Gas Ingress for CCIT throughout life-cycle

Using laser-based headspace analysis

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Overview

Part 1: Theoretical background

Part 2: CCIT in an existing process

Part 3: CCIT method development and validation

Part 4: Inherent integrity testing

Part 5: CCIT in package development

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:

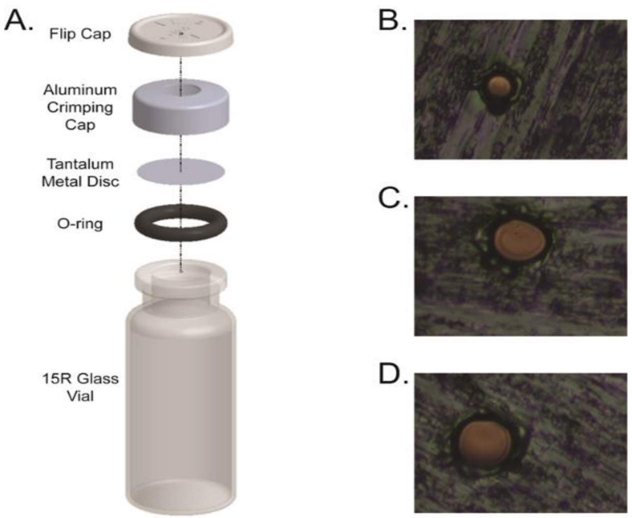
- **Effusion**: gas flow generated by a total pressure difference across the container defect
- **Diffusion**: gas flow of a particular gas generated by a partial pressure difference of that gas across the container defect

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

Validating headspace gas ingress methods

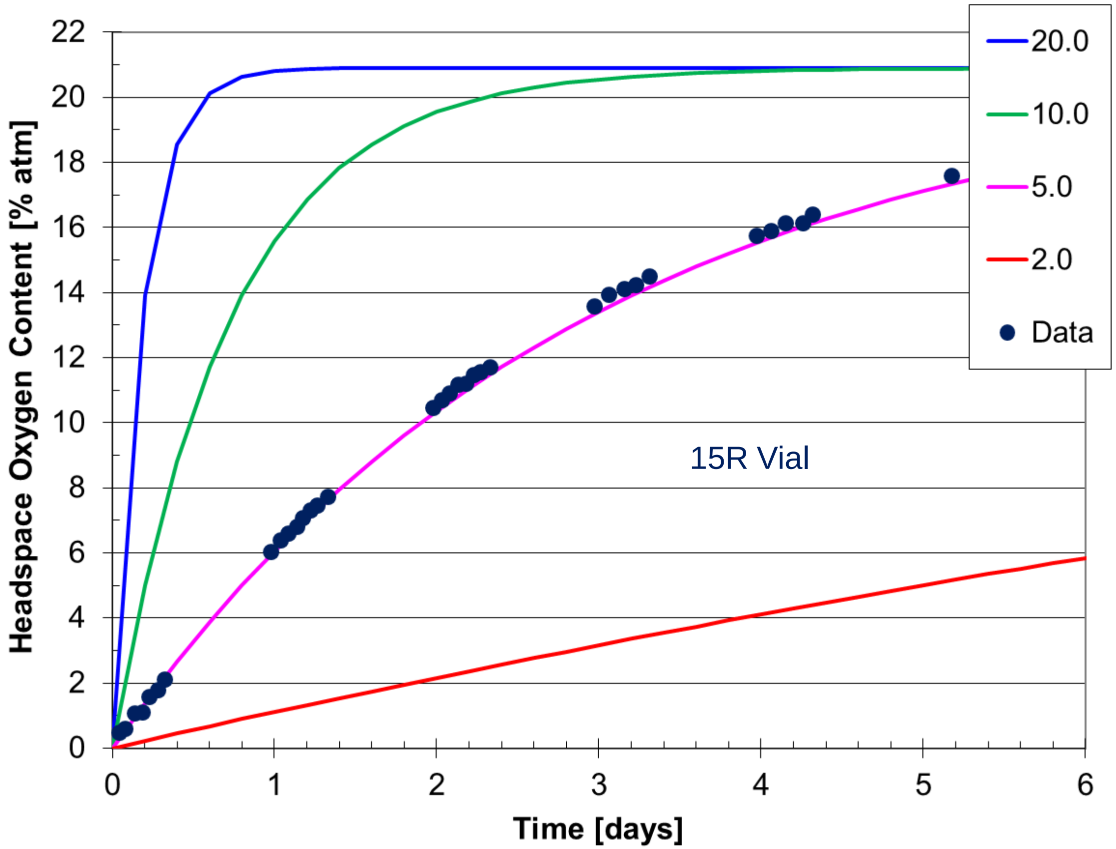
- CCIT methods based on detecting gas ingress into the headspace can be demonstrated and validated using known positive controls

- Gas flow physics model also enables calculation of test method sensitivity



Oxygen diffusion ingress model example

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

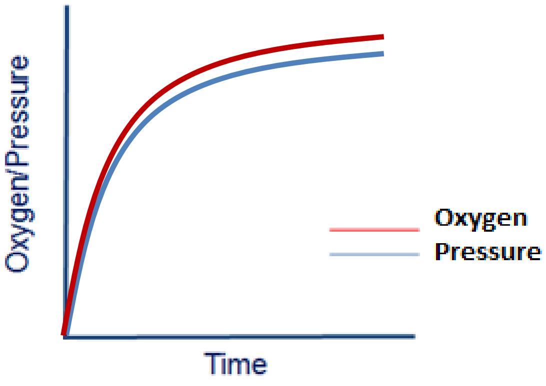


Defect diameter [μm]

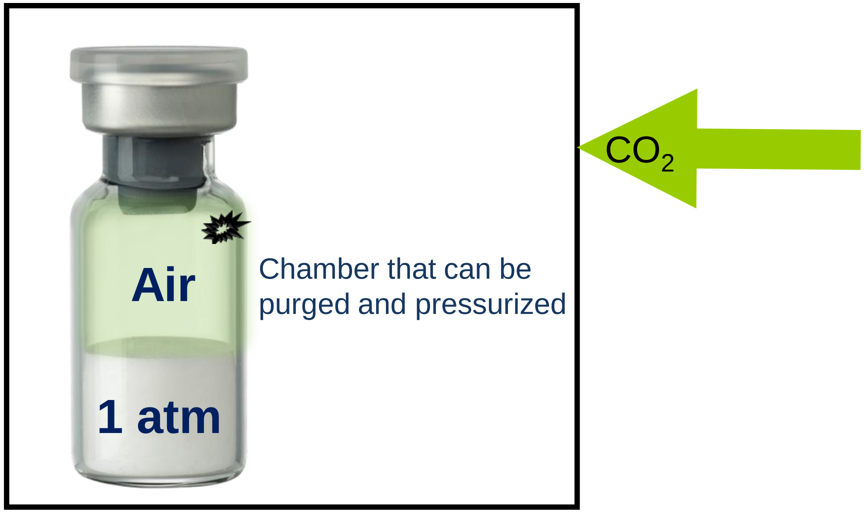
Published in PDA Journal Nov-Dec 2017 issue (71): 'Method Development for CCI Evaluation via Gas Ingress by Using Frequency Modulation Spectroscopy' [K. Victor]. p 429-453.

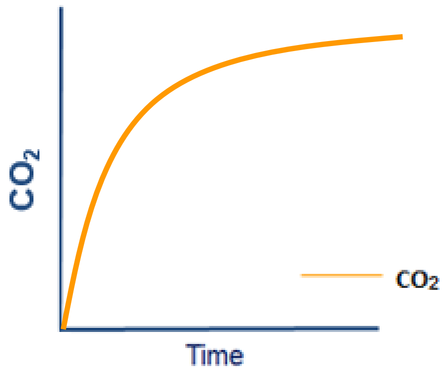
Headspace gas ingress as CCIT

Modified headspace



Non - Modified headspace





Headspace analysis systems

Laboratory and At-line Instruments and accessories

Automated Inspection Machines

SYNTEGON

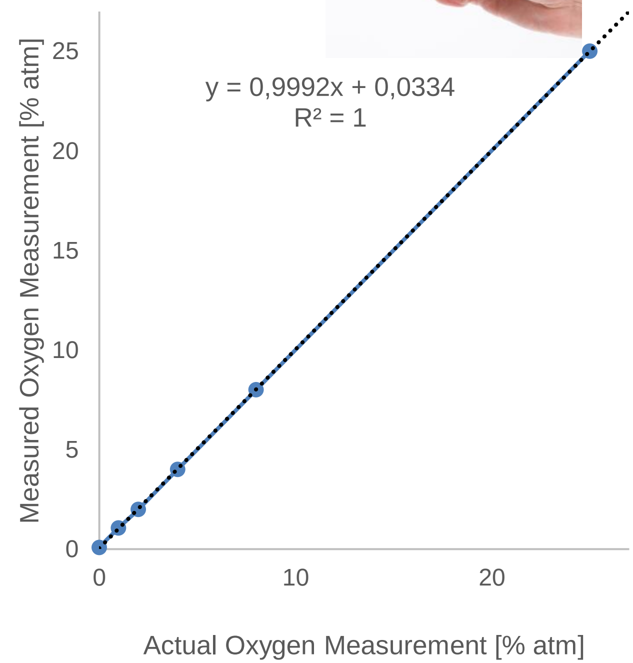
Strategic partnership with Syntegon (formally Bosch) for machines with Lighthouse laser measurement technology inside.

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 (Error) Precision (St. Dev.)



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

Part 2

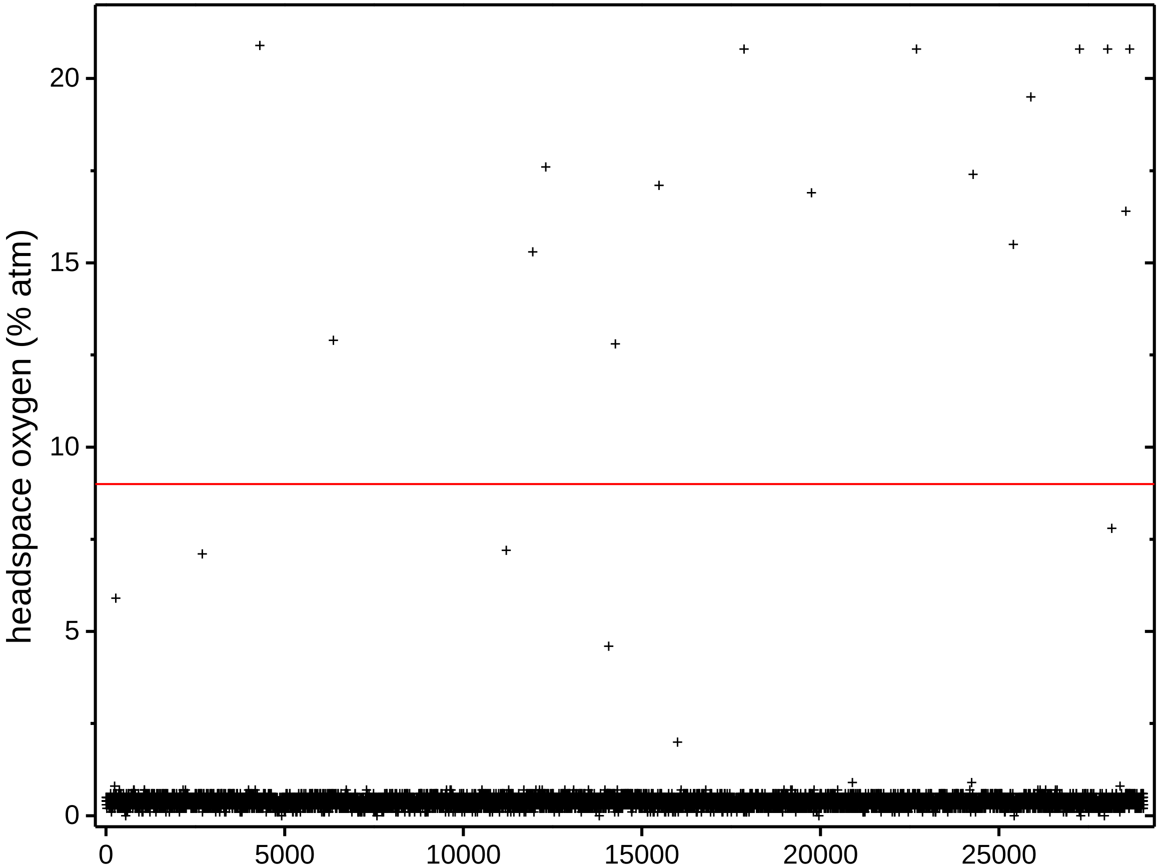
CCIT in an existing process

100% inspection of lyo product

Product: freeze dried
Headspace: 0.2 atmosphere nitrogen → 0% oxygen

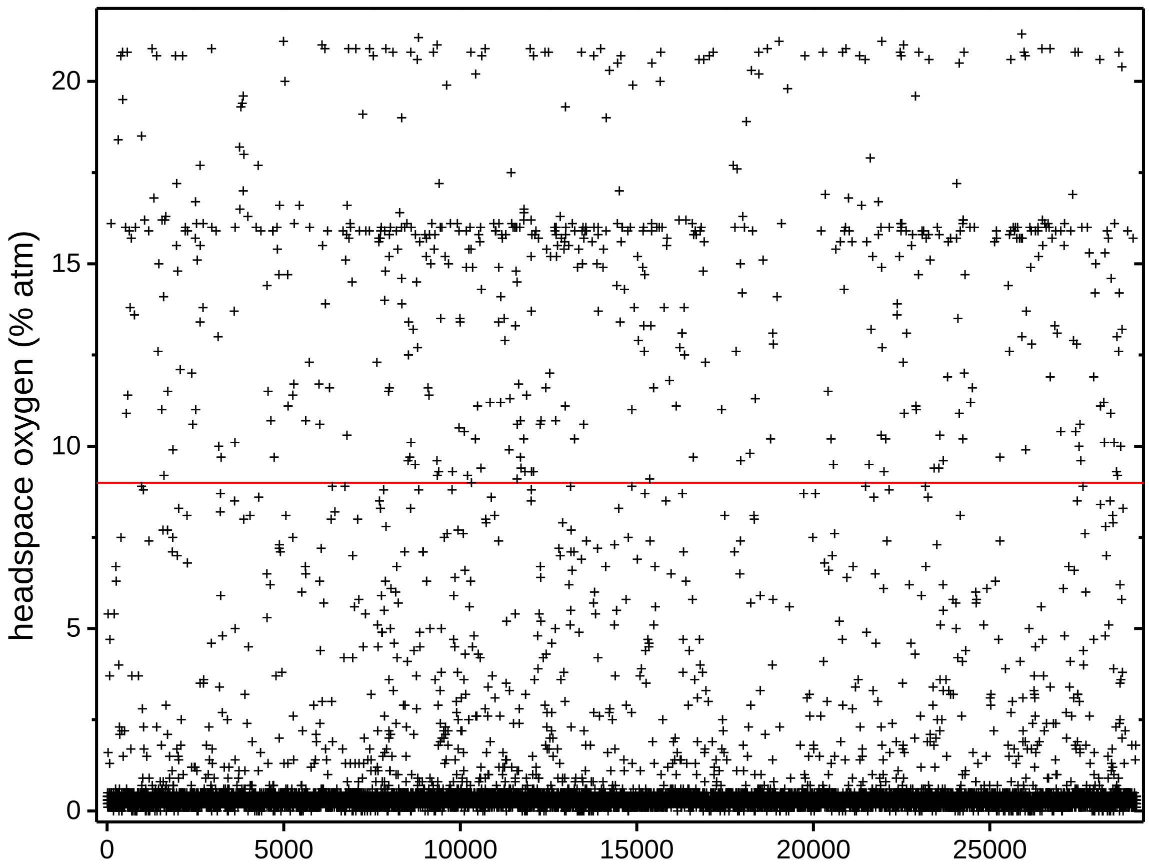
Problem: QC identified vials that had lost vacuum
Decision: Run 100% inspection in short timeframe

100% inspection of lyo product



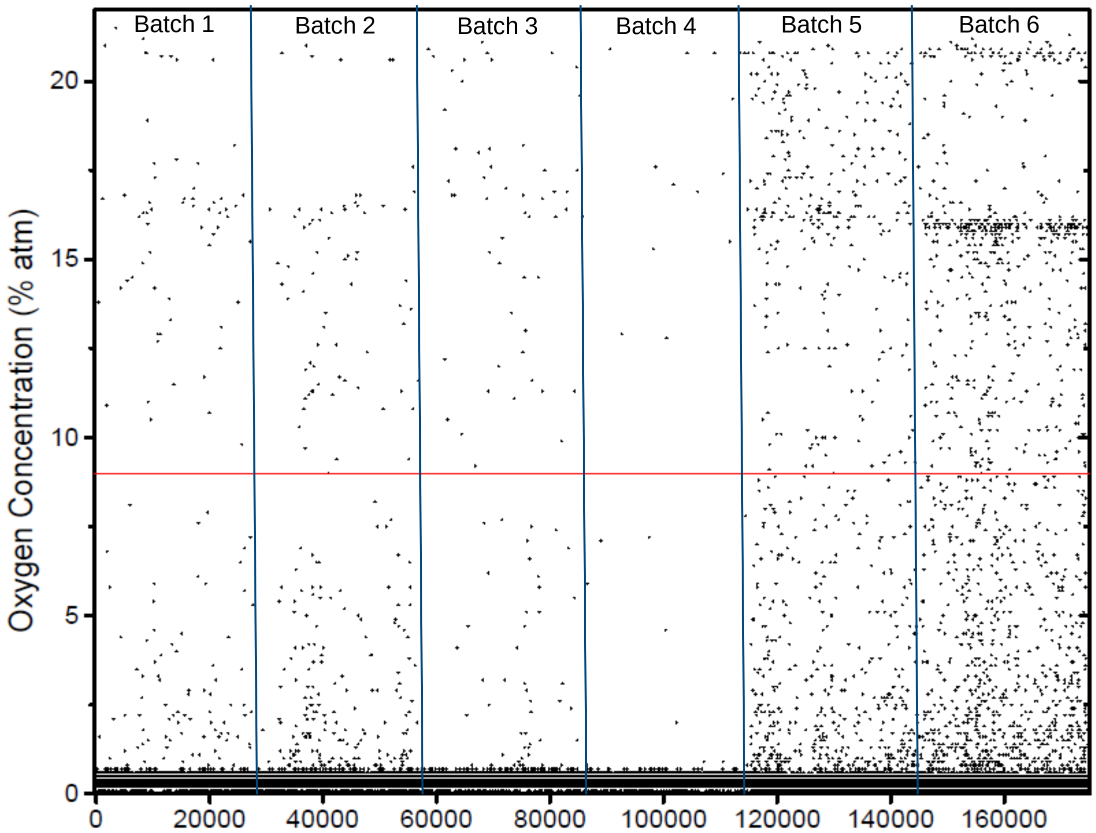
Total batch size: 29048
Number rejected: 16
Reject rate: 0.06%

100% inspection of lyo product



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

100% inspection of lyo product



Results of 6 chronological batches

Not a robust process

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?

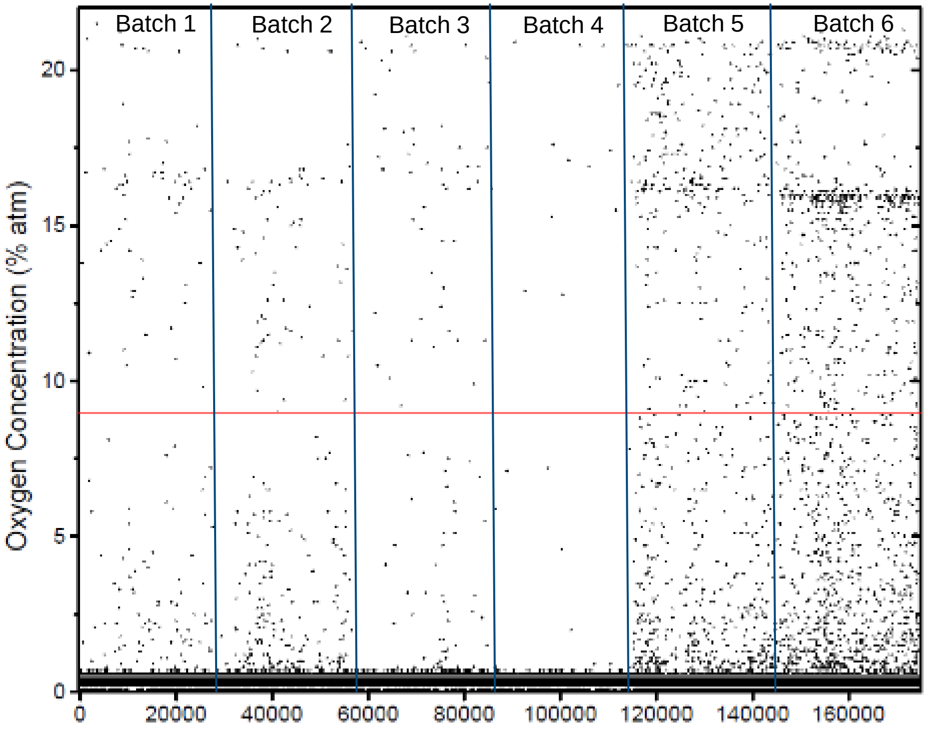
When would you know about it?

After 1 batch?

After 6 batches?

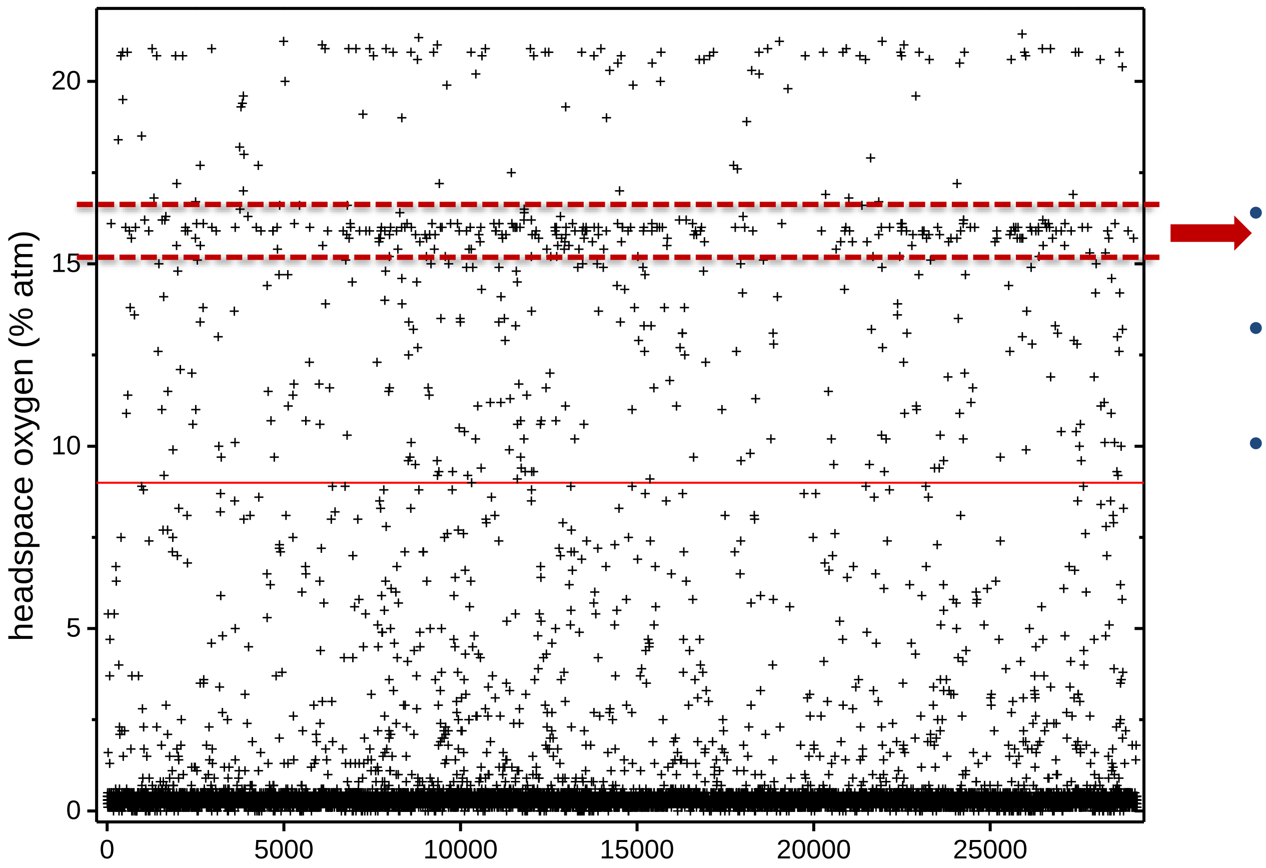
After 30 batches?

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



100% Inspection of lyo product

Temporary leaks

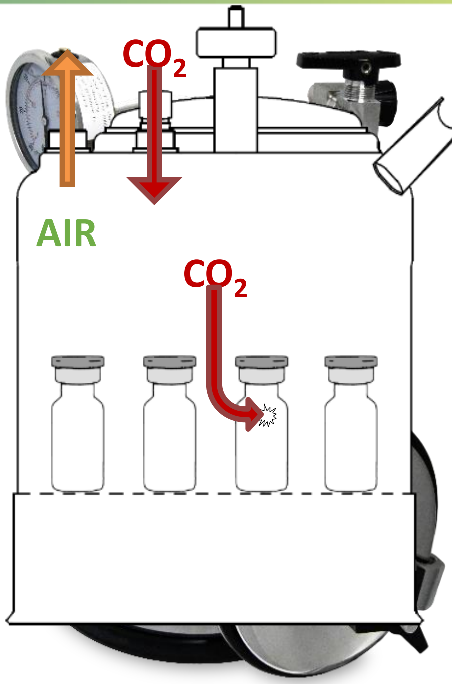


- Headspace specified to be 0.2 atm N_2
- If 0.8 atm air enters vial = **16% O_2**!
- Partial leaks stopped by capping

Part 3

CCIT method development and validation

Gas Ingress Testing for CCI



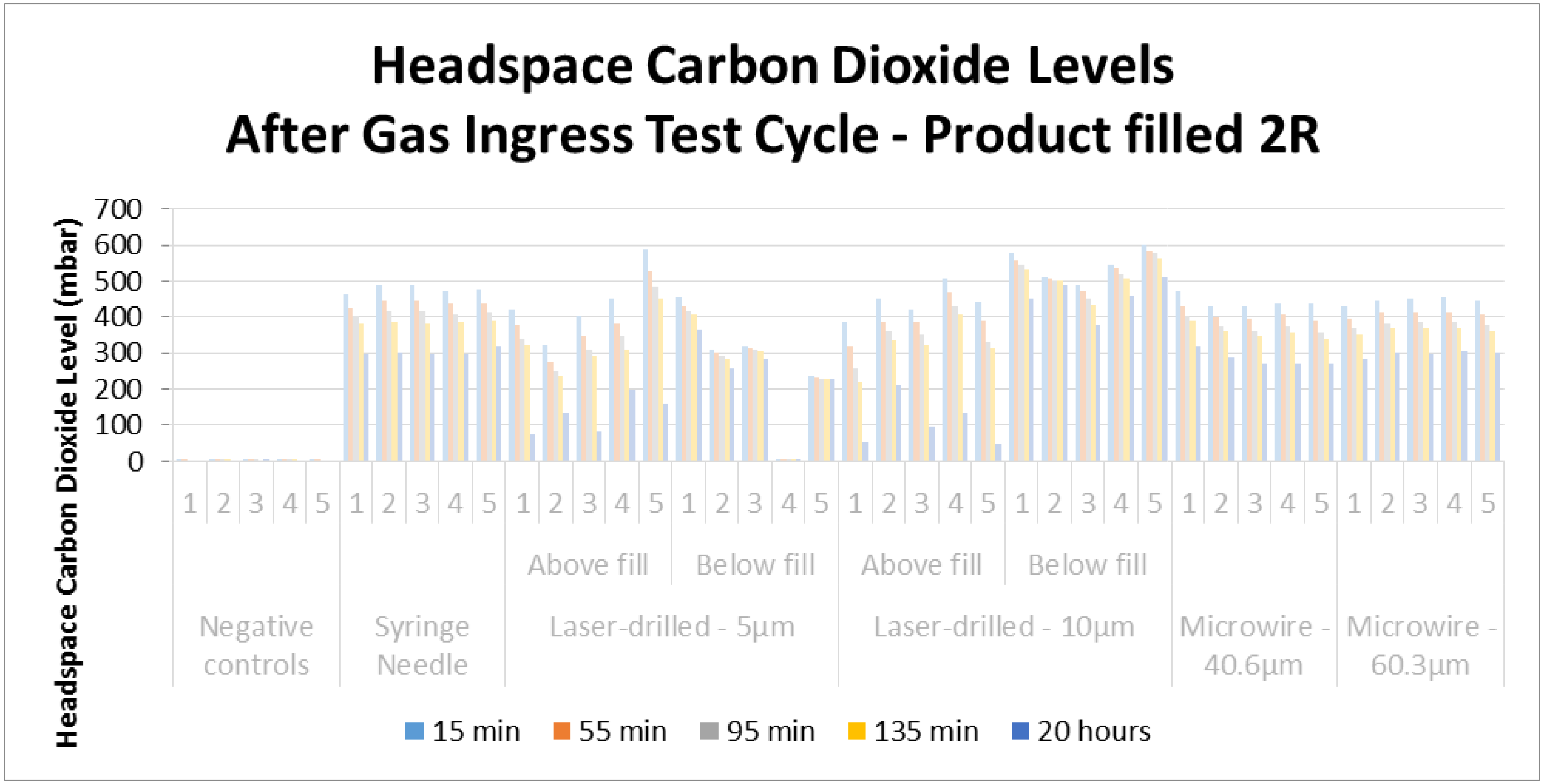
Objective

- Develop an approach similar to blue dye but better
- Reliably detect critical leaks above liquid level:
  5µm defect <15 min.

Sample preparation → Sample conditioning cycle → Measure headspace CO_2 levels

Gas bath instead of blue dye bath

CCI method development – CO_2 Headspace Gas Ingress



CCI method validation – CO_2 Headspace Gas Ingress

Three operators each tested:
5x 5µm laser-drilled positive controls
5x gross defect positive controls
5x negative controls

Control	Leak Detected?			CCIT result
	Operator 1	Operator 2	Operator 3	
5µm laser-drilled defect	5/5	5/5	5/5	Pass
16G needle gross defect	5/5	5/5	5/5	Pass
Negative controls	0/5	0/5	0/5	Pass

Part 4

Inherent integrity testing

Testing leak rates down to 10^{-8} sccs

Table 1. Gaseous Leakage Rate versus Orifice Leak Size[a]

Row	Air Leakage Rate[b] (std·cm³/s)	Orifice Leak Size[c] (µm)
1	$<1.4 \times 10^{-6}$	<0.1
2	1.4×10^{-6} to 1.4×10^{-4}	0.1 to 1.0
3	$>1.4 \times 10^{-4}$ to 3.6×10^{-3}	>1.0 to 5.0
4	$>3.6 \times 10^{-3}$ to 1.4×10^{-2}	>5.0 to 10.0
5	$>1.4 \times 10^{-2}$ to 0.36	>10.0 to 50.0
6	>0.36	>50.0

CO_2 headspace gas ingress method

- All samples stored in a CCIT vessel, 1 atm overpressure with CO_2
- Samples stored for 3 weeks and removed for measurement at 8 time points*

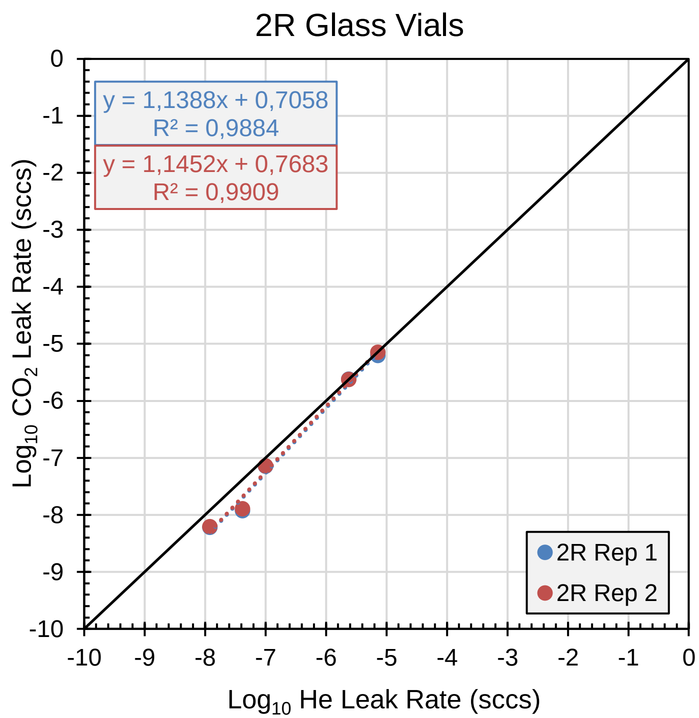
Helium Leak Rate testing method

- One sample tested per time
- Drill hole in container and purge with helium during test
- Draw vacuum on container (for vial, head with cap towards vacuum) and analyze pumped gas with helium leak detector.

Multiple measurements necessary for conversion of P_{CO2} to leak rate:
Victor et al. PDA J Pharm Sci and Tech **2017**, *71* 429-453

Testing leak rates down to 10^{-8} sccs

- Five different leak sizes
- Six samples per size tested
- Testing was repeated (Rep 1&2)



Headspace CO_2 gas ingress testing can detect defects as low as 10^{-8} sccs (corresponding to << 0.1µm orifice defect size)

C. Proff, H. Röhl, A. Caudill, J. Nunkaew, K. Victor, "Correlating CCI Leak Rates as Determined by Helium Leak Testing and Laser-Based Headspace Carbon Dioxide Analysis Using Modular Positive Controls", 2023 PDA Parenteral Packaging Conference, 18-19 April 2023.

Part 5

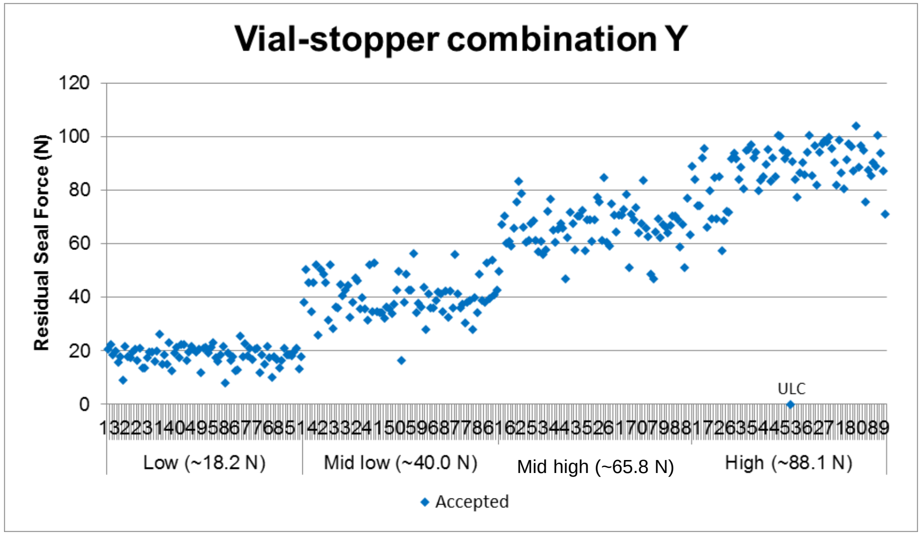
CCIT in package development

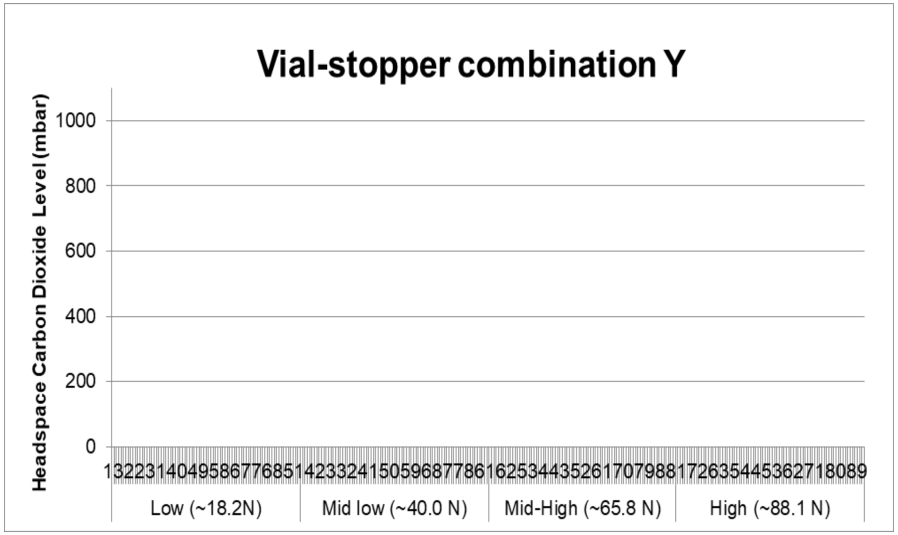
The curious case of temporary leaks

- Air filled vial at 1 atm at room temperature
- On dry ice (-80°C) the initial headspace condenses and creates underpressure
- The stopper can lose its elastic properties and closure can be lost
- Cold dense CO_2 from environment fills headspace
- Warming container to room temperature regains stopper elasticity and reseals closure

Dye ingress cannot detect this!

Primary packaging component selection

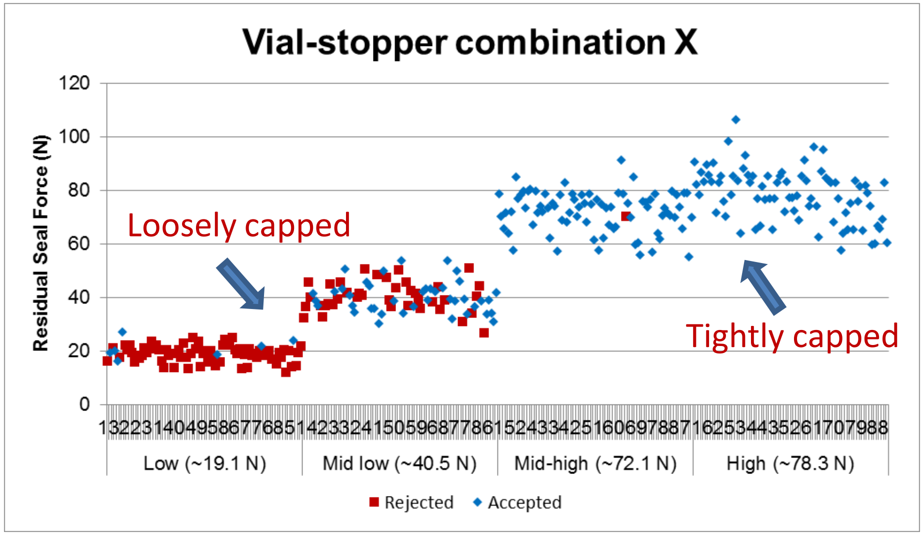


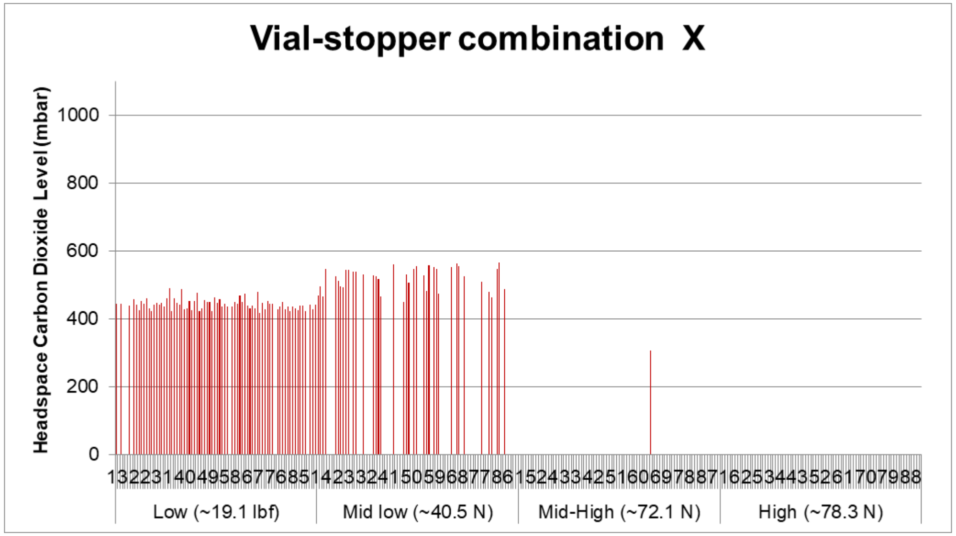


- Vial-stopper combination Y samples prepared at target RSF values and stored for 1 week at -80°C in a CO_2 rich environment
- None of the tested samples lost CCI at -80°C

** Ref. 'Mitigating Risk to Container Closure Integrity of a COVID-19 Vaccine Product During Ultra-Cold Chain Storage and Distribution' presentation PDA/FDA Joint Regulatory Conference', Michael Edey, Abriana Rozentsvayg, Derek Duncan*

Primary packaging component selection





Data-driven decision making on package components and process parameters

Ref. 'Mitigating Risk to Container Closure Integrity of a COVID-19 Vaccine Product During Ultra-Cold Chain Storage and Distribution' presentation PDA/FDA Joint Regulatory Conference', Michael Edey, Abriana Rozentsvayg, Derek Duncan

Product life cycle approach

Annex 1 focus:

- Using scientifically justified and validated methods.
- Having a scientifically valid sampling plan.
- Having knowledge and experience of the container and closure systems.
- Having a product life cycle approach

Questions?

Thank you!