Gas Ingress for CCIT

Using laser-based headspace analysis

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27-28 Feb 2020 - PDA CCIT Workshop Basel

Overview

Part 1: Theoretical background

- How does gas ingress work?
- How can theory be applied?

Part 2: Case study: products packaged under a modified atmosphere

- 100% inspection of lyophilized product

Part 3: Case studies: products packaged under a non-modified atmosphere

- Cold Storage CCI Study
- Gas Ingress Testing using CO_2 as a tracer gas

Part 1

Theoretical background

Gas ingress testing for CCI

Two different ways by which gas can flow through a defect in and out of a pharmaceutical container:

- **Effusion**: gas flow generated by a total pressure difference across the container defect
- **Diffusion**: gas flow of a particular gas generated by a partial pressure difference of that gas across the container defect

Understanding this gas flow enables the development of CCI test methods based on the measurement of gas ingress

Positive controls – validating headspace gas ingress methods

- CCIT methods based on detecting gas ingress into the headspace can be demonstrated and validated using known positive controls
- Gas flow physics model also enables calculation of test method sensitivity

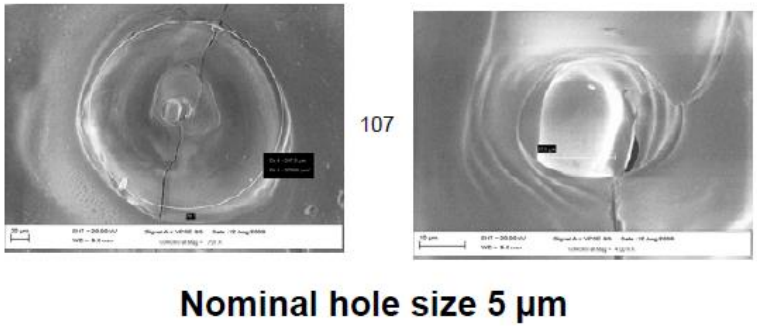
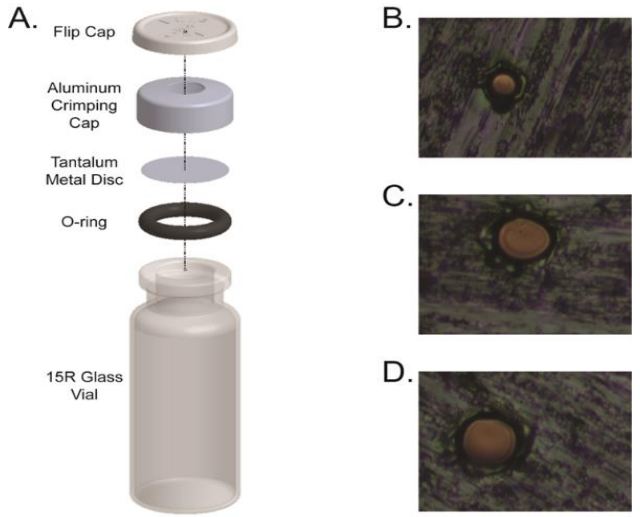
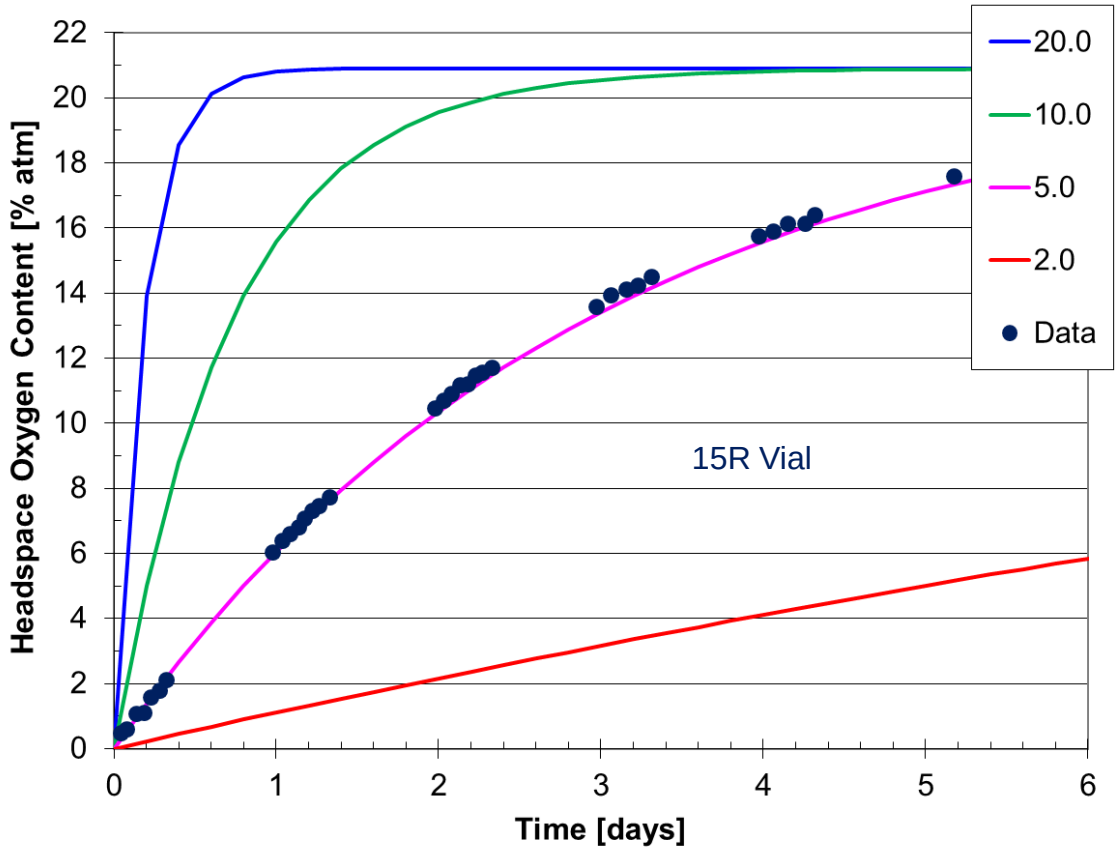


Image provided by Lenox Laser



Oxygen Diffusion Ingress Model Example

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

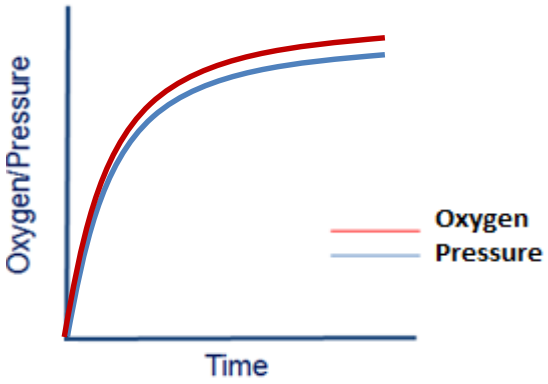


Defect diameter [μm]

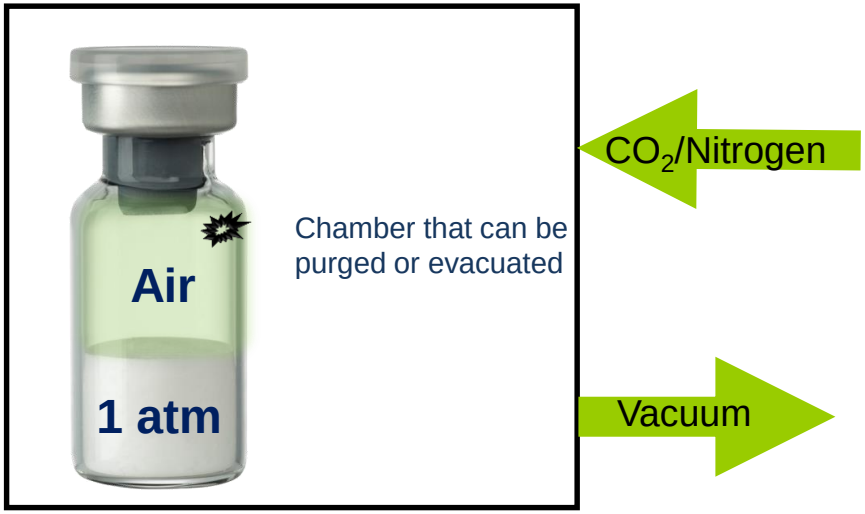
Published in PDA Journal Nov-Dec 2017 issue (71): 'Method Development for CCI Evaluation via Gas Ingress by Using Frequency Modulation Spectroscopy' [K. Victor]. p 429-453.

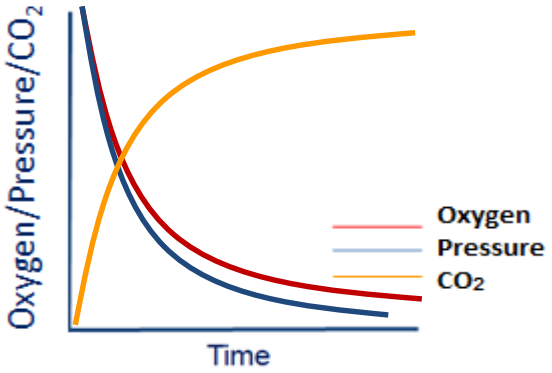
Headspace gas ingress as CCIT

Modified headspace



Non - Modified headspace

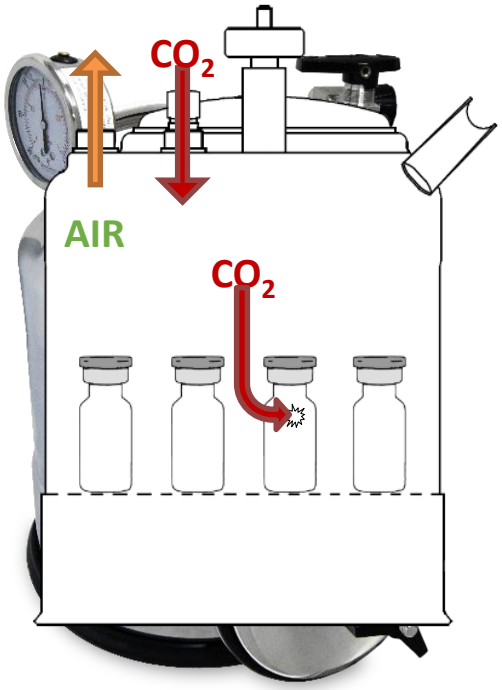




Gas Ingress Testing for CCI

Objective

- Develop an approach similar to blue dye but better
- Method must reliably detect critical leaks



Proposed Gas Ingress Test Method

- Vials placed in CCI Test Vessel
- Vessel pressurized with X bar of CO_2 for Y min
- Samples removed and tested for headspace CO_2

Gas bath instead of blue dye bath

Headspace Analysis Systems

Laboratory and At-line Instruments and accessories

Automated Inspection Machines

SYNTEGON

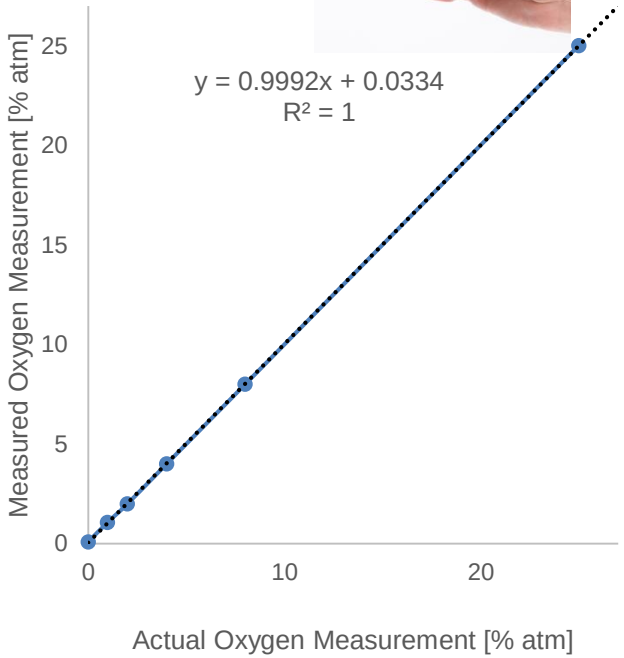
Strategic partnership with Syntegon (formally Bosch) for CCI machines with Lighthouse laser measurement technology inside.

Measurement performance

Instrument and machine qualification using NIST traceable standards.

N=100	Headspace Oxygen (% atm)			
Standard Label	Known Value	Meas. Mean	Error	St. Dev.
0	0.000	0.08	0.08	0.04
1	0.990	1.06	0.07	0.06
2	2.000	1.99	-0.01	0.07
4	4.000	4.00	0.00	0.05
8	8.000	8.00	0.00	0.07
25	24.99	25.02	0.03	0.07

Accuracy Precision

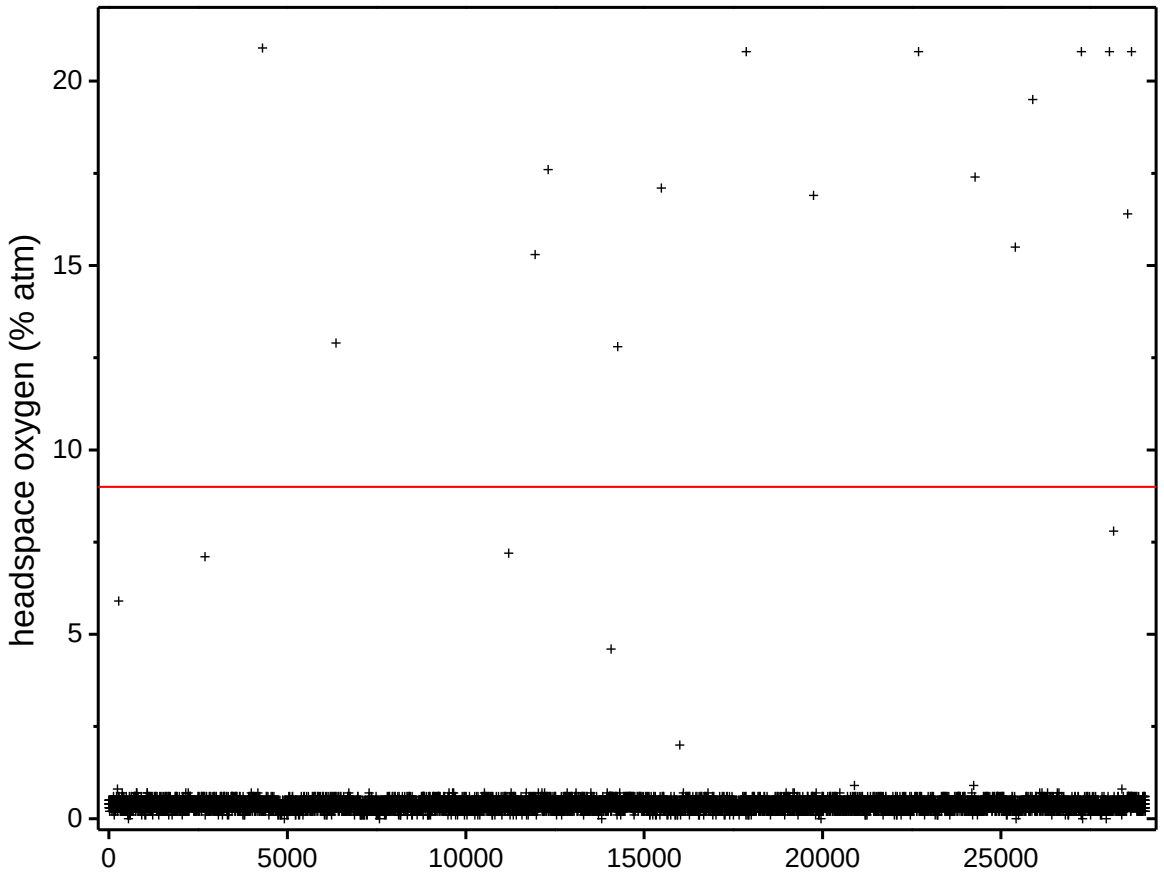


- Users and data managed in a database solution for 21-CFR-11 compliance and full audit trail
- Certificates of NIST traceable calibration standards
- Optional yearly re-certification of standards

Part 2

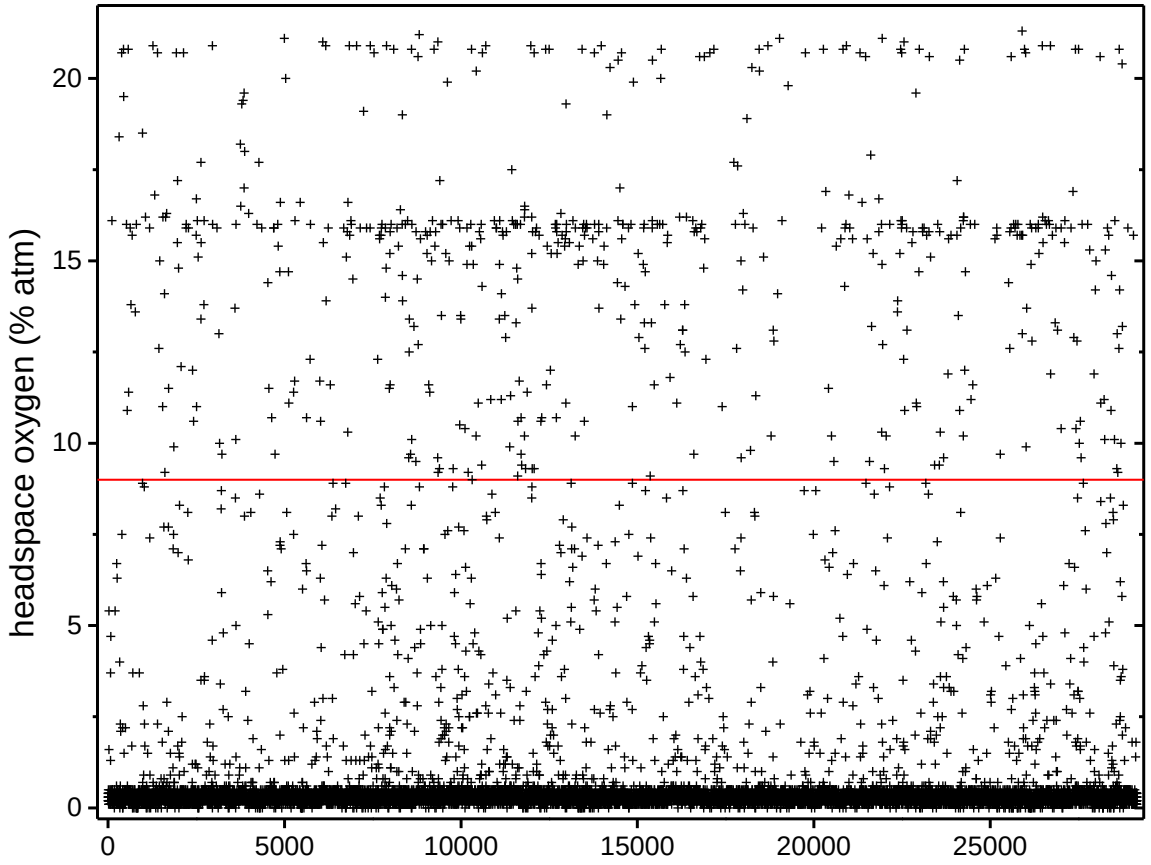
Case study – modified headspace

Case Study 1:
100% Inspection of lyo product



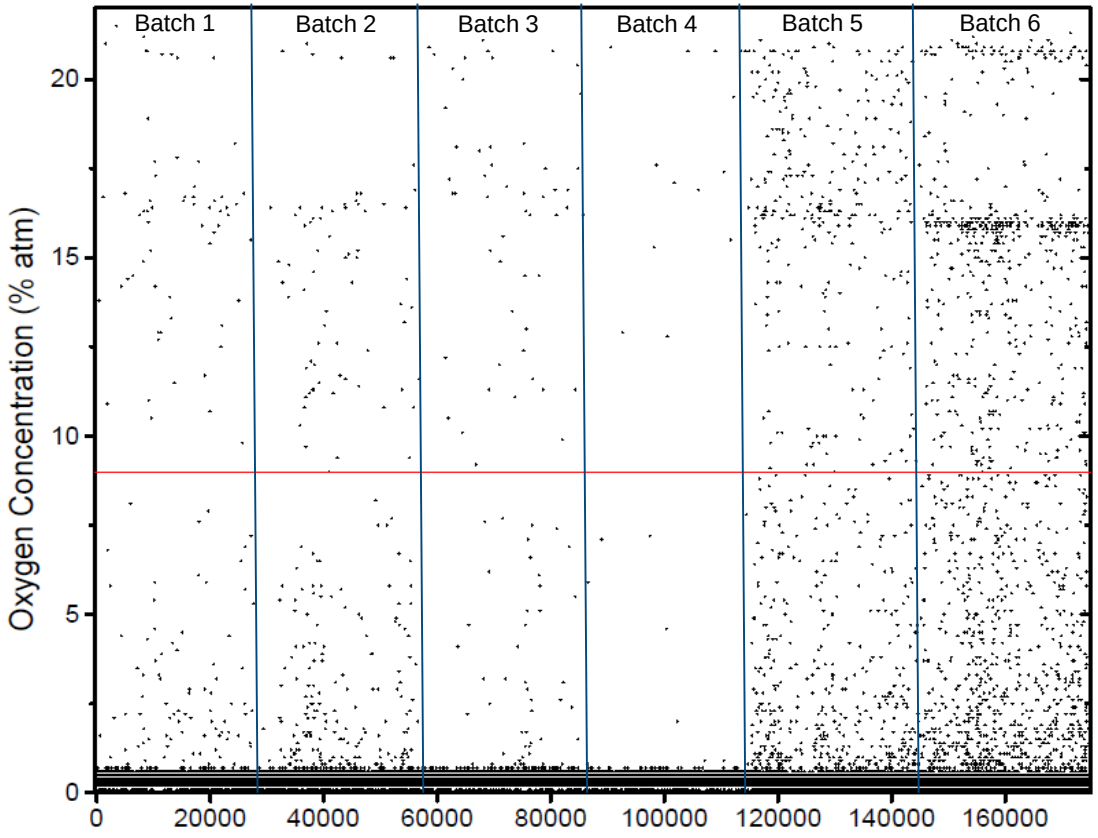
Total batch size: 29048
Number rejected: 16
Reject rate: 0.06%

Case Study 1:
100% Inspection of lyo product



Total batch size: 29156
Number rejected: 568
Reject rate: 1.95%

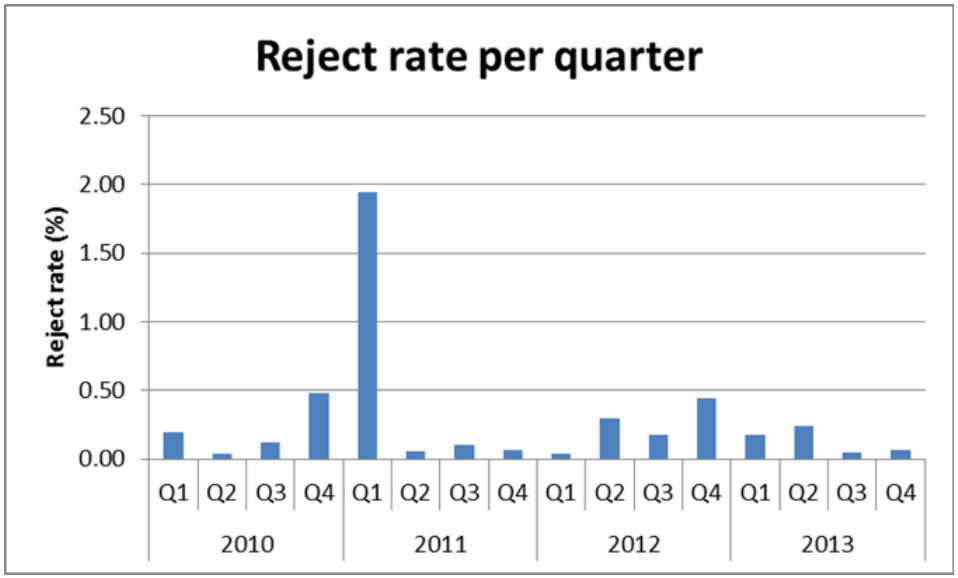
Case Study 1:
100% Inspection of lyo product



Results of 6 chronological batches

Not a robust process

Case Study 1: 100% Inspection of lyo product



Case 100% inspection

4 years of manufacturing data:

- 156 lots
- Total 1.6 million vials

Results

44-lots (28%) with zero rejects

3-lots had > 2% reject rate

Average reject rate was 0.27%

It is difficult to manufacture a perfect batch

Thought experiment: CCI control strategy

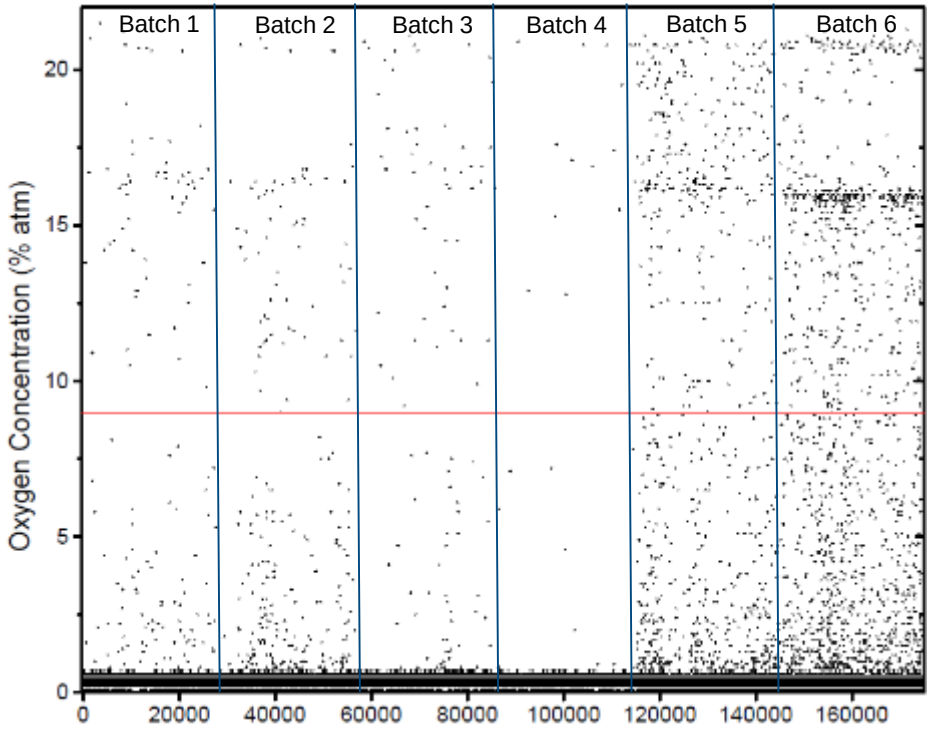
Think about the CCI control/testing strategy currently implemented in your company

If your lyo sealing process is doing this would you know about it?

When would you know about it?

- After 1 batch?
- After 6 batches?
- After 30 batches?

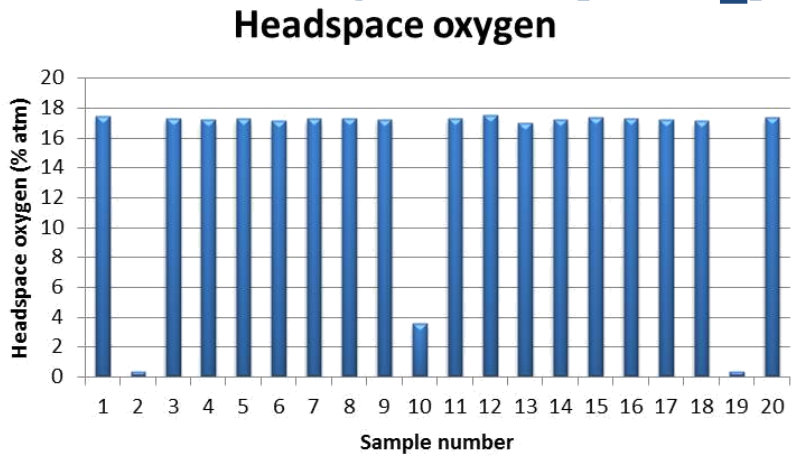
What would you need to do to prevent this from happening?

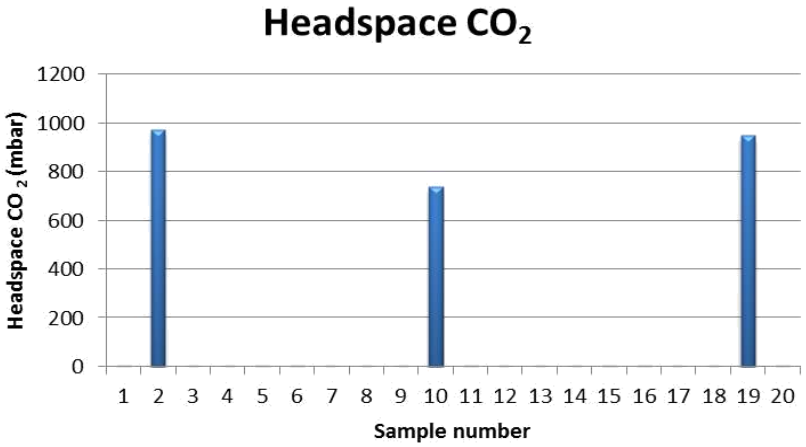


Part 3

Case studies – non-modified headspace

Case Study 2: CCI testing for vials stored on dry ice (CO_2)





Case

- Air headspace vials stored on dry ice (CO_2)
- Storage on dry ice increases risk of CCI loss (CO_2 ingress)
  - Conventional rubber stoppers lose elasticity (<Tg)
  - Differing material coefficients of expansion (interface gaps)

Result

- 3 containers revealed decreased oxygen levels
- Same vials revealed increased CO_2 levels

Gas Ingress Testing for CCI

Sample preparation → Sample conditioning cycle → Measure headspace CO_2 levels

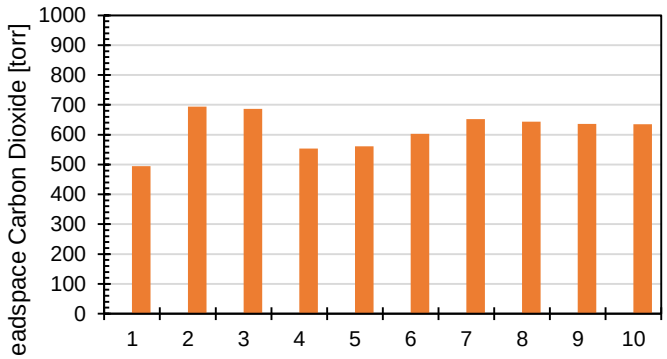
Gas Ingress Testing for CCI

- Gas ingress testing using CO2 overpressure easily identifies positive controls.
- Empty vials show almost total headspace gas exchange (600 – 700 torr of CO_2) with the chosen CCIT vessel cycle.

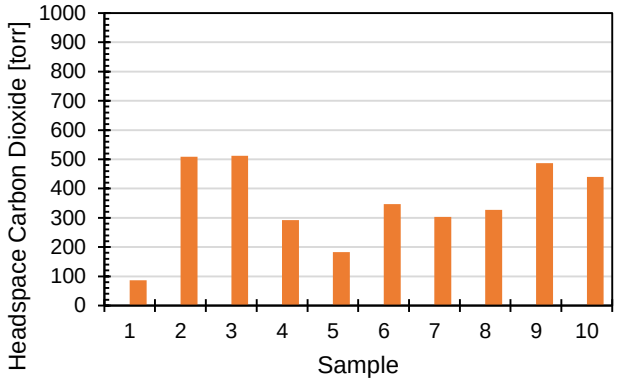
- Filled vials with defects below the liquid fill also detected but with less sensitivity.
- Further method development studies have shown cases where defects below the liquid level are not detected.

Results for 5 µm laser-drilled defects

Empty vials



Water Filled



Robust CCI method development and method validation can be done to define appropriate test methods with this approach.

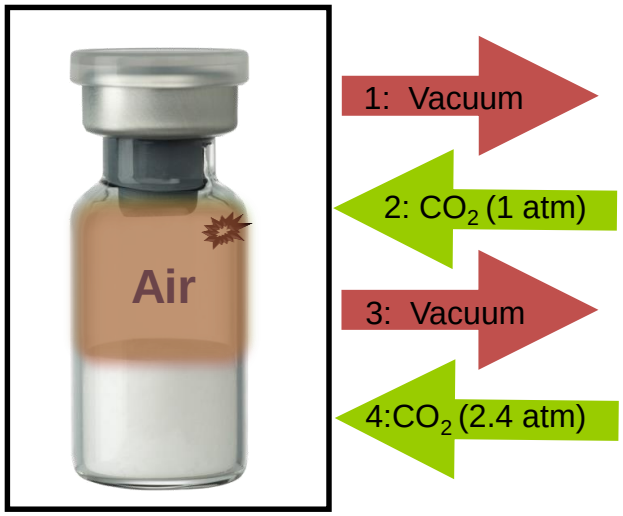
Case Study 3: CCI method development – CO_2 Headspace Gas Ingress

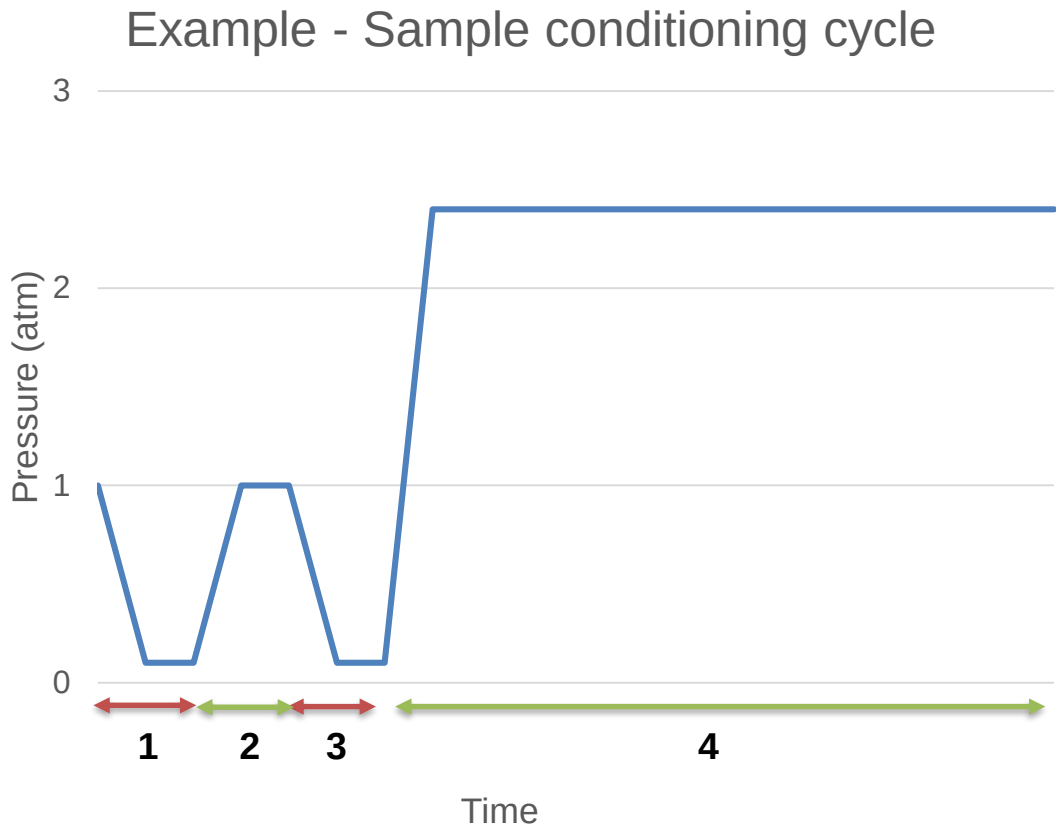
Objective: Detection of a 5µm laser-drilled defect within 15 min.

Sample set

- 2R DIN clear tubing vial – air headspace
  - 2mL PBS liquid filled (150mM)
  - 2mL BSA liquid filled (1mg/mL)
- Positive controls:
  - 2µm, 5µm and 10µm laser drilled glass defects above and below liquid level
  - 25G syringe needle punctured through stopper

Case Study 3: CCI method development – CO_2 Headspace Gas Ingress





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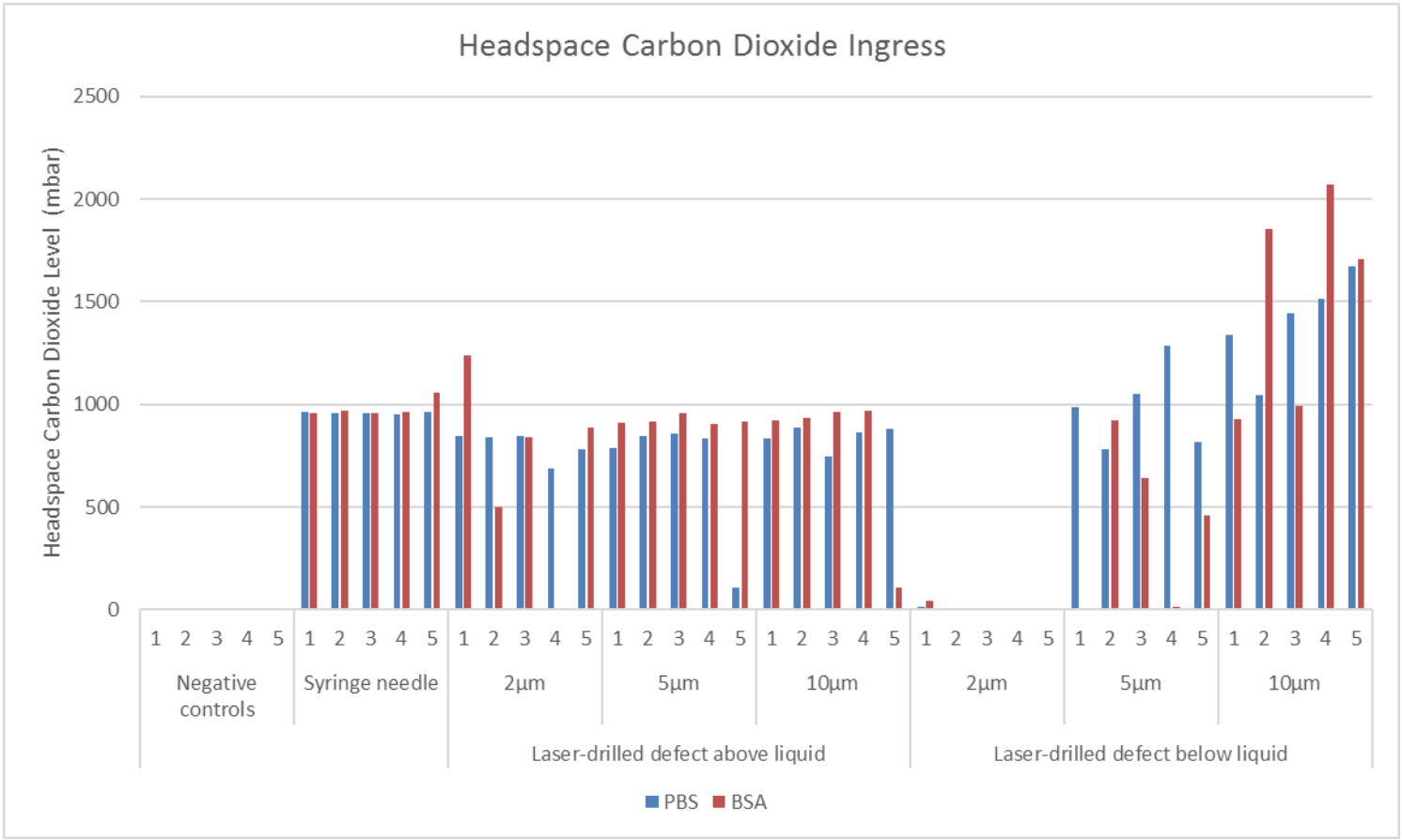

Case Study 3: CCI method development – CO_2 Headspace Gas Ingress

Results

Defect type	Defect location	Leak detected	
		PBS	BSA
2 µm laser-drilled	Above liquid	5/5	5/5
	Below liquid	1/5	1/5
5 µm laser-drilled	Above liquid	5/5	5/5
	Below liquid	5/5	4/5
10 µm laser-drilled	Above liquid	5/5	5/5
	Below liquid	5/5	5/5
Gross defect	Stopper	5/5	5/5
Negative control	NA	0/5	0/5

Presence of product can affect defect detection.
Defects type, size and location matters!

Headspace gas ingress as CCIT method

Blue dye test

- Ingress of methylene blue
- Qualitative visual inspection
- Destructive method
- Permanent leaks
- Useful for gross leak detection, CCI verification

Methylene blue:
$C_{16}H_{18}N_3SCl$

Laser-based headspace

- Ingress of O_2 , N_2 and/or CO_2
- Analytical measurement
- Non-destructive method
- Permanent *and* temporary leaks
- Sensitive to all leak sizes
- Quantitatively described by gas flow physics

Diatomic gas molecule

Similar to blue dye but much more sensitive, can be validated as an analytical method, can be used in all stages of the product life cycle

Thank you!