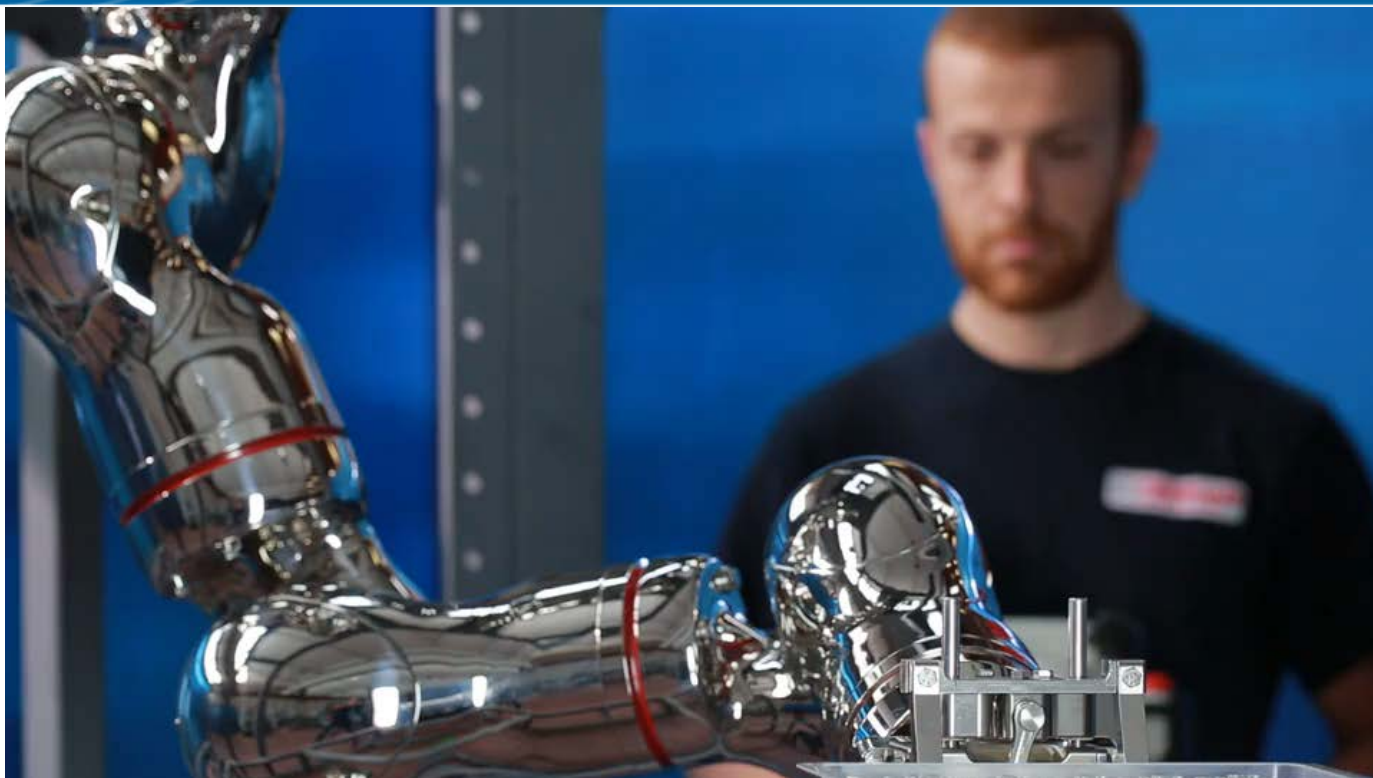
# Robotics



- Vast majority of robots are not designed to be air-tight and not to shed particles;
- Almost all are in aluminum;
- Surface coatings are less than optimal for hydrogen peroxide decontamination;
- Internal vacuum on arm limits use.



# The GMPs robot



- AISI 316 L stainless steel construction;
- 7 axis arm;
- “A” grade design with low particle shedding;
- IP67 rating, high pressure and temperature wash down resistant;
- Fully compatible with H<sub>2</sub>O<sub>2</sub> vapors decontamination;
- Hollow wrist design.

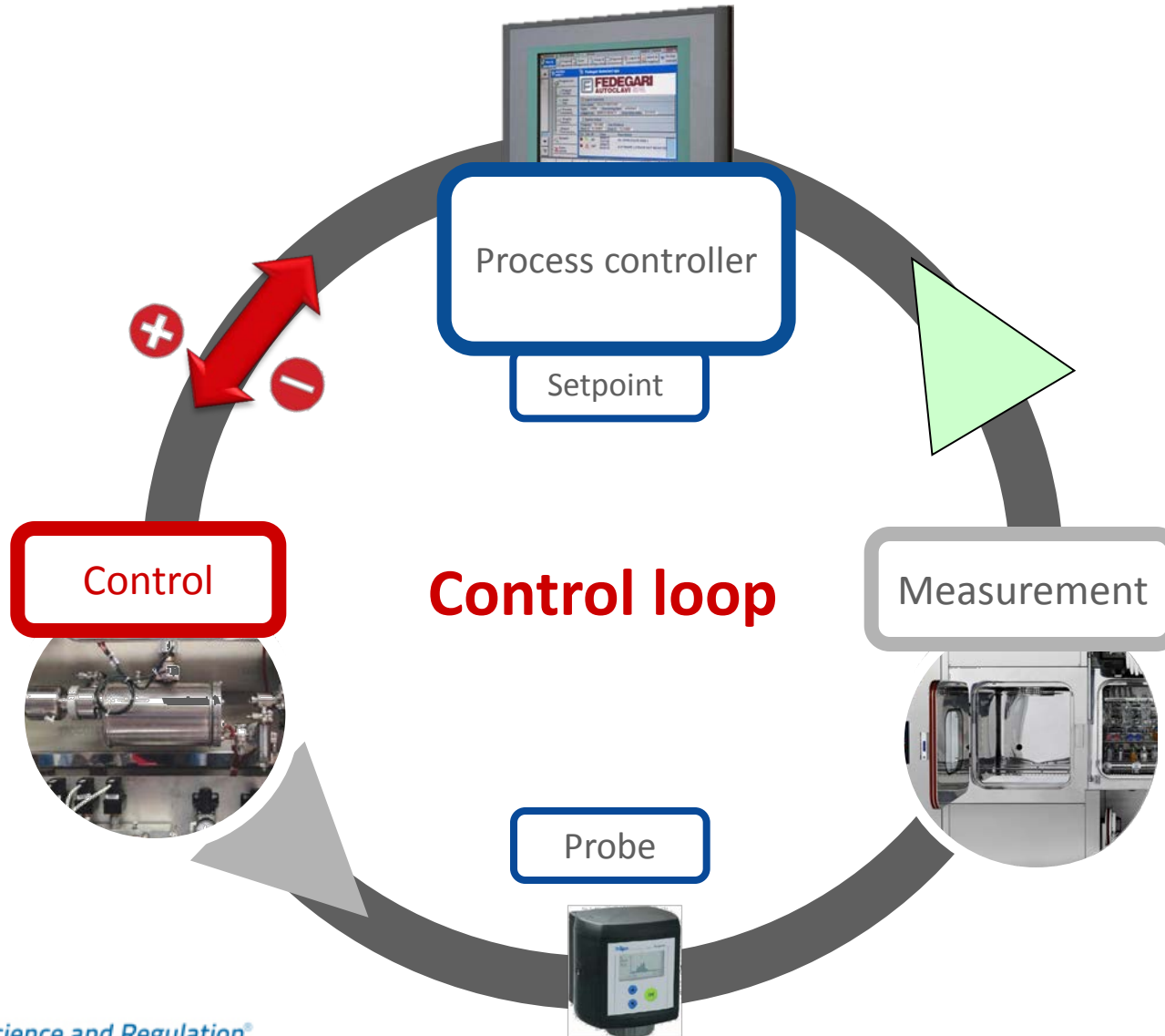


# Workcell spec's

- Flexibility – vial, syringe and cartridge filling from (1ml to 50 ml);
- Rate – 30 vials/min (10 ml), 10 syringes/min (1 ml);
- Steam sterilization, H<sub>2</sub>O<sub>2</sub>, decontamination, CIP & Wash down In Place (WIP);
- PC format change by programming;
- No glove ports and gauntlets;
- Disposable fill path;
- Peristaltic pump or CIP/SIP rotary piston pump



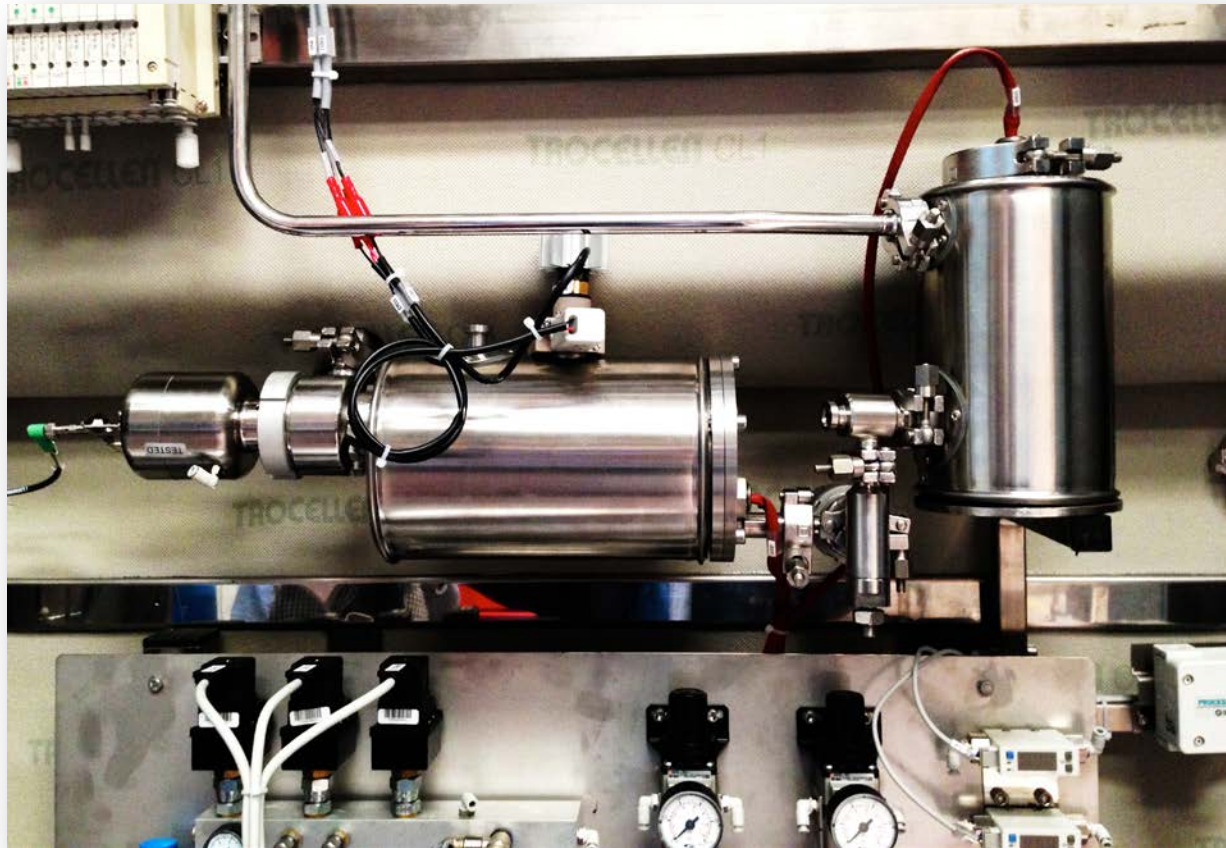
# PID-based H<sub>2</sub>O<sub>2</sub> vaporizer







# New generation H<sub>2</sub>O<sub>2</sub> Vaporizer







# New Material Formats



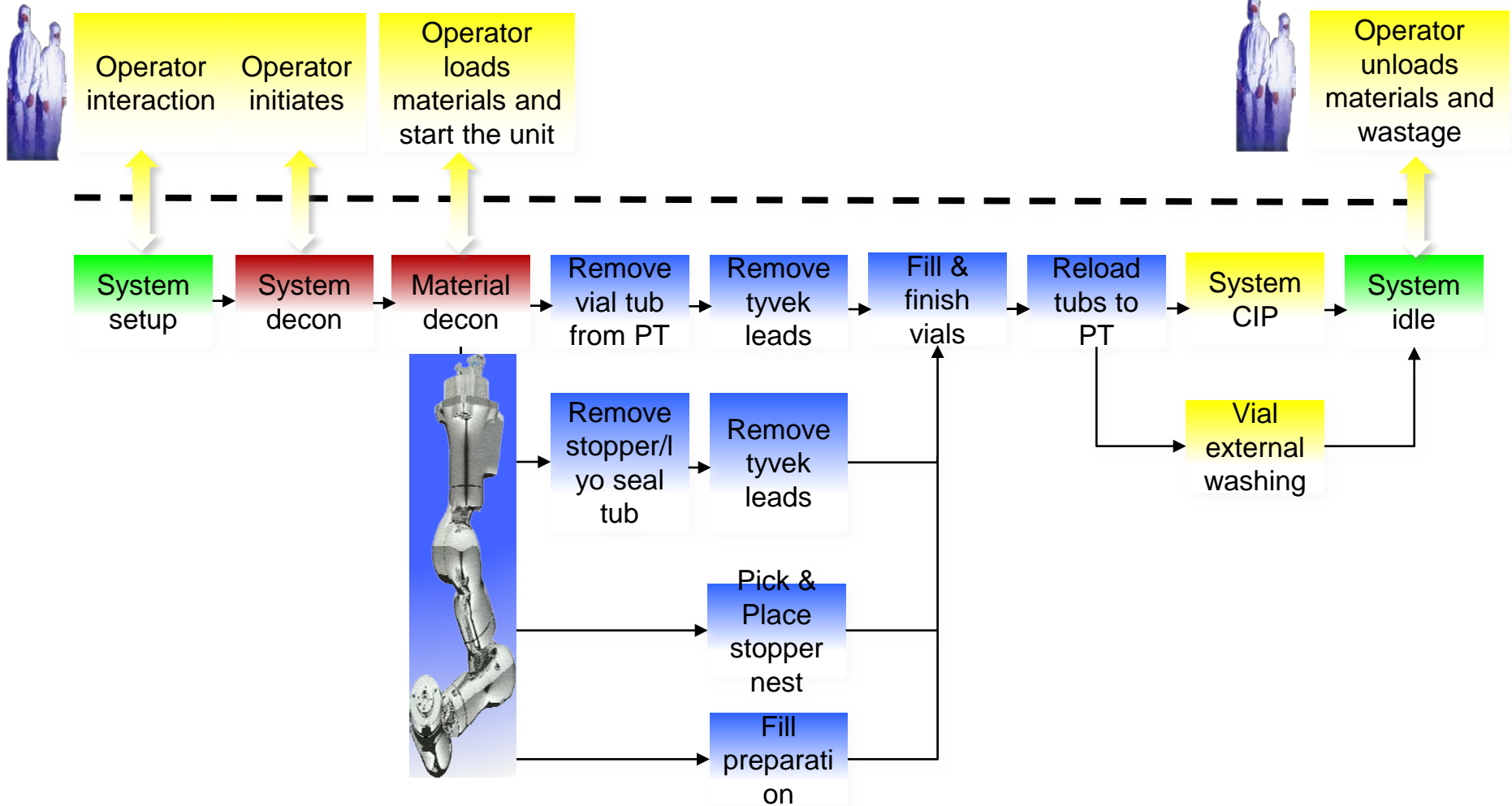


# GMP robot process simulation





# Conceptual Flow Diagram



# Summary



- Nothing is advanced with human intervention
- Don't be scared to redesign the aseptic process
- Complexity is the enemy of reliability
- Get rid of gloves
- Less moving parts means less problems and particles
- Looking outward provides new approaches



Thank you for your attention  
And now ready for your questions...

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