# CCI testing throughout the product life-cycle

Using laser-based headspace analysis


PDA Parenteral Drug Association

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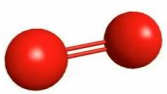
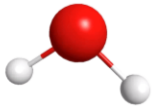
# What we do in a nutshell



Oxygen: 760nm



Moisture: 1400nm

$CO_2$: 2000nm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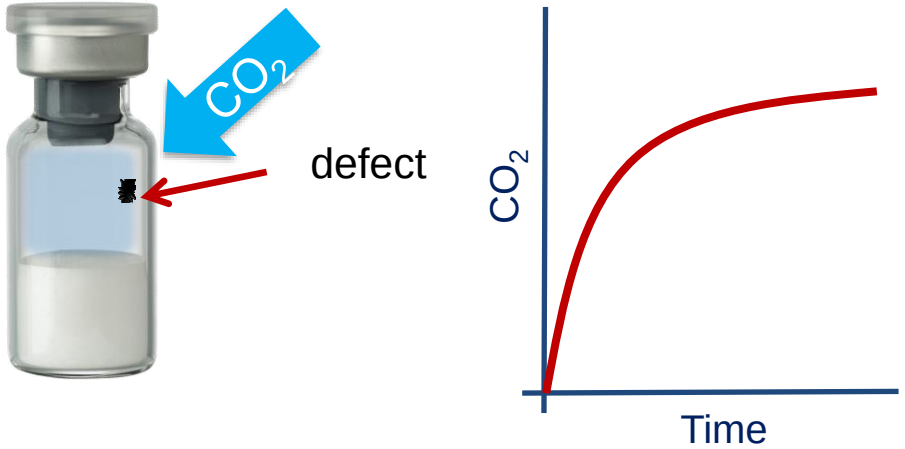
# We look at *change* in headspace

This can be:

- $O_2$ going in…or out
- $CO_2$ going in
- Pressure




Consider initial headspace and *what* will change when defect occurs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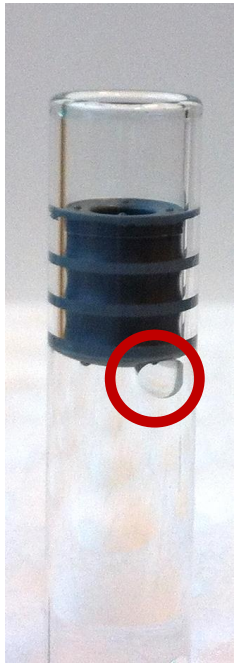
# What sort of packages?



- Anything that lets through laser light
- Can be plastic or glass
- Containing solid or liquid product
- Has a headspace…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# Case study 1
# CCIT in an existing process


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# 100% inspection of lyo product

Product specifications
Freeze dried with 0.2 atm nitrogen headspace

Problem
QC identified vials that had lost vacuum.

→ Run 100% inspection



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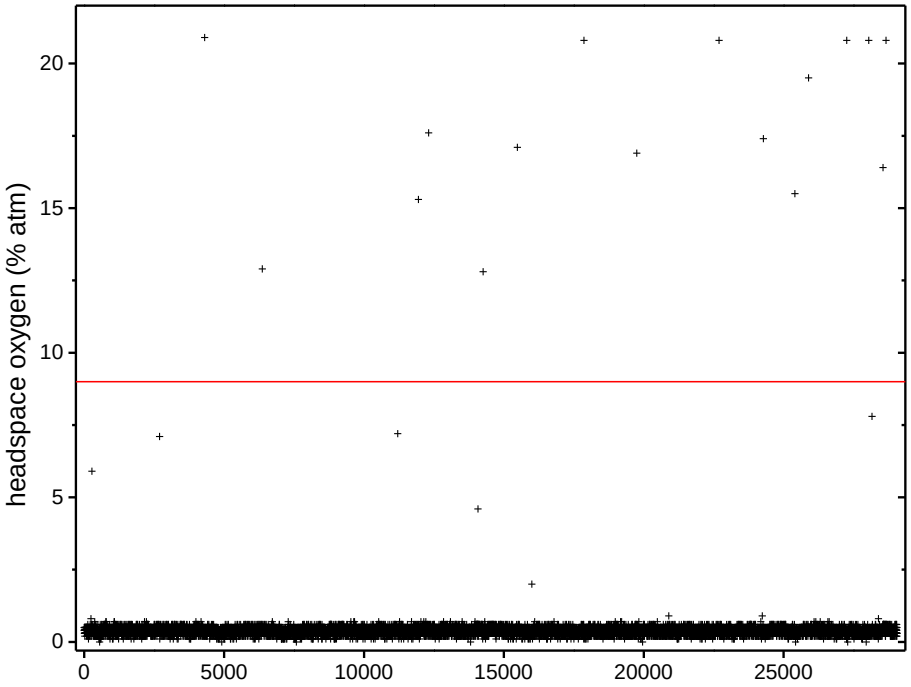
# 100% inspection of lyo product




- Total batch size: 29048
- Number rejected: 16
- Reject rate: 0.06%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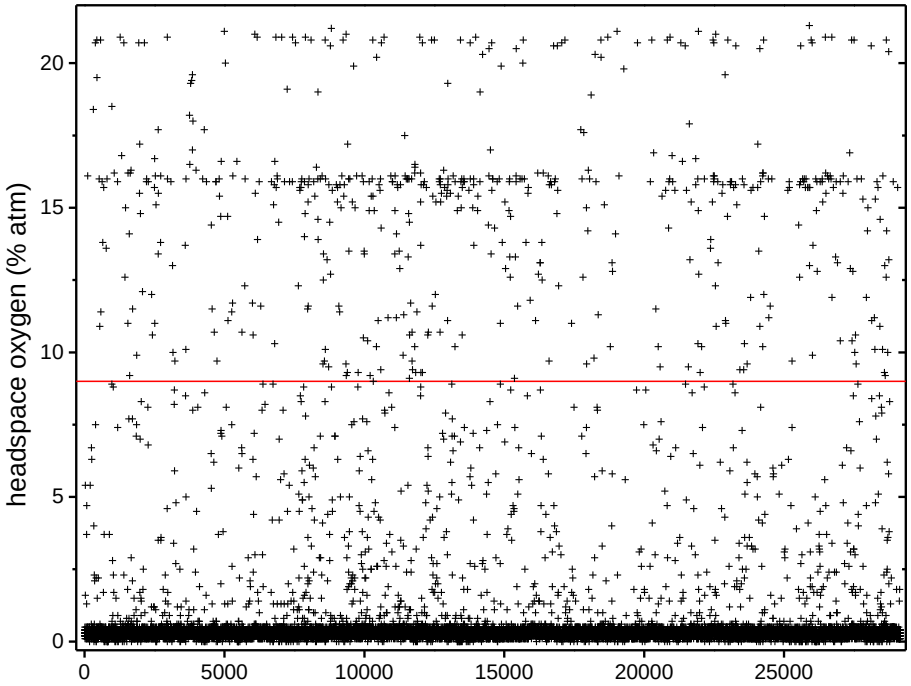
# 100% inspection of lyo product




- Total batch size: 29156
- Number rejected: 568
- Reject rate: 1.95%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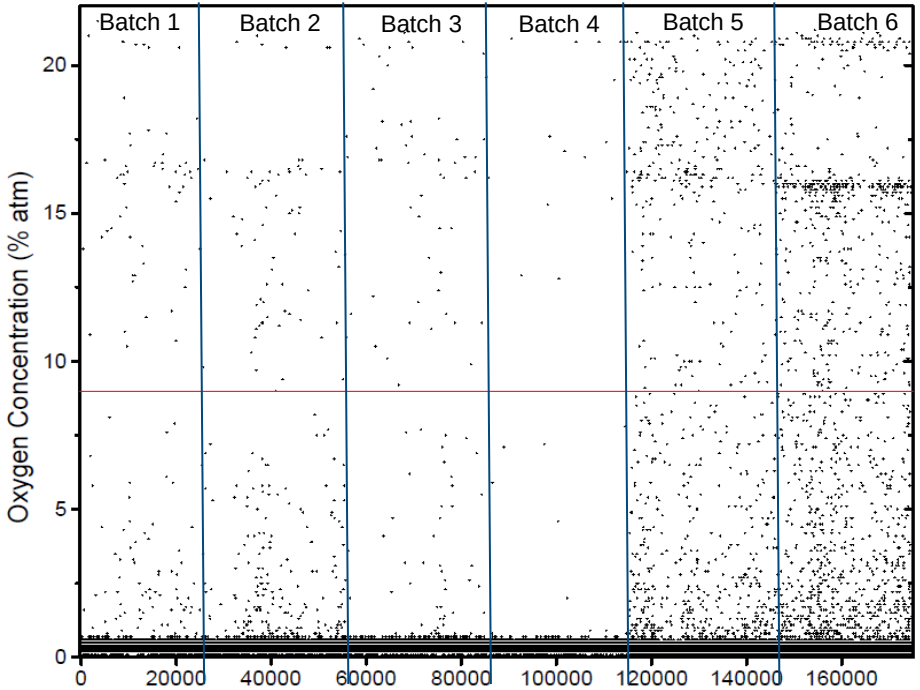
# 100% inspection of lyo product




Results of 6 chronological batches

Not a robust process

→ When would you discover this?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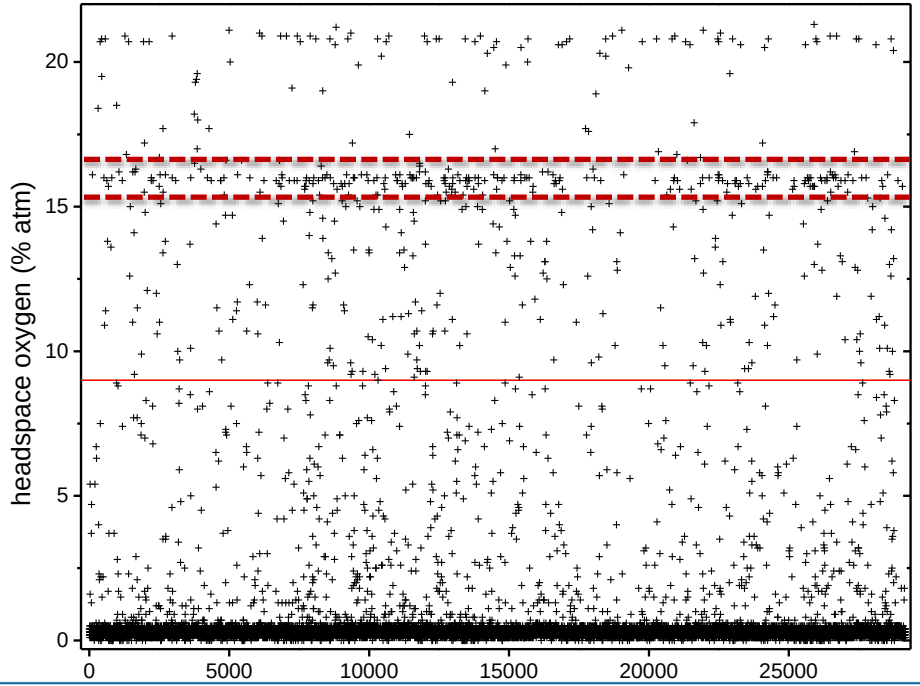
# 100% inspection of lyo product




- Headspace specified 0.2 atm $N_2$
- If 0.8 atm air enters vial = 16% $O_2$!
- Partial leaks stopped by capping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# Theoretical background

Gas flow dynamics


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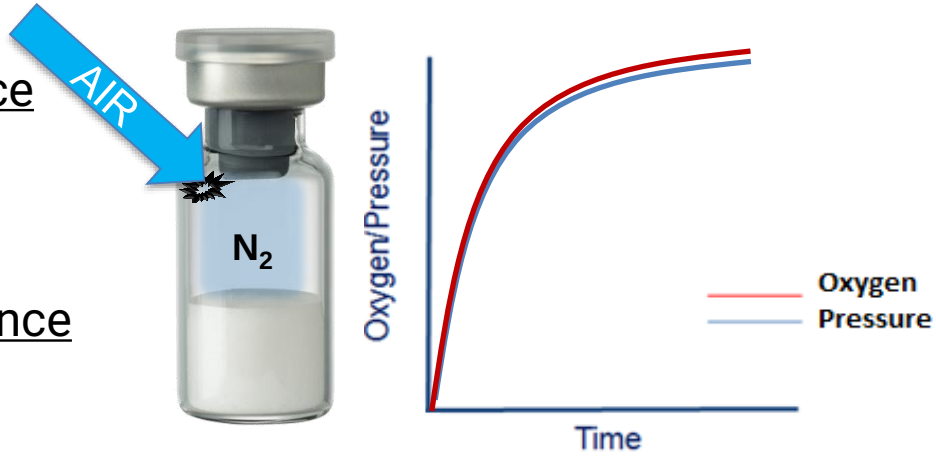
# Two ways gas can flow

**Effusion**
Gas flow driven by a total pressure difference across the defect

**Diffusion**
Gas flow driven by a partial pressure difference of that gas across the defect




**Understanding gas flow enables development of CCI test methods based on gas ingress**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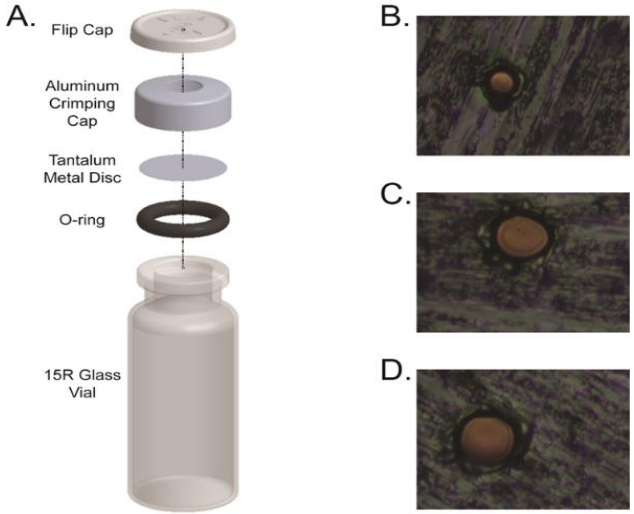
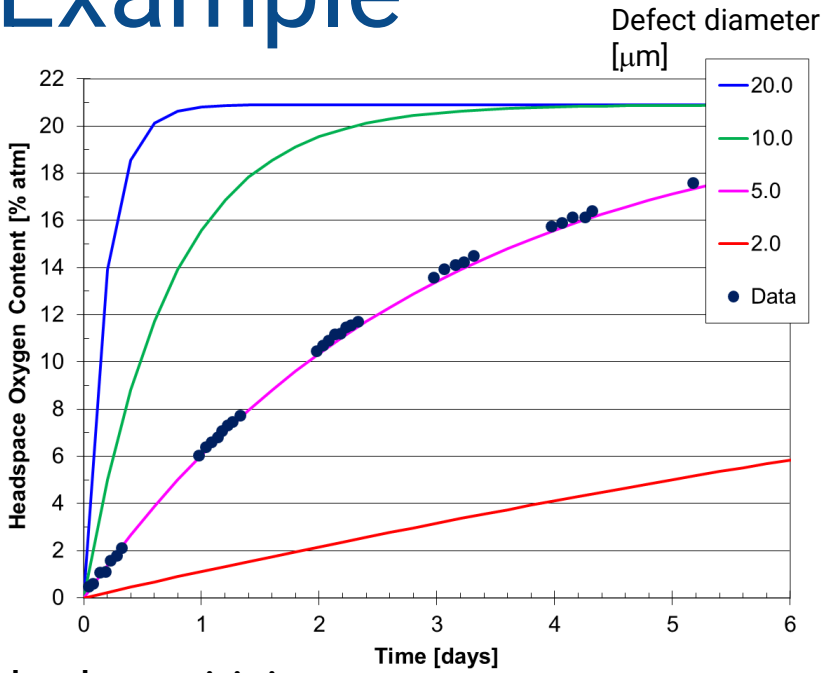
# Oxygen Diffusion Example




Theoretical model enables calculation of method sensitivity



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.

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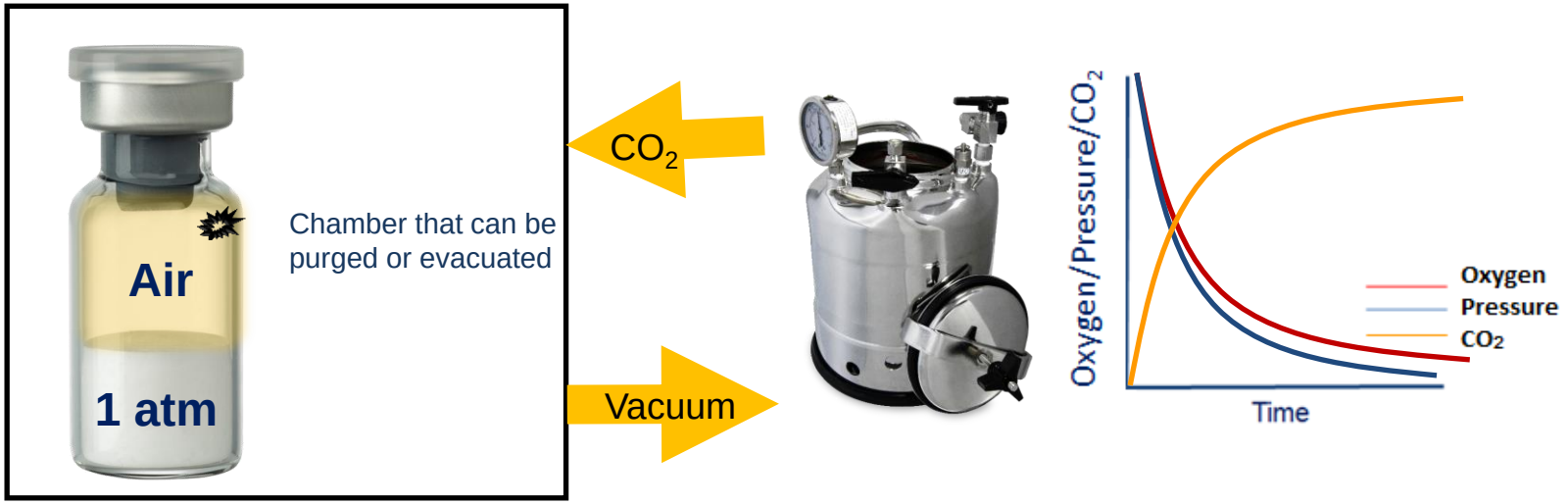
# What if the headspace is *unmodified*?




Use the same approach but change the ***outside*** environment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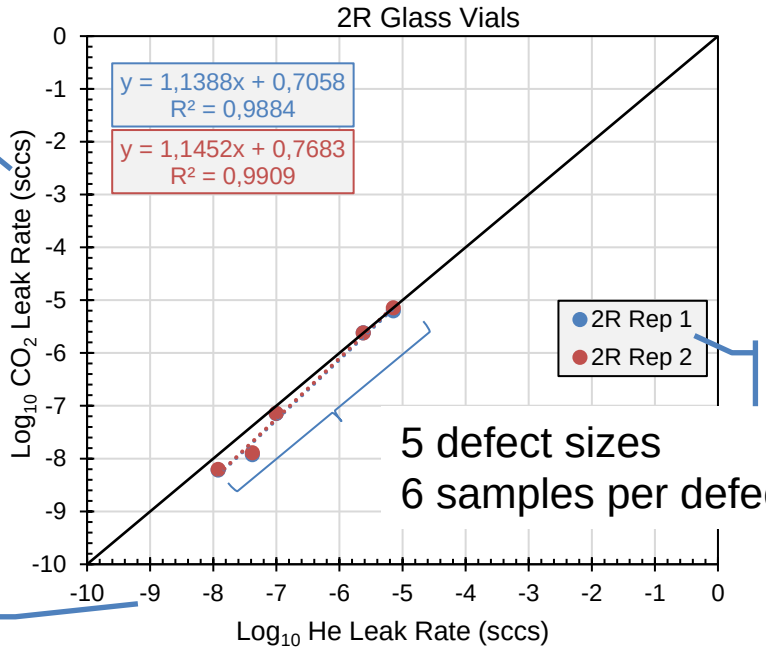
# You can detect very small leaks

Leak rate $CO_2$ gas ingress




Helium leak rate

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

We did 2 repetitions

5 defect sizes
6 samples per defect size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*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.*

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# Case study 2
# CCIT method development and validation


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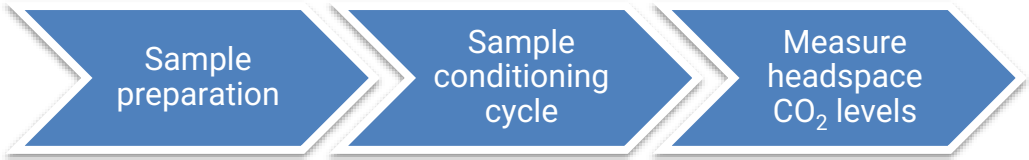
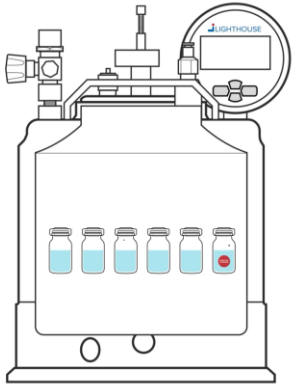
# Gas Ingress Testing for CCI

Objective

- Develop an approach similar to blue dye, but with $CO_2$
- Reliably detect critical leaks:

  5µm defect <15 minutes

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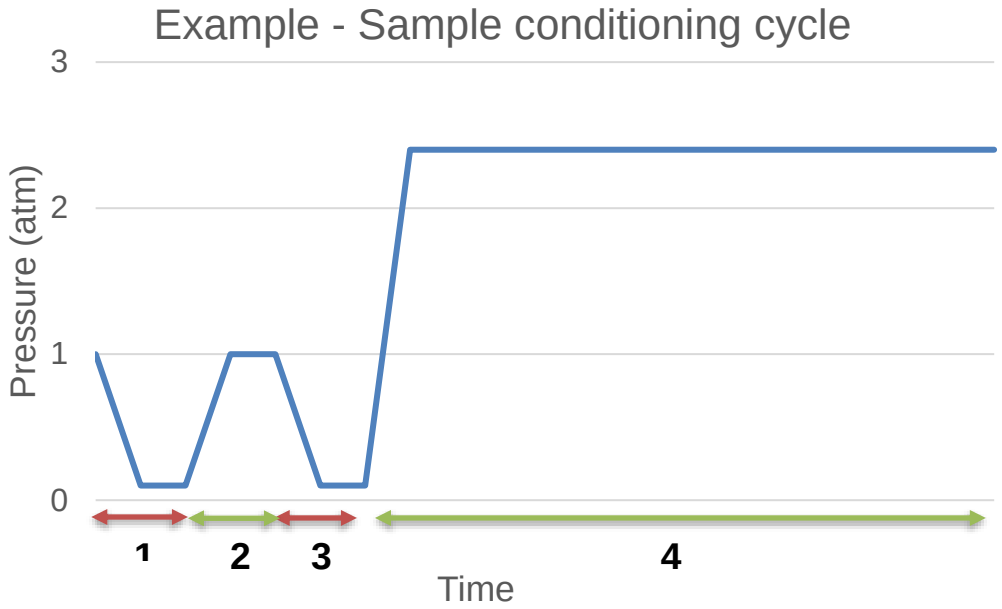
# Method Development


1: Vacuum

2: $CO_2$ (1 atm)

3: Vacuum

4:$CO_2$ (2.4 atm)





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# Method Development

Results:

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

| Defect type | Defect location | Leak detected | |
|---|---|---|---|
| | | PBS | BSA |
| 2 µm laser-drilled | | | |
| 5 µm laser-drilled | | | |
| 10 µm laser-drilled | | | |
| Gross defect | | | |
| Negative control | | | |


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# Case study 3
# CCIT in Package Development


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# The curious case of temporary leaks


- 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
- Creating an **overpressure**
- **Dye ingress cannot detect this!**


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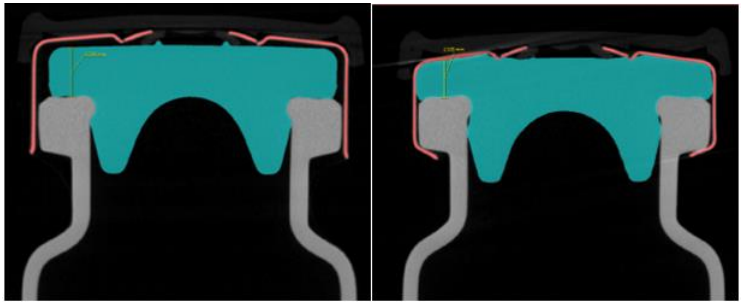
# Residual Seal Force

- In sealing rubber components, the **elastic property** is important.
- An applied stress (sealing force) induces a corresponding strain which creates a contact stress.
- This **stored internal energy** is the Residual Seal Force (RSF).



*Source: Genesis Packaging Technologies*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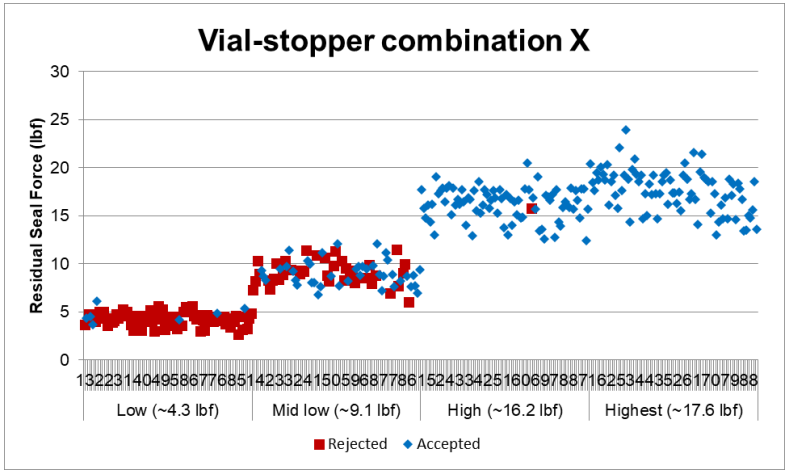
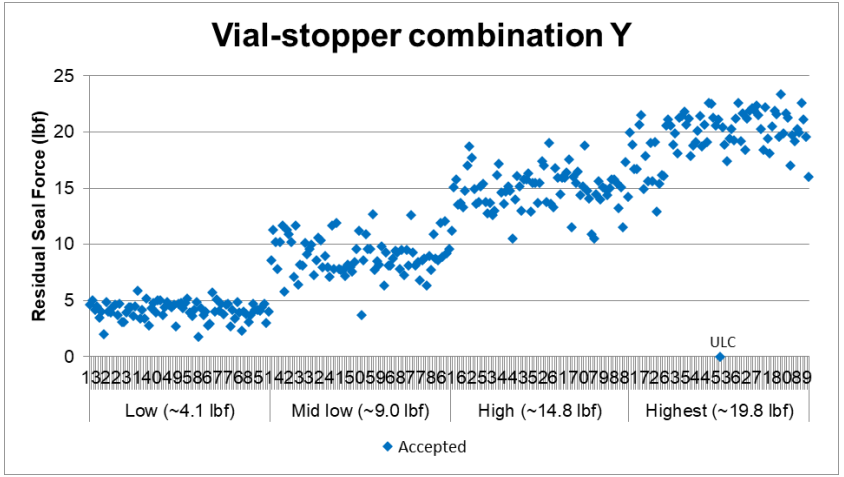
# Components for cold storage





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# Consider temperature excursions

Table 1: Headspace analysis of samples stored in freezer at -80°C for 48hrs.

| Crimp | Vial A | Vial B | Vial C |
|---|---|---|---|
| Low | 2000 ✓ | 2000 ✓ | 2000 ✓ |
| Medium | 2000 ✓ | 2000 ✓ | 2000 ✓ |
| High | 2000 ✓ | 2000 ✓ | 2000 ✓ |
| Min. temp. | -80°C | -80°C | -80°C |

Small decrease in temperature caused CCI issue.

Line qualification:

All the tests were carried out at exactly -80°C

Table 2: Headspace analysis of samples stored on dry ice for 48hrs.

| Crimp | Vial A | Vial B | Vial C |
|---|---|---|---|
| Low | 200 ✓ | 200 ✓ | 200 ✓ |
| Medium | 200 ✓ | 200 ✓ | 200 ✓ |
| High | 199/1 ✗ | 199/1 ✗ | 198/2 ✗ |
| Min. temp. | -94°C | -88°C | -91°C |


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# Summary


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# Headspace analysis for CCIT

- Analytical measurement
- Non-destructive method
- Permanent *and* temporary leaks
- Sensitive to all leak sizes
- Quantitatively described by gas flow physics



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# Generate data for safer drugs

## Analytical services

## Benchtop instruments


## Automated inspection machines



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# Thank you!

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