Ensuring Single-use Systems Integrity

Case study: Helium Integrity Test

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PDA TRAINING

Nathalie PATHIER,
Product Manager, Applied Services

SARTORIUS

Industry Challenges

Why is SUS integrity a topic ?

Impacts of a SUS integrity loss

Product contamination compromizing its sterility

Operator/environment exposure to hazardous substances

Loss of product

- Productivity and economical impact
- Shortage
- Planning disruption

SUS for drug substance / drug product processing are typically the most critical

What is an « integral » SUS ?

User's requirements

- No liquid leak, no contamination
- Closed systems

- What does it means for a SUS in terms of actual defect size ?
- Does it depend on the SUS use and process conditions ?
- How to define the relevant integrity test ?
- How to correlate this test to leaks or microbial contamination ?

How to demonstrate it to regulatory bodies ?

Industry Guidances and Standards

Main regulations & guidances

Standards for Final Drug Products

- **EU GMP Annex1 - Manufacture of Sterile Medicinal Products** (released August 25th, 2022), Contamination Control Strategy (CCS) including SUS Integrity
- **USP 1207 - Sterile Product Packaging – Integrity Evaluation** (Container Closure Integrity or CCI) of primary containers of sterile dosage forms

Recommendations for SUS

- **BPSA 2023 (vol. 2) and 2017 (vol. 1)** Design, Control, and Monitoring of SUS for Integrity Assurance
- **PDA TR 86 2021** Industry Challenges and Current Technologies for Pharmaceutical Package Integrity Testing

Standard Practice and Test Methods for SUS

- **ASTM E3244-20** Standard Practice for Integrity Assurance & Testing of SUS
- **ASTM E3251-20** Test Method for Microbial Ingress Testing on SUS
- **ASTM E3336-22** Test Method for Physical Integrity Testing of SUS

Definitions from ASTM E3244

Leak test

A test used to identify leaks not correlated to the defined barrier properties of a Single-Use System (SUS)

Integrity test

A test used to confirm the defined barrier properties of a SUS

Maximum Allowable Leakage Limit (MALL)

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 to assure that a SUS maintains its integrity prior to and during use

ASTM E3244 Standard Practice for Integrity Assurance and Testing of SUS

Approach for Assurance of Integrity

The supplier:

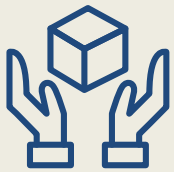
- Ensures the SUS robustness and integrity by applying Quality by Design (QbD) principles and validation during product development phases
- Performs process controls during the SUS manufacturing and optional Supplier Integrity Tests (SIT) upon request and when applicable

The end-user:

- Performs a risk analysis considering the SUS application and the impacts of an integrity breach on the drug quality, operator exposure or business continuity
- Mitigates the risk of compromising the SUS integrity by:
  - Visual inspections, operator trainings for handling, installation and use
  - Optional Point-of-use Integrity Tests (POU-IT) or Leak Tests (POU-LT) of the SUS at his site, when applicable

A joint responsibility applicable across the whole lifecycle of the SUS

How to ensure that no product leakage or microbial ingress can occur during the process?



SU Product Robustness

QbD, validation tests & studies, process & quality controls

SU System Integrity Science

Understand leak & microbial ingress mechanisms

Integrity Testing Technology

Supplier integrity tests
Point of use tests

Three pillars to reduce the risk of leakage or microbial ingress during the drug manufacturing process

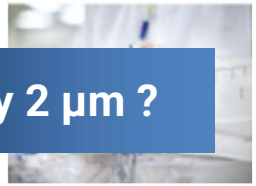
Testing strategy must be adapted to the criticality of the application – Example for 2D bag assemblies

Supplier

Bag chamber leak test

SU assembly integrity test (2 µm)

Why 2 µm ?



End-user

Point-of-use integrity or leak test

Discard defects from bag chamber manufacturing operations

Discard additional defects from bag chamber manufacturing and assembly operations

Discard additional defects from transportation & handling operations

Case study: Helium Integrity Test

Original questions

What is the leak size of concern for a given SUS application ?	1
When does a SUS liquid leak ?	2
When can the product be contaminated by microorganisms ?	3
How are test methods validated and what does a leak test result mean ?	4

Sciences studies on integrity of single-use system (container)

SUS applications and pressure ranges

Hydrostatic pressure in storage

~0.7m / 2'

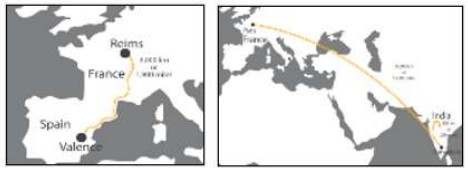
Max pressure 70mbar

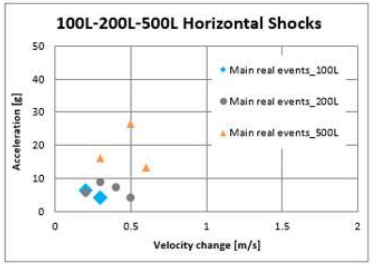
Flexboy® 20 L

Flexsafe® 500 L

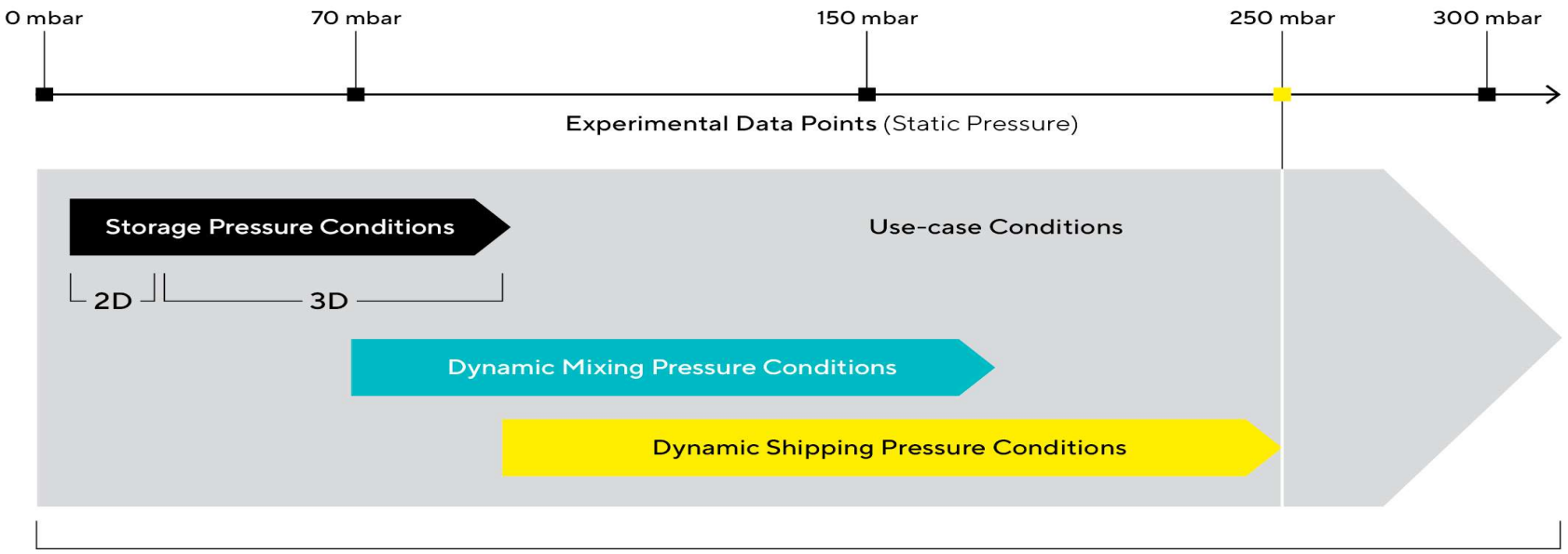
Application	Pressure range
Storage	~10 – 100 mbar
Shipping	~100 – 250 mbar

Shipping can generate up to 20g acceleration





Pressure ranges for our integrity science studies



Range of pressures covered by integrity sciences experiments (0 - 300 mbar) exceeds most severe use-case conditions (max. 250 mbar).

Identifying conditions leading to liquid leak

Liquid leak results for PE film at 300mbar imposed pressure

	Hole size µm	2 µm	3 µm	5 µm	10 µm
Water	Number of samples	3	3	3	3
	Number of leaks	0	2	2	3
TSB*	Number of samples	3	3	3	N/A
	Number of leaks	0	1	1	N/A

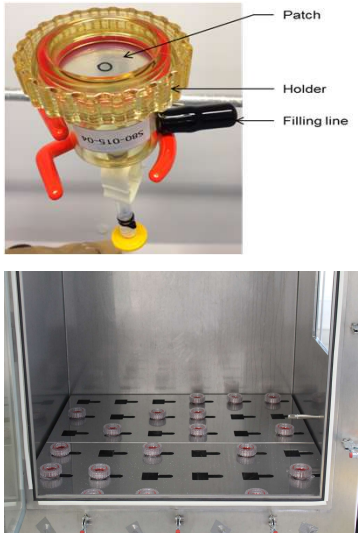
* Trypticase soy broth (growth media for BCT trials)

Liquid tests on film show no leaks on 2µm defects at 300 mbar

Identifying conditions leading to microbial ingress

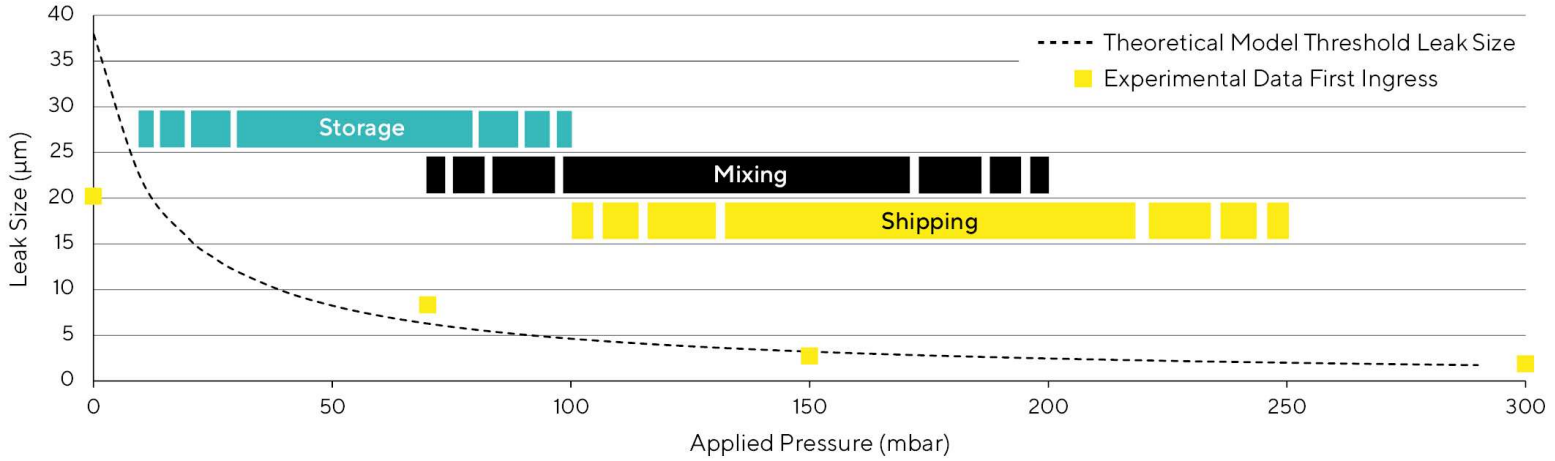
BCT results at 300mbar imposed pressure

	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



Microbial aerosol tests on 300 film samples show no ingress for 1µm defects at 300 mbar

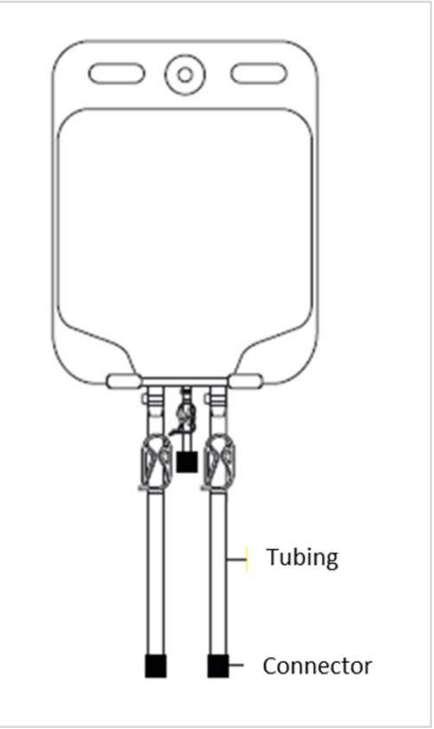
Relationship between microbial ingress and liquid leaks for Flexsafe® products



2 micrometers is the MALL for liquid leaks and microbial ingress for all use-case conditions up to 250 mbar

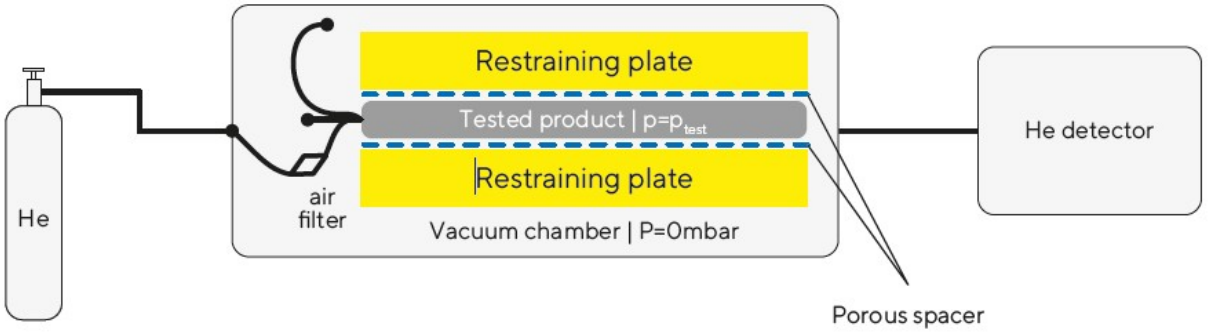
Test method main requirements

- Test of **product assembly** (bag chamber incl. tubing lines & connectors*)
- **100% non-destructive** testing (deterministic approach)
- **Sensitivity** that can be correlated to **microbial ingress** (2 µm)
- Capable to be implemented in-line **in routine production of SU assemblies**



*Note: some connectors are not suitable for the helium test, e.g. membrane connectors

Test method concept



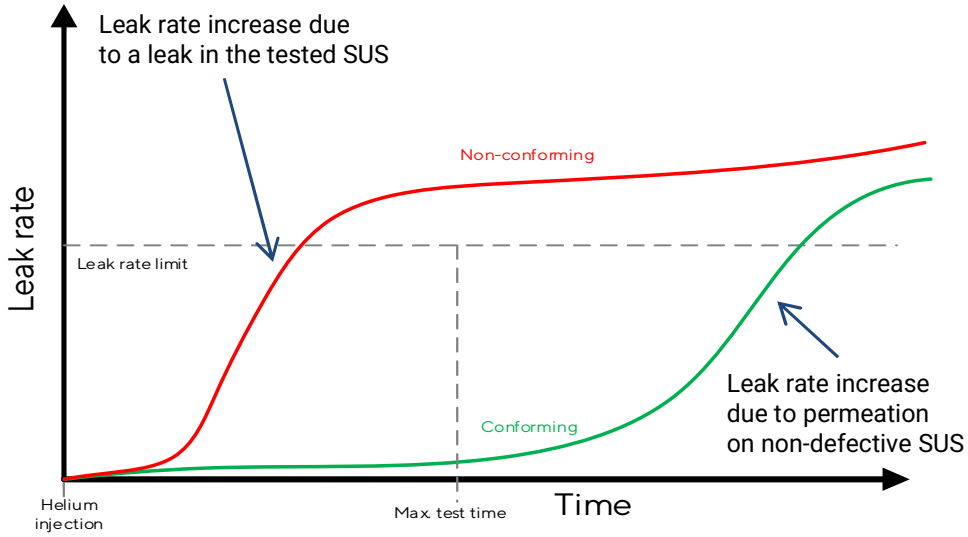
Schematic Diagram of the Helium Test

- Helium used as a tracer gas to detect a leak
- Test performed in a vacuum chamber
- Porous spacers avoid masking effect
- Restraining plates reduce stress on bag
- Test on SU bag assembly

Test working principle

- **Vacuum drawing** in the test chamber
- **Background monitoring** to achieve a suitable helium level
- **Helium injection** in the SUS, compare helium leak rate to limit (threshold)
- **Evacuation** of helium from the SUS, flooding to ambient pressure

Link to SIT video
https://www.sartorius.com/en/products/fluid-management/proven-integrity



Validation approach for the test of SUS at 2 µm

Determination of the type of defect to be used for the validation

Evaluation of the impact of different product (SUS) designs

Determination of the reject threshold with a 6 sigma confidence interval for the differentiation between defective and non-defective samples

Determination of the type of defect

2µm MALL for most stringent use-case conditions

- 2 µm defined target for the helium test validation

Two types of defect tested:

- Patches of film with defect
- Capillary tubes

Defects calibrated and placed at worst-case locations

Parameters study

- Evaluate impact of different product designs

Volume

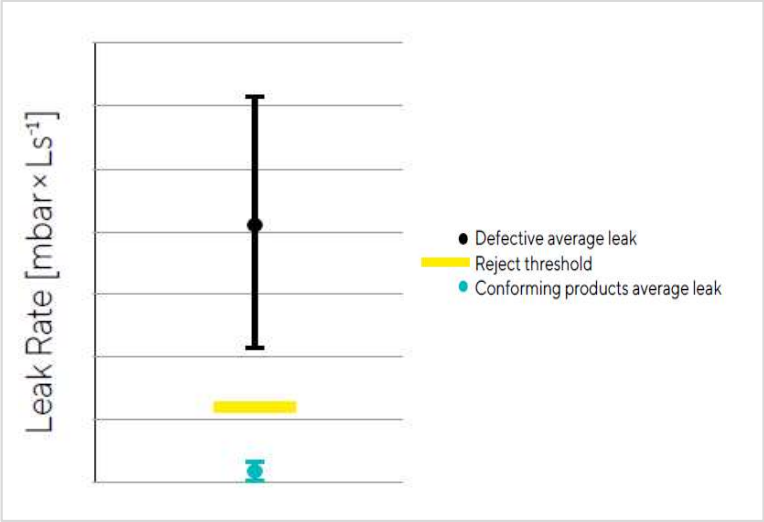
Components

Material

- Determine test parameters for worst-case product configuration

Validation study

- Verification of the previously determined test parameters
- Tests on a statistically significant number of test samples
- **Determine pass/fail criteria**
  - Segregate negative from positive controls with a confidence interval of six times the standard deviation (6 sigma)



Confirmation of defect type → **Parameters study** → **Validation**

Proven Integrity of Single-use Systems with Helium Integrity Testing

- Physical test performed on SUS assemblies at our manufacturing site upon request, non destructive test
- Reliable validation of the test with a 2 µm detection limit allows a correlation to both liquid leak and microbial ingress
- Recommended for critical SUS applications (eg aseptic processing)

No Liquid Leak

No Microbial contamination

Meeting quality and regulatory requirements for critical BDS/BDP* applications

*BDS/BDP: Bulk Drug Substance / Bulk Drug Product

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Acknowledgement

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PDA Parenteral Drug Association
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Q & A

Contact: nathalie.pathier@sartorius.com

Reference publications in PDA Journal of Pharmaceutical Science and Technology

- 1st publication: 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
- 2nd publication: Single-Use System Integrity II: Characterization of Liquid Leakage Mechanisms https://journal.pda.org/content/early/2020/11/16/pdajpst.2020.012088
- 3rd publication: 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
- 4th Publication: Single-Use System Integrity IV: A Holistic Approach Based on Compiled Scientific Study Data | PDA Journal of Pharmaceutical Science and Technology