Container Closure Integrity of Sterile Pharmaceutical Containers

Laser-based Headspace Analysis

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Definition

Sterile product Container Closure Integrity (CCI)

The ability of a container (vial, ampoule, syringe, cartridge, bottle etc) to:

- Keep the contents **IN**
- Keep the contaminants **OUT**

Container Closure Integrity impacts…..

PRODUCT QUALITY

STERILITY | **STABILITY** | ***RECONSTITUTION***

What is changing in the guidance & regulations?

- A new revised USP <1207> was implemented in August 2016
- EU Annex 1 undergoing revision
- FDA has announced a revision of their container closure guidance*

* Container Closure Systems for Packaging Human Drugs and Biologics 1999 and 2002

What does it mean for the Industry?

- Regulators increasingly critical of CCI data from legacy methods (blue dye, microbial ingress)
- Trend towards quantitative (deterministic) analytical methods
- Emphasis on Science-based justification
- Drive towards a coherent CCI strategy across the Product life cycle

USP <1207.1>
Leak Detection Index

	Detectable Leaks	
Limit of Detection Index	**Air Leak Rate (std cc/S)**	**Orifice Leak Size (um)**
Class-1	**$<1\ 10^{-6}$**	**<0.1**
Class-2	**10^{-6} to 10^{-4}**	**0.1 to 1**
Class-3	**6 $x10^{-4}$ to 4 $x10^{-3}$**	**2 to 5**
Class-4	**5 $x10^{-3}$ to 1.6 $x10^{-2}$**	**6 to 10**
Class-5	**0.017 to 0.360**	**11 to 50**
Class-6	**>0.360**	**>50**

Air leak rate at 1-atm differential pressure at 25 C, i.e. vial at full vacuum

USP <1207.2> Leak Detection Summary

	Leak Detection Class	Measurement Outcome
Tracer-gas	Class 1-4	Helium Loss
Laser-Headspace	Class 1-6	Gas Composition or Gas Pressure
HVLD	Class 3-6	Electrical Current
Pressure Decay	Class 3-6	Pressure Drop
Vacuum Decay	Class 3-6	Pressure Rise
Mass Extraction	Class 3-6	Mass Flow

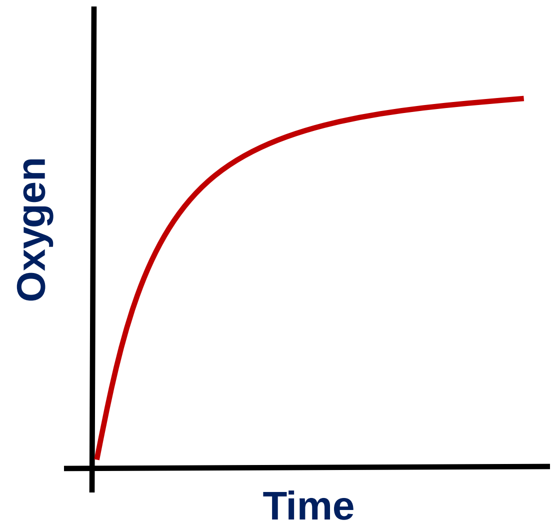
While no single method is appropriate for all types of containers, Laser Headspace analysis is the only method for all sizes of defects

Characterizing the headspace non-destructively

What gases can be measured?

- Headspace oxygen
- Headspace carbon dioxide
- Headspace moisture (water vapor)
- Headspace total pressure levels

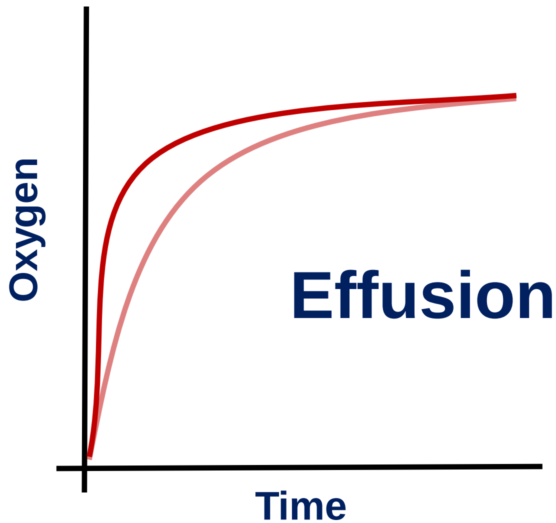
CCI testing – how?

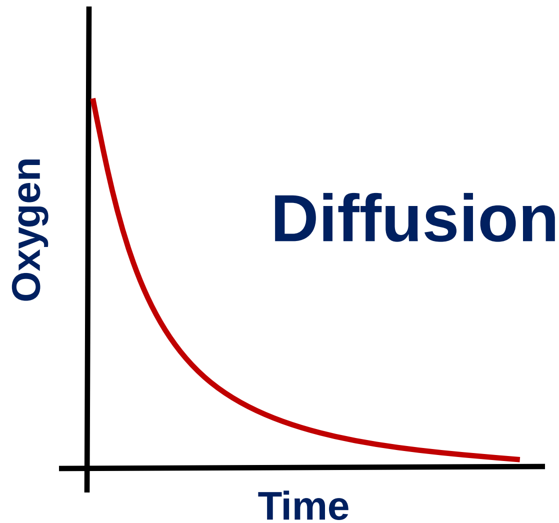


Headspace Measurement

Exchange of gas between the container and the outside environment through a defect

CCI testing: other situations





What type of product-packages?

- Sterile liquid, or lyophilized, or dry-powder filled
- Transparent rigid containers:
  - Clear or amber glass
  - Transparent plastics
- Vials, syringes, ampoules, cartridges
- Nominal volume ranging from 0.2mL to 250mL

Advantages & disadvantages

Advantages	Disadvantages
• Non-destructive • Rapid • Quantitative results • Deterministic method • Operator independent • Applicable over whole leak range • Permanent & temporary leaks detectable	• Not all fill levels • Sample needs to be transparent to laser • Inline production inspection needs modified headspace

Equipment

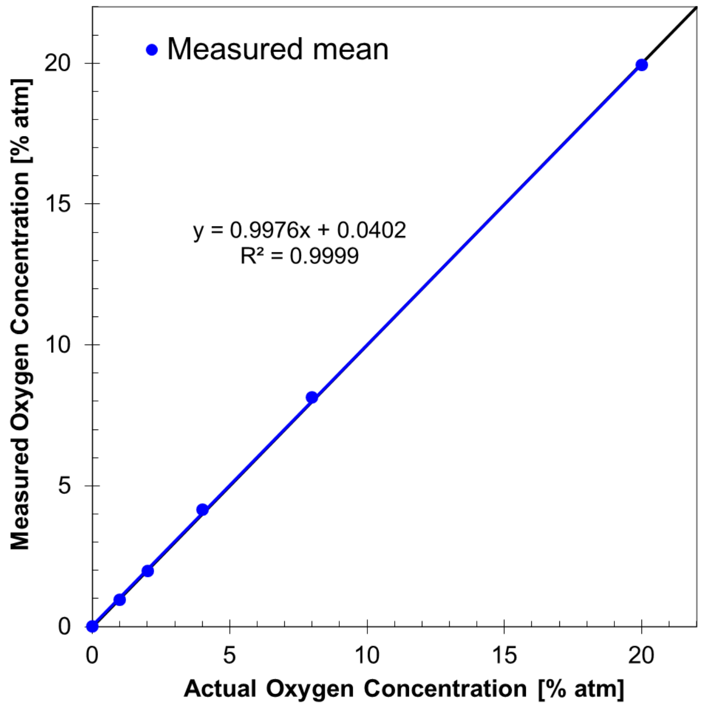
100% inspection
Multiple heads for total headspace analysis.

Each system comes with calibration and reference standards prepared from your glassware.

Measurement performance

N=100	Headspace Oxygen (% atm)			
Standard Label	Known Value	Meas. Mean	Error	St. Dev.
0.0	0.000	0.01	0.01	0.02
1.0	1.005	0.96	-0.04	0.03
2.0	2.004	1.98	-0.03	0.03
4.0	3.998	4.02	0.02	0.04
8.0	7.999	8.13	0.13	0.03
20.0	20.00	19.93	-0.06	0.04

Accuracy   Precision



Part 2

GAS DIFFUSION THEORY

CCI testing: Gas diffusion theory

$$\vec{J} = -D\vec{\nabla}n$$

Fick's 1st Law

$$\frac{\partial P_i(t)}{\partial t} = \frac{-D \cdot A_0}{V} \frac{\partial P_i(z,t)}{\partial z}$$

New USP <1207> states:

"Mathematical models appropriate to leak flow dynamics may be used to predict the time required for detecting leaks of various sizes or rates."

$$\%Oxygen(t) = 20.9\% \cdot \left[1 - \mathbf{exp}\left(-\frac{\alpha_{Diff}}{V} t\right)\right]$$

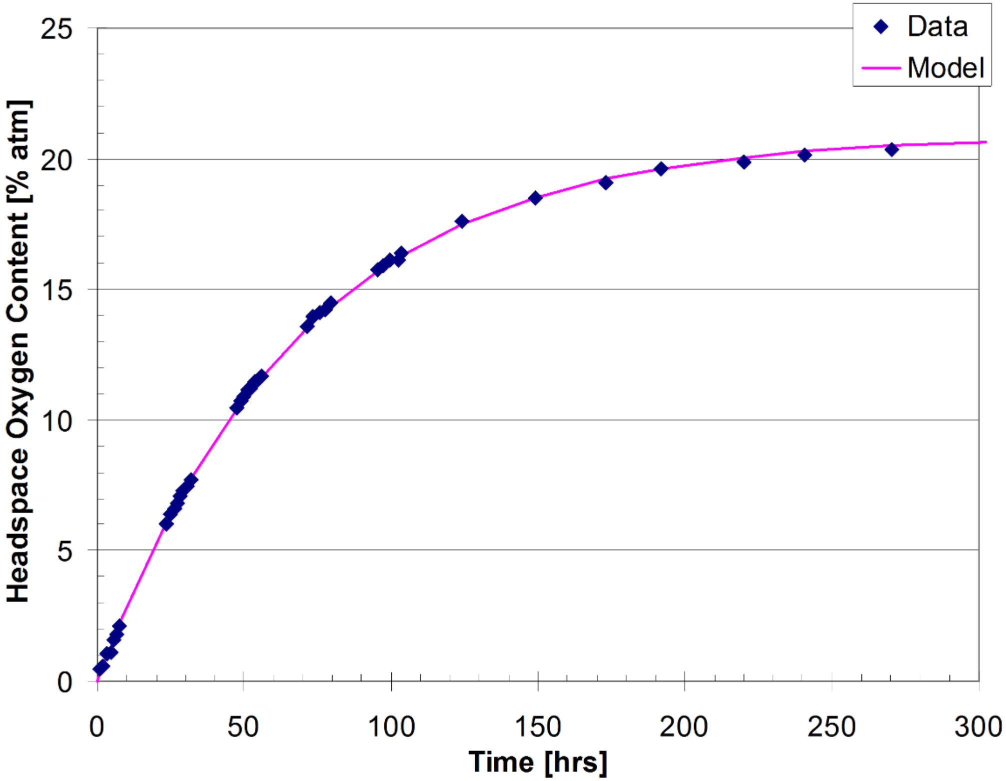
The change in oxygen concentration will be exponential with respect to time

Diffusion Parameter

$$\alpha_{Diff}\left[\frac{cm^3}{s}\right] = \frac{D \cdot A_0}{L}$$

The Diffusion Parameter is a function of the Diffusion Coefficient, *D*, the defect cross-sectional Area, A_0, and Depth, *L*.

Validation of Oxygen Ingress Model



With fixed values for:

$D = 0.22\ cm^2/s$
$A_0 = 20\mu m^2$ ($5\mu m$ ø)
$V = 18cc$ (15R)

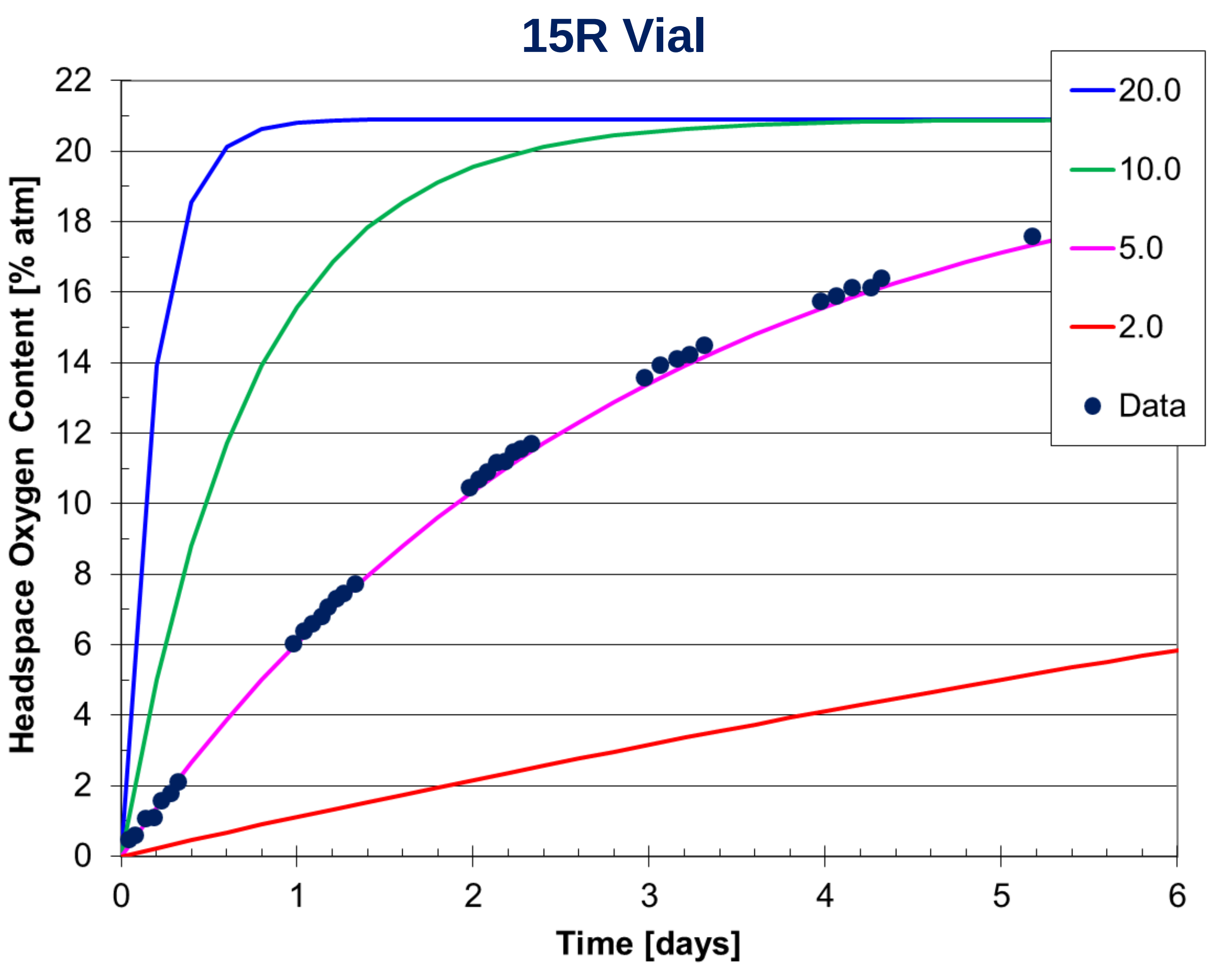
Obtain an empirical **depth parameter value:**

$L = 6\ \mu m$

Model matches the data ±0.3 %-atm oxygen at every point

Oxygen Ingress Model Example

Predicted oxygen concentration versus time for **ideal defects**



Defect diameter [µm]

Part 3

INDUSTRY CASE STUDIES AND EXAMPLES

Overview of CCI case studies

1. Method development
2. Process optimization
3. Biologics Cold Storage CCI Study
4. 100% inspection of lyophilized product

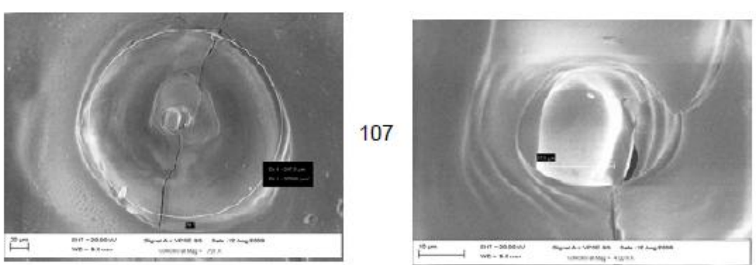
Case study 1:
Method Development

Objective

- Detection of 5 micron leak within 30 minutes

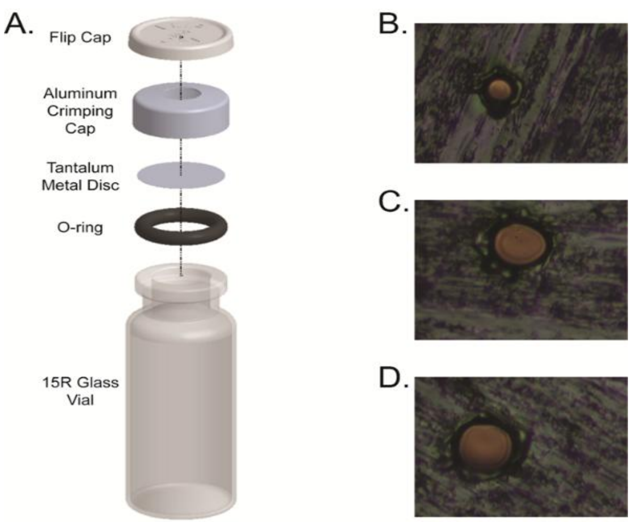
Sample set

- 6R DIN clear tubing vial – 1.5mL product
- Positive controls: 2µm, 5µm,10µm and 15µm laser drilled defects
  - Glass defects
  - Metal plate defects



Nominal hole size 5 µm

Image provided by Lenox Laser



Case study 1:
Method Development

– **Phase 1: Manufacturing conditions**
  - Determine nitrogen purge conditions

– **Phase 2: API reactivity**
  - Oxidation rate

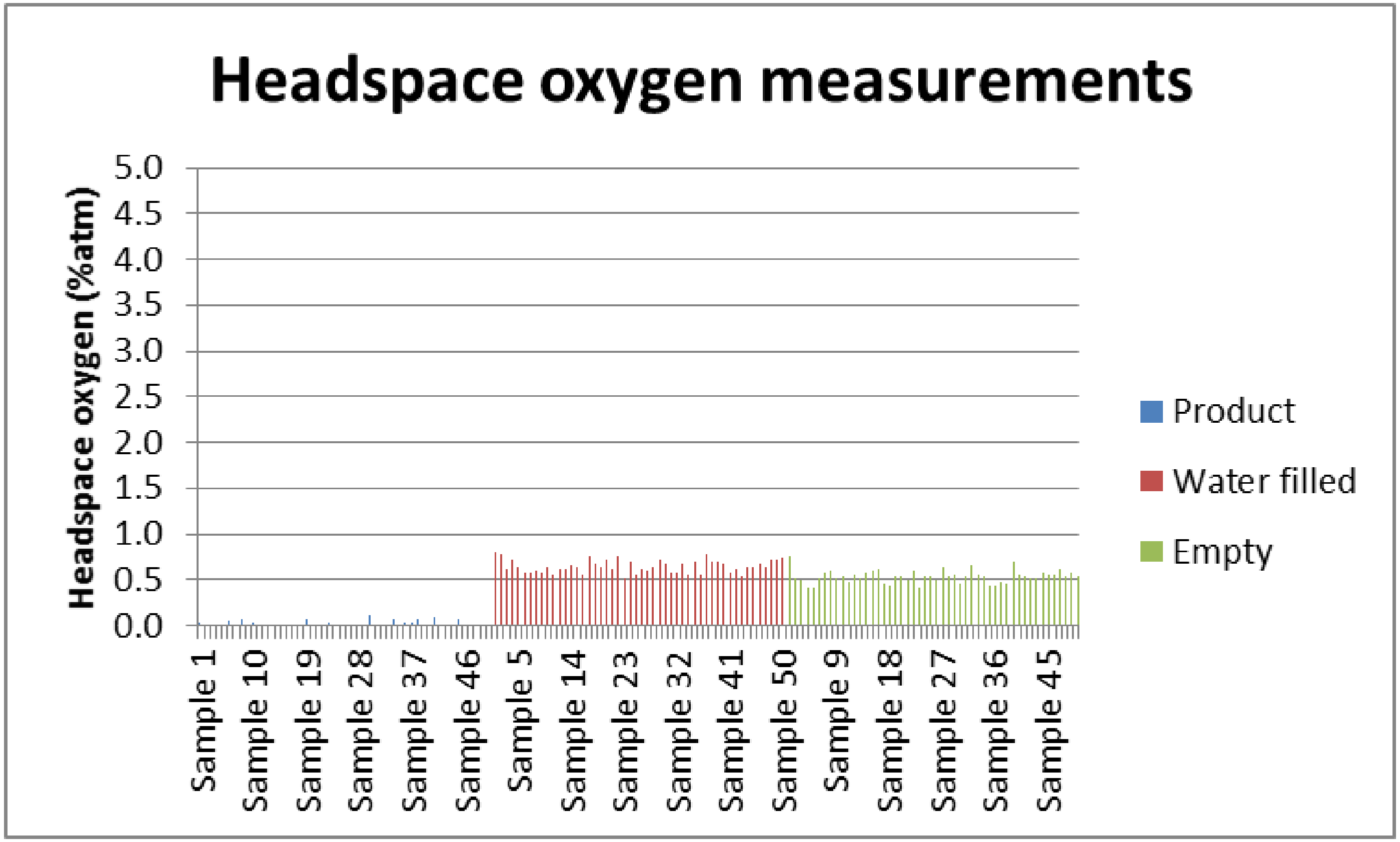
– **Phase 3: CCI Method development**
  - Diffusion test with vials with know defects (+ve controls)
  - Effusion test with vials with know defects (+ve controls)
  - Method protocol

Case study 1:

Method Development

Phase 1: Manufacturing conditions

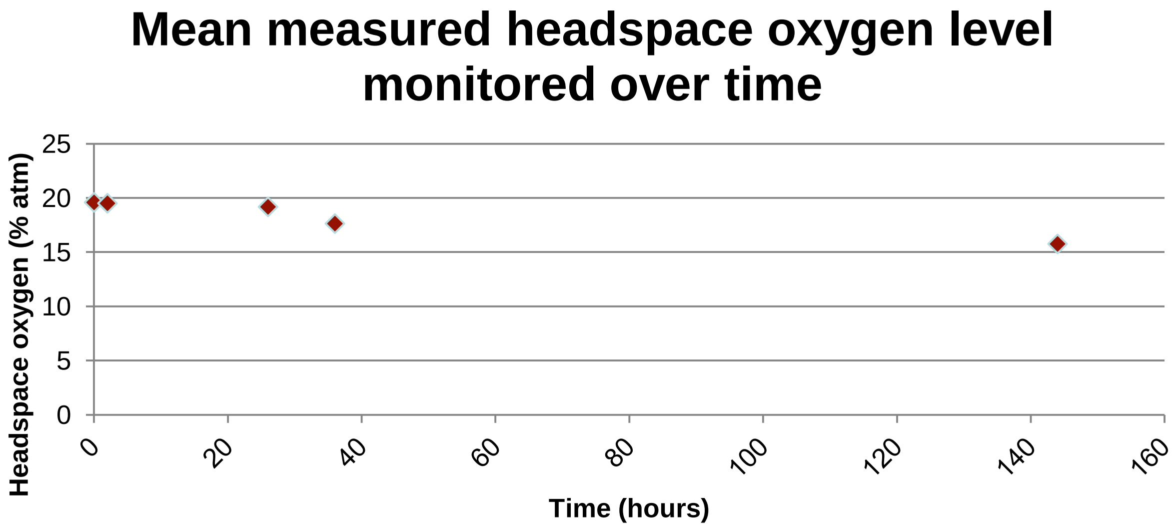
- 50 product, water-filled and empty samples



Case study 1:
Method Development

Phase 2: API reactivity

- 50 product samples opened to air and followed over time



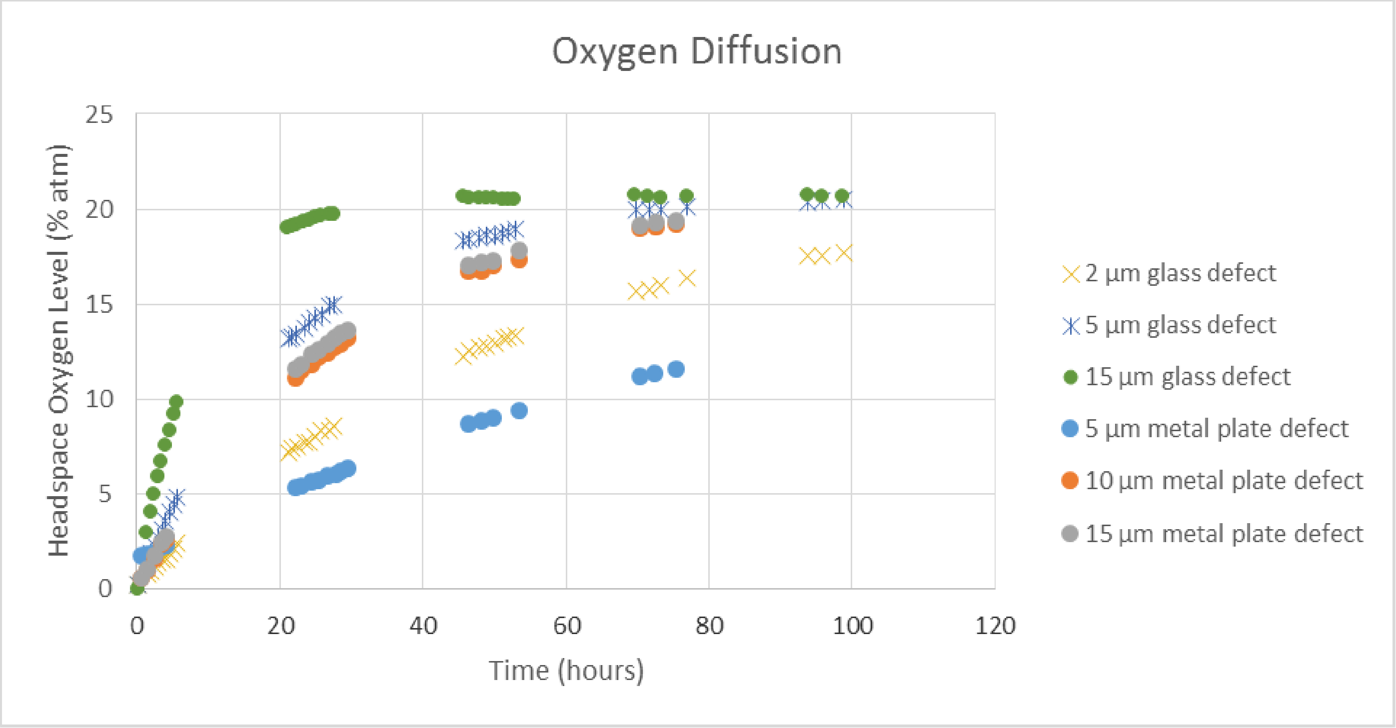
	Oxygen (% atm)
Start	19.59
2 hours	19.50
26 hours	19.18
36 hours	17.63
144 hours	15.76

Case study 1:

Method Development

Phase 3: CCI method development

- Diffusion tests with vials with known defects

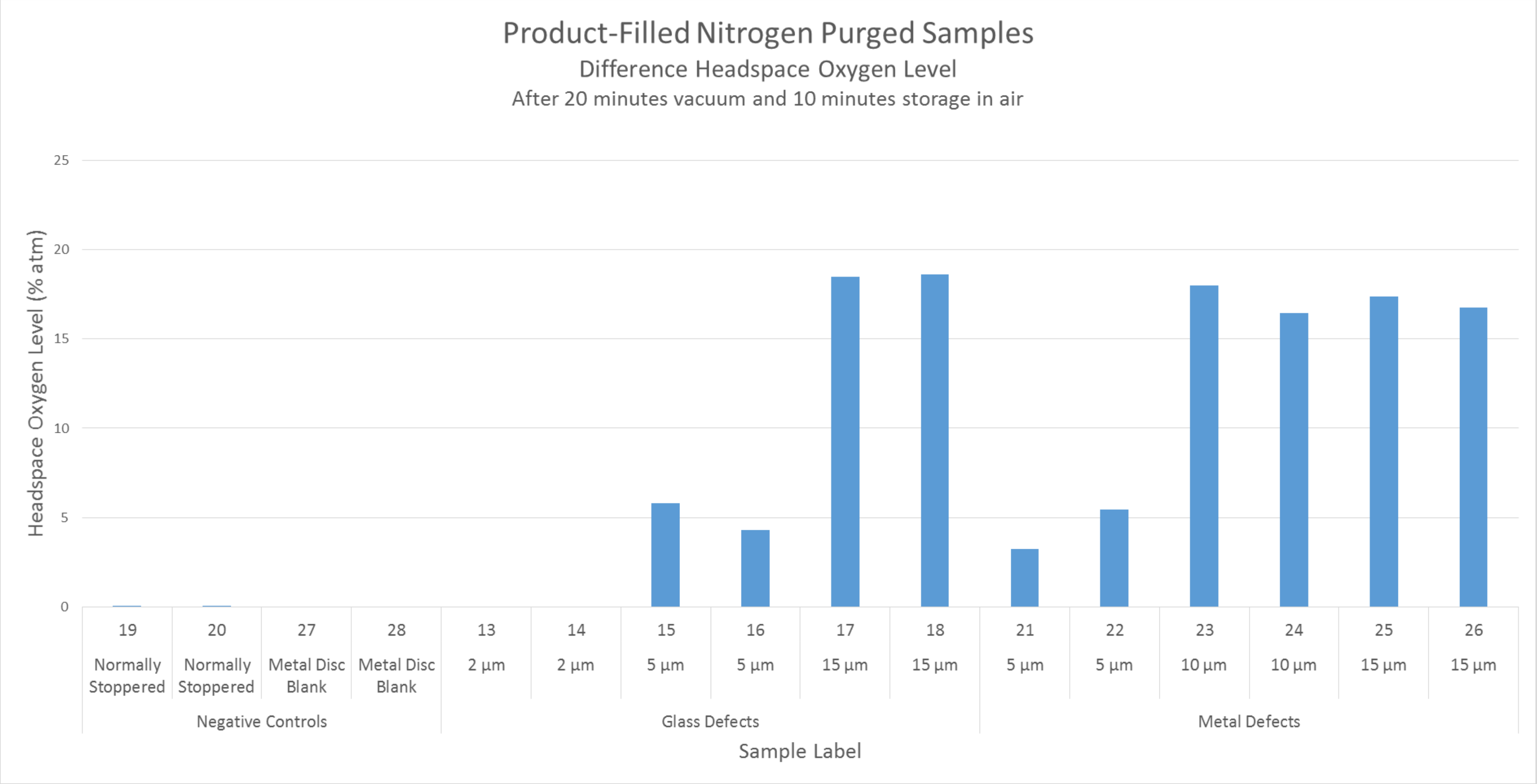


Case study 1:

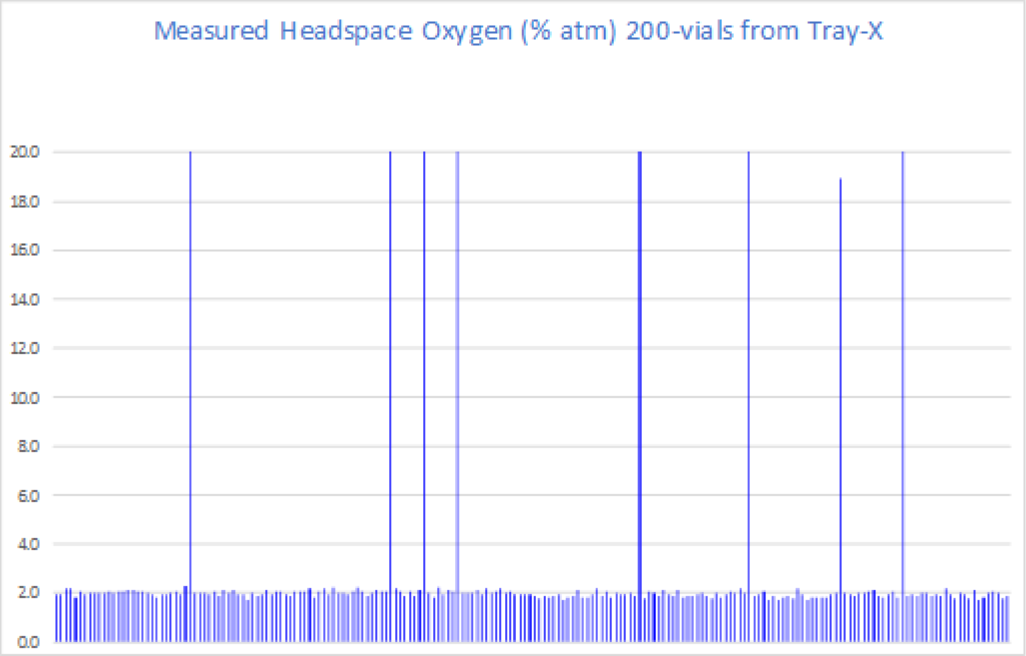
Method Development

Phase 3: CCI method development

- Effusion tests with vials with known defects



Case study 2:
Process optimisation



Case

- Liquid product in glass vial under N_2 atmosphere.
- All 200 vials passed visual inspection.

Result

- 192 accepted vials < 2% O_2
- 8 rejected vials ≈ 20% O_2
- Total test time for 200 vials: < 45 minutes

Conclusion

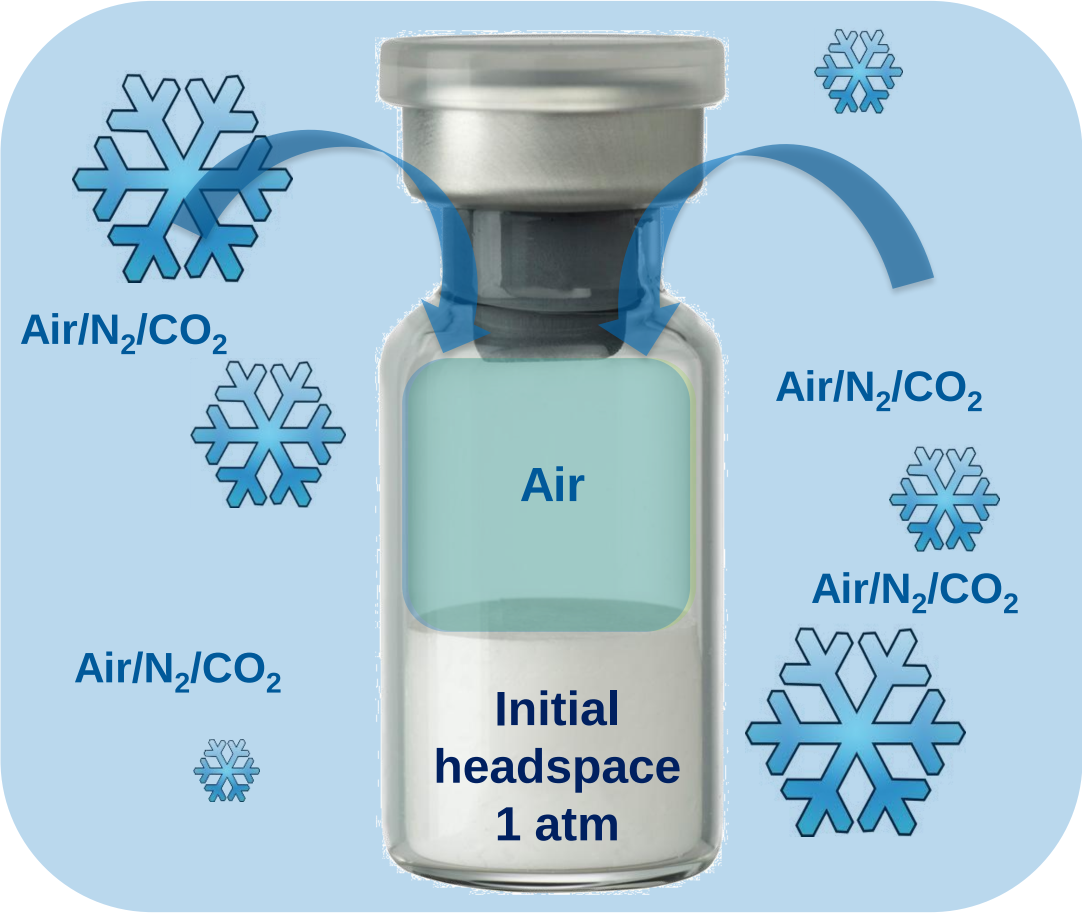
Ineffective crimping caused defective vials with permanent leaks.

Case study 3:
CCI testing for vials stored on dry ice (CO_2)

- 2R vials containing a Biologic, headspace 1 atm of air
- Stored on dry ice for 7 days.
- Thawed to room temperature (RT).
- Headspace conditions analyzed.
  - *Any change in the headspace condition would indicate a loss of CCI during deep cold storage*

Case study 3:
CCI testing for vials stored on dry ice (CO_2)

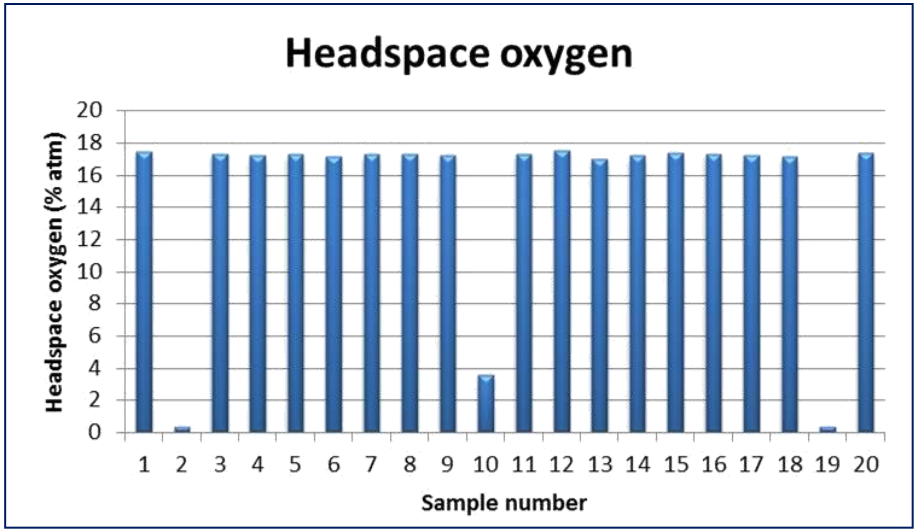
- Air headspace vial at 1 atm at RT
- At low T, initial headspace condenses and creates underpressure
- Stopper can lose elastic properties & closure can be lost
- Cold dense gas from storage environment fills headspace
- Warming container to RT, stopper regains elasticity and reseals trapping the cold dense gas in the vial

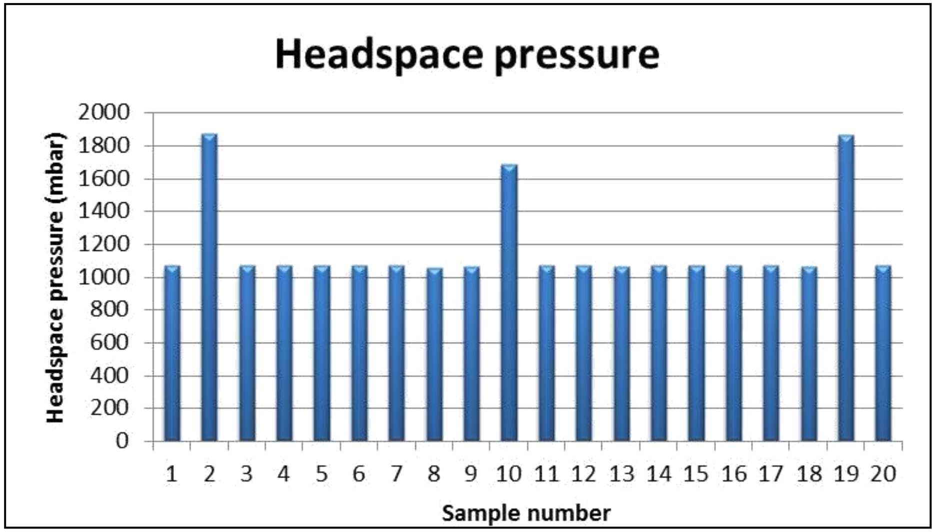


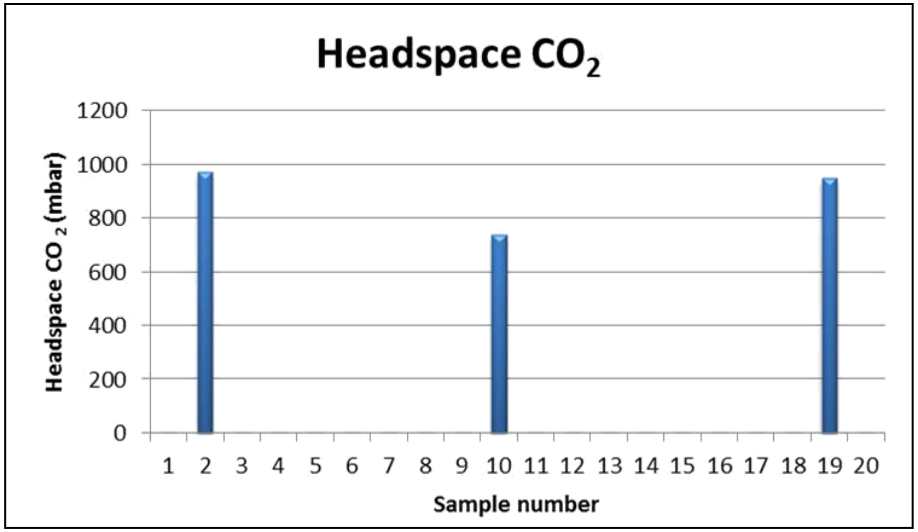
Case study 3:
CCI testing for vials stored on dry ice (CO_2)

- The cold dense gas trapped inside, expands as temperature increases creating overpressure
- Headspace gas composition could also change depending on storage environment
- Maintenance of changed headspace conditions can be monitored over time to verify that the leak was temporary.

Case study 3:
CCI testing for vials stored on dry ice (CO_2)







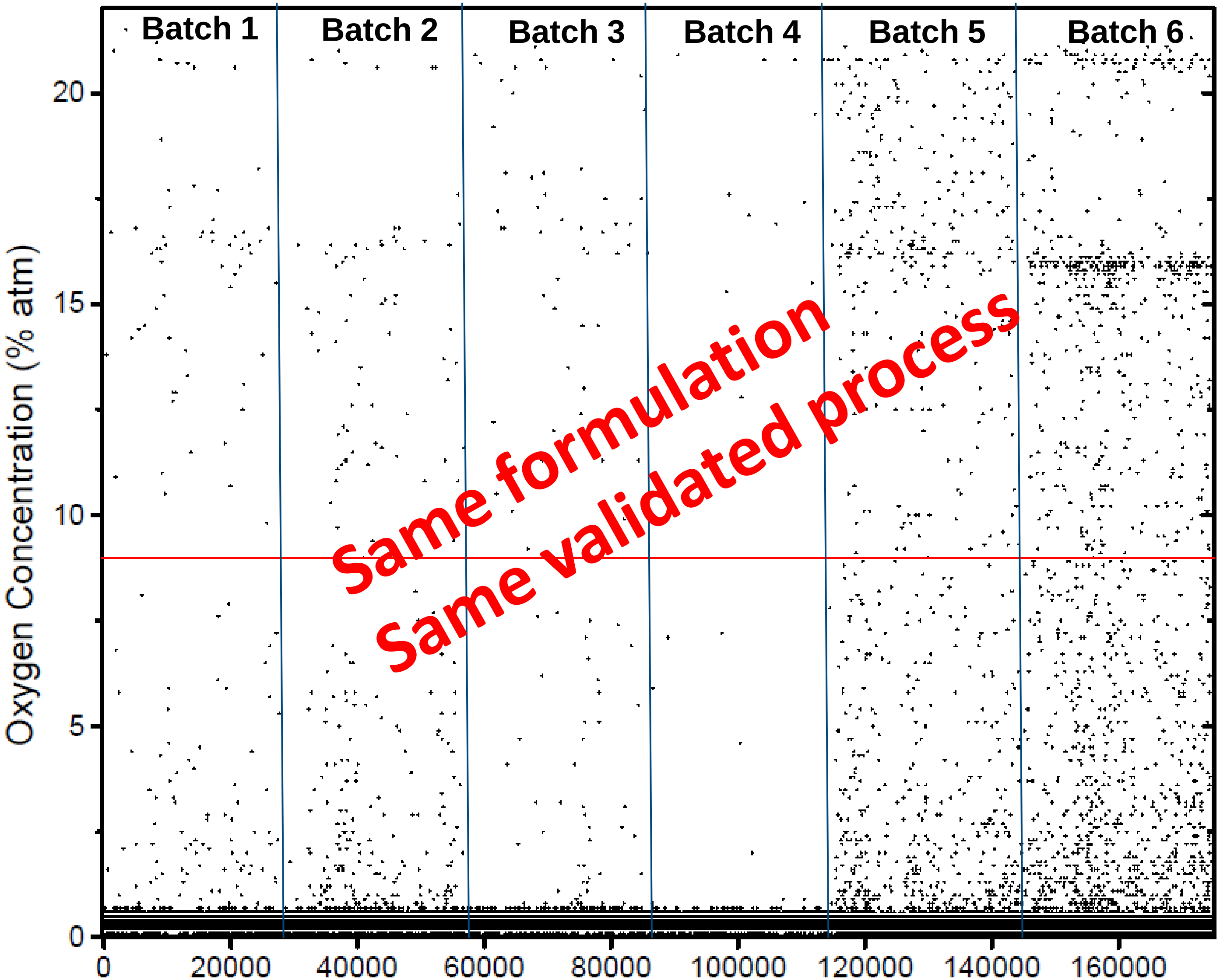
Three different headspace measurements identify the same 3 vials as having CCI issues.

Case study 3:
CCI testing for vials stored on dry ice (CO_2)

Some important comments on these results:

- Leaks during deep cold storage are usually temporary!
- CCI methods requiring an active leak *(blue dye, microbial ingress, pressure/vacuum decay)* will NOT identify these vials having temporary leaks.

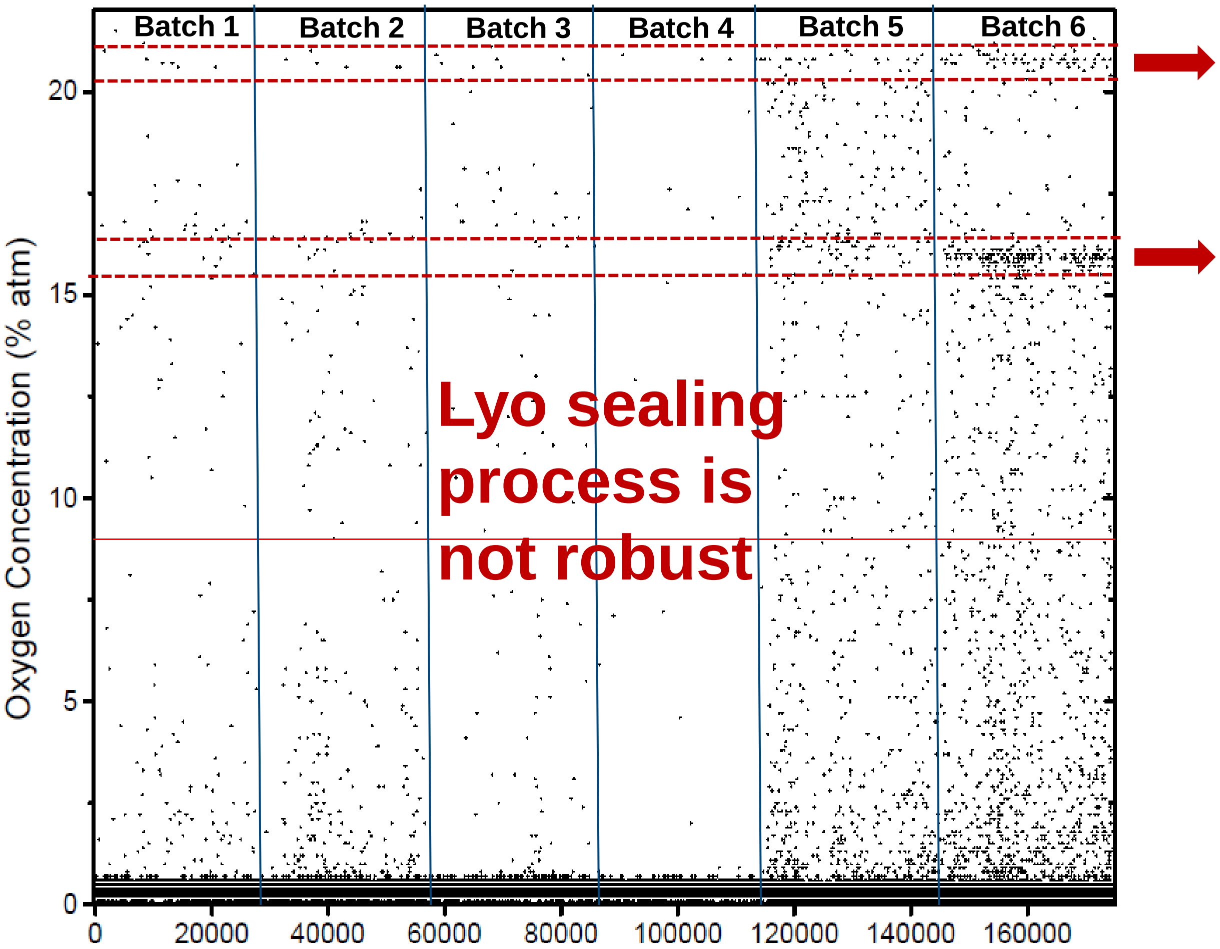
Case study 4:
100% CCI testing of lyo product



Lyophilised Product closed at 200 mbar of N_2

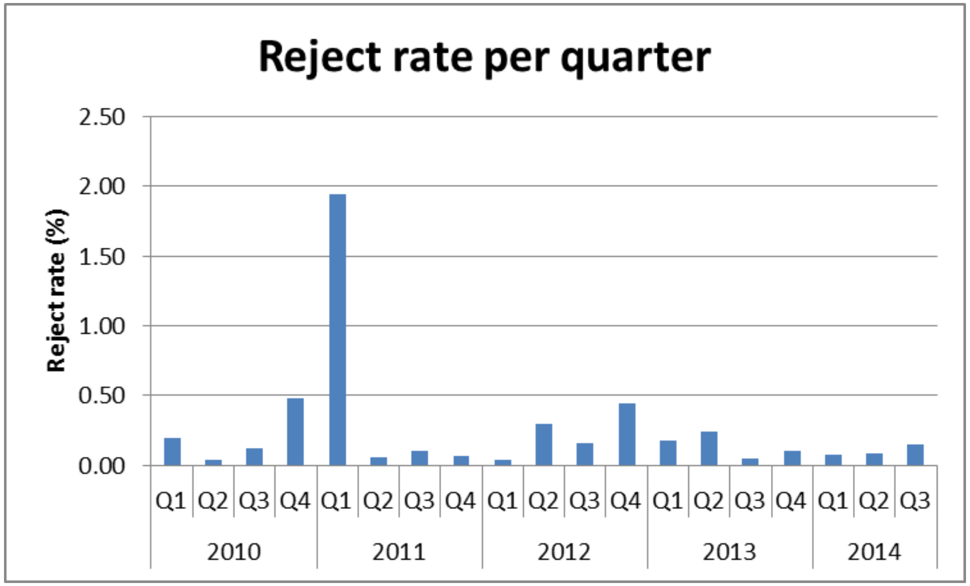
Results of 6 consecutive batches

Case study 4:
100% CCI testing of lyo product



- 1 atm air vials, gross (permanent) leaks
- Lyo headspace specified to be 200 mbar N_2
- If 800 mbar air enters vial = 16% O2!
- Partial leaks stopped by capping

Case study 4:
100% CCI testing of lyo product



Case 100% inspection

5 years of manufacturing data:

- 156 lots
- Total 1.9 million vials

Results

44-lots (28%) with zero rejects

Average reject rate was 0.25%

Difficult to manufacture a perfect CCI lyo batch

Thank you for your attention

Demonstration

Let's consider the following product-package:

- Product ampoule closed at 500mbar N_2

- What are the headspace oxygen levels when the…

A) … container has retained CCI?

B) … container has just lost closure?

C) … container has permanently lost closure for some time?