# Gas Ingress for CCIT throughout life-cycle

## Using laser-based headspace analysis

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PDA
Parenteral Drug Association

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# What we do in a nutshell


Quantify headspace gas composition, non-destructively

# Case study 1

# CCIT in an existing process

# 100% inspection of lyo product

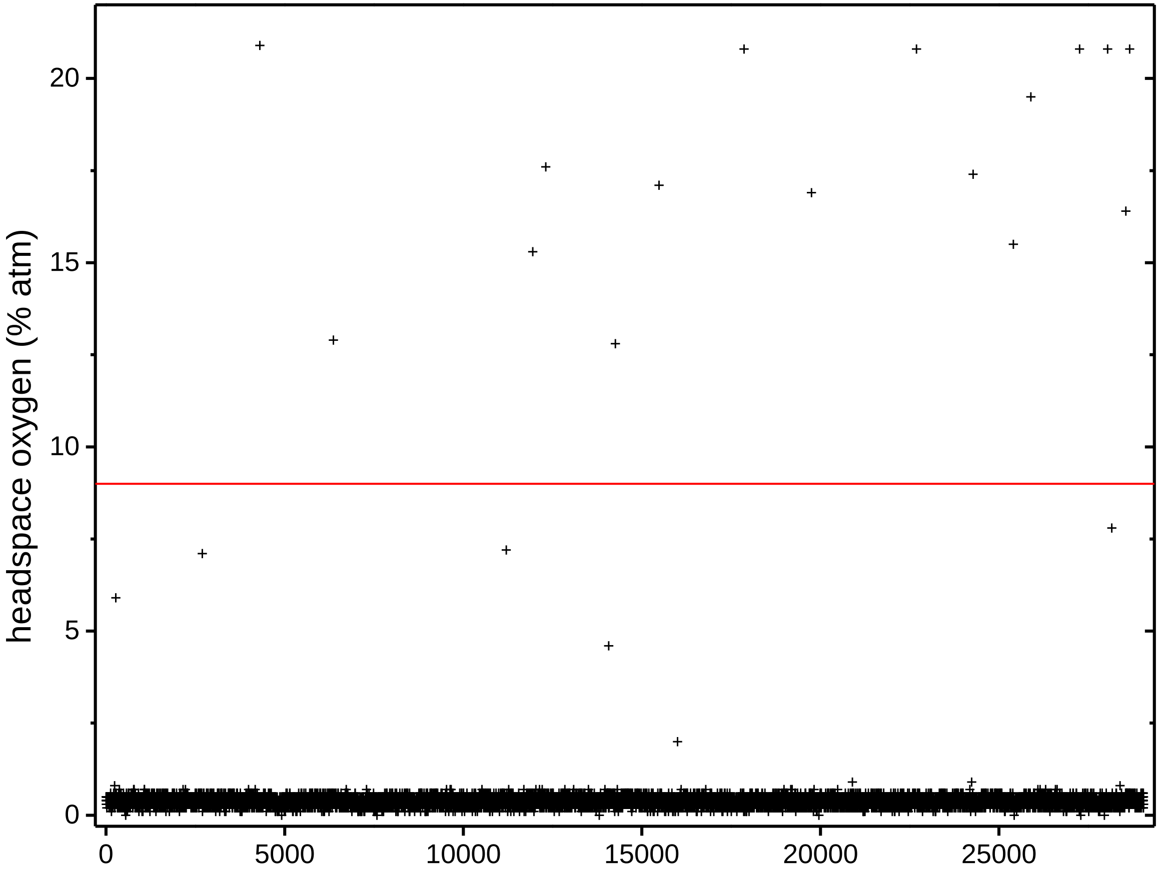

**Product:** freeze dried

**Headspace:** 0.2 atmosphere nitrogen → 0% oxygen

**Problem:** QC identified vials that had lost vacuum

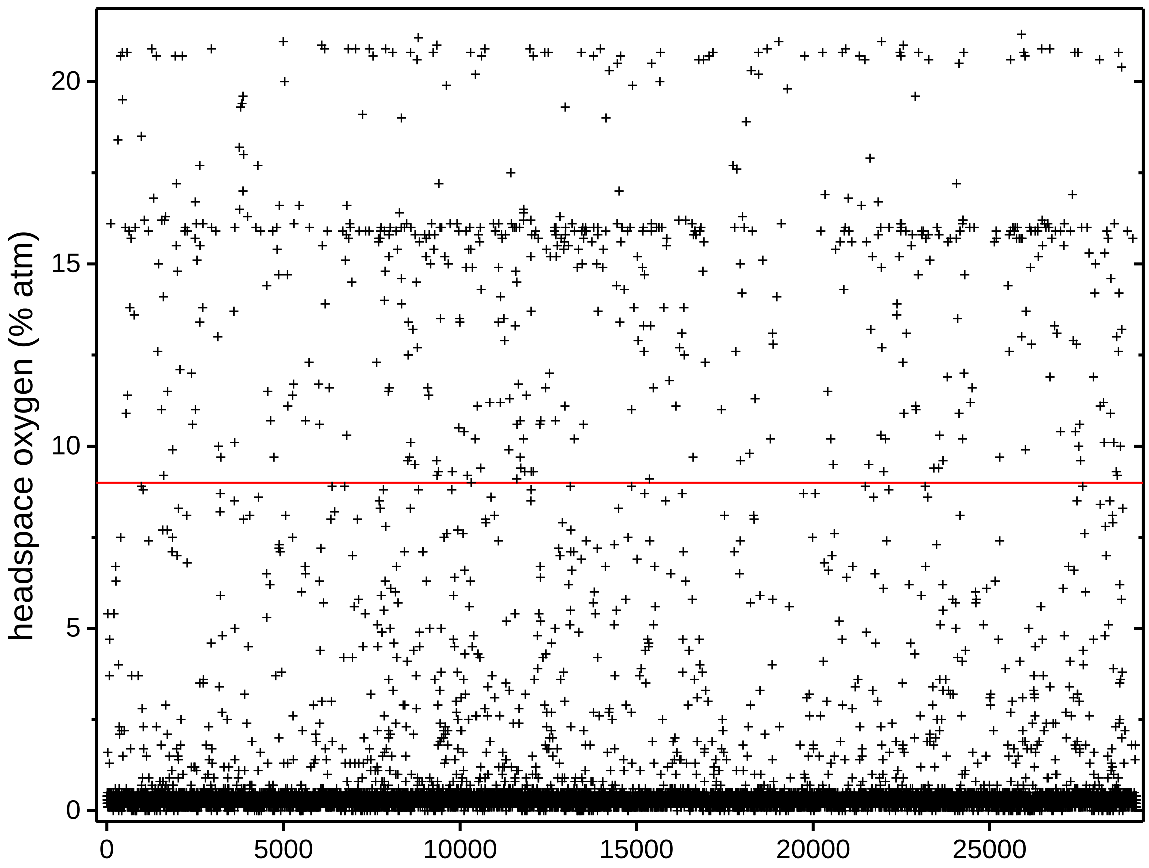
**Decision:** Run 100% inspection in short timeframe

# 100% Inspection of lyo product



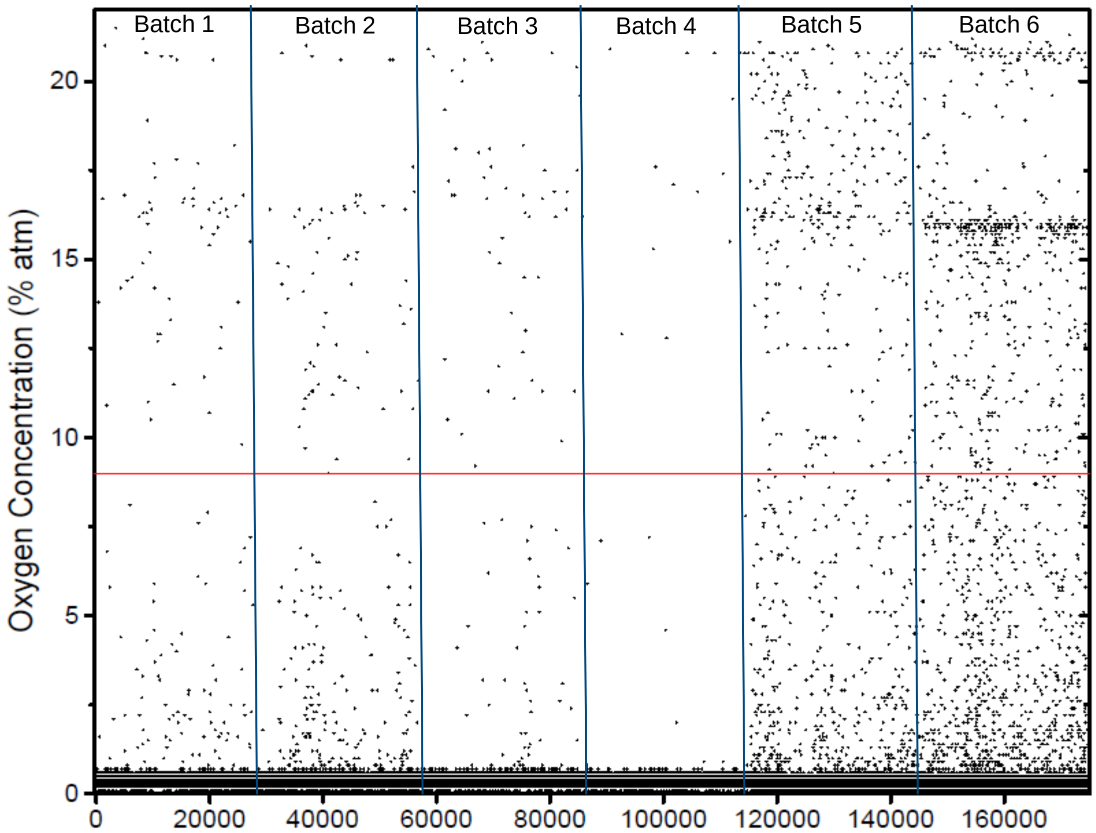

Total batch size: 29048
Number rejected: 16
Reject rate: 0.06%

# 100% Inspection of lyo product




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

# 100% Inspection of lyo product



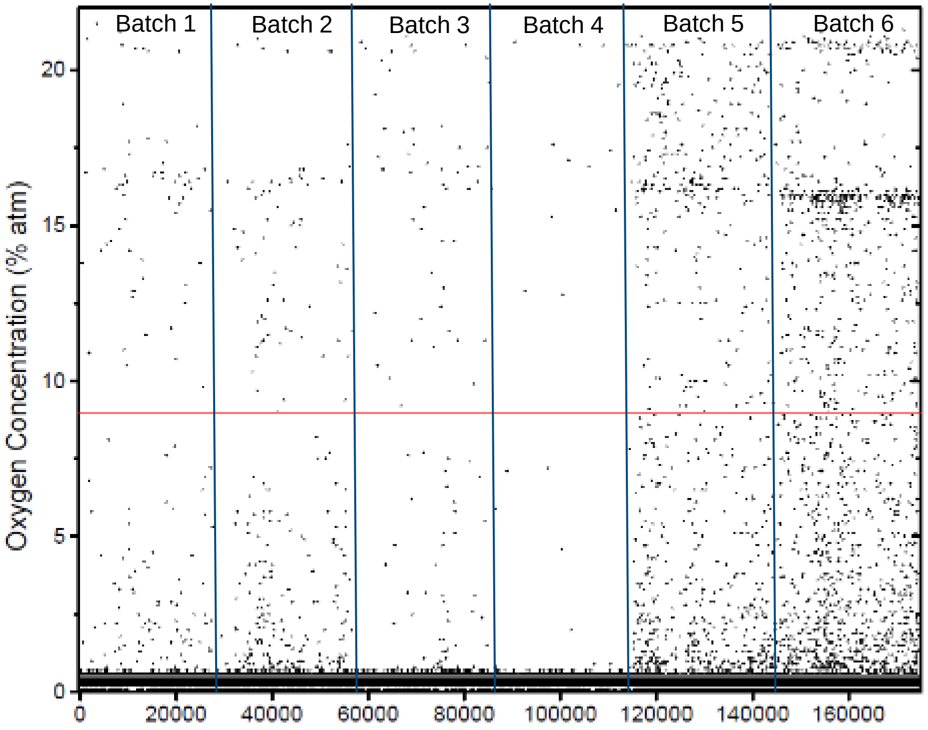

Results of 6 chronological batches

**Not a robust process**

# Thought experiment: CCI control strategy

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

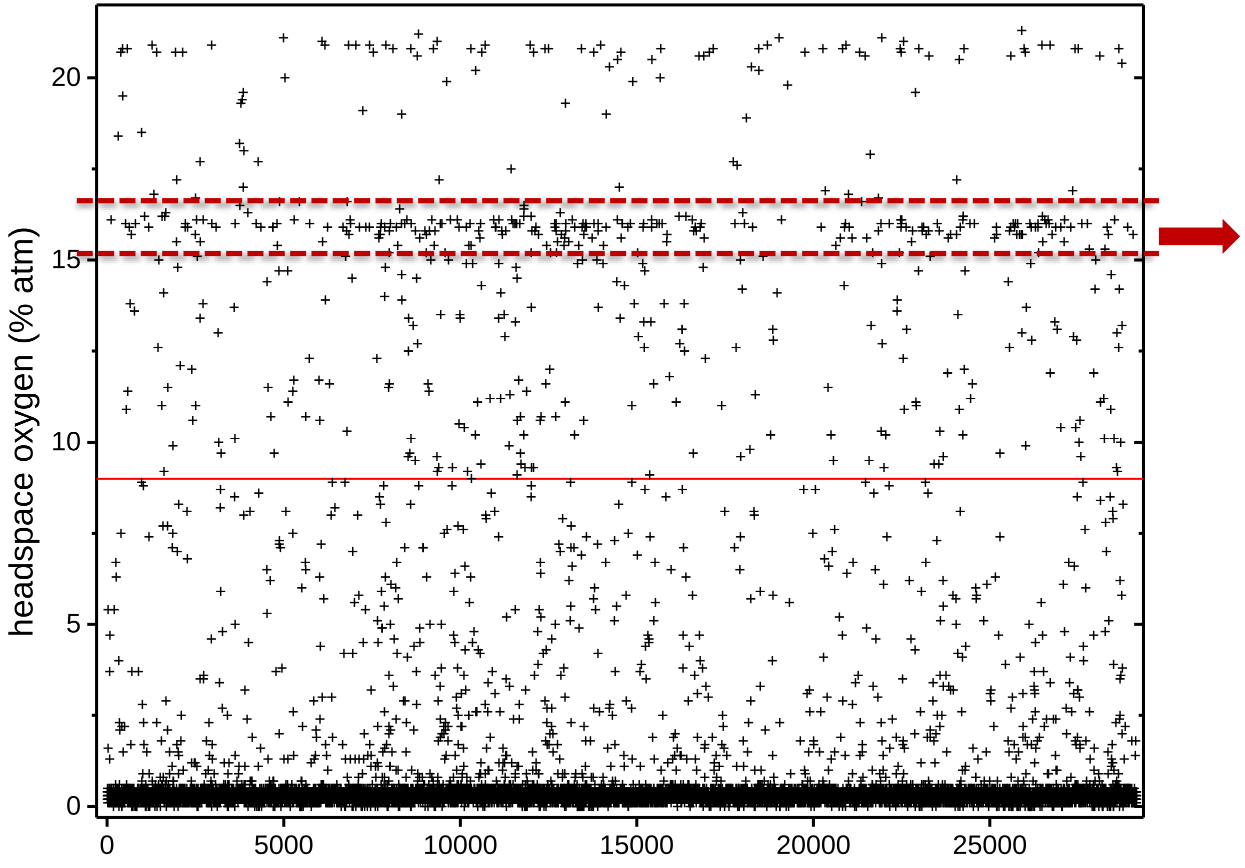
If your lyo sealing process is doing this would you know about it?




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



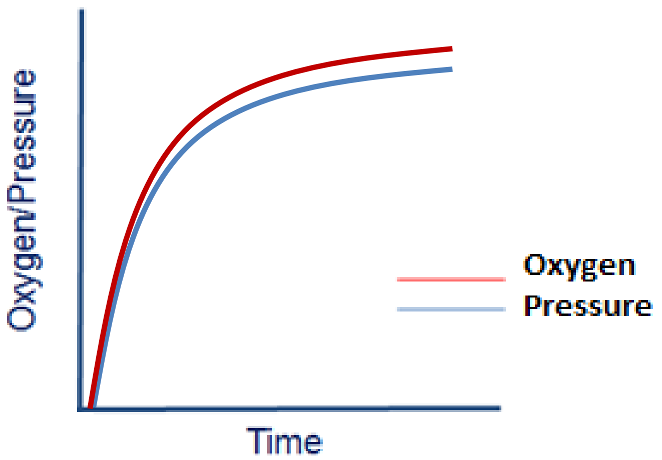

- Headspace specified to be 0.2 atm $N_2$
- If 0.8 atm air enters vial = **16% $O_2$**!
- Partial leaks stopped by capping

# Theoretical background

# Headspace gas ingress as CCIT

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

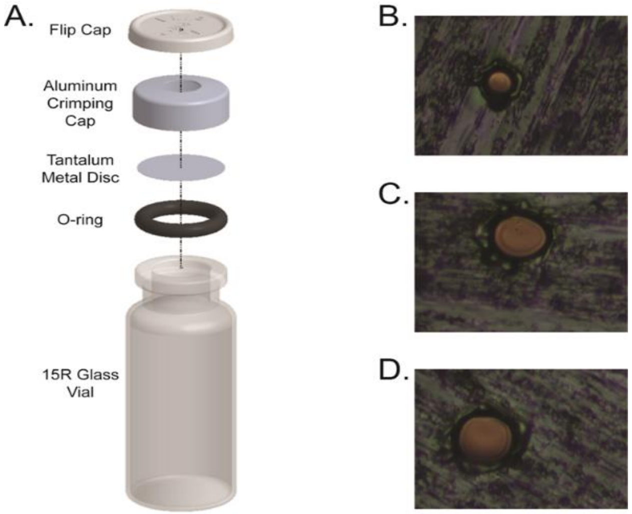
- **Effusion**: gas flow generated by a total pressure difference across the container defect
- **Diffusion**: gas flow of a particular gas generated by a partial pressure difference of that gas across the container defect


**Understanding gas flow enables development of CCI test methods based on gas ingress**

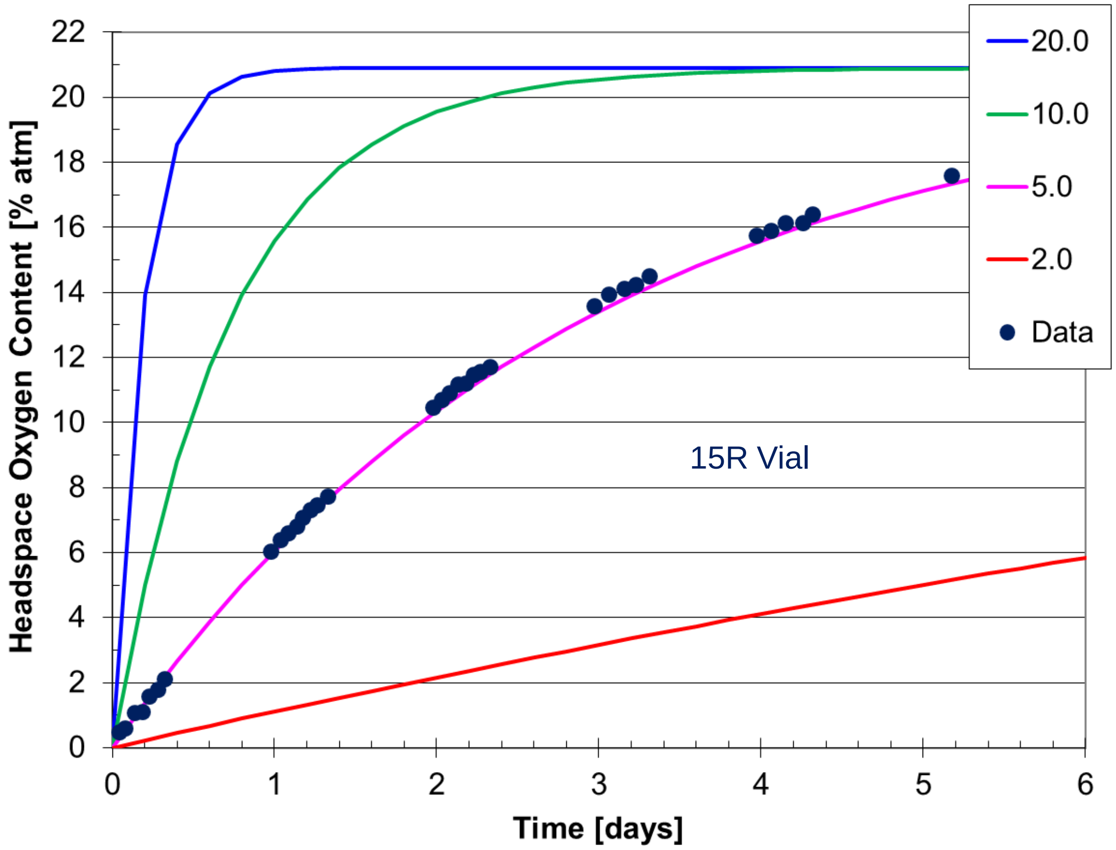
# Positive controls – validating headspace gas ingress methods

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



# Oxygen Diffusion Ingress Model Example

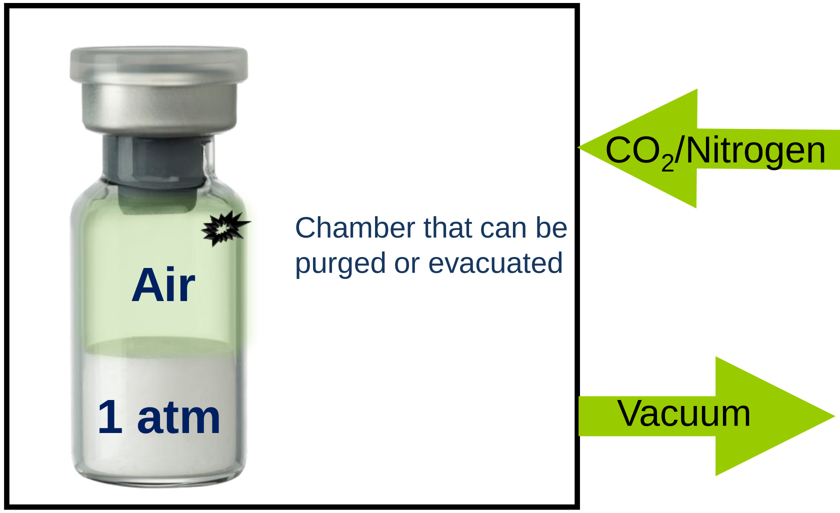
**Predicted** oxygen concentration versus time for **ideal defects**

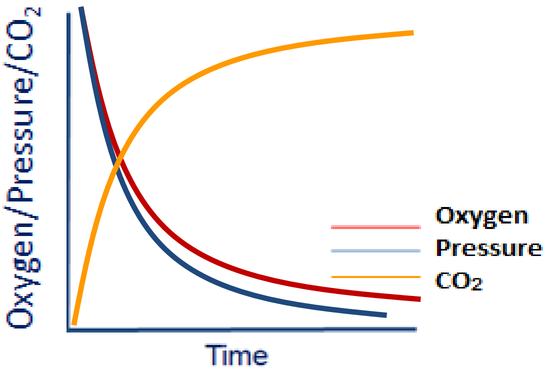



Defect diameter [μm]

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.

# What if the headspace is *unmodified*?

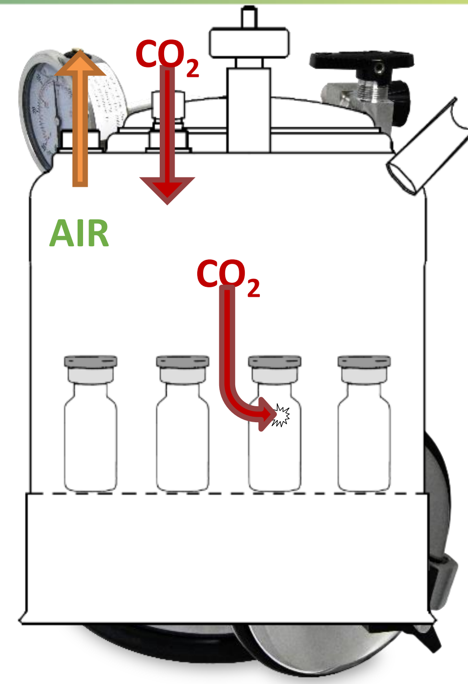



**You can use the same approach as before by changing the environment outside the sample.**

# Case study 2
# CCIT method development and validation

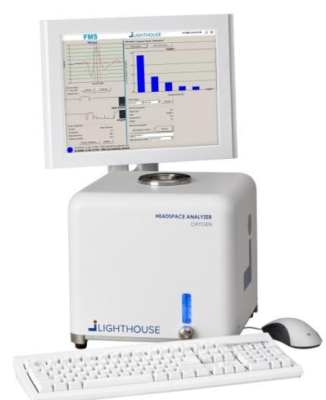
# Gas Ingress Testing for CCI




## Objective

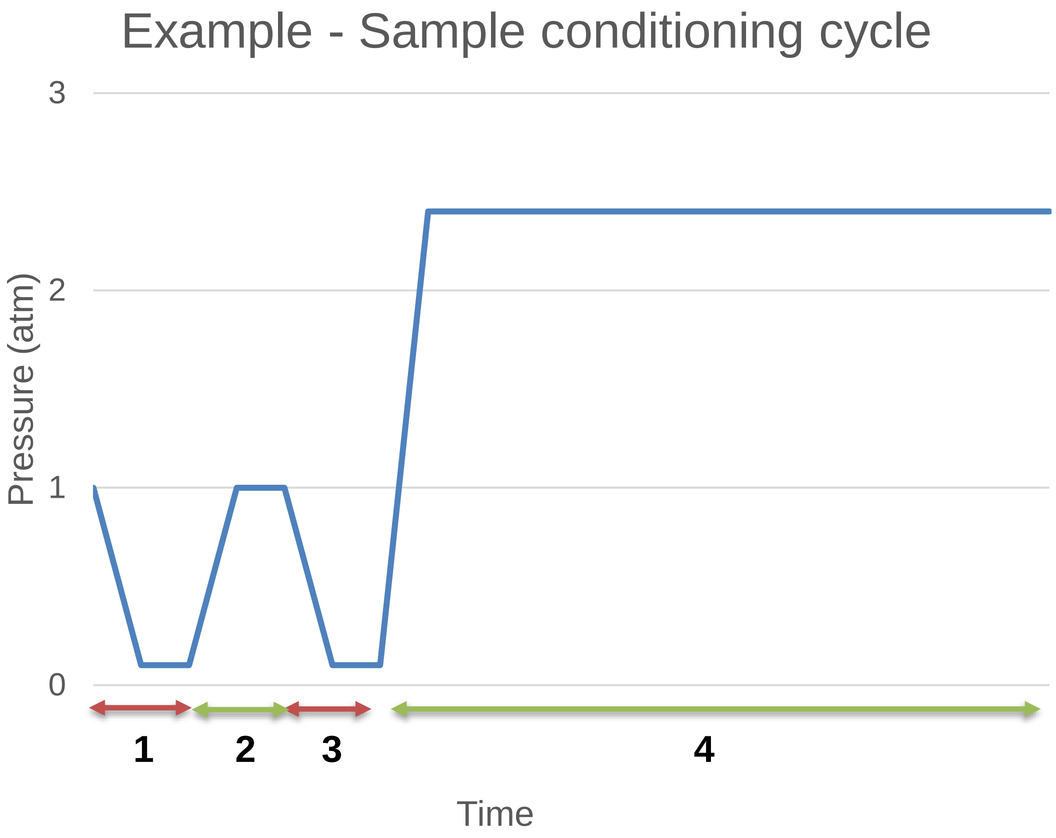
- Develop an approach similar to blue dye but better
- Reliably detect critical leaks: 5µm defect <15 min.

1. Sample preparation
2. Sample conditioning cycle
3. Measure headspace $CO_2$ levels


**Gas bath instead of blue dye bath**

# Method development: $CO_2$ Headspace Gas Ingress

# 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!**

# Case study 3
# 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!**

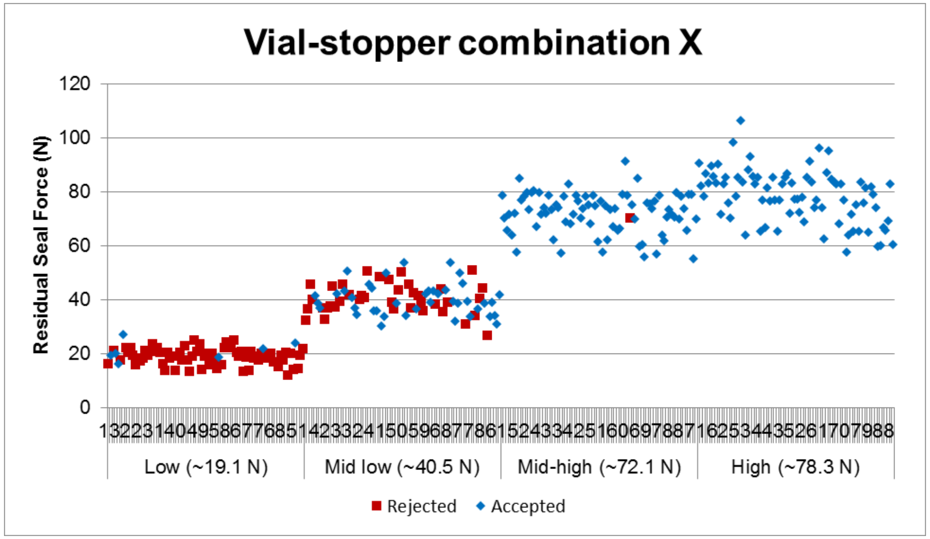
# CCI testing for vials stored on dry ice

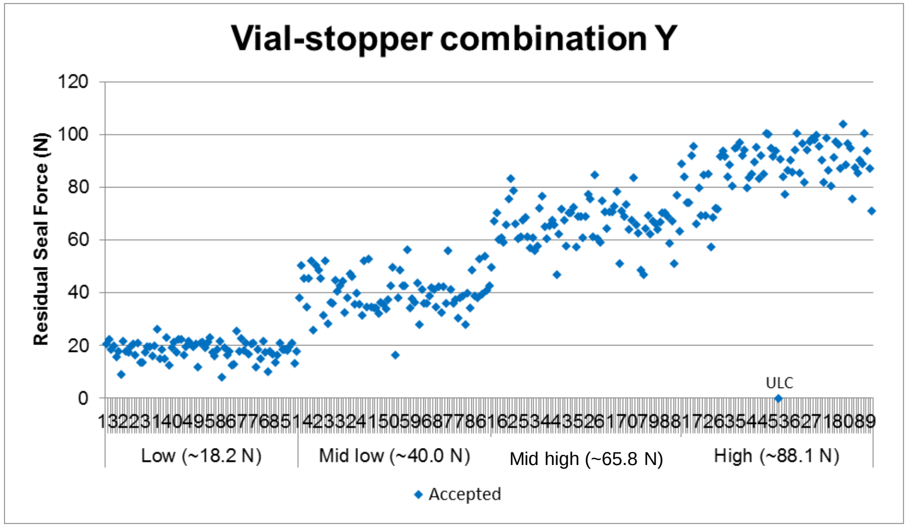
**Objective:**
Determine optimal packaging components and process parameters to prevent loss of CCI during deep cold storage

**Study setup:**

- Investigate 2 vial/stopper combinations
- Investigate 4 crimping pressure settings
- Correlate CCI to measured seal quality (Residual Seal Force)

# CCIT during package development




**Data-driven decision making on package components and process parameters**

# 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**

# Headspace Analysis Systems

Laboratory and At-line Instruments and accessories


Automated Inspection Machines


SYNTEGON

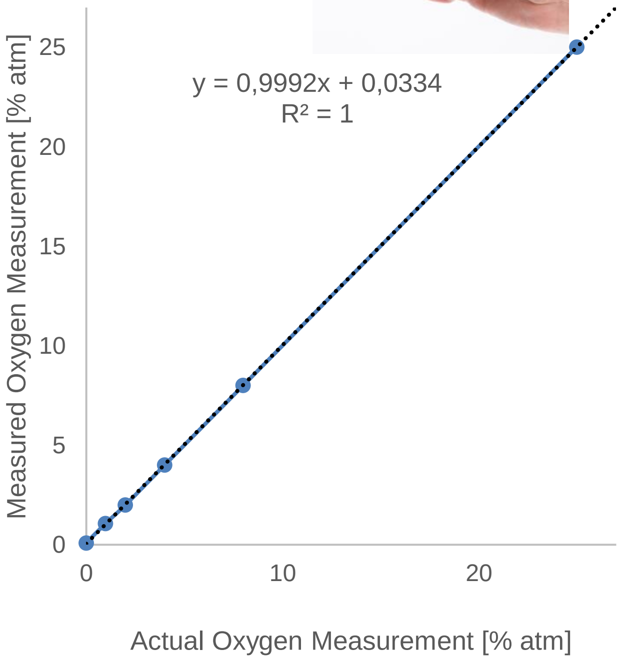
Strategic partnership with Syntegon (formally Bosch) for CCI machines with Lighthouse laser measurement technology inside.

# 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 (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

# Thank you!