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2018 PDA Container Closure Performance and Integrity Conference

Assuring Packaging Quality in Delivery Systems

June 13-14, 2018 | Bethesda, MD
Exhibition: June 13-14
#PDACCPI

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

Carole Langlois, Senior Product Manager

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SUS in more critical cGMP processes

- Bag integrity failures significantly impact:
  - Patient & operator safety
  - Drug availability
  - Cost
- Increasing regulatory scrutiny on SU Container Closure Integrity Testing (CCIT)
- Lack of common understanding

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

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Current Industry Standard & Guidance

USP<1207> 2016 *package integrity evaluation – sterile products*

2 NEW ASTM E55 work items on integrity kicked-off to combine and replace existing WKs launched in 2014

- ***standard practice*** *for integrity assurance & testing (supplier & end-user combined)*
- ***test method*** *for microbial ingress testing on SUS*

PDA TR27 1998 *Pharmaceutical package integrity (under re-write)*

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

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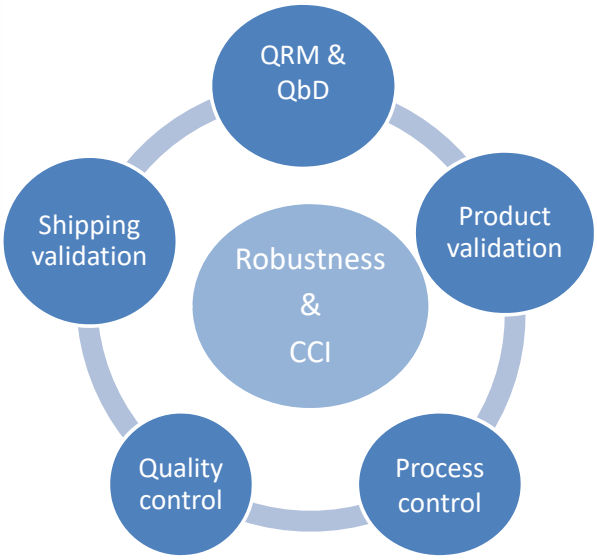
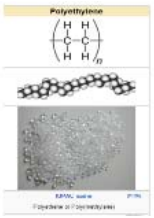
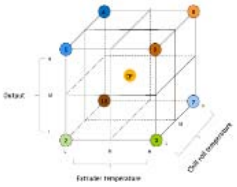
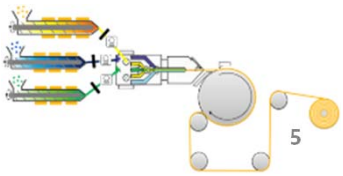
Robustness & Closure Integrity by Design: The Foundations









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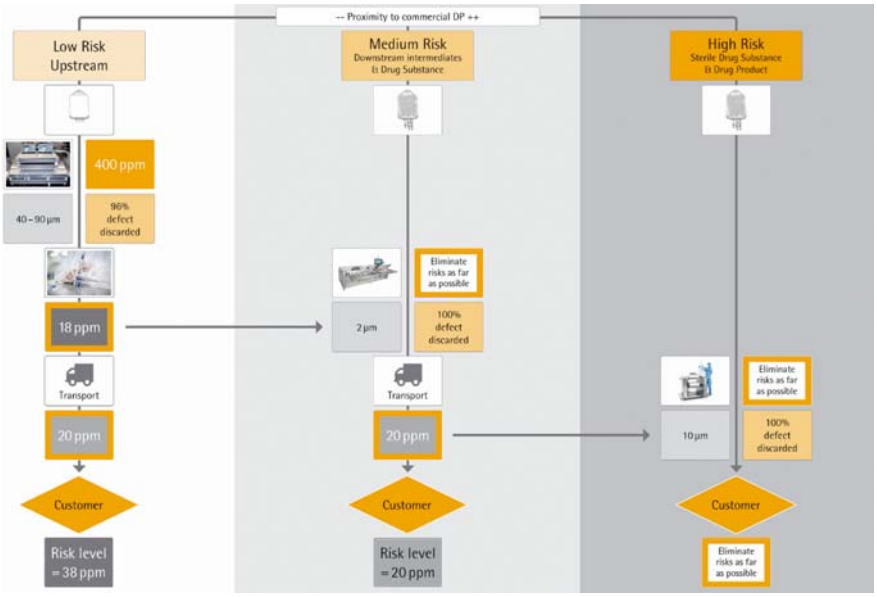
Risk Mitigation along product life cycle



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Enhanced process integrity for patient & operator

- *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*

FDA-ASTM Workshop on Standards for Manufacture of Pharmaceutical and Biopharmaceutical Products Single Use Systems (SUS): A Microbiology Product Quality Perspective.
Patricia F. Hughes, Ph.D. Branch Chief (Acting) CDER/OPQ/OPF/DMA
October 11, 2016

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Understanding liquid leaks & microbial ingress mechanisms

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

- Close relation between microbial ingress and liquid leak
- Defect sizes depend on processes & liquid attributes
- Microbial ingress not found with micro-tube of 2 µm under any test conditions

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Close Relation between Liquid Leaks & Microbial Ingress

MALL (Maximum Allowable Leakage Limit) *is the greatest leak size tolerable [...] that poses no risk to product safety [...]**

Author	Keller	Gibney
Microbial test	Aerosol	Aerosol
Tube length	0,7 cm	0,7 cm
Challenge micro-organism	P. Fragi	P. Fragi
MALL liquid leaks	2 µm	5 µm
MALL microbial ingress	2 µm	5 µm
Pressure - bar	-0,21 / + 0,21	-0,35
Material	Nickel	Nickel

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* USP<1207> Package Integrity Evaluation-Sterile Products

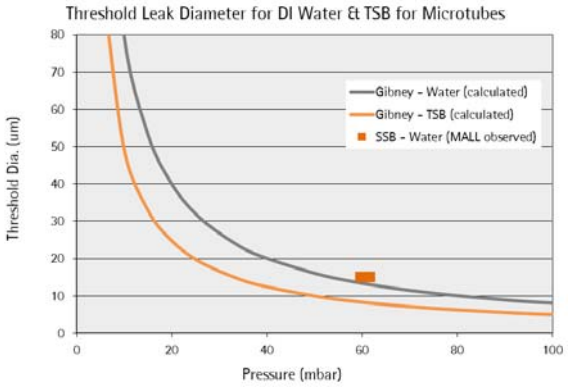
Defect size depends on processes & liquid surface tension

Threshold leak diameter using microtubes:

- ~15 µm for DI water at 70mbar
- ~10 µm for TSB at 70mbar
- ~3 µm for DI water at 300mbar
- ~2 µm for TSB water at 300mbar

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

Gibney, 2000



Fluid surface tension impact leak size

44 mN/m for Tryptic Soy Broth (TSB)[2]

71 mN/m for DI water[3]

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2µm MALL for microbial ingress at any tested pressure

- Microtubes with IDs of 2, 5, 7, 10, 20, 50µm were tested
- Pressures used in the range of ±20.7kPa
- No growth for microtubes with ID of 2µm

TABLE 1. *Microbial ingress into test cells as a result of bioaerosol exposure and imposed pressures at 25 °C.*

Microtube ID Size (µm)	Imposed Pressure (kPa)							Total Positives
	-20.7	-13.8	-6.9	0	6.9	13.8	20.7	
50	4/9	8/9	1/9	2/9	3/9	1/9	3/9	22/63
20	6/9	4/9	0/9	0/9	1/9	6/9	6/9	23/63
10	1/9	4/9	0/9	0/9	0/9	3/9	3/9	11/63
7	0/9	1/9	0/9	0/9	0/9	3/9	1/9	5/63
5	1/9	2/9	0/9	0/9	0/9	3/9	1/9	7/63
2	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/63
Total Positives	12/54	19/54	1/54	2/54	4/54	16/54	14/54	68/378

Source: Keller

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Create data on SUS used in sterile product manufacturing

- Demonstrate the relation between microbial ingress and liquid leaks
- Determine the Maximum Allowable Leakage Limit (MALL)* under process conditions of SUS
- Develop and validate the physical test methods with detection limits that confirm the absence of liquid leaks/microbial ingress in SUS

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

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Process conditions impact liquid leaks & microbial sizes (1/3)

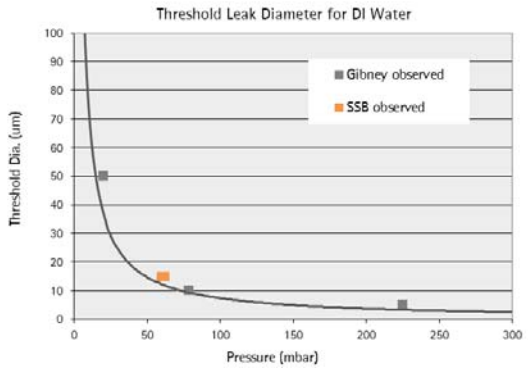
- **Hydrostatic pressure in storage**

Flexboy® 20 L

Flexsafe® 500 L

Observed data at 70mbar of water static head pressure on S71 and S80 films fall within Gibney Model

- **10µm is the MALL for storage & mixing**



10µm is the tolerable leak size for product safety in storage and mixing applications

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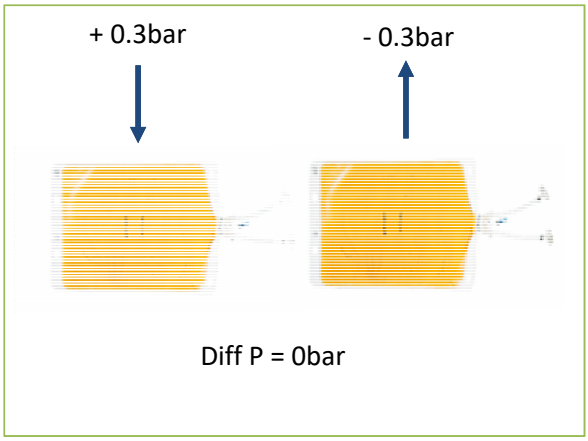
Air shipment does not impact the MALL (2/3)

- No significant gas head space in liquid filled bags
- No pressure in the system as liquids are not compressible



E. Post, CCIT: Cross Validation of the Microbiological vs. a Physiological Chemical CCIT, PDA Europe Conference Berlin, 2000

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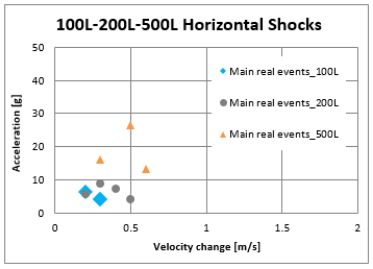
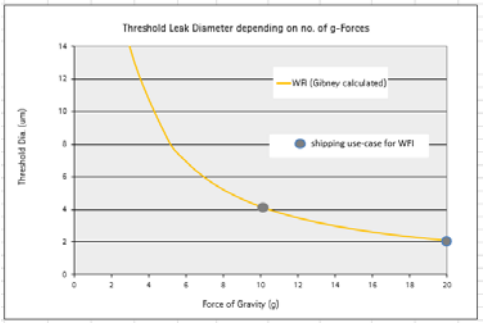
Acceleration in liquid shipping does impact the MALL (3/3)

- **Shipping can generate 20g acceleration**



- **2µm is the MALL for liquid shipping**



~0.7 m

Bags used in shipping require a 2µm integrity testing sensitivity

$$P_e > P_{max} + \left[\left(\frac{4\sigma}{D_L} - \rho g L\right) \times 0.390\right]$$

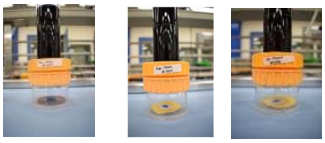
From theory to collected data on films

Liquid leak study – trial and intermediate results

MALL observed: 15µm at 70mbar and 2µm at 300mbar test pressure

Pressure	Model solution	2µm	3µm	5µm	10µm	15µm	20µm	25µm	30µm
70mbar	Water + 0.5% methylene blue dye	0/1	-	-	-	0/1	1/1	1/1	1/1
	TSB	On going							
300mbar	Water + 0.5% methylene blue dye	0/3	2/3	2/3	3/3	-	-	-	-
	TSB	On going							

Leak type: free flow, drip-fled flow, one drop



MALL

Leak

- Not tested

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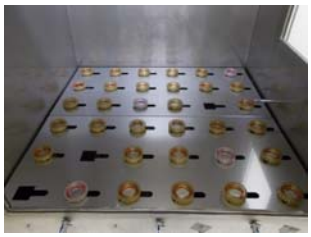
From theory to collected data on films

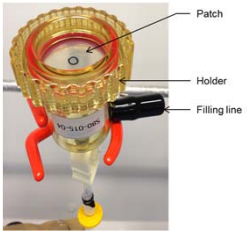
Aerosol microbial study – trial and intermediate results

MALL observed: 40µm at atmospheric pressure

Pressure	Model solution	2	3	5	10	15	25	30	40	50	80	100
0mbar	TSB	0/30	-		0/30	0/30	0/30	0/30	0/30	6/30	14/30	22/30
70mbar	TSB	On going										
300mbar	TSB	On going		10/30	22/30	-	-	-	-	-	-	-

Hole sizes given in microns





MALL

Leak

- Not tested

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Interim conclusion on liquid and microbial studies on SUS

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

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Helium Supplier Integrity Test for SUS

- Test of finished products (bag chamber incl. lines & connectors)
- 100% non-destructive testing (deterministic approach)
- Sensitivity down to 2µm correlated to microbial ingress
- Capable to be implemented in-line in routine production

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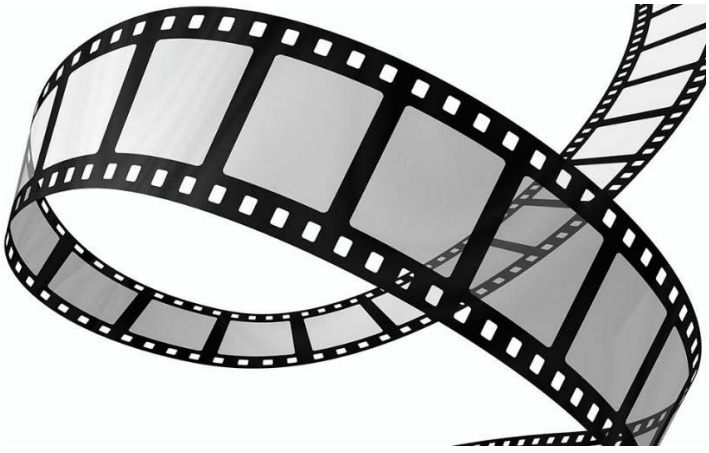
Helium Supplier Integrity Test for SUS



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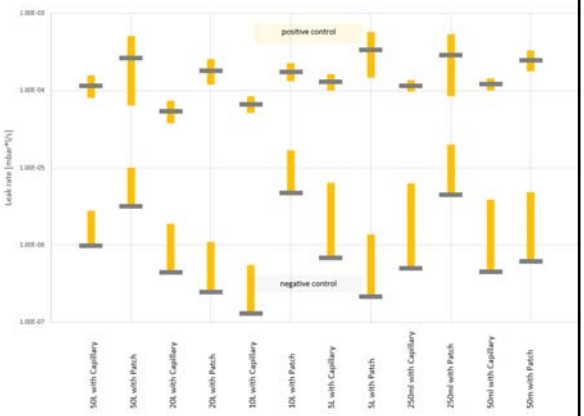
Robust validation to reliably detect down to 2µm defects

- 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

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Integrity Testing along product life cycle as a QRM approach

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

1 Bag Chamber Leak Test (BC-LT)

100% BC-LT
Pressure Decay
ASTM F2095[6]

Detection limit:
40-90 µm for 2D
50-100 µm for 3D

2 Final Product Supplier Integrity Test (SIT)

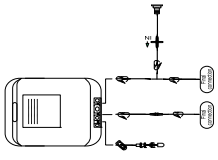
100% SIT
Helium Test

Detection limit
2µm

3 Point of Use Leak Test (PoU-LT)

Pressure Decay ASTM F2095[6]

Detection limit:
10µm on 2D bags
100-200µm on 3D bags



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Summary

- Growing adoption of SUS in critical cGMP processes
- Leaks introduced along SU product life cycle as a main challenge
- Increased regulatory scrutiny
- Robustness and closure integrity by design
- Lack of common understanding and guidance for SUS integrity testing
- Helium-based gas test method offering the highest sensitive results correlated to microbial ingress for SUS

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Thank you!

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