Ensuring Container Closure Integrity Throughout the Product Lifecyle

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Agenda

1. Introduction to CCIT

- What is CCIT?
- Factors to Consider – MALL & QRM
- Status Quo

2. Regulatory Landscape

- Regulatory guidance and updates
- Deterministic vs Probabilistic
- Key Approaches to Validate a Solution

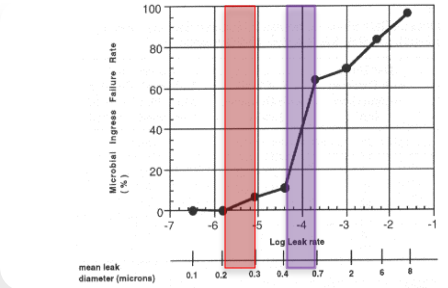
3. CCIT Throughout the product lifecycle

- Appropriate Test Methods
- Sampling plans
- Summary

What is CCIT?

Container Closure Integrity Testing

… evaluates the adequacy of container closure systems to maintain a sterile barrier against potential contaminants including microorganisms, reactive gases, and other substances. (USP <1207>)



Smallest leak to allow ingress determination
Lee Kirsch, et al, PDA J Pharm Sci & Technol, Vol. 51, No. 5, 1997

Understanding Maximum Allowable Leakage (MALL)

- Each product has a specific set of needs
  - Maintain Sterility
  - Maintain Headspace
  - Maintain Formulation

Stability

Critical Leak: What level of leakage poses risk?
Definition of MALL

Approximate Hole Diameter	Leak rate (mbar-L)/S
1.0 cm	10^{4}
1.0 mm	10^{2}
0.1 mm	10^{0}
0.01 mm	10^{-2}
1.0 micron	10^{-4}
0.1 micron	10^{-6}
0.01 micron	10^{-8}
1.0 nanometer	10^{-10}
1.0 Angstrom	10^{-12}

Leak Size	Flow rate
Does not articulate depth/length	Assumes partial pressures, viscosity, leak geometry.
Singular focus	Cumulative in nature
Verified against flow	Self verified
Measurement is the physical defect	Measurement dependent on the physical defect

What is QRM?

Quality Risk Management

QRM principles provide a proactive means of **identifying, scientifically evaluating and controlling potential risks to quality**. The evaluation of risk to quality should be **based on scientific knowledge** and **ultimately link to the protection of the patient**.

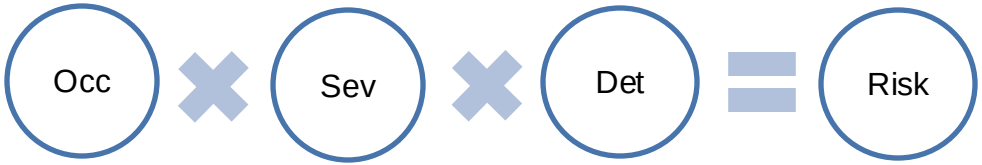
Severity: A measure of the possible consequences of a hazard.

Likelihood/Frequency of Occurrence: the condition of being likely or probable; probability.

Detectability: The ability to discover or determine the existence, presence, or fact of a hazard.

- Parenteral CCI consider high-risk.
- Quality inspection of all inputs & controlled manufacturing processes

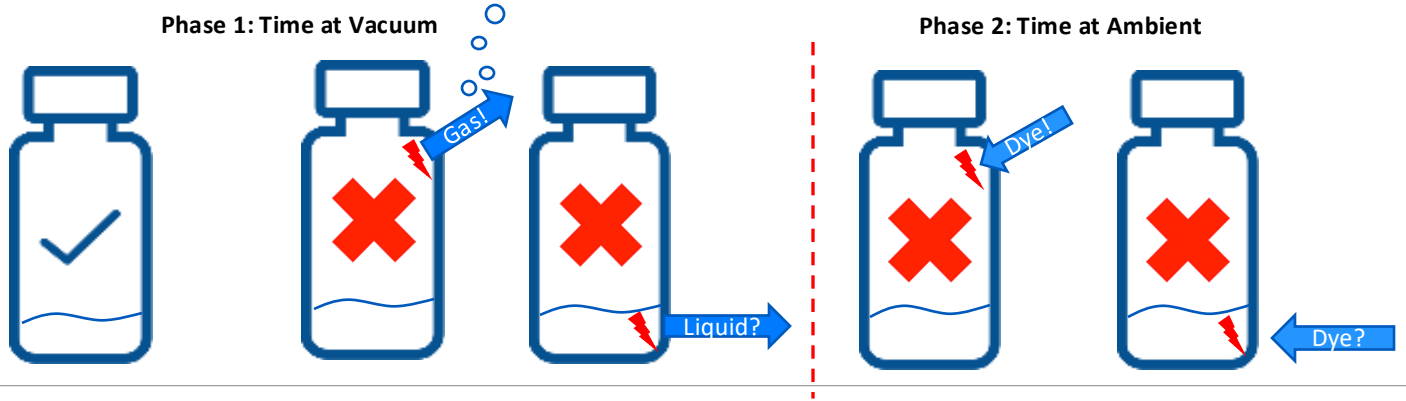
  → Systematic quality vs. random quality
- Critical defect sizes in the single digit micron range.



A. McFarland, ValSource, 2023

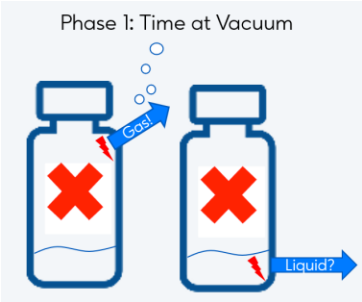
Dye Ingress: Method Comparison

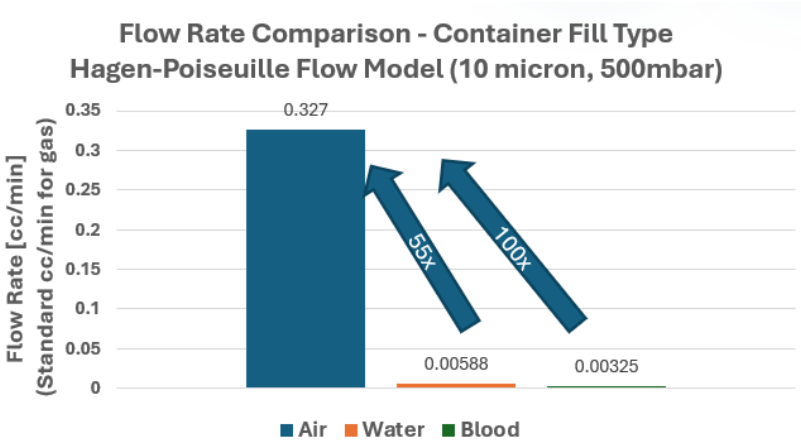
Closure Re-seal Method Parameters	USP 31 <381> Ph.Eur. 3.2.9	ISO 8362-5 Annex C	Modified ISO
Dye	0.1% aq. Methylene Blue		
Vacuum	-27 KPa	-25 KPa	-37 KPa
Time at Vacuum	10 min	30 min	30 min
Time at Ambient	30 min	30 min	30 min
Detection method	Visual inspection		



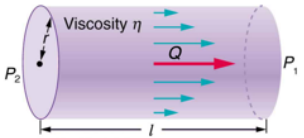
Viscosity, Headspace & Dye Ingress

- Dye ingress significantly more effective for gas space defects.
- Optimal liquids at optimal test conditions still show flow rates less than 2% compared to that of air.
- Containers with limited headspace and viscous product will vastly underperform.





$$Q = \frac{(P_2 - P_1)\pi r^4}{8\eta l},$$



Contents	Flow [cc/min *10^3]	Viscosity [Cp]
Air	0.327	0.0181
Water	0.00588	1.001
Blood	0.00325	1.81

Shifts in CCIT Regulation

FDA Guidance for Industry

Container and Closure System Integrity Testing in Lieu of Sterility Testing

USP Chapter 1207

Package Integrity Evaluation – Sterile Products

USP Chapter 382

Elastomeric Closure Functionality in Injectables Packaging/Delivery Systems

EMA Annex 1

Manufacture of Sterile Medicinal Products

PDA TR 86

Industry Challenges & Current Technologies for Pharmaceutical Package Integrity Testing

USP <1207> Deterministic Package Integrity

Deterministic: the leakage event is based on phenomena that follow a ***predictable*** chain of events, and leakage is ***measured*** using ***physicochemical technologies*** that are readily ***controlled*** and ***monitored***, yielding objective ***quantitative data***.

Probabilistic: its stochastic in nature in that it relies on a series of sequential and/or simultaneous ***events*** each associated with ***uncertainties***, yielding ***random outcomes*** described by probability distributions.

Deterministic methods	Probabilistic methods
Electrical Conductivity and Capacitance (HVLD)	Bubble Emission
Laser-Based Gas Headspace Analysis	Microbial Challenge, Immersion Exposure
Mass Extraction	Tracer Gas Detection, Sniffer Mode
Pressure Decay	Tracer Liquid
Tracer Gas Detection, Vacuum Mode	
Vacuum Decay	

Aspects of Method Variations

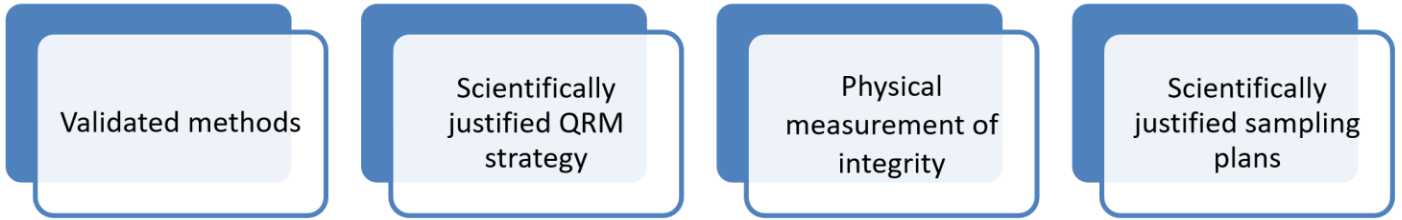
Probabilistic		Deterministic
includes elements of randomness. Every time you run the model, you are likely to get different results, even with the same initial conditions.		does not include elements of randomness. Every time you run the model with the same initial conditions you will get the same results.
✗	Non-Destructive	✓
✗	Quantitative	✓
✗	Non-Subjective	✓
✗	Repeatable	✓

CCIT and the Validation Challenge

USP 37 – NF 32 S2 <1225>	ISO 17025:2005 (E)
Accuracy	Accuracy
Precision	Repeatability / Reproducibility
Specificity	Selectivity
Detection Limit	Detection Limit
Quantitation Limit	
Linearity	Linearity
Range	Range
Robustness	Robustness

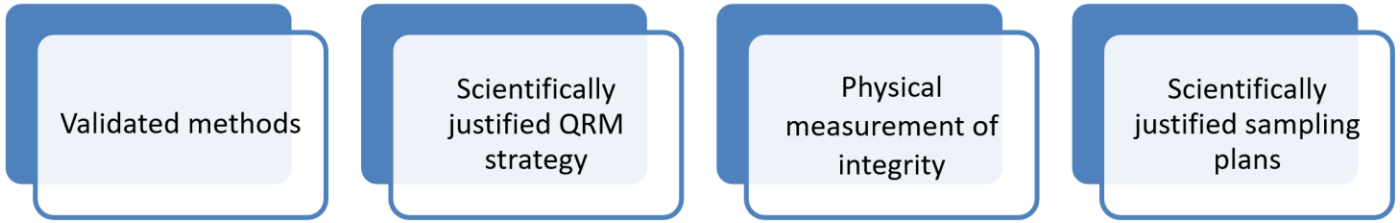
Annex 1 – CCI – Fusion Sealed

- 8.22 Where final containers are closed by fusion, e.g. Blow-Fill-Seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, the **critical parameters and variables** that affect seal integrity **should be evaluated, determined, effectively controlled and monitored** during operations. Glass ampoules, BFS units and small volume containers (≤100 ml) closed by fusion **should be subject to 100% integrity testing using validated methods**. For large volume containers (>100 ml) closed by fusion, **reduced sampling may be acceptable where scientifically justified and based on data** demonstrating the consistency of the existing process, and a high level of process control. It should be noted that **visual inspection is not considered as an acceptable integrity test method**.



Annex 1 – CCI – General Guidance

8.23 Samples of products using systems other than fusion should be taken and checked for integrity using **validated methods**. The **frequency of testing** should be **based on the knowledge and experience** of the container and closure systems being used. A **scientifically justified sampling plan** should be used. The **sample size** should be **based on information** such as supplier management, packaging component **specifications** and **process knowledge**.



QbD Lifecycle for Container Quality

Scenario - 2ml vial (Various product fills):

- *Large molecule*
- *Small molecule liquids*
- *Lyo powders*

Component & Design

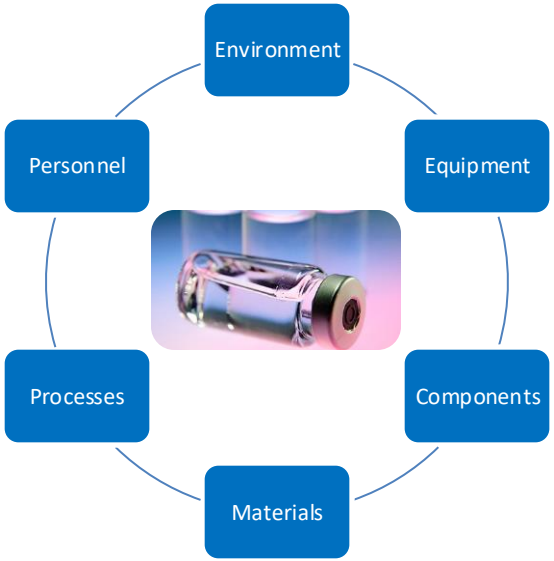
- Component & material selection
- Lifecycle performance

Equipment & Process

- Process, equipment and personnel qualification
- Process performance

In-Process Control Strategy

- Statistical
- Quantitation



Helium Leak Detection (HLD)

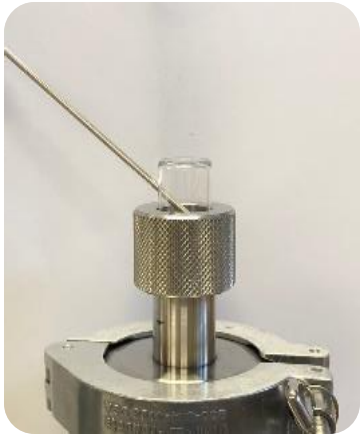
- Validation of components
- Sensitive below 1 micron (10^{-8})
- Permeation for O_2 sensitive products
- Extremely accurate flow measurement

Fill

Stopper

Crimp

Sample

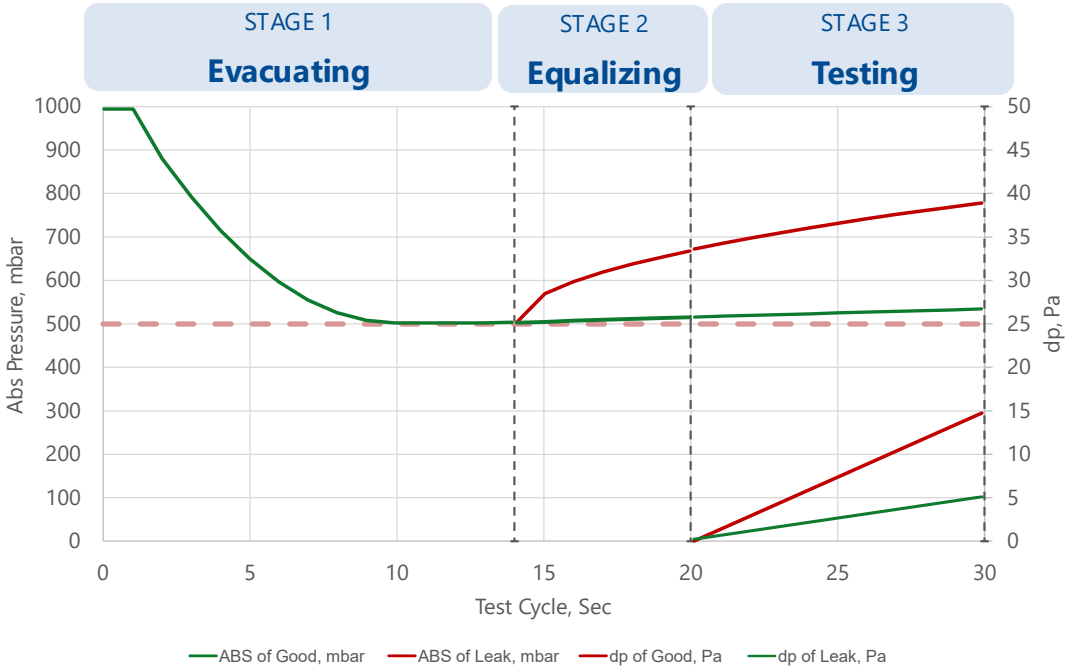


100% Helium Fill

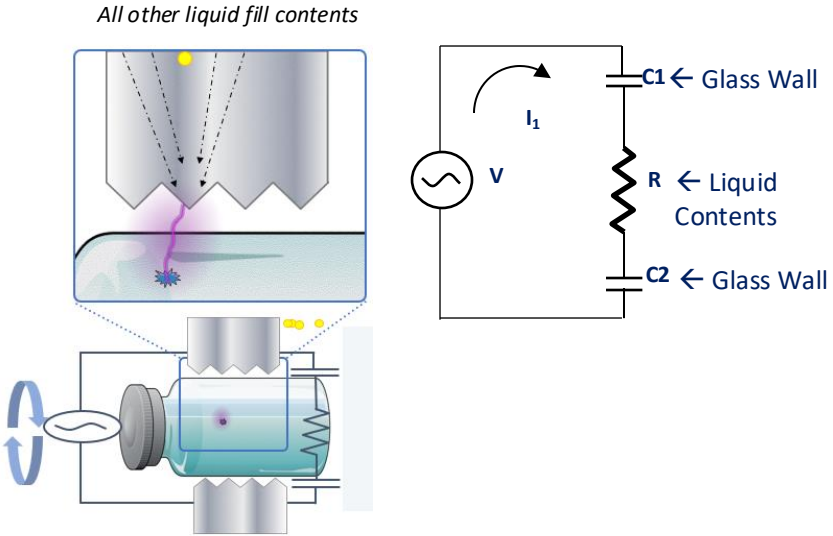
Vacuum Decay

- Practical & sensitive leak test
- Measurement correlates to leak size
- Pressure decay option

All small molecule, non-viscous, non-proteinacious fill contents



High Voltage Leak Detection (HVLD)



Deterministic Technologies

Helium Leak Detection	High Voltage Leak Detection	Vacuum / Pressure Decay
Inherent integrity evaluation & component selection	Rapid and sensitive CCI method	Practical effective approach
Highly sensitive, effective for barrier property inspection	Effective for all liquid filled parenterals	Wide range of product classes and package formats
Typical manual process can be fully automated	Effective with active product	Results correlate to leak size
Ideal for container development	Ideal for biologics and low headspace presentations	Ideal for lyophilized products, small molecule products and applications with headspace

Sampling Plans & Quantitation

- Deploying quantitative solutions improve test result confidence level
- Quantitative methods provide deterministic levels of assurance
- Attribute data requires larger sample sets for similar confidence levels
- Sampling Plans
  - Zero acceptance number sampling plans (Squeglia)
  - Reduced zero acceptance sampling plans (ANSI/ASQ Z1.4 & ISO 2859-1:1999)
  - Rule of 3 Sampling Plans (Coleman et al.)

	per 10,000	1	1.5	2.5	4	6.5	10	15	25	40	65	100	150
	Defect Rate %	0.01	0.015	0.025	0.04	0.065	0.1	0.15	0.25	0.4	0.65	1	1.5
Lot Size													
2-8		*	*	*	*	*	*	*	*	*	*	*	*
9-15		*	*	*	*	*	*	*	*	*	*	13	8
16-25		*	*	*	*	*	*	*	*	*	20	13	8
26-50		*	*	*	*	*	*	*	*	32	20	13	8
51-90		*	*	*	*	*	*	80	50	32	20	13	8
91-150		*	*	*	*	*	125	80	50	32	20	13	12
151-280		*	*	*	*	200	125	80	50	32	20	20	19
281-500		*	*	*	315	200	125	80	50	48	47	29	21
501-1,200		*	800	500	315	200	125	80	75	73	47	34	27
1,201-3,200		1250	800	500	315	200	125	120	116	73	53	42	35
3,201-10,000		1250	800	500	315	200	192	189	116	86	68	50	38
10,001-35,000		1250	800	500	315	300	294	189	135	108	77	60	46
35,001-150,000		1250	800	500	490	476	294	218	170	123	96	74	56
150,001-500,000		1250	800	750	715	476	345	270	200	156	119	90	64
>500,001		1250	1200	1112	715	556	435	303	244	189	143	102	64

The Number of Samples Needed to Ensure a Type 1 Error Rate of 5%. Here $T = \log_{10}(6 \times 10^{-6}) = -5.22$, $C = -8$, and $L = \log_{10}(\frac{1}{2}LLOV) = -8.30$

p	Sample Sizes		
	Rule of 3	DR_0	DR_1
0.01	300	6	10
0.001	3000	6	11
0.0001	30,000	7	12
0.000003	1,000,000	8	13

Coleman et al. PDA J Pharm Sci and Tech, Vol. 75, 465-473, 2021

Summary

- QRM & MALL
- Status quo
- Shifts in regulation – USP 1207 and Annex 1
- Deterministic test methods
- Validating a CCIT method
- CCIT through the life cycle of a product
- Statistical sampling plans

Thank You!

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