Single-use System Integrity

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PDA
Parenteral Drug Association

CONNECTING PEOPLE SCIENCE AND REGULATION®

Agenda

- **Introduction**
- Industry & Regulatory Framework
- SUS Robustness
- Science Behind Integrity of SUS
- Technologies for Leak or Integrity Testing of SUS
- Summary

Leak vs. Integrity Testing & Definitions

- **Leak test** – a test used to identify leaks of any sizes in a SUS.
- **Integrity Test** – a test used to confirm the defined barrier properties of a SUS.
- **Maximum Allowable Leakage Limit** – the greatest leakage rate (or leak size) tolerable for a given product package to maintain its barrier properties under its use-case conditions (e.g. prevent any risk to product safety, product quality or operator and environmental safety).
- **Integrity Assurance** – a holistic approach of risk analysis and mitigation by means of product and process robustness, quality and process control and integrity testing.
- **Non-destructive test method** – a test method that maintains the tested SUS in a condition for further use, without impacting its quality attributes.
- **Destructive test method** – a test method that may destroy the tested SUS during the test and not allow further use.

Barrier Properties as Measure for Integrity

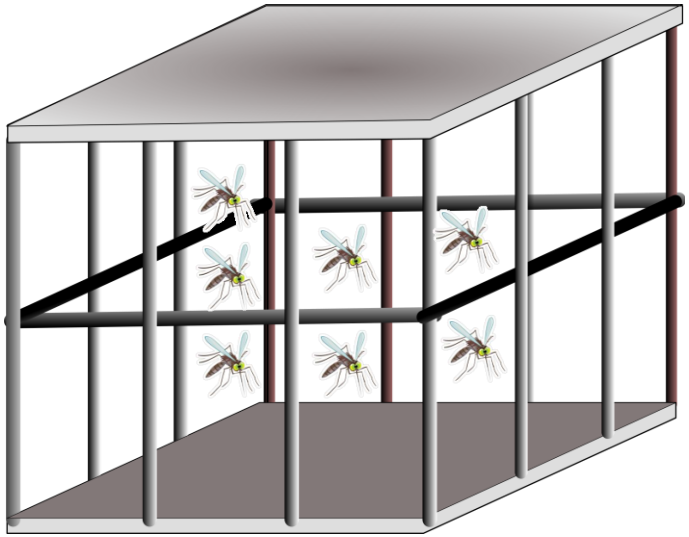
- **Barrier property** of this cage (container) is to keep the lion in.

- **This container is integral.**

Barrier Properties as Measure for Integrity

- Is the same container integral if its **barrier property** is to keep mosquitos in?

- **This container is not integral.**



What's the Best Approach to Ensure Integrity?

IF windows keep out birds, **THEN** should we detect a defective window by checking homes for birds?

REMEMBER: Single-use System Integrity…

- **…IS NOT** passing a microbial ingress test.
- **…IS** the absence of a defect that puts product quality or operator and environmental safety at risk.
- **…IS** the conformance of the package the maximum allowable leakage limit (MALL).

What's the Best Approach to Ensure Integrity?

- **INSTEAD** of checking for birds…

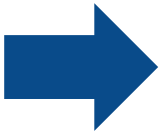
- **Design and make** windows that close well based on meaningful, reliable tests.
- **Test** for absence of defects that could permit birds.
- **Monitor** to ensure control over materials and processes.

SUS Integrity Approach

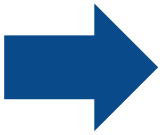
- QbD & validation to reach consistent SU system robustness
- Process control, quality control & integrity testing

- Understand liquid leakage & bacteria ingress mechanisms
- Correlate integrity testing detection limits to liquid leaks & microbial ingress under process conditions

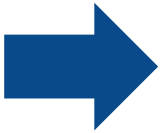
- Implement 100% physical supplier integrity testing
- Provide point of use testing



SU System Robustness



SU System Integrity Science



Integrity Testing Technology

Combined with the robustness of our self-deploying bags, our integrity tests ensure that no product leakage or microbial ingress can occur during drug manufacturing process

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Current Main Industry Guidance and Standards Initiatives

Annex1 - Manufacture of Sterile Medicinal Products (Revision – Not yet published)

ASTM E3244 2020 Standard Practice for Integrity Assurance & Testing of SUS

ASTM E3251 2020 Test Method for Microbial Ingress Testing on SU

ASTM WK74440 Proposed Test Method for Physical Integrity Testing for SUS

PDA TR 86 2021 Industry Challenges and Current Technologies for Pharmaceutical Package Integrity Testing

BPSA 2017 Design, Control, and Monitoring of SUS for Integrity Assurance

The Challenge is to Ensure That No Product Leakage or Microbial Ingress Can Occur During the SUS lifecycle

- QbD & validation to reach consistent SU system robustness
- Process control, quality control & integrity testing

- Understand liquid leakage & bacteria ingress mechanisms
- Correlate integrity testing detection limits to liquid leaks & microbial ingress under process conditions

- Implement 100% physical supplier integrity testing
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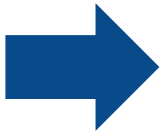
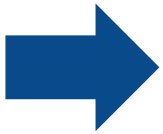
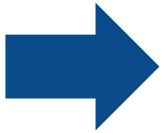


SU System Robustness



SU System Integrity Science



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Combined with the robustness of our self-deploying bags, our integrity tests ensure that no product leakage or microbial ingress can occur during drug manufacturing process

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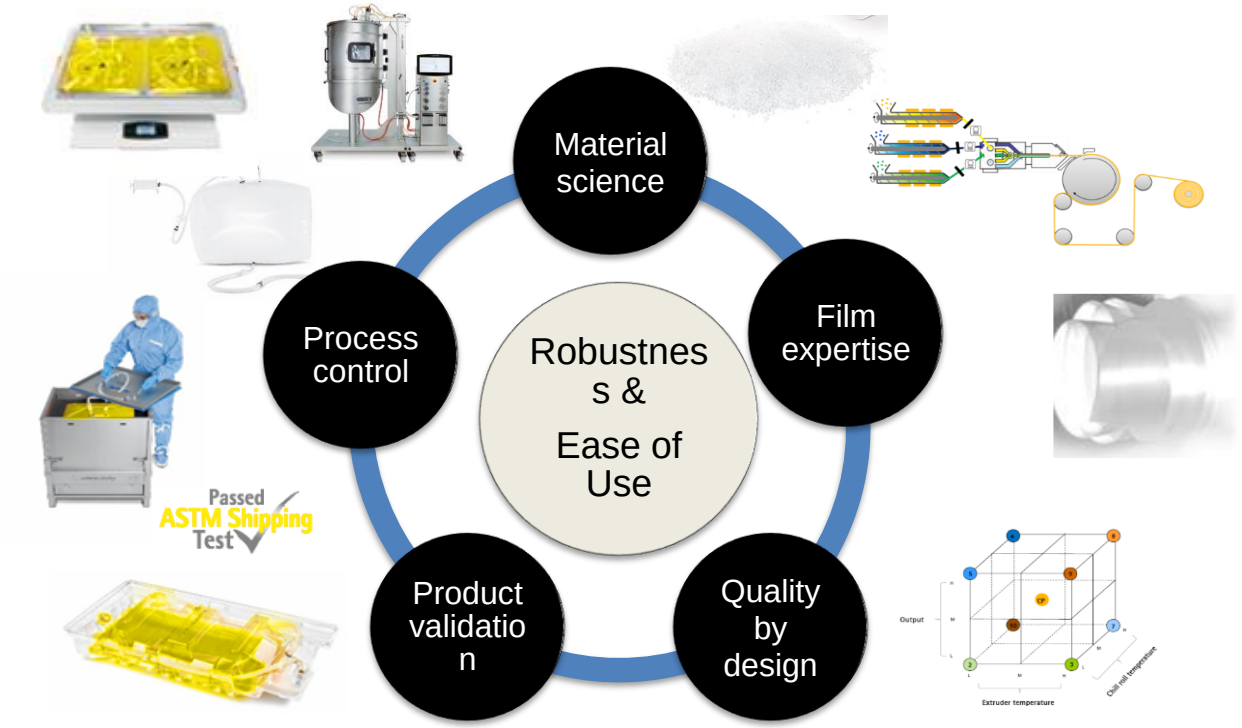
Material Science Expertise for Robustness & Safety by Design

Flexsafe® Film & Bags

Material science &
film expertise
Raw material selection
& film layer combination

QbD & product validation
> 3000 mechanical tests
ASTM D4169 shipping test

Process control
Control of raw materials,
film extrusion & welding
leak test on bags



Continuous Integrity Improvement by Developing More Sensitive Leak Detection Technologies

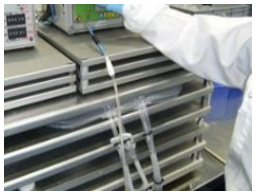
- Identifying smaller defects help understand failure mode & improve process capabilities

Supplier Process Validation	Supplier Process Control	End-User Process Validation & Controls
• Mechanical tests • Microbial immersion • Packaging validation • Shipping validation • Microbial ingress test & liquid leak test using calibrated defects **to identify the MALL* and correlate physical integrity testing**	• Seal tests • Visual inspections • 2D bag chamber leak test, sensitivity ≥ 40 µm • **Finished product Supplier Integrity Test *(upon request),* sensitivity ≥ 2 µm**	• Package integrity • Visual inspection • Media hold & media fill • Microbial immersion test • Operator training to best practices • **2D pre-use point of use leak test, sensitivity ≥ 10 µm** • **3D post-installation point of use leak test, sensitivity ≥ 50 µm**

*MALL: the greatest leakage rate (or leak size) tolerable for a given product package to maintain its barrier properties under its use-case conditions, *(ASTM E3244)*

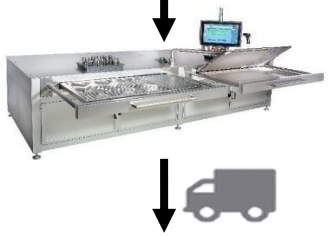
Intermediate Process Control, Quality Control & Final Product Integrity Testing – Example for Flexboy & Flexsafe 2D Bags

100%
Bag chamber
leak test
~40 – 90 µm



Discard defects from bag chamber manufacturing operations

Upon request
Final assembly
integrity test
2 µm



Discard additional defects from bag chamber manufacturing and assembly operations

Upon request Point-
of-use
integrity test
10 µm

Discard additional defects from transportation & handling operations

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Understand Liquid Leakage and Microbial Ingress Mechanisms on Film Materials Used in Single-use Biomanufacturing

- Demonstrate the relation between microbial ingress and liquid leak
- Establish a predictive model to determine the Maximum Allowable Leakage Limit (MALL*) under any process conditions
- Establish a correlation between liquid leak/microbial ingress and physical integrity testing
- Develop and validate the physical test methods with detection limits that guarantee the absence of liquid leak/microbial ingress in SUS

*MALL: the greatest leakage rate (or leak size) tolerable for a given product package to maintain its barrier properties under its use-case conditions, *(ASTM E3244)*

Process Conditions May Impact Liquid Leak & Microbial Ingress

Hydrostatic pressure in storage

~0.7m / 2’

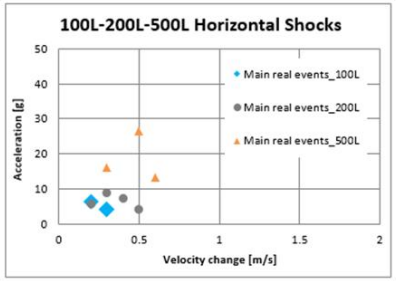
Max pressure 70mbar

Flexboy® 20 L

Flexsafe® 500 L

Application	Pressure range
Storage	~10 – 100 mbar
Shipping	~100 – 250 mbar

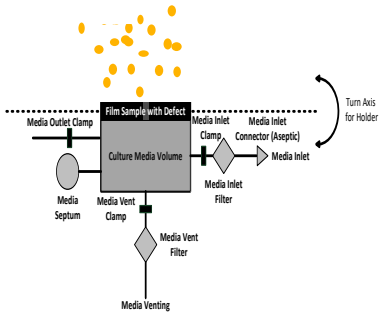
Shipping can generate up to 20g acceleration

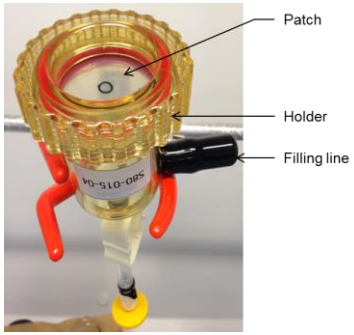


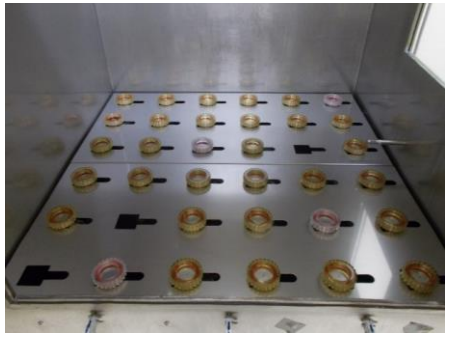
Microbial Aerosol Tests on 300 Film Samples Show No Ingress For 1 & 2 µm Defect at 300 mbar

Microbial ingress results at 300 mbar imposed pressure

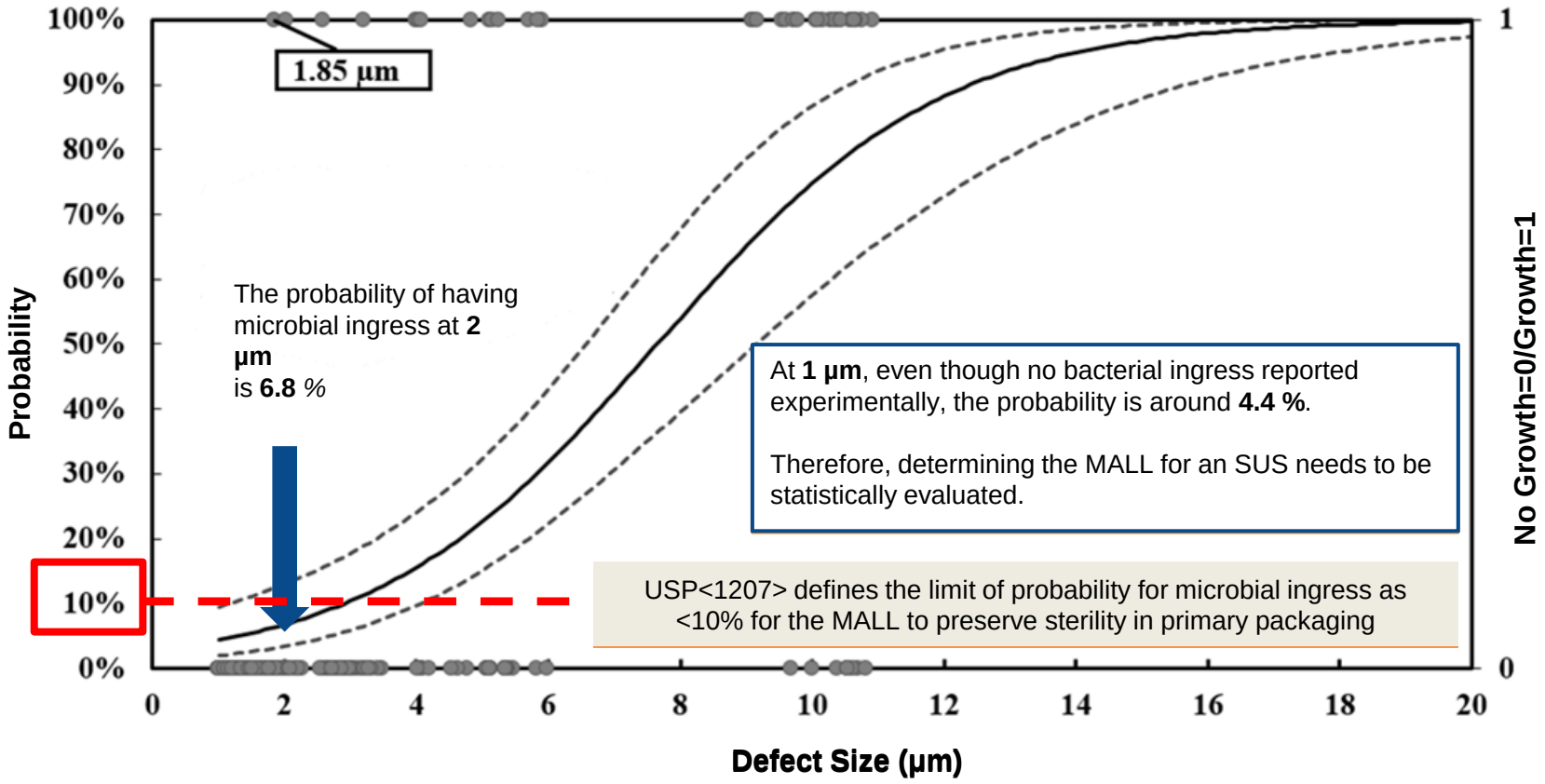
	Hole size µm	1µm	2µm	3µm	5µm	10µm
PE film	Number of samples	30	30	30	30	30
	Number of ingress	0	2	2	10	22
EVA film	Number of samples	30	30	30	30	30
	Number of ingress	0	0	9	17	13





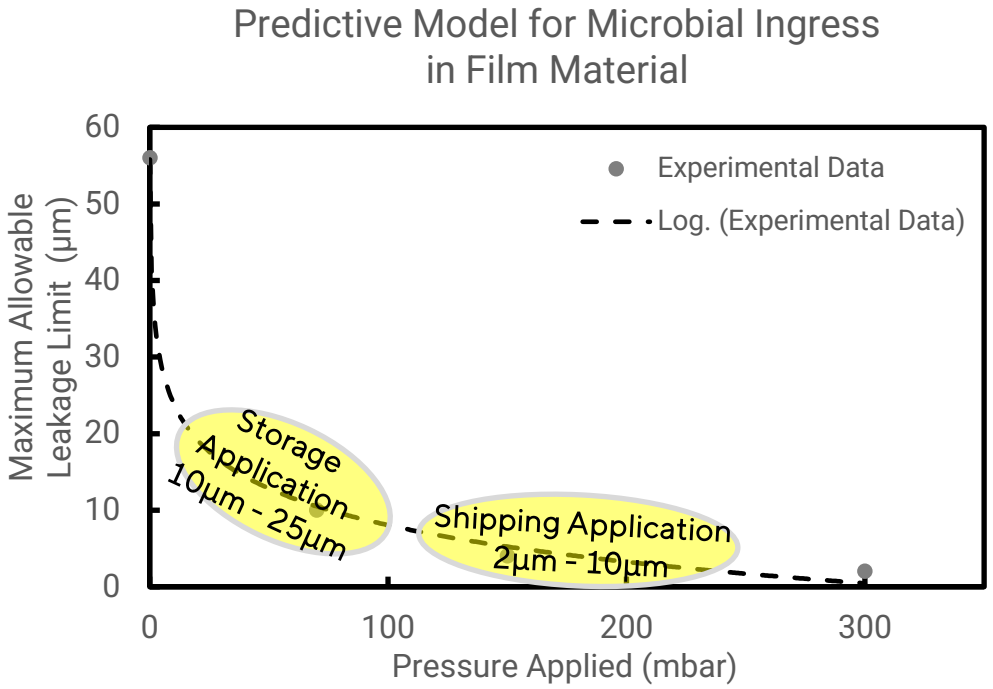


Probability for Microbial Ingress at 300 mbar Pressure on PE Film



Predictive Model to Define Application-specific MALL

- Establishes the MALL for any process condition
- Based on observed data for microbial ingress at various pressure conditions
- MALL defined as a probability of for microbial ingress of <10%



Conclusion from Results Obtained on Liquid Leak & Microbial Ingress Studies on SUS

- Results obtained on film materials fall into the existing models for sterile package using micro tubes
- Both studies, liquid leak and microbial ingress ones, tend to confirm that leak sizes for liquid flow are not significantly different from leak sizes for sterility loss
- The conditions of use (pressure) does significantly impact the Maximum Allowable Leakage Limit (MALL)
- 2 µm is the MALL under any conditions and both, for liquid leak and microbial ingress

PDA Journal Publication Series:

Single-use System Integrity I: Using a Microbial Ingress Test Method to Determine the Maximum Allowable Leakage Limit (MALL) https://journal.pda.org/content/73/5/459

Single-use System Integrity II: Characterization of Liquid Leakage Mechanisms https://journal.pda.org/content/early/2020/11/16/pdajpst.2020.012088

Single-Use System Integrity III: Gas Flow Rate Through Laser-Drilled Microchannels in Polymeric Film Material
https://journal.pda.org/content/early/2021/06/15/pdajpst.2021.012631

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Integrity Testing With Detection Limits Correlated to Microb. Ingress & Liquid Leaks

- Helium supplier integrity test with detection limit of 2µm.
  - Smallest defect size detectable by integrity test
  - Confirms the integrity of the complete assembly
- Pressure decay test confirms the absence of defects at the point-of-use.
  - Can also correlate to liquid leaks & microbial ingress

1 Bag Chamber Leak Test (BC-LT)

100% BC-LT
Pressure Decay
2D bags ≤50L

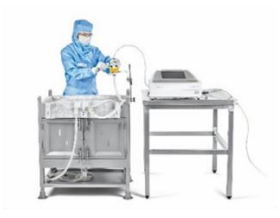
Detection limit
40-90 µm
(no claim)

2 Final Product Supplier Integrity Test (SIT)

100% SIT
Helium Test
2D bags ≤50L
3D bags ≤500L
Mixers ≤650L

Detection limit
2µm (claim)

3 Point of Use Leak/Integrity Test (PoU-LT/IT)

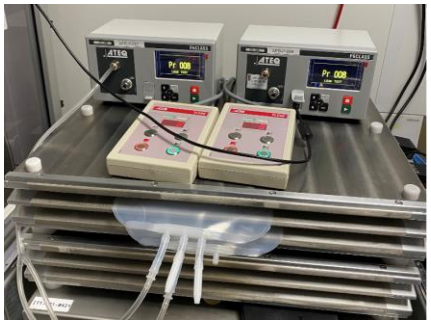


Pressure Decay

Detection limits
10µm on 2D bags ≤50L
100-200µm on 3D bags ≤500L
50-400 µm on Mixing bags ≤1.000L
50–600µm on STR bags ≤2.000L

Bag Chamber Leak Test Ensures the Absence of Leaks on Film Surface as well as Bag & Port Welding for 100% of Our 2D Bags

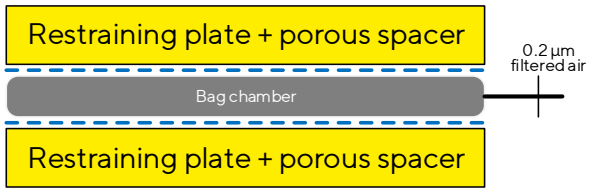
- **ASTM F2095 Pressure decay testing**
- Restraining plates
  - Reduce stress on bag
  - Provide small inflation volume
  - Allow high test pressure: **500 mbar**
- Porous spacer avoid masking effect of potential leaks



20-year experience in leak testing.

20 million bags produced.

Combining small volume, high test pressure and spacers provides a reproducible, accurate and sensitive test.
Detection limit: **40 – 90 µm (no claim)**



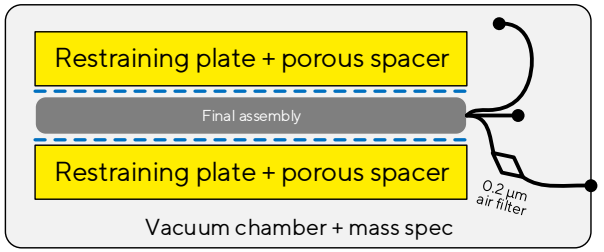
Bag making → 1 BC-LT → Final assembly → 2 SIT → Sterilization & shipment → 3 PoU-LT / PoU-IT

Finished Product SIT to Test 100% of 2D & 3D Bag Assemblies for Storage, Shipping & Mixing Used in Critical DS & DP Applications

- Helium gas tracer in vacuum chamber
- Restraining plates
  - Reduce stress on bag
  - Provide small inflation volume
  - Porous spacer avoid masking effect of potential lea

With low background noise and dynamic leak rate measurement helium gas tracer is the best method to achieve reliably highest sensitivity

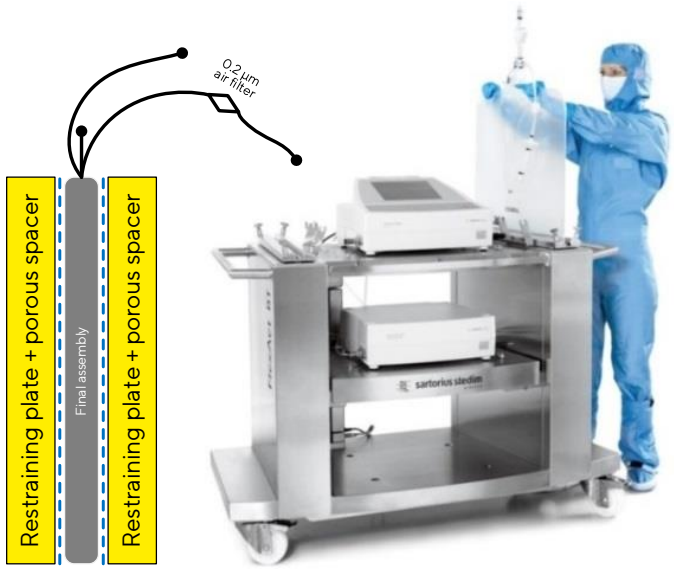
Detection limit (claim): **2 µm correlated** to microbial ingress and liquid leaks at shipping pressure conditions



Bag making → 1 BC-LT → Final assembly → **2 SIT** → Sterilization & shipment → 3 PoU-LT / PoU-IT

PoU-IT for 2D Bags Ensures that No Defects Have Been Generated During Shipping & Handling

- **Pressure decay** with restraining plates & porous spacers
- Restraining plates
  - Reduce stress on bag
  - Provide small inflation volume
  - Allow high test pressure: **300 mbar**
- Porous spacer avoid masking effect of potential leaks

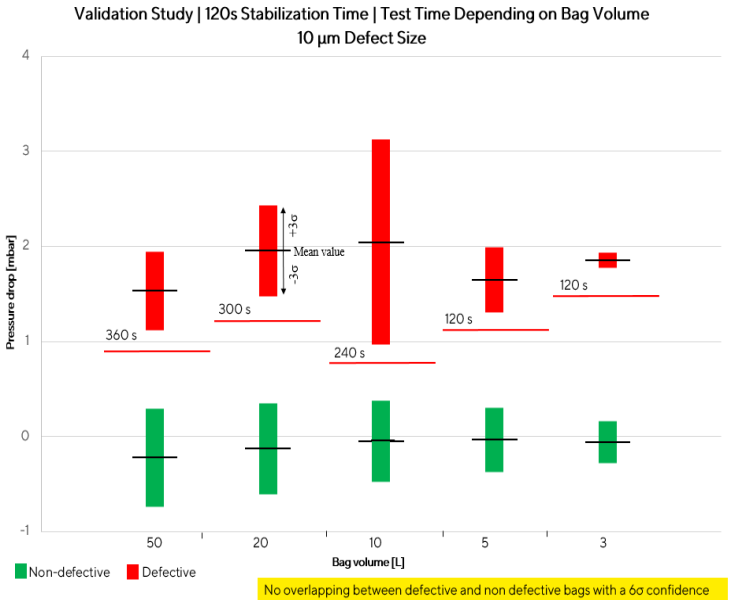


Combining small volume, high test pressure and spacers provides a fast, reproducible, accurate and sensitive test.
Detection limit: **10 µm correlated** to microbial ingress and liquid leaks at storage pressure conditions

Bag making → 1 BC-LT → Final assembly → 2 SIT → Sterilization & shipment → 3 PoU-LT / PoU-IT

Strong Validation of Physical Test Methods Example: Point-of-use Integrity Test for 2D Bags

- Measurement of defective & non-defective samples
- Use of representative and deliberately calibrated defective bag film patches for defect simulation
- Reliability proven using samples from multiple batches
- **10µm detection validated** applying a **6 sigma confidence interval**



Validation study with >700 tests to establish test specifications

Bag making → 1 BC-LT → Final assembly → 2 SIT → Sterilization & shipment → 3 PoU-LT / PoU-IT

PoU-LT for 3D Bags Ensures that No Gross Defects Have Been Generated During Shipping, Handling & Installation

- **Pressure decay** with porous spacers after installation inside the final container
- Porous spacers avoid masking effect of potential leaks
- Container mechanically supports the bag
- Fast filling kit available to shorten test times for large volumes
- Test is performed after installation, directly before use to detect leaks caused during complex handling & installation steps
- Detection limit: **100 - 200 µm for storage & shipping bags**
  50 - 400 µm for mixing bags

Bag making → 1 BC-LT → Final assembly → 2 SIT → Sterilization & shipment → 3 PoU-LT / PoU-IT

PoU-LT Ensures that No Gross Defects Have Been Generated During Shipping, Handling & Installation | SU STR Bioreactor

- **Pressure decay** with porous spacers after installation inside the final container
- Porous spacers avoid masking effect of potential leaks
- Container mechanically supports the bag
- Test is performed after installation, directly before use to detect leaks caused during complex handling & installation steps

Volume (L)	Max. test time (min)	Limit of detection (µm)
50	40	50
200	55	100
500	65	200
1000	85	400
2000	120	600

Bag making → 1 BC-LT → Final assembly → 2 SIT → Sterilization & shipment → 3 PoU-LT / PoU-IT

Proven Integrity of your process improves patient safety, regulatory compliance, production costs and drug availability

- Enhances patient and operator safety
- Prevents any risk of high value product loss at commercial phase
- Meets cGMP regulatory expectations for single-use system integrity
- Speeds up drug product manufacturing capacity and market availability with SU proven process integrity

Application: Gross Leaks Detection prior to Mixing

Point of Use Leak Test ensures that no gross defects have been generated during shipping, handling and installation

- A risk-based approach indicates that creating a defect of a size < 200 µm during the transportation, handling, storage and installation of is very unlikely to happen
- Test is performed after bag installation, directly before use to detect leaks caused during complex handling and installation steps
- Accurate pressure decay leak measurement
  - derived from ASTM F2095* test method
  - using Sartocheck® 4 plus Bag tester

* ASTM F2095-07: “Standard Test Methods for Pressure Decay Leak Test for Flexible Packages with and without Restraining Plates.”

Components Needed for Bag Testing

Magnetic Mixer bag with PoU-LT line

Testing tube for 3D bags

Palletank and Filter holder

Sartocheck® 4 plus Bag tester

Sartocheck® Fast filling kit (Optional)

Bag tester fleeces

Bag tester clamps

Porous Spacers I Fleeces Avoids False Passed Results

Porous spacers avoid masking effect due to direct contact of the bag onto the stainless steel panels of the Palletank

- Patented porous spacer I Bag tester fleeces
- The fleeces are designed to perfectly fit the shape of the Palletank and fixed using Bag tester clamps
- Fleeces can be easily removed after the test, important for heat transfer in jacketed Palletanks

Air Filling at Low Pressurization Stabilization I Test

- The Bag Tester fills directly to 50 mbar and stabilizes afterwards
- Air filling through pre-assembled gamma stable Air filter to avoid any sterility breakage
- All clamps can remain open during the test thus leak test also includes lines and connections
- This is not true if lines are fitted with filter, open tube, connections with membranes (Opta, KPC etc.), then clamp must be closed
- After stabilization time valves close and the pressure drop is measured

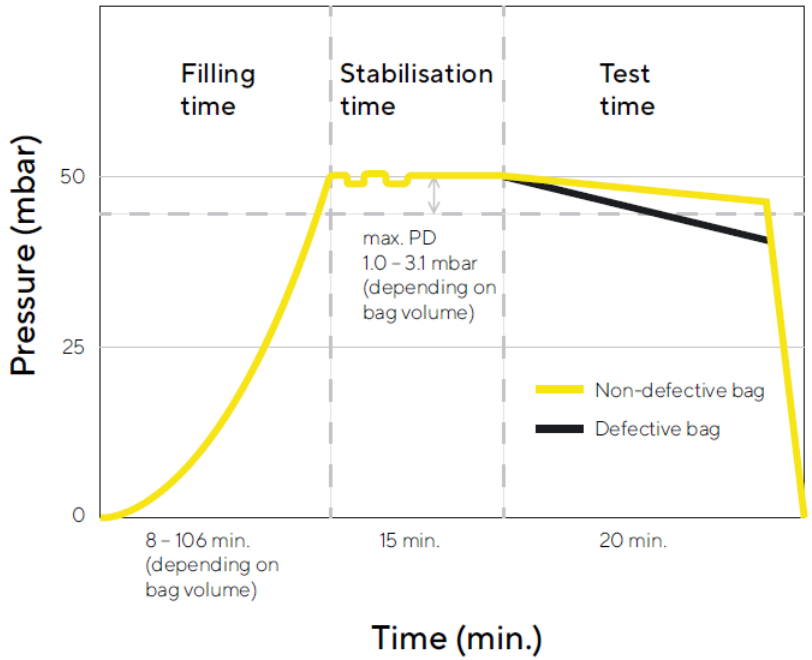
Mixing Point-of-Use Leak Test: Pass or Fail?

Test PASS

- Pressure drop remained below threshold limit, the test passed
- The bag is non-defective
- Mixing process can start

Test FAIL

- Pressure drop exceed the limit, the test failed
- Leak detected, the bag shall not be used



SUSI and Annex 1 [1]

- 8.129 Appropriate measures should be in place to **ensure the integrity** of components us
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.

- 8.131 SUS are those technologies used in manufacture of sterile products [...].

- 8.132 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. [...]

  vi. The risk of holes and leakage.

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

*Contamination Control Strategy

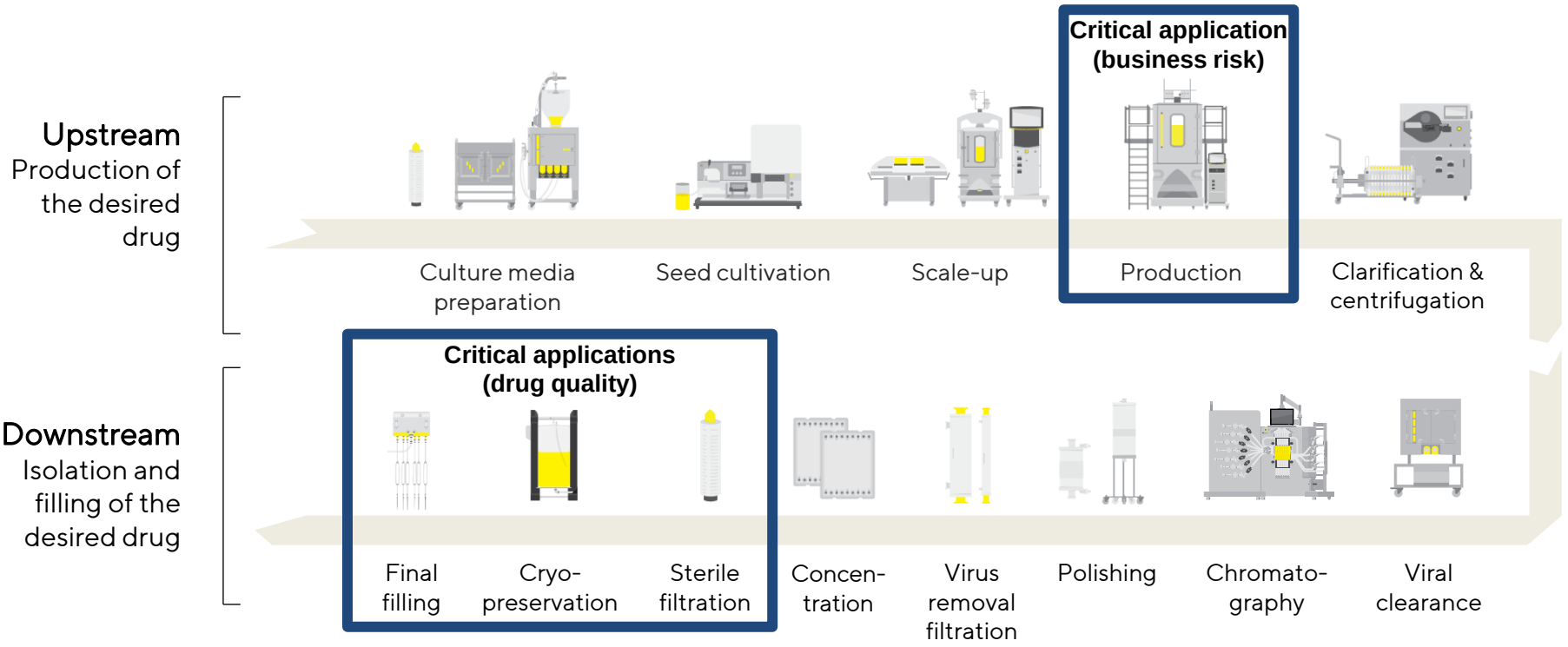
SUSI and Annex 1 [2]

- 8.134 For sterile SUS, verification of sterility assurance should be performed as part [...].

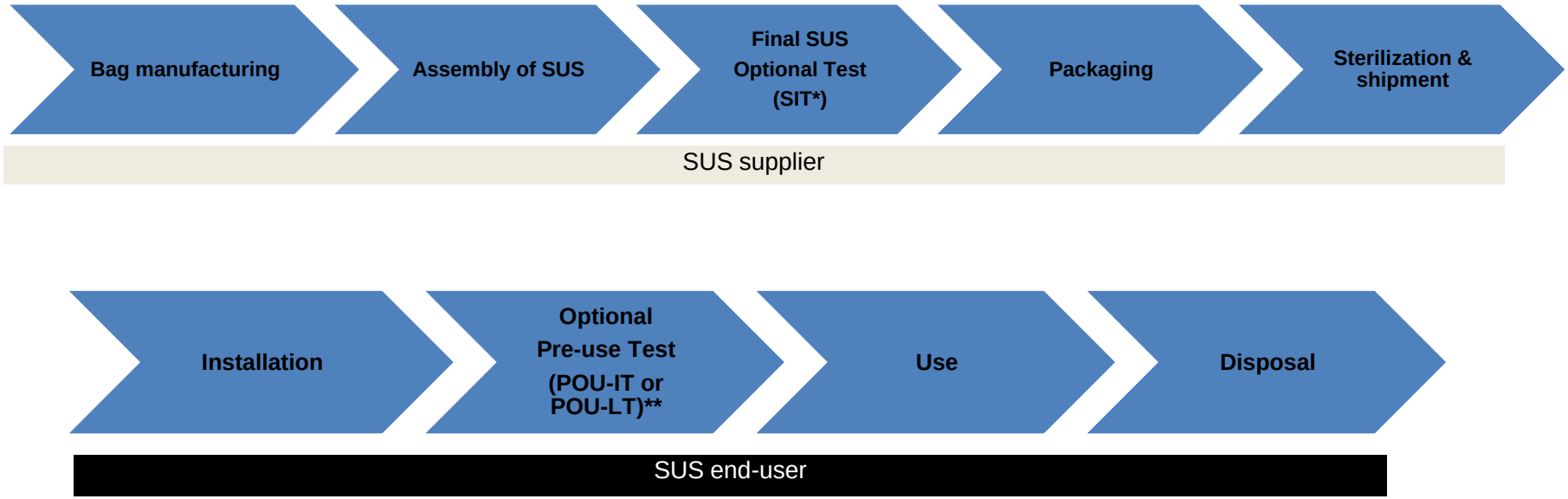
- 8.137 SUS should be designed to maintain integrity throughout processing under the intended operational conditions. Attention to the structural integrity of the single use components is necessary where these may be exposed to more extreme conditions (e.g. freezing and thawing processes) either during routine processing or transportation. This should include verification that intrinsic sterile connection devices(both heat sealed and mechanically sealed) remain integral under these conditions.

- 8.138 Acceptance criteria should be established and implemented for SUS corresponding to the risks or criticality of the products and its processes.

Typical Biotech Process and Main Critical Applications for SUS Integrity



QRM Principles Must Be Applied Along the Entire Life-Cycle of the SUS



*SIT: Supplier Integrity Tests
**POU-IT : Point-of-use Integrity Tests, POU-LT: Point-of-use Leak Tests

Sartorius' Testing Solutions Overview

Tests at Sartorius (supplier tests)

2D bags and 3D bags and mixers integrity offer Supplier Integrity Testing (2 µm SIT) : the corner stone to build your integrity strategy during the QRM

Tests at end-user (point of use tests)

Enhanced process safety by pre-use testing of STR single-use bioreactors

Leak test of Flexsafe® 3D storage and shipping bags, Flexsafe® mixers in a safe, fast & easy way

Integrity test of Flexboy® and Flexsafe® 2D bags for bulk drug substance or bulk drug product storage and/or shipping

Summary of Integrity Assurance Staratego

Robust design, manufacturing processes and controls

Specific optional tests when justified by the SUS application

Appropriate level of assurance of SUS integrity (SUSI)