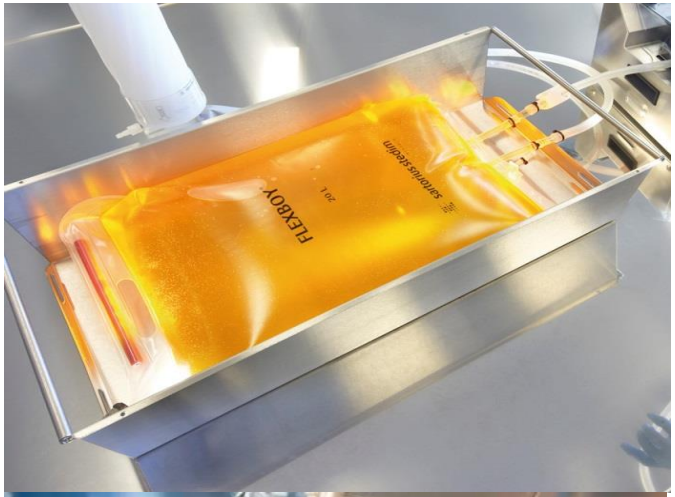
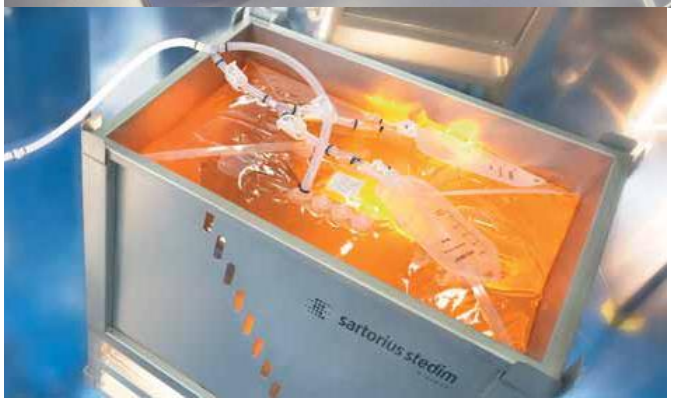
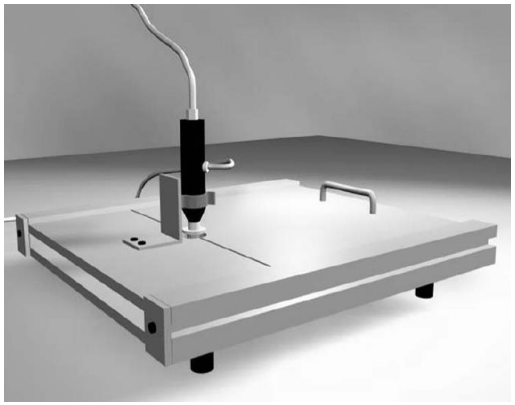




SU Container Closure Integrity via QbD, Process Validation, Process Control & Supplier/End User Integrity Testing

Single-Use (SU) Container Closure Integrity (CCI)



1. Regulatory & Industry Requirements
2. SSB Position Statement on SU-CCI
3. Quality Risk Management, Process Validation and QC
4. Supplier bag chamber leak test and Integrity Testing
5. Pre Use Leak Testing for Flexboy®
6. Conclusions

SU-FMT Increasingly Used in All Process Steps & Applications of cGMP Production Leading to More Stringent Requirements

UPSTREAM PROCESSING	DOWNSTREAM PROCESSING	FORM/FILL & FINISH
Media preparation **Cell Culture harvest**	**Buffer preparation**	**Buffer preparation**
SU-FMT have grown on cell culture harvest, media & buffer preparation & early process intermediate steps	**Purification & Polishing of Drug Substance**	**Formulation & Filling of Drug Product**

SU-FMT implemented on more critical process steps:
Process Intermediates, Drug Substance & Drug Product

Different Criticality of Process & Applications Clusters (PACs) Call for Different Container Closure Integrity Approaches

PAC-definition	**PAC 1** Media, buffer, harvest	**PAC 2** Drug substance	**PAC 3** Drug product
PAC-specific Integrity testing requirements	Supplier in process control	Supplier integrity test end user leak test	Supplier integrity test end user leak test

A Growing Requirement for Single-use Container Closure Integrity Testing (CCIT)

There is a growing use of Single-Use Systems (SUS) in critical process steps and applications

Risk of integrity loss remains a hot topic

Authorities support the creation of standard practices:

USP<1207> proposed revisions, ASTM E55 WK's

CCIT for SUS requires Quality Risk Management approach throughout the product life cycle

Standard & Guidance

PDA TR 27 1998 *Pharmaceutical package integrity* (re-write)

USP<1207> 1998 *Sterile product packaging – integrity evaluation* Proposed Revisions to General Chapter

FDA guidance 2008: *Container and Closure System Integrity Testing in lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products*

ASTM E55 WK43741 2014 *Standard Practice for Testing Integrity of Single-Use Systems at Vendors Manufacturing Facilities*

ASTM E55 WK47355 2014 *Standard Practice for Controlling Integrity of Single-Use Systems during Biopharmaceutical manufacturing process at End-user factory*

End User Requirements for Single-Use Container Closure Integrity

There is no industry consensus yet on SU Container Closure Integrity requirements

- **Supplier test** and/or
- **Pre use** at point of use and/or **Post use** at point of use?
- Correlation with bacterial ingress testing – **Immersion** or **Aerosol**?

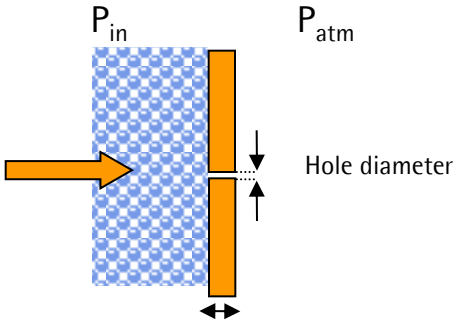
Most current end users require a **point of use leak test** to mitigate the risk of product loss

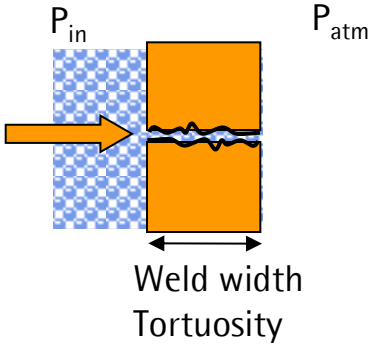
- **Pre-use** post installation test in associated container and
- Leak detection requirement depending on the PAC

Emergent need for **post-use testing** in final filling of drug products for **regulatory compliance**

- Point of use leak test is required in complement to a supplier Integrity Testing
- 100% test on the **full SU assembly**
- **Higher sensitivity** detection test correlated to a **Bacterial Ingress Testing**

Quality Risk Management at Supplier
Potential Leak Risks in a Single-Use 2D Bag Assembly





Pinhole leak at the **film** surface

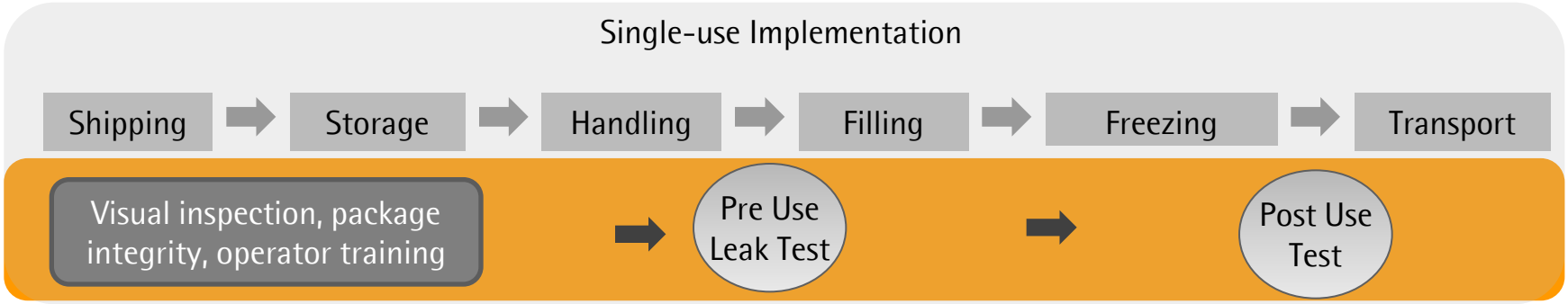
Channel leak in bag **seals**

Channel leak at the junction **weld** between the port tube and film

Channel leak at the Hose barb **connections**

We understand the leak failure mode at each stage of the process and mitigate the risk with process validation, process control and quality control

Quality Risk Management at End User
Most of Defects before Use are in the 200µm to 5mm Range



Our track record shows that defects due to mishandling during transportation, storage and installation could be in the range of 200µm to 5mm before use

Main defect modes

- Film cuts due to use of sharp tools
- Tears due to tough manipulation of bags
- Hose barb leaks due to tough manipulation of tubing lines

Smallest acupuncture needle is 100µm

Smallest leak detection is required at supplier for continuous process improvement, Detection limit target range for Point-of-use leak test can be higher, 15 – 500µm

Different PACs Require Different CCIT Approaches

PAC/ Critical Level	GMP application & process step	Supplier Test	PoU Pre-use	PoU Post-use
PAC 2 & 3 High	• **Downstream of sterilizing grade filtration step** • Bags shipped **outside** of clean rooms	X		X
PAC 2 & 3 Medium	• **Upstream of sterilizing grade filtration step** • Bags stay in clean room environment	X	X	
PAC1 Low	• Intermediate **sterilizing grade filtration step**	Rely on product quality (QC, robustness)		

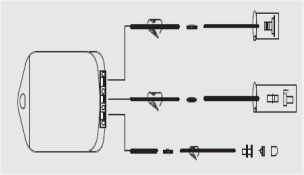
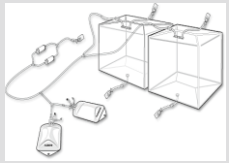
The highest sensitive physical test methods need to be developed to grow critical drug product & drug substance process steps for SUS

SU-CCI is the Result of Quality by Design, Process Controls and Quality Controls Along the Entire SUS Life Cycle

Compliant with ICH Q9 HACCP concept described in section I.5

	Supplier Qualification Tests	Supplier Production Controls	End-User Process Validation & Controls
Current	• Mechanical tests on film and weld • Microbial immersion test • Packaging validation • Shipping validation	• Seal quality tests • Visual inspections • Microbial immersion test • **100% 2D Bag Chamber Leak Test by Pressure Decay**	• Package integrity • Visual inspection • Media hold & media fill • Microbial immersion test • Operator training • **Pre-Use Leak Testing 2D bags - pressure decay**
in Progress	• Microbial aerosol test – correlated to leak size • Liquid leak test – correlated to leak size	• **100% 3D Bag Chamber Leak Test – pressure decay** • **Finished product Supplier Integrity Test – Helium test**	• **Pre-Use Leak Testing 3D bags – pressure decay**

CCIT Involves 2 Different Testing Methods, Pressure Decay & Gas Tracer Test at 3 Stages in Product Life Cycle

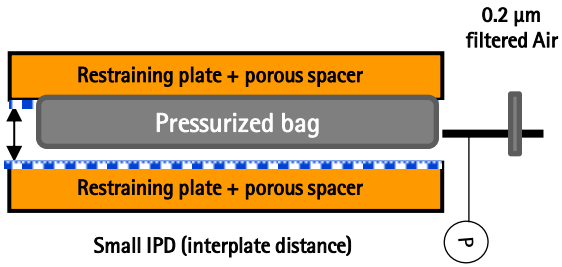
	1 Bag Chamber Making (BC)		2 Finished Product Assembly (FP)	
Product Family	100% Bag Chamber Leak Test (BC-LT) **Pressure Decay** For all PACs		100% Supplier Integrity Test (SIT) **Gas Tracer** for PACs 2 & 3	
Flexboy Flexsafe Celsius OctoPlus FF Up to 50L	2D 	Implementation for all bag chambers in production ALL PACS Detection limit 30 – 100 µm	2D Assemblies 	In development for 2D flexboy For PACs 2&3 Detection limit 2µm
Flexsafe & Mixers Up to 500L	3D 		3D Assemblies 	

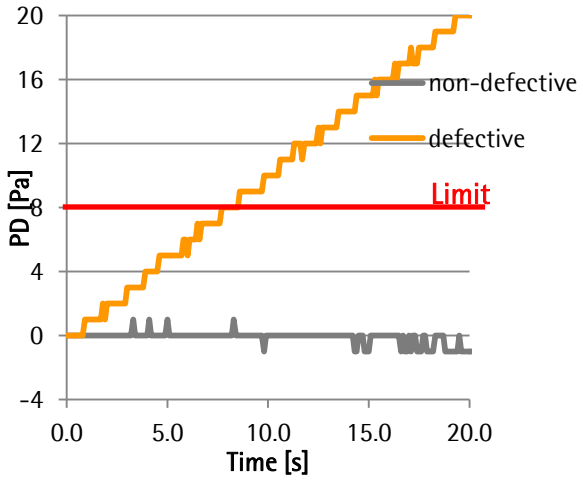
3 **Pressure Decay** Pre Use Leak Test (PU-LT): Detection limit 15 – 30µm on 2D

Bag Chamber Leak Test Performed in-Process on 100% of Bag Chambers For All PACs to Verify the Absence of Leaks on Film and Weld

Test methodology is pressure decay within restraining plates and porous spacers

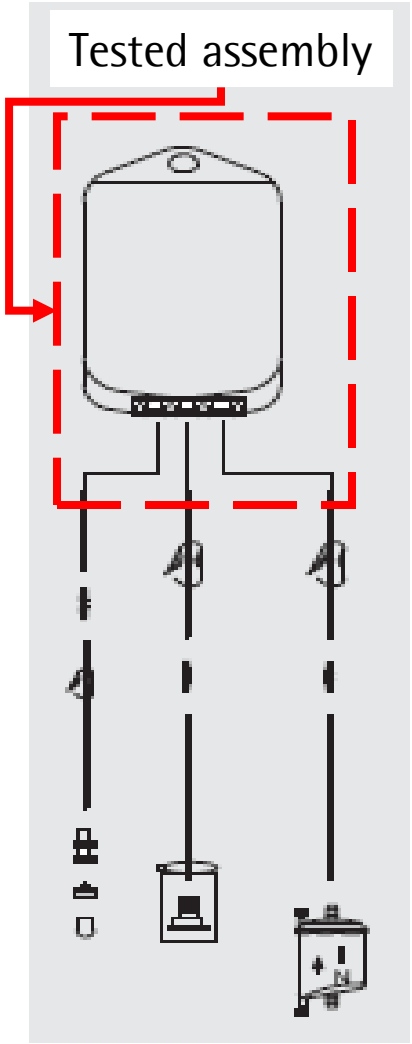
- Porous spacer cover 100% of film surface to avoid masking effect of potential leaks
- Restraining plates reduce stress on bag, provide small inflation volume & allow high test pressure - 500 mbar
- The combination of the small volume, high test pressure and spacers provides a reproducible, accurate and sensitive test
- Detection limit **30 – 100 µm**





Bag welding → Tube welding → 1 Bag chamber leak test → Bag connections → Final assembly → Packaging

Flexboy® Bag Chamber Leak Test Documented in Certificate of Release



CERTIFICATE OF RELEASE

Product Description

Reference :	FXB113196	Batch Number :	09A06437
Product description :	Std flexel® palletank® 200l (leak test)	Quantity :	5
Expiry Date :	2012/03		
Revision level :	00*		
Irradiation batch number :	*14110001*	*Certificate enclosed*	

Specifications :

STATEMENTS :

Biological Reactivity Tests In vitro and In vivo :	SARTORIUS STEDIM Biotech flexel bags have passed USP <87> and USP <88> testing and are classified USP Class VI.
Physicochemical Test :	SARTORIUS STEDIM Biotech flexel bags have passed current USP<661> tests for plastic Containers. PE, the contact layer of the S40 film passes current EP 3.1.5 (Polyethylene with additives) and complies with U.S. FDA21CFR177.1520(c)3.2a.
TSE-BSE status :	Conform to the European Guidance EMEA /410/01 and European Pharmacopoeia (EP) 5.2.8.

MONITORING :

Endotoxins :	Representative Finished Product has been sampled and tested according to current USP <85> Bacterial Endotoxins test by LAL and EP 2.6.14 method C. Passes the acceptance criteria of < 0.125 EU /mL.
Particulates :	Representative Finished Product has been sampled and tested according to current USP <788> and EP 2.9.19. Passes the Large Volume Injectables limits.
Bioburden :	Representative Finished Product has been sampled and tested according to ISO11737 method by filtration. Passes the acceptance limits determined by validation.
Sterility :	According to ISO 11137 and EN 552 with a 10-6 Sterility Assurance Level (SAL).

BATCH TESTING :

Visual Inspection :	100 % of these bags are inspected and pass the SARTORIUS STEDIM Biotech specifications.
Leak testing :	100 % of these bags are leak tested.
Product conformity :	Technical drawing compliance and Batch record review.
Gamma Irradiation :	25 kGys minimum. The Gamma Irradiation Certificate from the approved contractor is enclosed.

We certify that this batch has been manufactured in compliance with our internal procedures and that all the test results conform to our specifications. This batch has been manufactured by SARTORIUS STEDIM Biotech following applicable cGMP regulations.

Date of Release : 2009/04/21

** Modification : please note that this batch is manufactured without bottom line*

Nicole Lasserre
QUALITY DEPARTMENT

ISO 9001 : 2000
ISO 13485 : 2003
FDA audited

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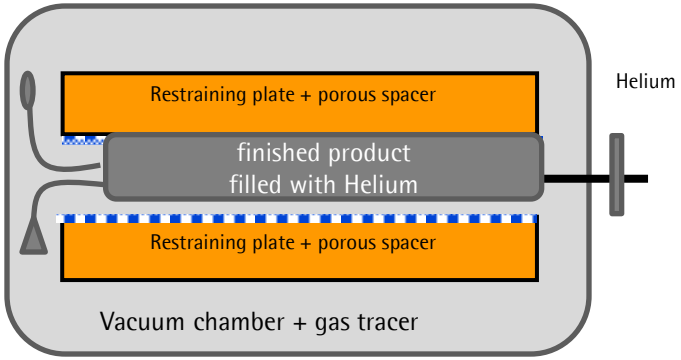
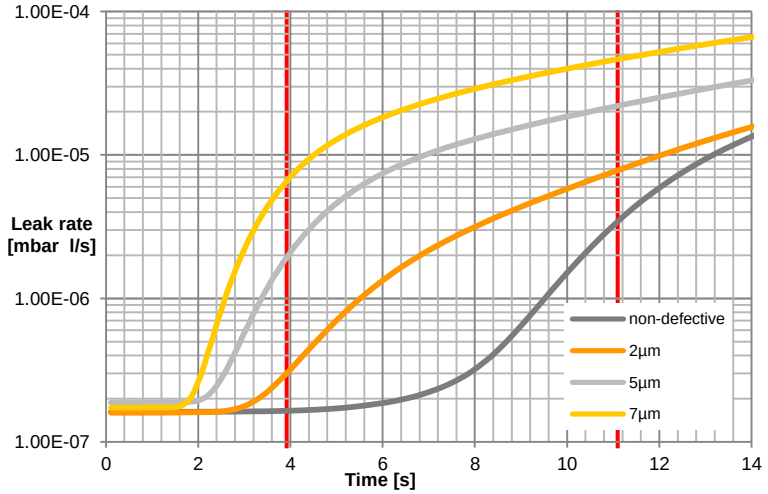
Fax : +33 (0)4.42.84.56.19
Web site : www.sartorius-stedim.com
S.A. au capital de 10 310 944,63 EUR
SIRET : 314095520 00073 APE 2222Z
TVA FR FR94314095552
GAMFLEX1

Finished Product Integrity Test Performed Prior to Packaging on 100% of Single Bags or Final Assembly Used in Critical PACs 2 & 3

Test methodology is gas tracer within a vacuum chamber with restraining plates and porous spacers

- Porous spacer avoid masking effect
- Restraining plates reduce stress on bag
- No background noise in the vacuum chamber
- Use of helium for most sensitive sensor technology



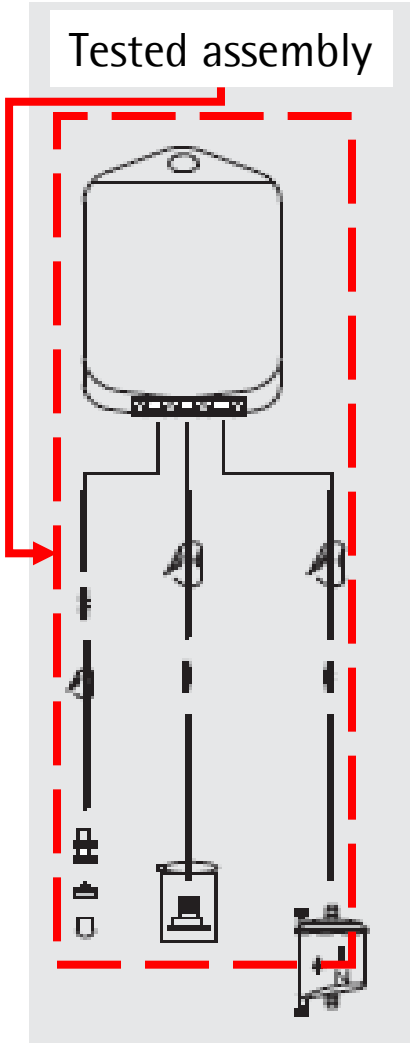


Helium leak rate can be correlated to a leak size

The optimal test method to achieve a **detection limit of 2 µm**

Bag welding → Tube welding → 1 Bag chamber leak test → Bag connections → Final assembly → 2 Supplier integrity test → Packaging

Helium Supplier Integrity Testing Documented in Certificate of Release



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Date of Release : 2009/04/21

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ISO 13485 : 2003
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SIRET : 314095520 00073 APE 2222Z
TVA FR FR94314095552
GAMFLEX1

Point-of-use Leak Testing Ensures that No Gross Defects Have Been Generated during Shipping, Installation & Handling

Test methodology is pressure decay within restraining plates and porous spacers

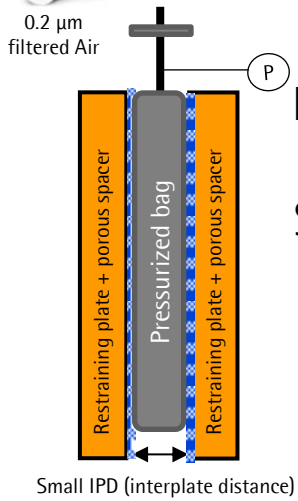
- Porous spacers avoid masking effect of potential leaks
- Restraining plates reduce stress on bag, provide a small inflation volume and allow high test pressure - 300 mbar
- The combination of the small volume, high test pressure and spacers provides a reproducible, accurate and sensitive test in 7 minutes total test time

Detection limit of **30µm validated for 3 min test time**

Test time can be extended to improve detection limit **to 15 µm**

Microbial aerosol test correlation to leak size in progress

FlexAct® BT
Sartocheck® 4 Plus Bag tester

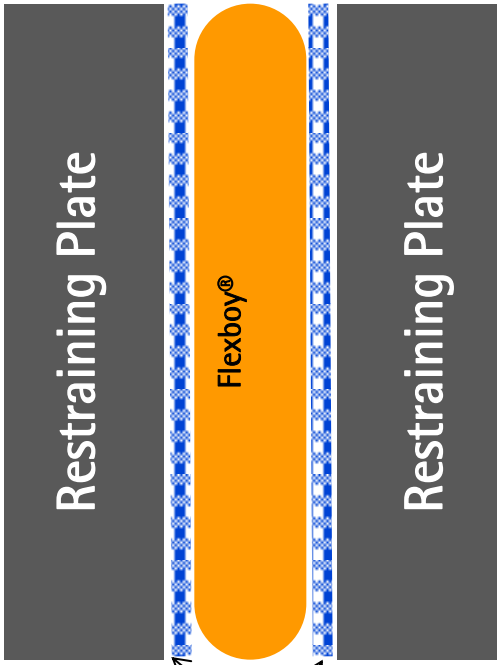


High pressure
+
Small volume
=
High
Sensitivity

Overview FlexAct® BT components

FlexAct® BT with
Sartocheck® 4 plus Bag tester & MultiUnit Inside

Filter holder



Weight: 375kg

(826 lbs)

Porous spacer

Point-of-use Leak Test Validated for 30µm Sensitivity with 6 Sigma Confidence Interval Between Defective and Non Defective Bags

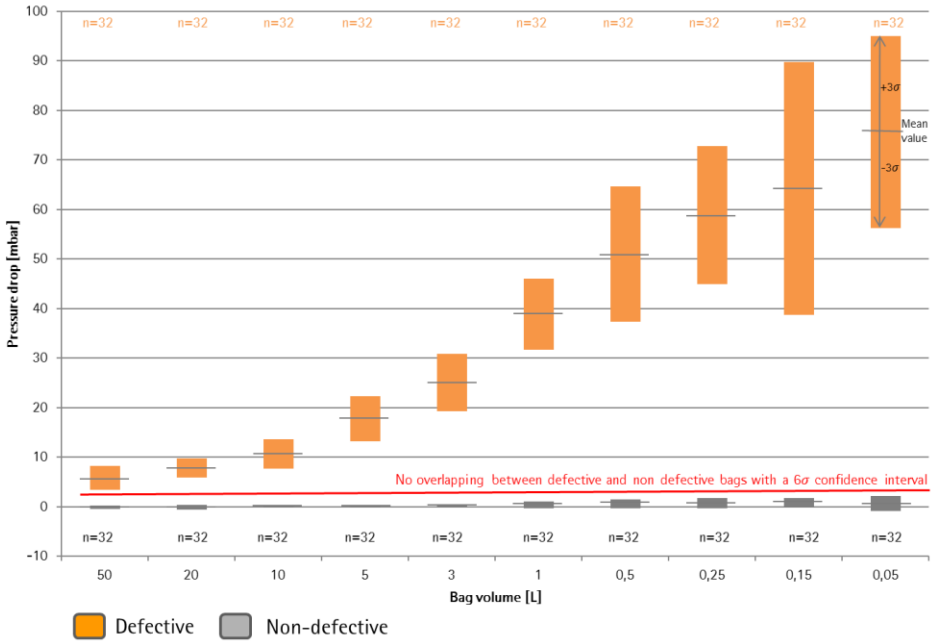
30µm limit based on risk assessment in line with ICHQ9 HACCP approach

- Analyzed failure modes over 20 years and 20 million of bags produced
- Defect < 30µm are very unlikely to happen during transport & use of Flexboy® bags.

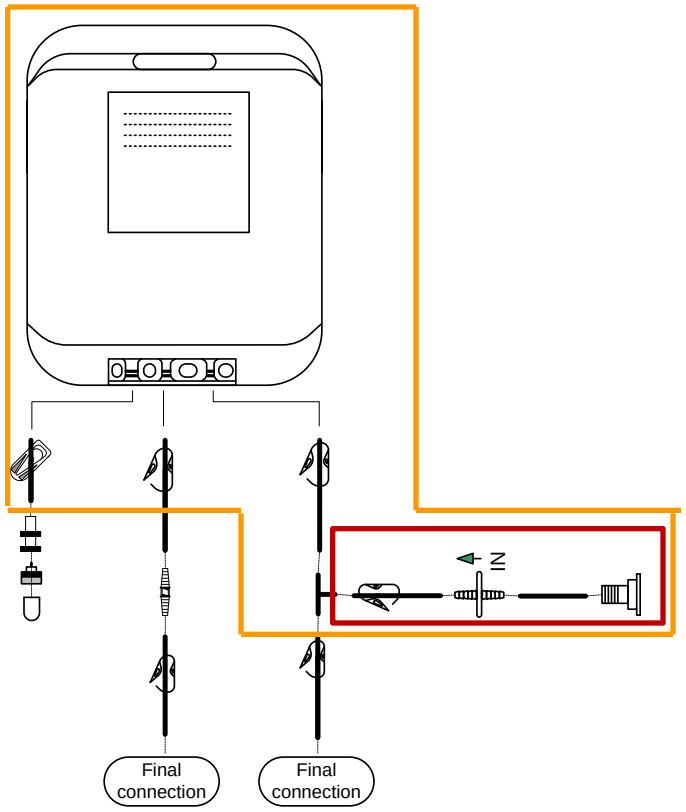
Leak detection of 30µm validated across the full range of Flexboy® 2D bags from 50mL to 50L

Reliability proven using samples from multiple batches and performing **700 tests.**

Sensitivity validated using 30µm defect film samples and applying a 6 sigma confidence interval between defective & non defective bags.



Flexboy® 2D Bags Point-of-use Leak Test : design rule for testing



scope of the validation for the 30µm leak detection

Filter Test Line

Standard products available with appropriate design, the SOP and the test specification

- Stabilization & test time
- Test pressure and pressure decay limit

The leak test specification apply for the qualified design (see drawing)

The handle is removed for the test to maintain small inter-plate distance and high sensitivity

Custom configurations leak testing (including lines), can be developed on a case by case basis

- Design definition
- Setting of test parameters, Pressure, time and maximum pressure decay

FlexAct® BT Supplied with a Robust Validation Package and an Integrated Service for the IQ/OQ/PQ, SOP development & Training

FlexAct® BT Installation Qualification and Operational Qualification performed by Service Dpt

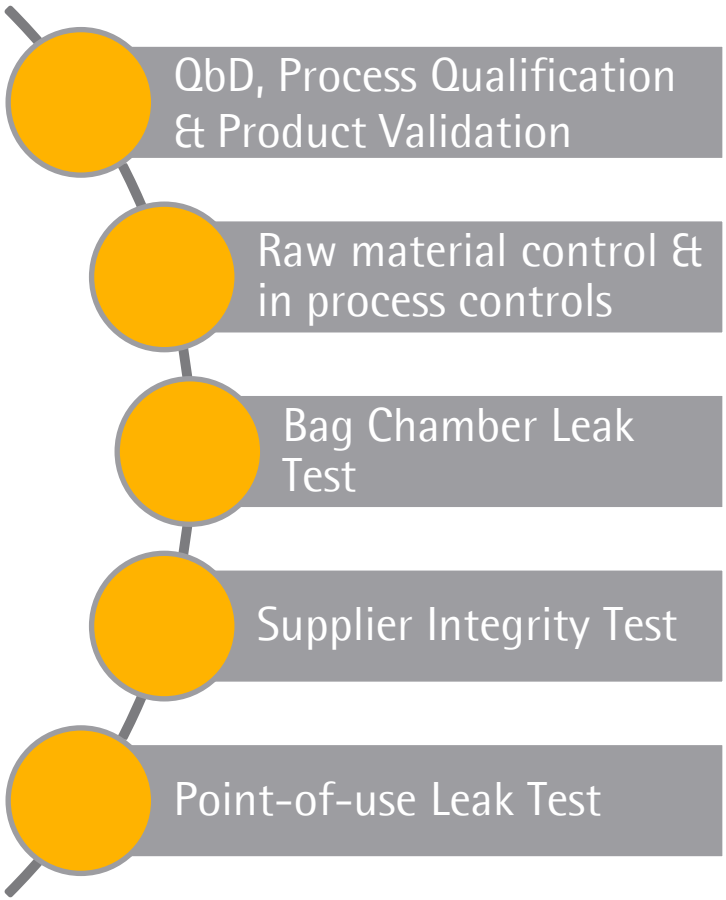
Performance Qualification performed by Application Specialist FMT using Standard Flexboy® configurations

- Test reproducibility with non defective bags
- Test sensitivity with calibrated master leaks
- On-site training service

Additional service to establish test parameters and specifications for custom Flexboy® 2D bags with different volumes, tubing lengths and connections or,

Smaller leak size detection, down to 15µm, can also be validated for small volume bags or with a longer test time

Conclusion: Single-use Container Closure Integrity is the Result of Multiple Controls Performed by Both The Suppliers and End Users



Our Bag Chamber Leak Test performed on all bags garanties that no leaking bags are used to manufacture final products

Our Supplier Integrity Test performed on final products used in critical applications garanties that no defect > 2 µm occur in our production

Our Pre Use Leak Testing with detection limits 15-500 µm can be performed at end user to check the correct installation of bags and mitigate the risks of product loss.

These three tests in conjonction with the control of our manufacturing process ensure the strongest level of bag closure integrity