GMP–
PHARMA
CONGRESS

#sharing challenges
and solutions in practice

Aseptic Sterile Filtration using Single Use and Isolator Technologies

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– Merck Biopharma (Bari Site) –

Part of PharmaCongress – Düsseldorf/Neuss, 31 May–1 June 2022

MERCK

AGENDA

1. **Project: facility and equipment pre-requisites, qualification and implementation of SUS;**
2. Risk identification when using SUT and mitigation strategy;
3. Single Use Integrity test at the point of use (method development & qualification);

Merck Bari Plant

The facility is located in Bari industrial area (Modugno), close to the airport, the main transport routes (airport, highways, harbors, railroads)

...and the most beautiful places in the world according to Lonely Planet travel guide ☺!

Merck Bari Plant Capabilities

Global site for Biotech Drug Product & Finished Product manufacturing for all Biotech products supporting clinical / launch and commercial

Scope

Biotech DP, FP manufacturing

Technologies

Liquid & solid aseptic filling (vial, cart., syr.) under isolator, device assembly, packaging, QC and MSAT;

Franchises

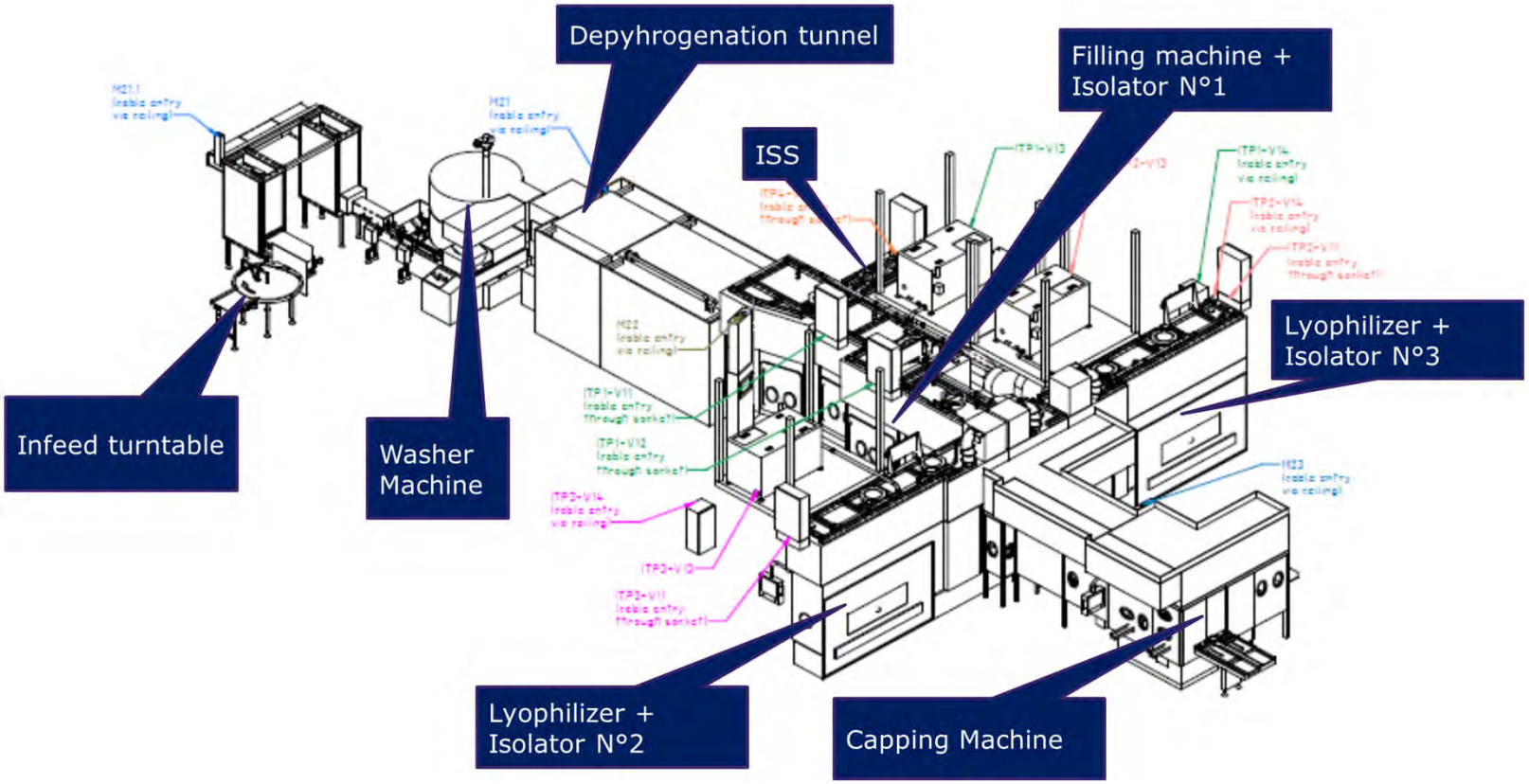
N&I, Oncology/immuno-oncology, Fertility, Endocrinology, Biosimilars

Investments

Around 160 million € have been invested in Bari Site moving all the manufacturing lines from sterile cleanrooms to isolator technology to pursue Merck purpose.

Merck purpose: To create, improve and prolong lives as one for patient

Merck Bari line isolator



Merck Bari line isolator

Vials washing machine

CIP/SIP Cabinet

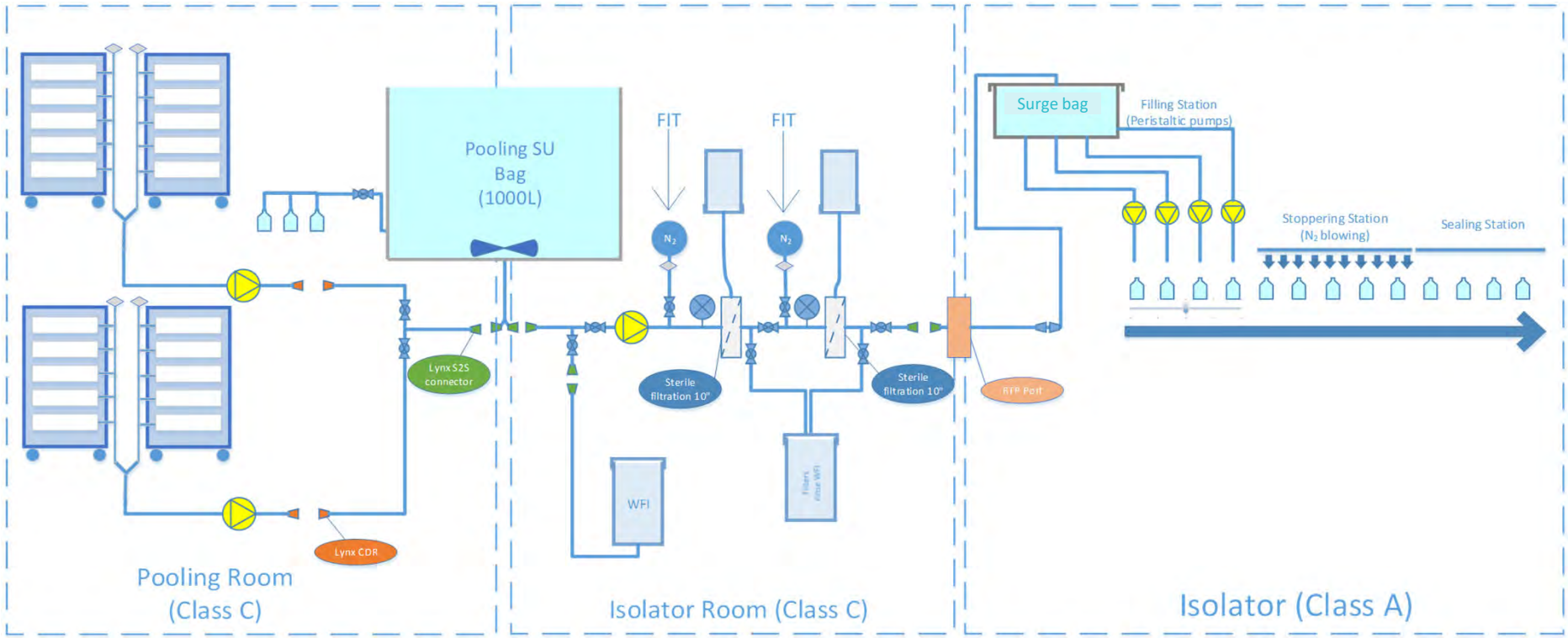
Depirogenation tunnel

Stopper vessel loading station

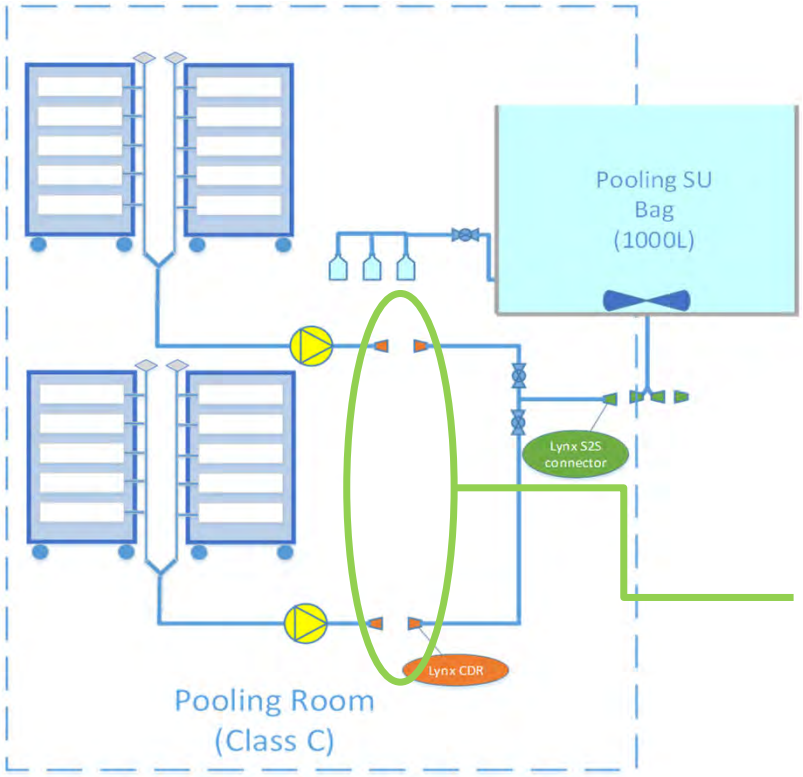
Merck Bari line isolator

Filling Unit

Process: pooling, filtration, filling

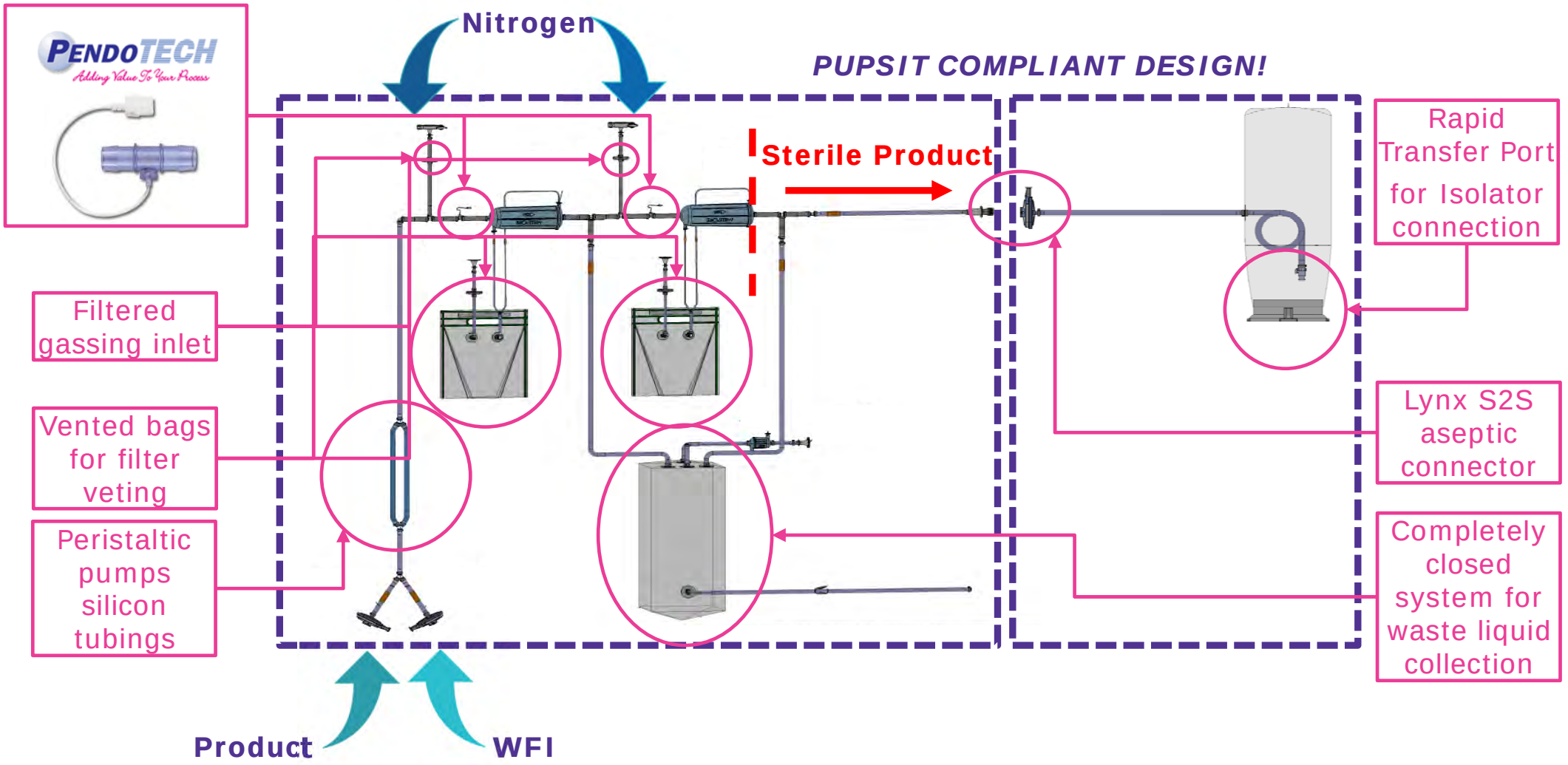


Process: pooling, filtration, filling

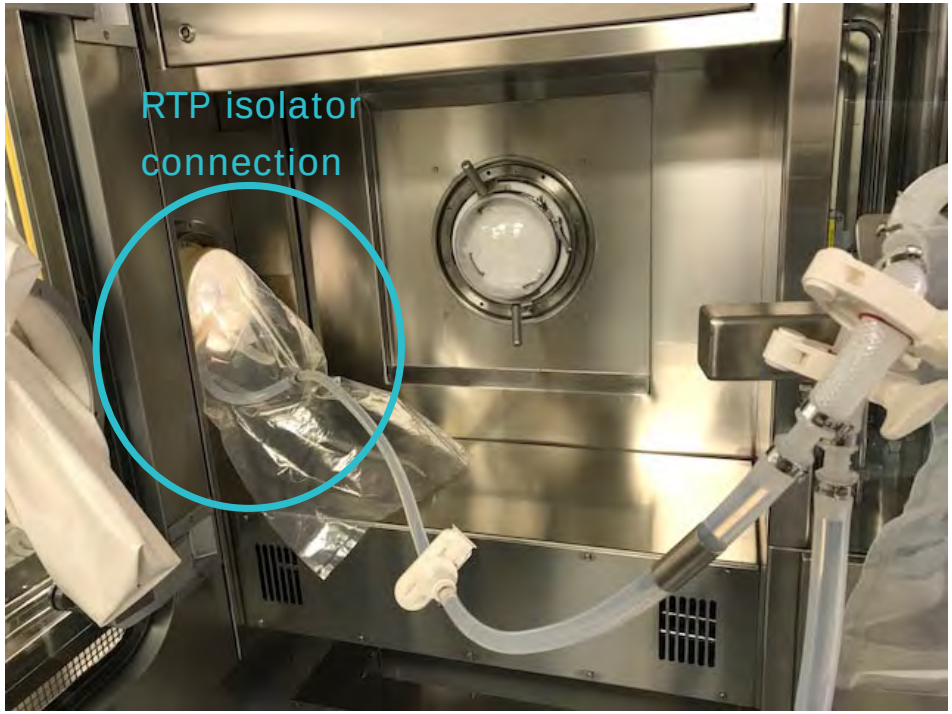


With Lynx® CDR Sterile Connectors, you can connect, disconnect and reconnect your single-use and hybrid systems both wet and under pressure while remaining sterile.

Filtration assembly with a redundant Sterile filtration



Filtration assembly with a redundant Sterile filtration



New Annex 1 requirements when using SUS

Facility pre-requirements

Annex 1 draft: Manufacture of sterile products

Focus on SUS integrity

8.120 The background in which closed systems are located should be based on their design and the processes undertaken. For aseptic processing and where there are any risks that system integrity may be compromised, the system should be located in a Grade A zone. If the system can be shown to remain integral at every usage (e.g. via pressure testing and/or monitoring) then a lower classified area may be used. If the closed system is opened (e.g. for maintenance of a bulk manufacturing line) then this should be performed in a classified area appropriate to the materials (e.g. Grade C for terminally sterilization processes, or Grade A for aseptic processing) or be subject to further cleaning and disinfection (and sterilization in case of aseptic processes).

8.118 It is critical to ensure the sterility of all product contact surfaces of closed systems used for aseptic processing. The design and selection of any closed system used for aseptic processing should ensure maintenance of sterility. Connection of sterile equipment (e.g. tubing / pipework) to the sterilized product pathway after the final sterilizing filter should be designed to be connected aseptically (e.g. by intrinsic aseptic connectors or fusion systems).

New Annex 1 requirements when using SUS
Personnel pre-requisites

Focus on SUS integrity

Annex 1 draft: Manufacture of sterile products

8.117 The use of closed systems can reduce the risk of extraneous contamination such as microbial, particulate and chemical from the adjacent environment. Closed systems should always be designed to reduce the need for, and complexity of manual interventions.

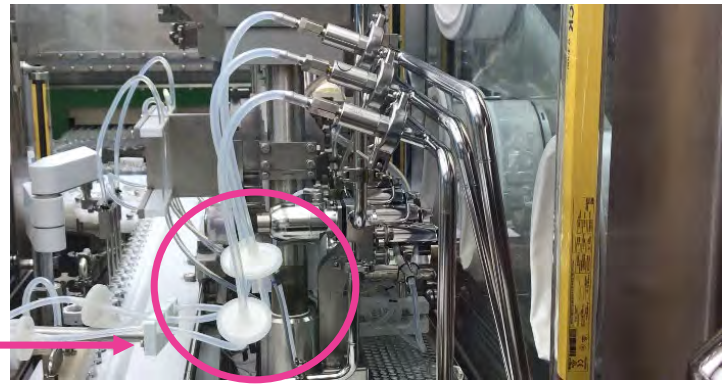
Simple SUS design & Operators training are key!

Premises & equipment pre-requisites

1. Nitrogen connection at 6bar close to the line for SUS device & filter integrity tests;
2. Rapid Transfer Port for SUS connection close to the filling pumps;
3. Filling line predisposition to SUS connection (peristaltic pumps);
4. Hybrid configuration Stainless Steel & SUS are super critical and must be properly managed:

SITUATION:

The gassing station installed between vials filling station and stoppering station receive nitrogen from Syntegon cabinet (SS);
The cabinet is sterilized only when rotary pumps are installed and for this reason it was not possible to sterilize the nitrogen Line when using peristaltic filling pumps.
A sterile filter has been added between gassing station & nitrogen line as shown.



ISSUE: *observed during Media Fill Run*

A limited overpressure remained in the nitrogen* stainless steel line and during the Aseptic Process Simulation the filters popped up creating a potential critical issue for the isolator aseptic core (No contamination observed during Media Fill and on ad hoc sampling of the gas line).

* substituted with oxygen during Media Fill.

SUS Supplier selection & qualification

Tool: *Questionnaire with score for each request*

- *Biological Safety Tests availability;*
- *Mechanical Properties of the film (on film samples);*
- *Gas Transmission Property (on film samples);*
- *Physical-chemical tests results;*
- *Sterility Test Gamma irradiation & validation package;*
- *Quality Assurance Lot Release Criteria;*
- ***Container Closure Integrity ->LEAK TEST execution before shipment & minimum leak validated;***
- *pH measurement - Temperature measurement methods (specify probe characteristics);*
- *Productive capacity (How many production sites?);*
- *Need for audits on production sites;*
- *Lead time - Standard Product;*
- *Lead time - Customized Product;*
- *Post-sale: lead time for urgent intervention (for equipment);*
- *Post-sale: lead time for non urgent intervention (for equipment)*
- *Extractable studies availability (documentation provided)*
- *Shipping validation studies (documentation provided)*
- *Allergens declaration, Toxicological studies (documentation provided)*

SUS Supplier selection & qualification

Vendor Qualification:
- Risk Assessment of the material and the vendor;
- Supplier questionnaire;
- Supplier Audit;
- Validation packages review (ex Sterilization process);

Material Qualification (3 batches):
- Check of Certificate of Quality & Integrity;
- Sterility indicator check;
- Sterility conformity during Media Fill;
- Visual check (outer/inner package & label variable data);
- Assembly integrity test*;
- E&L & subvisible particles studies during GMP batches;

As robust as possible

Routine Incoming control:
- Check of Certificate of Quality & Integrity;
- Visual check (outer packaging + label variable data);

Before production control:
- Visual check (label variable data);
- Sterility indicator check;
- Assembly integrity test*;

limited

*Assembly integrity test performed on the filtration set only;.

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Risk identification when using SUT and mitigation strategy

Annex 1 draft: Manufacture of sterile products

8.122 There are some specific risks associated with SUS which should be assessed as part of the CCS. These risks include but are not limited to:

i. The interaction between the product and product contact surface (such as adsorption, or the formation of leachables and extractables).

ii. The fragile nature of the system compared to fixed reusable systems.

iii. The increase in the number and complexity of manual operations (including inspection and handling of the system) and connections made.

iv. The complexity of the assembly.

v. The performance of the pre-use integrity test for sterilizing grade filters (refer to paragraph 8.88).

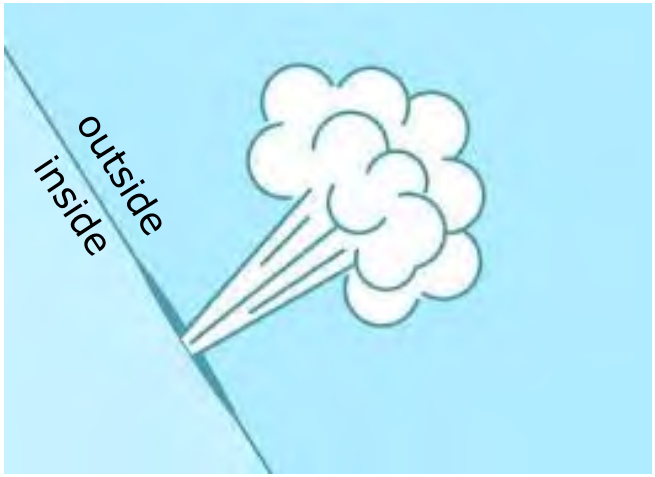
vi. The risk of holes and leakage.

vii. The potential for compromising the system at the point of opening the outer packaging.

viii. The risk of particulate contamination.

Risk identification when using SUT and mitigation strategy

Integrity is a Critical Quality Attribute of a SUS!

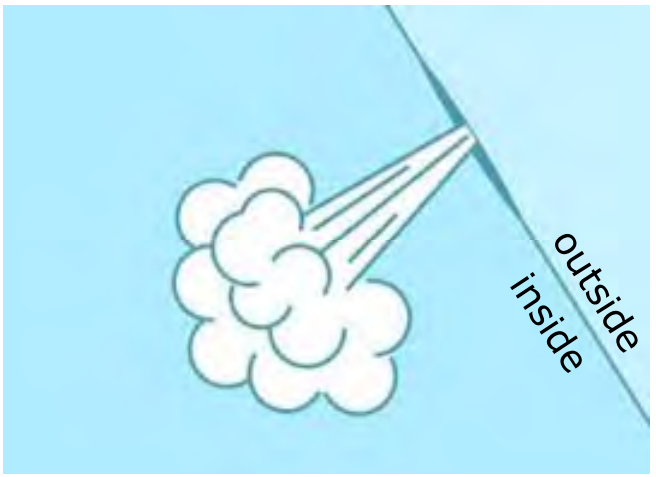


Product spill & potential risk for Operator safety

BUSINESS & SAFETY RISK

Product contamination

QUALITY RISK



ASTM Guideline:
WK64337 New Guide for Integrity Assurance and Testing of Single-Use Systems (astm.org)

Risk identification when using SUT and mitigation strategy

Focus on SUS integrity

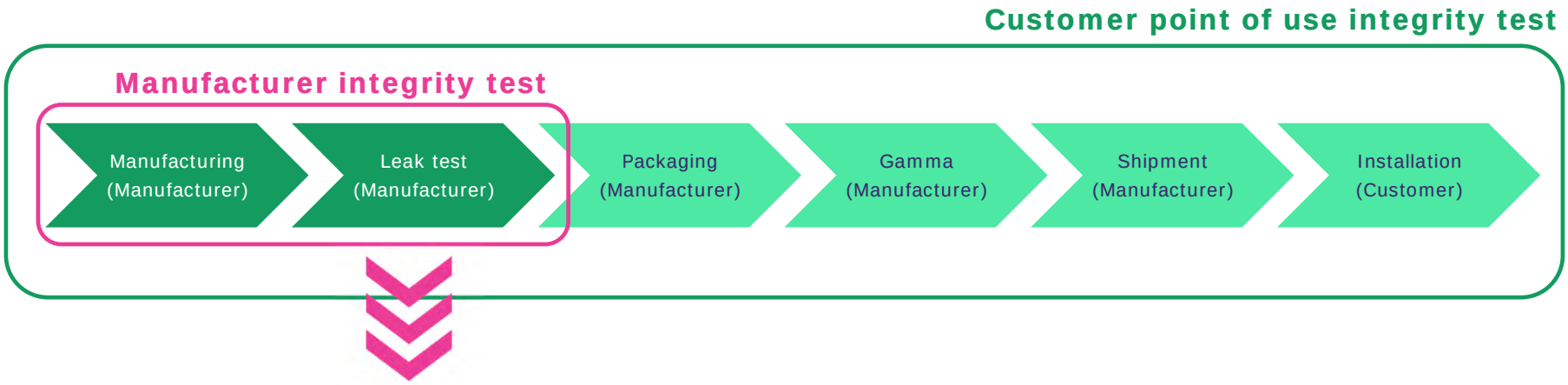
New Annex 1 requirements when using SUS

8.116 Closed systems can be single use systems (i.e. disposable systems) and fixed systems (such as vessels with fixed pipework). Guidance in this section is equally applicable to both systems.

8.119 Appropriate measures should be in place to ensure the integrity of components used in aseptic connections. The means by which this is achieved should be determined and captured in the CCS. Appropriate system integrity tests should be considered when there is a risk of compromising product sterility. Supplier assessment should include the collation of data in relation to potential failure modes that may lead to a loss of system sterility.

Integrity test approach SS vs SUS	
STAINLESS STEEL PIPING (Cabinet)	**SINGLE USE SYSTEM**
Leak Test	/
CIP (cold/hot WFI)	/
Product Filters installation	Assembling at supplier
Leak Test	Leak Test at supplier (optional)
SIP	Gamma sterilization
Leak Test	**Leak Test at Site**
Keep in overpressure	/

How leaks in Single Use Systems are handled by Suppliers



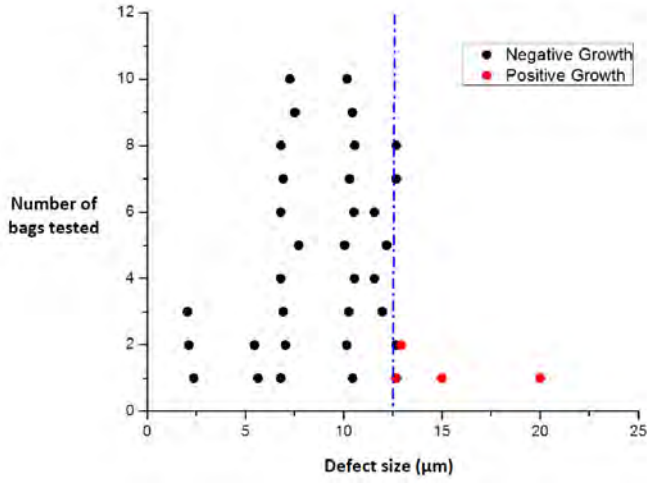
Different suppliers have **different approaches and capabilities** on integrity assurance (**KEY**):

- Leak testing just during SUS Manufacturing **Process Validation** + **annual check**;
- Leak testing **on samples** taken from the Bacth Manufactured;
- Leak testing **on 100%** SUS manufactured;

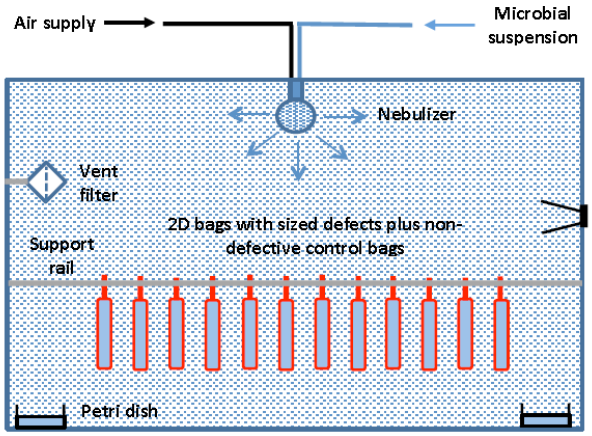
Maximum Allowable Leakage Limit (MALL)

The "***Design, control, and monitoring of single-use systems for integrity assurance"*** Guideline, ***written by Bio-Process System Alliance (BPSA) in 2017***, describes two different microbial trials to identify the MALL – SUS liquid immersion vs **SUS aerosol challenge**.

Microbial results after 60 minutes of aerosol challenge



12,65 µm identified as leak check to guarantee sterility – aerosol contamination



Feature	Properties
Test bag	2D with 2 L volume
Defect size range	4 µm - 20 µm
Growth media	600 mL trypticase soy broth
Challenge organisms	*Escherichia coli* *Staphylococcus aureus* *Bacillus spizizenii* *Candida albicans* *Aspergillus brasiliensis*
Microbial aerosol concentration	10^6 cfu/mL
Aerosol exposure times	60 minutes
Incubation temperature	$30^0 – 35^0$ C
Incubation time	14 days

BPSA white paper Design, Control, and Monitoring of Single-use Systems for Integrity Assurance, July 2017

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STEP 1: to identify the right SUSIT Method

KEY: All the above-mentioned tests are **Pre-use** and not post use Integrity Test –> indeed Drug Product could clog leaks causing faulse passed test!

Decay test methodology

The leak size is measured using the pressure decay on the pressurized container

PROs:

- Sensitivity above 10µm
- Easy to implement/ manage/ calibrate;
- Cheap system;

CONs:

- sensitivity is dependent on the SUS volume and test pressure -> low on large volumes and low pressure;
- Sensitivity is temperature fluctuation dependent;

Flow measurement methodology

The leak size is measured using the flow loss & quantified by a flow sensor

PROs:

- Easy to implement;
- Sensitivity is independent from device volume;

CONs:

- Sensitivy to fluctuation in gas supply pressure and ambient pressure;
- Less suitable for very small leak;
- Sensitivity is temperature fluctuation dependent;

Helium test methodology

The leak size is measured with the Helium quantification in the chamber using a mass spectrometer.

PROs:

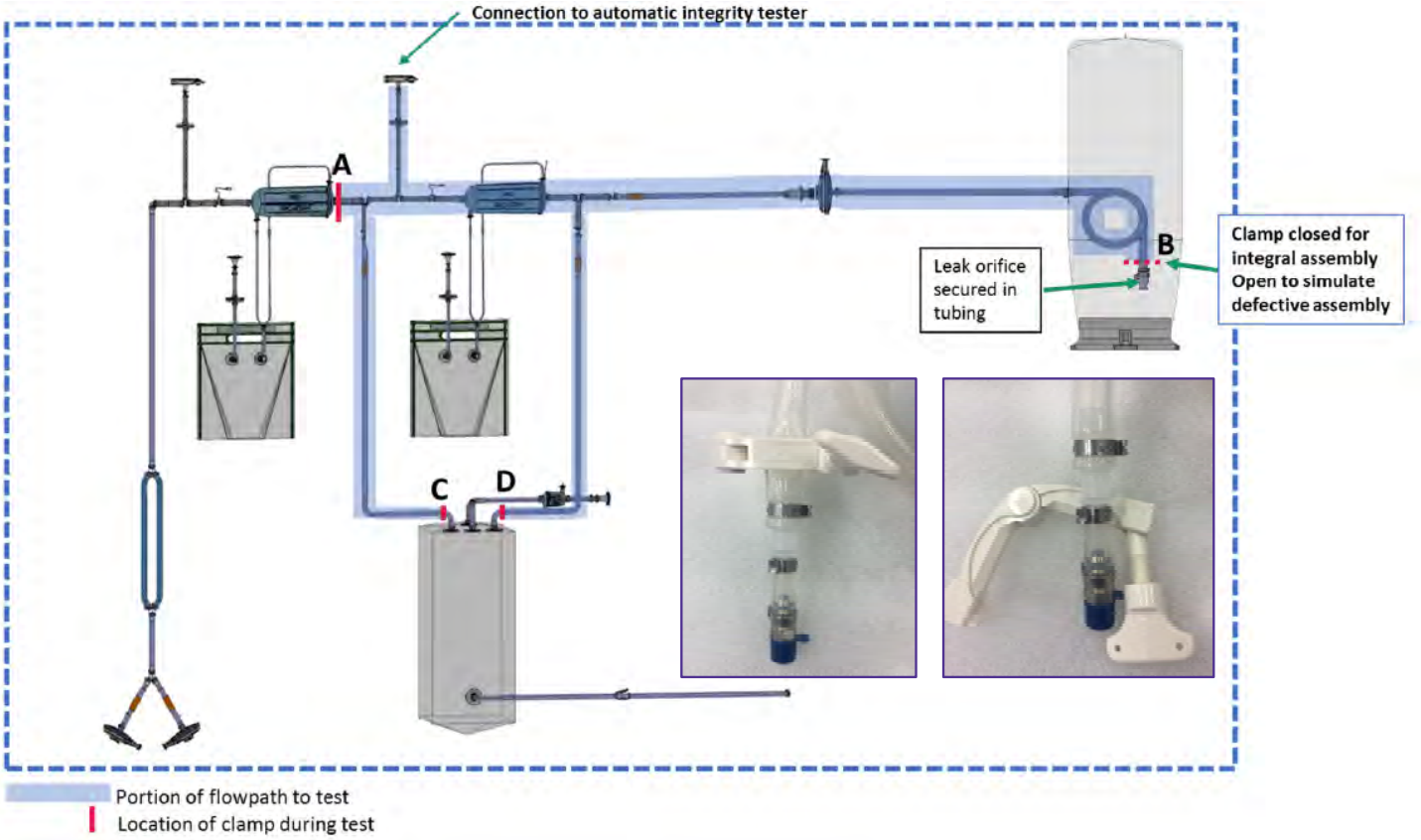
- Sensitivity above 2µm;
- Sensitivity is independent from device volume, temperature & pressure fluctuation;

CONs:

- Equipment costs;
- Challenging implementation/ management/calibration;
- Natural film permeability to Helium could generate faulse passed test;

Palltronic Flowstar LGR

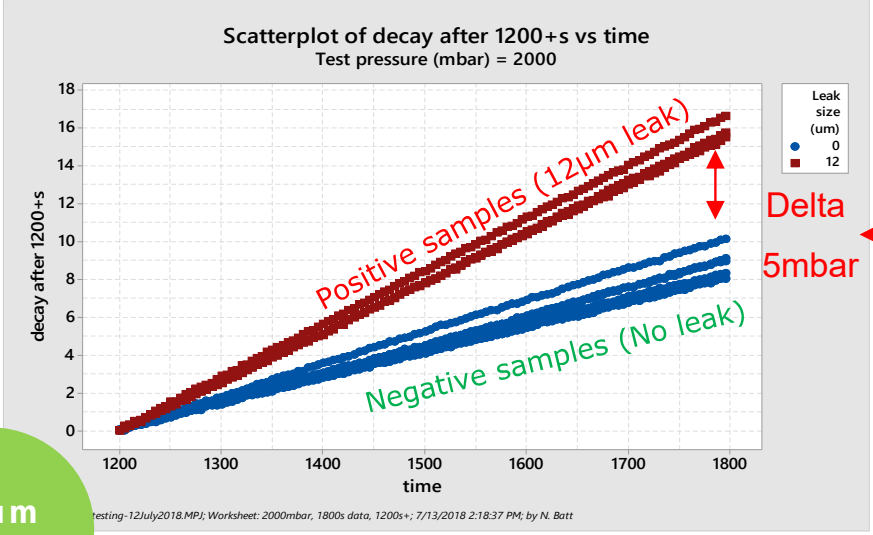
STEP 2: To develop the Method making tests



STEP 2: To develop the Method making tests

12µm leak - decay test development trials:

- Test pressure: 2 bar **Risk for SUS integrity**
- Decay test duration: 1800 sec (30m)
- Stabilization time 1200 sec (20m) - to reduce the adiabatic heating effect
- Test Time: 600 sec (10m) **Potential lack of test reliability**

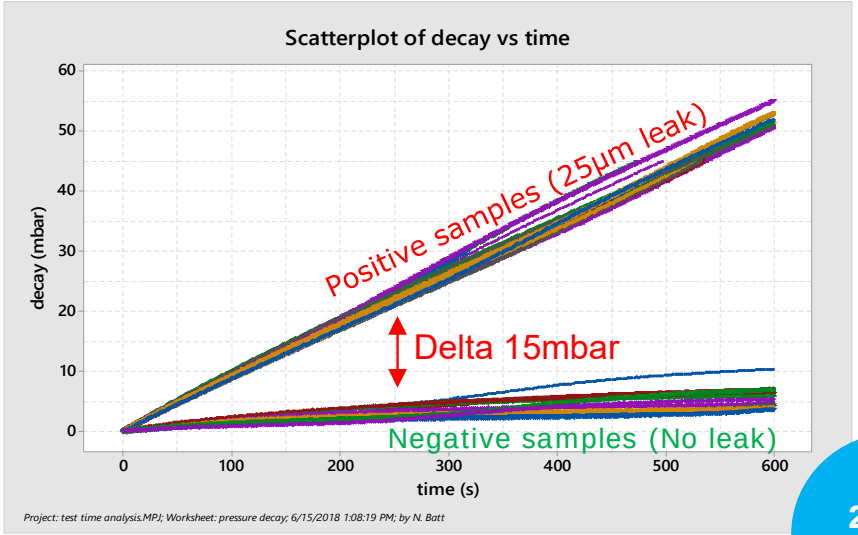


12µm leak

Good separation observed after 1800s

25 µm leak - decay test development trials:

- Test pressure: 1 bar
- Decay test duration: 250 sec (≈5 m)
- Stabilization time 100 seconds;
- Test Time: 150 seconds



25µm leak

Good separation observed after 150s

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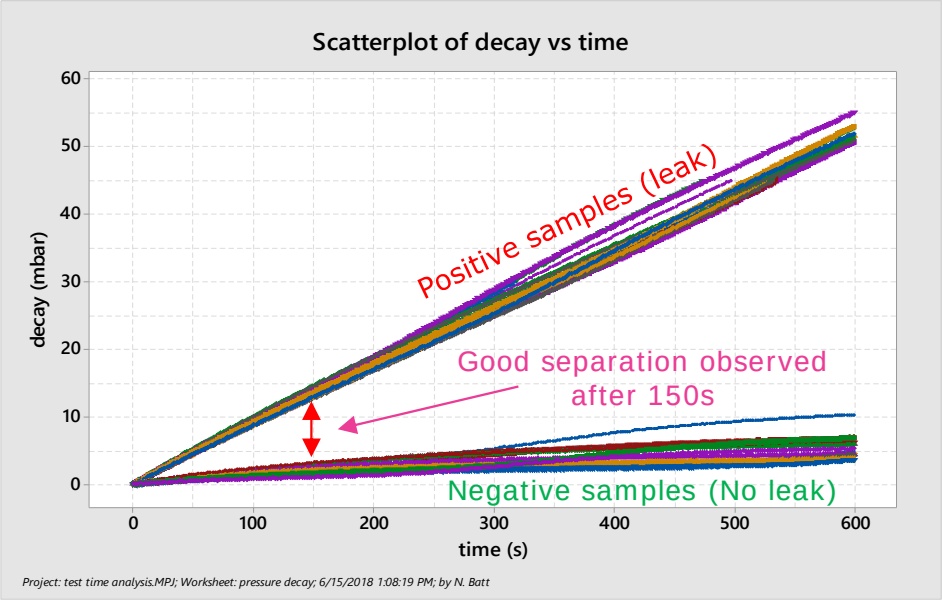
STEP 3: To identify the most sensitive method recipe

FINAL DECAY TEST METHOD RECIPE:

- Calibrated orifice to simulate leak defect;
- Test pressure chosen of 1 bar
  - Process pressure max during filling;
  - Maximize test sensitivity while maintaining all components within recommended pressure range;
- Test time chosen is 150 seconds:
  - Repeat tests conducted out to 10 minutes test time, data analyzed every 30 seconds to show separation. Minimal improvement seen after 150 seconds

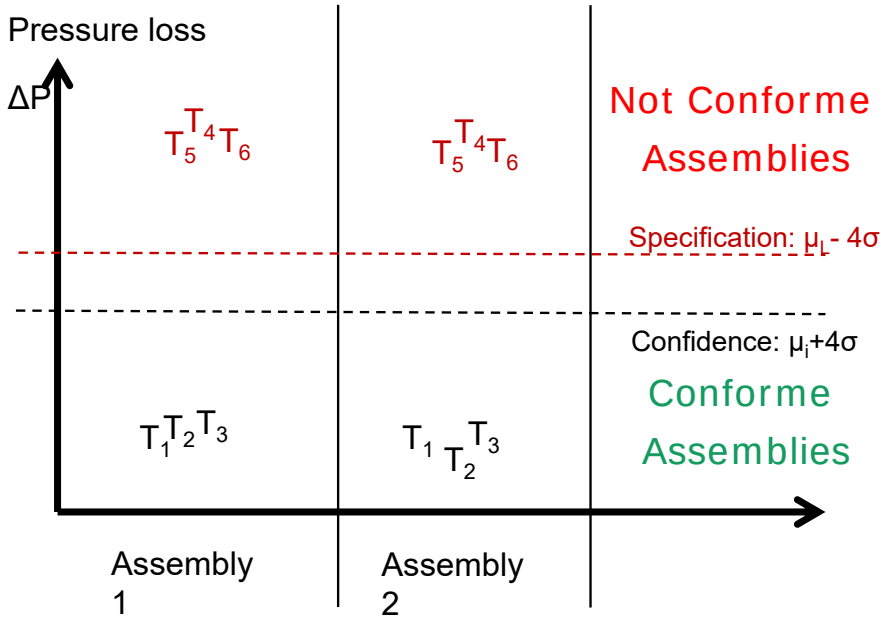


STEP 4: To validate the test method developed

How to Validate from a GMP prospective the Decay Test:

- **To prepare a Validation Protocol with a clear acceptance criteria:**
  - Test specification set at overall mean of non defective assemblies + 4σ (σ standard deviation);
  - Clear separation between non defective and defective data population;

  N.B. Mean +/- 4σ = 99,9968% of values represented by the population.
- **To prepare a Validation Protocol with a clear operative Procedure:**
  - 2 assemblies for 3 different supplier batches tested by 3 operators in 3 different days (W & W/O leak defect);
- **To prepare the test execution with an effective training;**

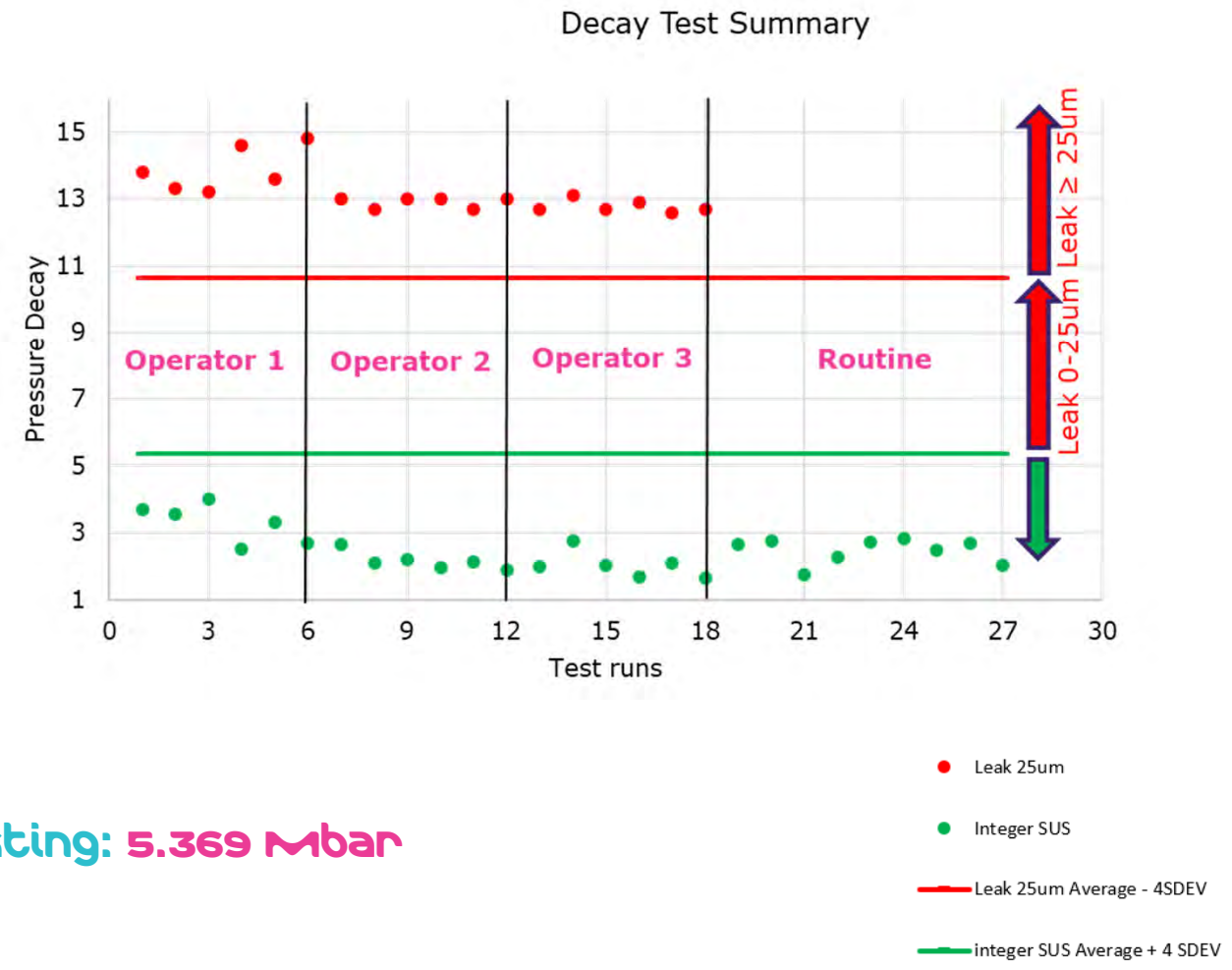


STEP 4: To validate the test method developed

Results Observed:

25 um defect tests	
Mean	13.189 mbar
Standard Deviation	0.638 mbar
Mean–4 standard deviation	10.637 mbar

Intact device tests	
Mean	2.497 mbar
Standard Deviation	0.718 mbar
Mean+4 standard deviation	5.369 mbar



Limit identified for routine testing: 5.369 Mbar

Thank you!

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