Ensuring the Product Robustness, the Science and the Technologies for **Proven Single-Use Container Closure Integrity**

Case Study: Helium Integrity Test

Marc Hogreve
Senior Engineer Integrity Testing
Sartorius Stedim Biotech

Industry Challenges

Single use process integrity is a key industry & regulatory challenge

Validated SU Container Closure Integrity (CCI) required to:

- Strengthen regulatory compliance
- Improve patient safety

> Bag failures cost ~$100K to $1M per bag
>
> R. Wong, Bayer

SU container integrity testing (SU-CCIT) is meaningful when it correlates to liquid leaks & microbial ingress

- Lack of understanding of defect size causing liquid leaks and microbial ingress under real life conditions
- Current CCIT not correlated to leaks & microbial ingress

> Leaks have been reportedly responsible for up to $20M worth of products per year at some larger facilities.
>
> Bioplan

Users cannot show real proof of process integrity to regulatory organizations

Why are concerns about Integrity a key industry challenge for SUS?

SUS Used in Drug Substance & Drug Product Process Steps Require Higher Assurance of Container Closure Integrity (CCI)

> We're very much concerned about the integrity of SUS used in final filling applications.
>
> FDA Inspector 02|2018

FDA-ASTM Workshop - Oct 2016 [1]
Examples of SU validation activities and Integrity testing

Validation for SU fill finish sterile product manufacturing

- **Physical integrity test correlated to microbial ingress**
- Packaging integrity at the supplier, post shipping & post-installation

Microbiological challenge testing

- Identification of defect size that would allow ingress of bacteria **under process conditions**

[1] SUS: A Microbiology Product Quality Perspective - Patricia F. Hughes, Ph.D.., Branch Chief (Acting), CDER/OPQ/OPF/DMA

FDA-ASTM Workshop - Apr 2018 [1]
SUS fill finish assemblies for sterile products

Must meet requirements to ensure flow-path sterility and integrity

- Supporting sterilization validation summary data and information on the gamma irradiation process

- **Integrity tests are also reviewed during the review of the BLA and on inspection**

An example of an information request sent to an applicant is as follows:
"You have submitted supplier's leak testing data and method qualification information for the single use assembly. Implement a leak integrity test for the single use assembly prior to use for filling at the facility."

[1] Sterile drug product, New developments - Patricia F. Hughes, Ph.D.., Branch Chief (Acting), CDER/OPQ/OPF/DMA

Industry Challenges

- **USP<1207> 2016** *package integrity evaluation – sterile products*
- **ASTM E55 WK64337 2018** *Standard Practice for Integrity Assurance & Testing of Single-use Systems*
- **ASTM E55 WK64975 2018** *Test Method for Microbial Ingress Testing on Single-use Systems*
- **New PDA TR** *on Pharmaceutical package integrity (to replace existing TR27 from 1998)*
- **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 process

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

» SU Product Robustness

- Understand liquid leakage & bacteria ingress mechanisms
- Correlate detection limit to liquid leaks & microbial ingress

» SU Container Integrity Science

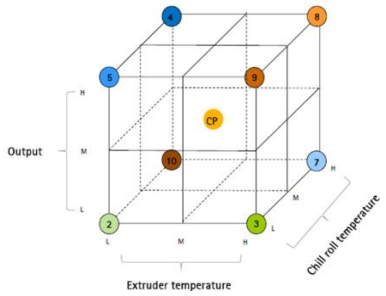
- Implement 100% physical supplier integrity testing
- Provide point of use testing

» 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 the process

Single-use Product Robustness

QbD, process control and quality control to reach consistent robustness



~ 3000 robustness tests

Tensile Strength: 930

Elongation at break: 930

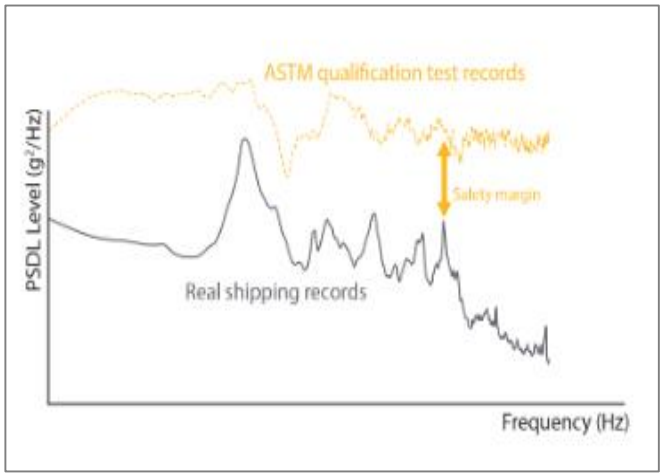
Puncture tests: 930

Flex durability: 186

Water burst tests : 26

Most stringent standards:

ASTM D4169



Passed ASTM Shipping Test

Self-deploying bag after installation

Avoid mishandling

&

reduce bag failures

Process & Quality Controls Ensure CCI along our **Entire Production Cycle**

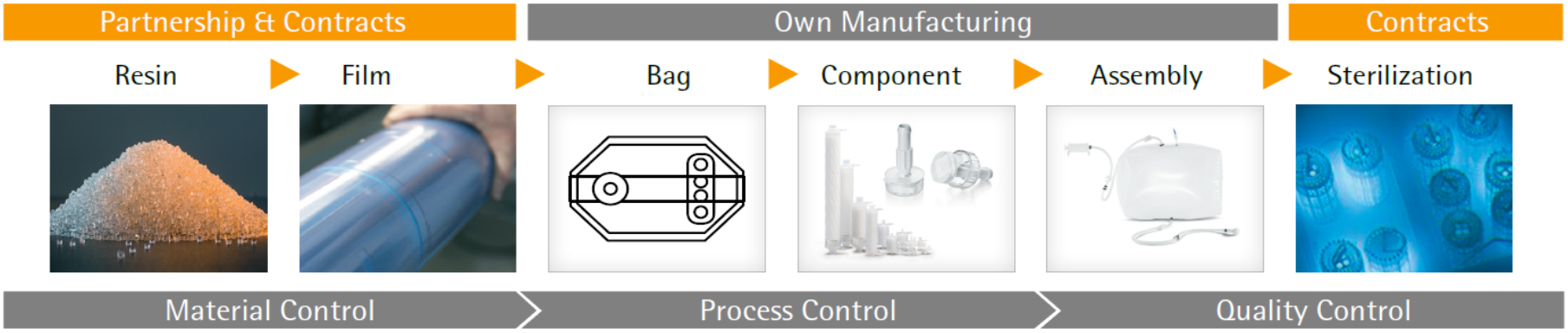
Process control reduces the risks of defects on film, seals, welds & connections

- Extrusion temperature & speed,
- Weld & seal temperature & time

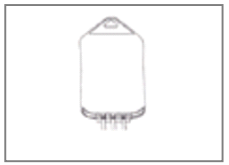
> SU-CCI is the Result of Process Qualification and Quality Controls Along the Entire Product Life Cycle

Quality controls confirm the absence of leaks

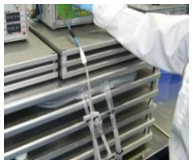
- Film & seal strength integrity,
- Microbial Ingress Testing – ISO15747 - Immersion in B. Diminuta
- 100% Bag Chamber Leak Test (BC-LT)



Intermediate process control, quality control & final product integrity testing



Bag chamber leak test
40 – 90 µm



Discard 400ppm defects from manufacturing operations
Integrity Assurance Level (IAL) 10^{-4}

Assembly
Helium SIT
2 µm

Discard 500ppm additional defects from manufacturing operations
Integrity Assurance Level (IAL) 10^{-5}

But, why 2µm?

PoU-IT
10 µm
FlexAct® BT

Discard 20ppm additional defects from transportation & handling
Integrity Assurance Level* (IAL) 10^{-6}

Existing data in peer-reviewed publications on **critical leak size for sterile package using micro tubes**

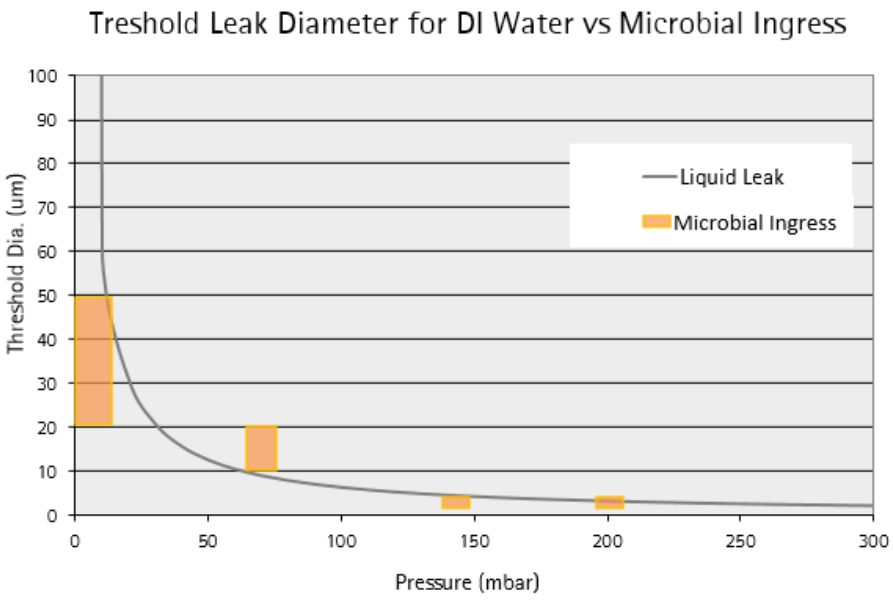
Liquid leak & bacterial ingress depend on

- Process & applications conditions
- Liquid properties (mainly surface tension)
- Size of defect

Correlation between liquid leak & bacterial Ingress

- Microbial ingress cannot occur without liquid flow (Kirsch & Morton, 1989)

Gibney, 2000 $P_o > P_{atm} + \left[\left(\frac{4\sigma}{D_h} - \rho g L\right) \times 0.390\right]$



2µm is the maximum allowable leakage limit that never produce liquid leak or microbial ingress in any process conditions using micro tubes

Single-use Container Integrity Science

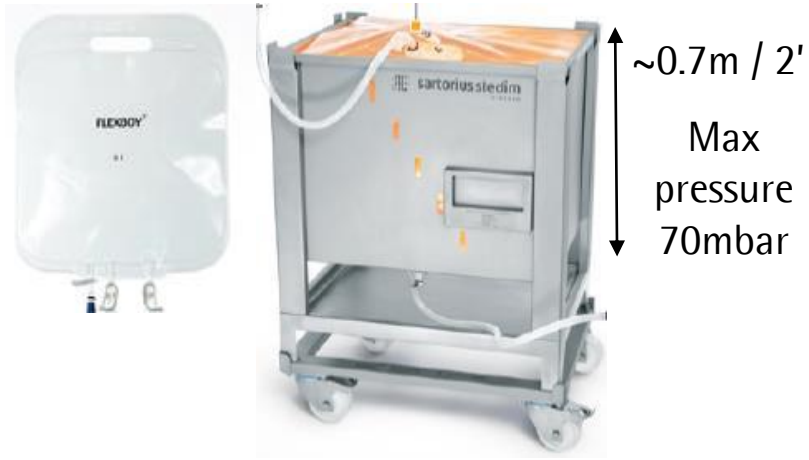
Understand liquid leakage and microbial ingress mechanisms on film materials used in single use biomanufacturing

- 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: is the greatest leak size tolerable that poses no risk to product safety, USP<1207>

Process Conditions Impact Liquid Leaks & Microbial Sizes

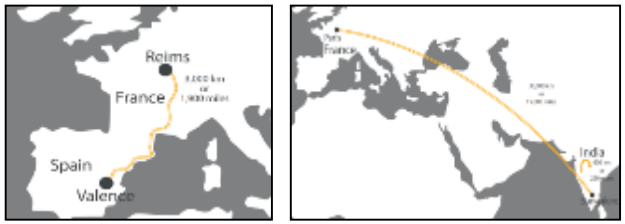
Hydrostatic pressure in storage

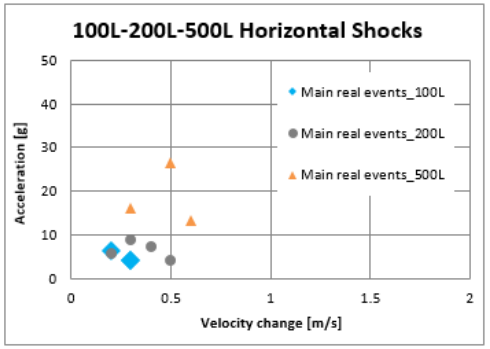


Flexboy® 20 L Flexsafe® 500 L

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

Shipping can generate up to 20g acceleration





Interim conclusion from results obtained on **liquid leak & microbial ingress studies** on SUS

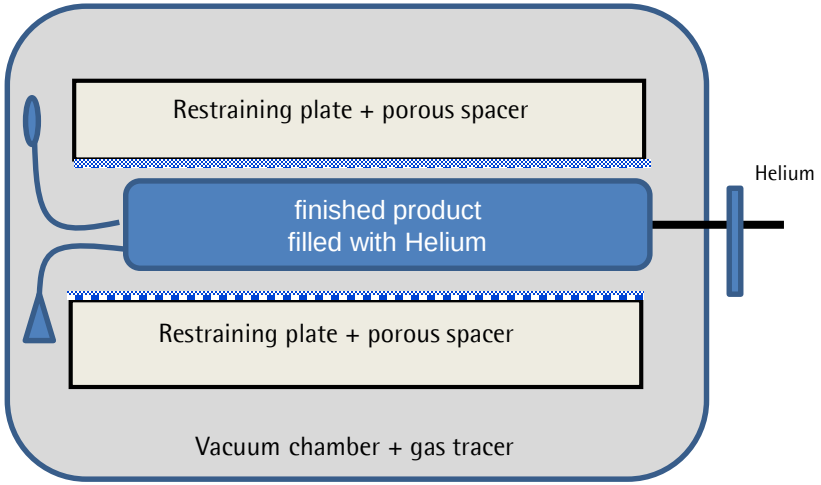
- Results obtained on film materials fall into the existing models for sterile package using micro tubes
- Both studies, liquid leak and microbial ingress ones, tend to confirm that leak sizes for liquid flow are not significantly different from leak sizes for sterility loss
- The conditions of use (pressure) 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

Main Requirements

- Test of **finished product** (bag chamber incl. lines & connectors)
- **100% non-destructive** testing (deterministic approach)
- **Sensitivity** that can be correlated to **bacterial ingress**
- Capable to be implemented **in-line in routine production**

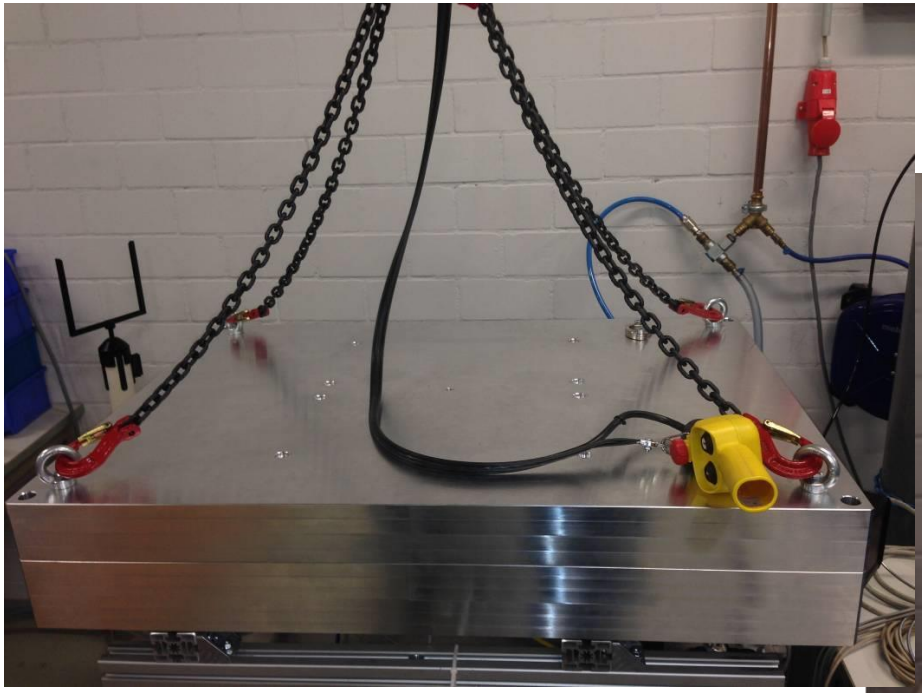
Test Concept

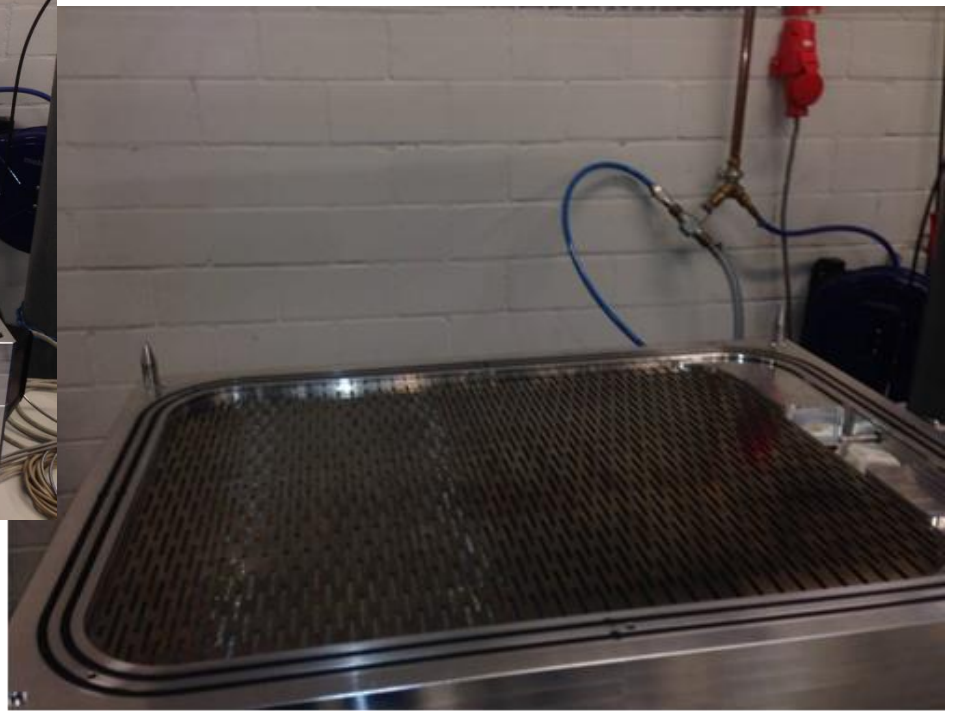
- Porous spacers avoid masking effect
- Restraining plates reduce stress on bag
- Test can be used as “Integrity Test” covering the whole SUS
- Gas leak rate can be correlated to a leak size of 2µm



small inflation volume + high test pressure = best sensitivity

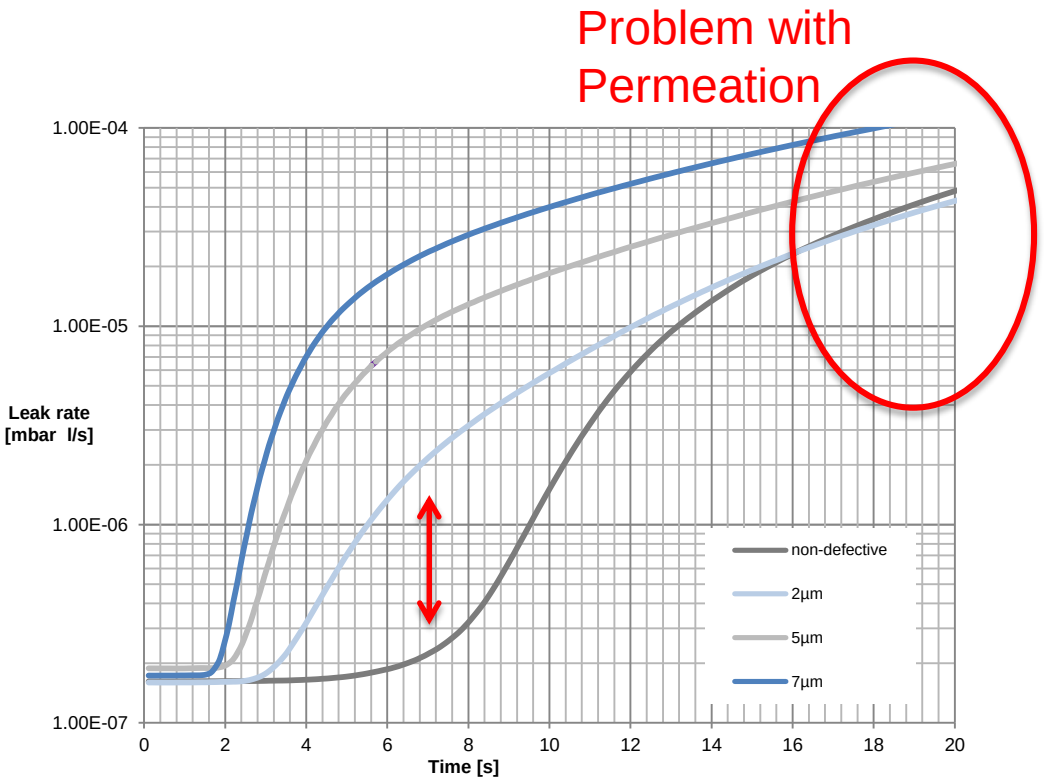
Feasibility Tests





Feasibility Tests

- Feasibility tests done with three different test gases
- Results based on 20 samples per leak size (50l bags)
- One decade differentiation in the time frame between 4-10 s
- Helium gas tracer was the best test method to achieve a level of detection **down to 2 µm**



Results for helium testing

Challenges for Industrialization

- High permeability of helium through the thin bag film
- Outgassing of volatile components
- Vacuum level vs. tact time
- Helium background concentration & absorption

Solutions for Industrialization

- Machine concept with fast helium filling to measure before the start of permeation
  => dynamic leak rate evaluation
- High vacuum to get lowest background level
- High vacuum pump capacity to reach vacuum in a reasonable time frame
- 2 chamber design for alternating operation to reach target tact time
- Flexible chamber design to cover different product families

Finished Product SIT to Test **100%** of 2D Bag Assemblies Used in Critical DS & DP Applications

- **Helium Gas Tracer in Vacuum Chamber**
- Restraining plates
  - Reduce stress on bag
  - Provide small inflation volume
  - Allow high test pressure: **300 mbar**
- Porous spacer avoid masking effect of potential leaks

- With low background noise and dynamic leak rate measurement helium gas tracer is the best method to achieve reliably highest sensitivity
- Detection limit: **2 µm correlated** to microbial ingress and liquid leaks at 300mbar pressure (shipping pressure conditions)

Validation Approach

- A **reliable** test method using samples from multiple production lots
- A **reproducible, accurate** and **robust** test method using a 6 sigma confidence interval for the differentiation between defective and non-defective samples
- A **sensitive** test method using defective samples, calibrated on a pinhole equivalent
- A **One-for-all** validation procedure, whatever the test method is

Definition of Defect

- Aerosol BCT & liquid leak studies performed on different bag film materials
- Identification of MALL for microbial ingress & liquid leak under **different process conditions**
- 2µm estimated as MALL for worst-case (shipping) conditions -> target for the helium test validation
- Deliberate defects manufactured and confirmed with flow calibration

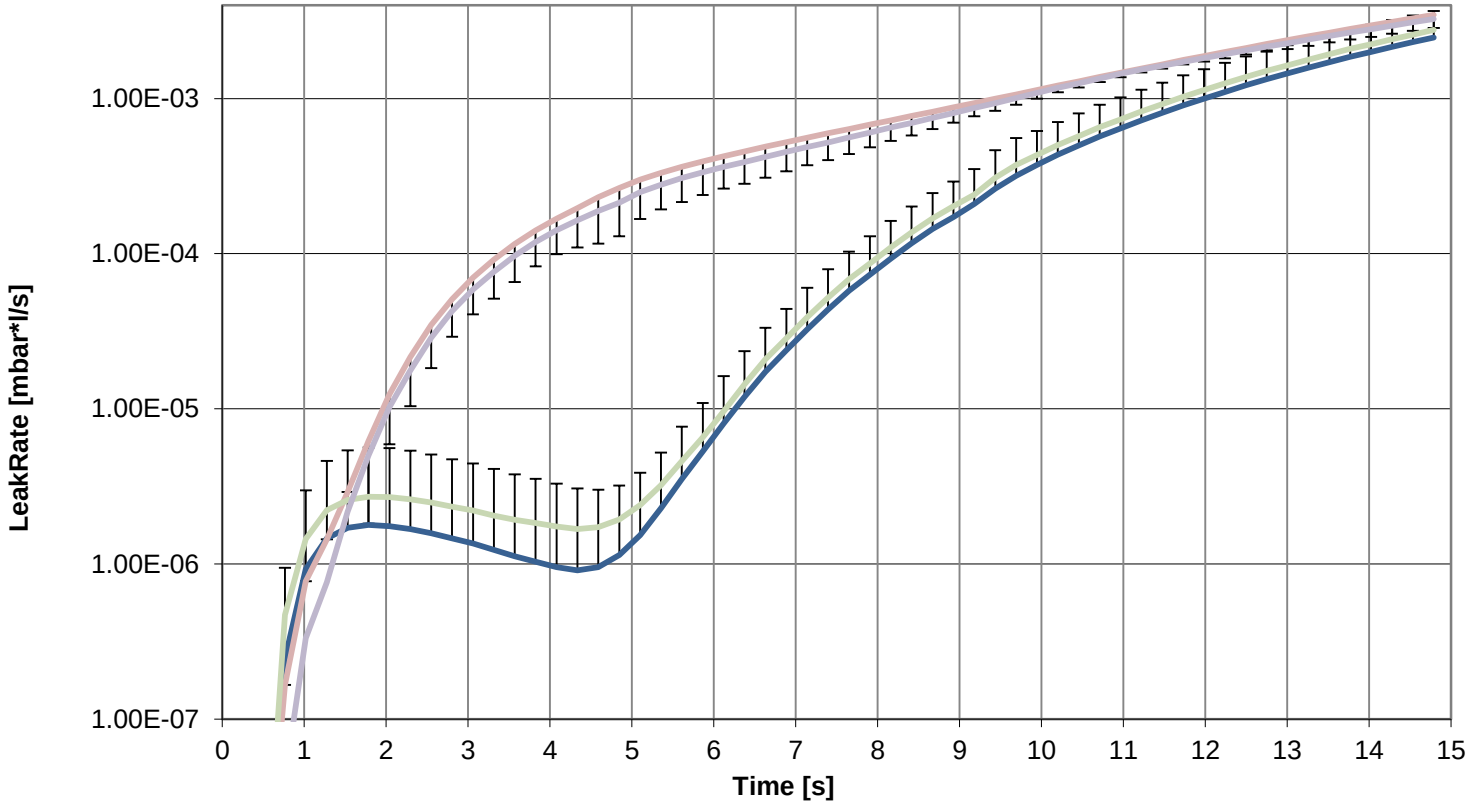
Definition of Defect

- Different types of defects tested: patches and capillaries
- Defects placed at worst-case positions

Parameter Study

- Evaluate impact of different product designs
  - Volume
  - Components
  - Material
- Determine optimum test parameter set(s)
- Tests on a limited number of test samples

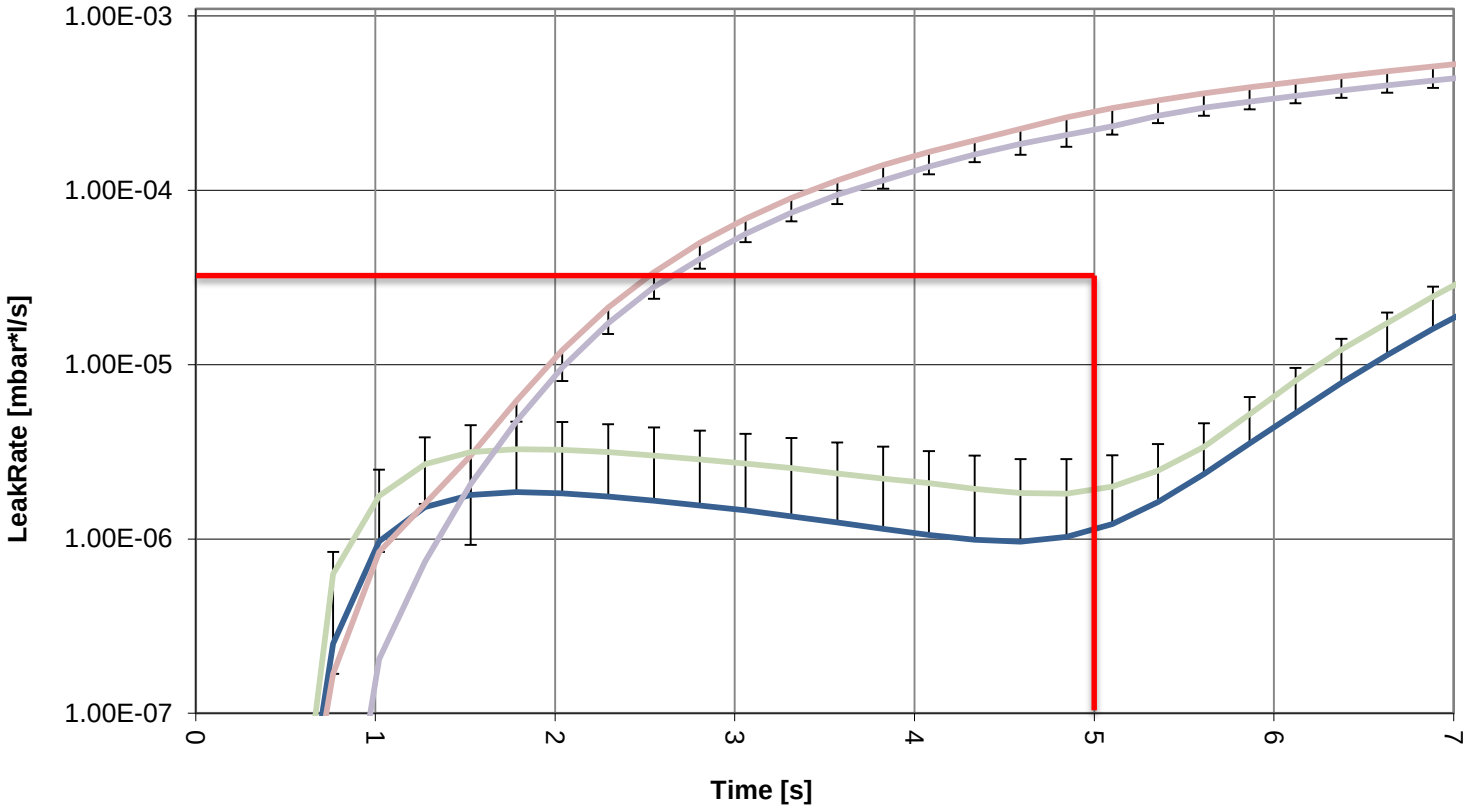
Parameter Study Results on 50L Bags



Validation Study

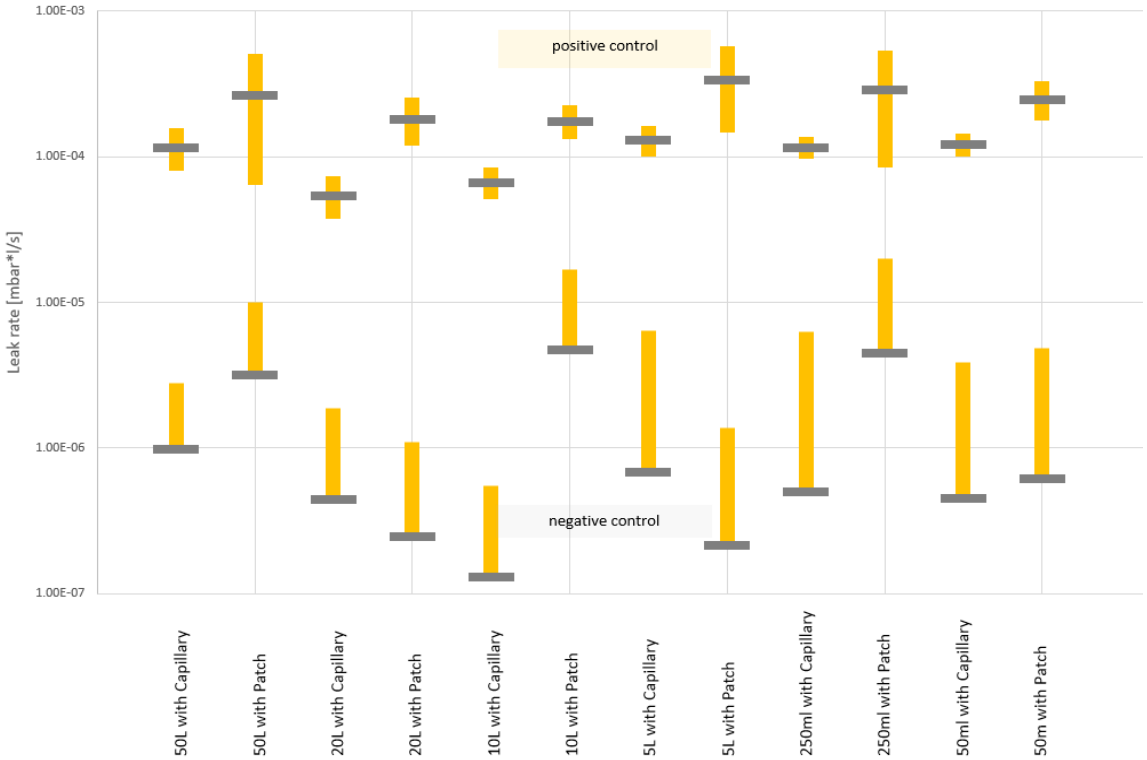
- Verification of selected test parameter set(s)
- Determine pass/fail criteria (time & leak rate limit) **=> dynamic leak rate**
- Tests on a statistically significant number of test samples

Validation Study Results on 50L Bags



Validation Study Result Overview

- Measurement of defective & non-defective samples
- Use of different types of artificial defect, like film patches & capillaries
- Defects deliberately calibrated
- Reliability proven using samples from multiple batches
- **2µm detection validated** applying a **6 sigma confidence interval**



Validation study with >380 tests to establish test specifications

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

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

- Questions?