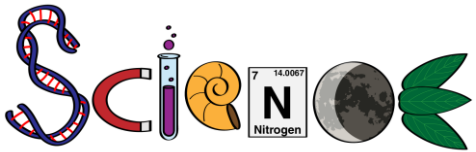
CCI testing throughout the product life-cycle

Using laser-based headspace analysis

PDA Parenteral Drug Association

PDA TRAINING

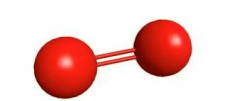
What we do in a nutshell



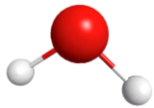
Better and safer drugs for patients!

How we do that in a nutshell

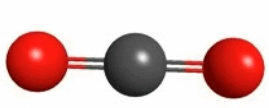
Quantify headspace gas composition – non-destructively



Oxygen



Water (vapor)



Carbon dioxide

Case study 1
CCIT in an existing process

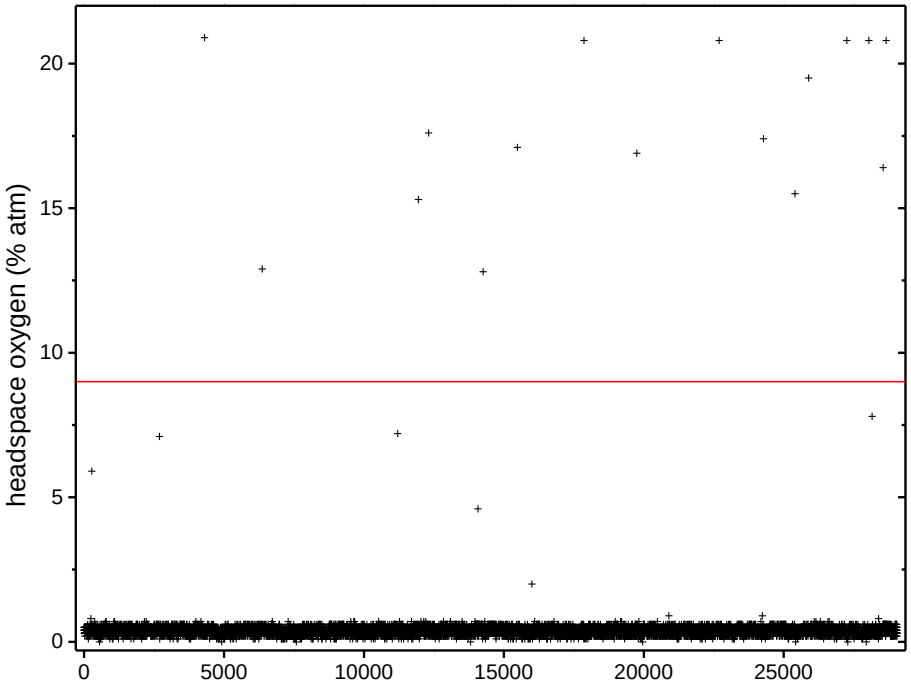
100% inspection of lyo product

Product specifications
Freeze dried with 0.2 atm nitrogen headspace

Problem
QC identified vials that had lost vacuum.

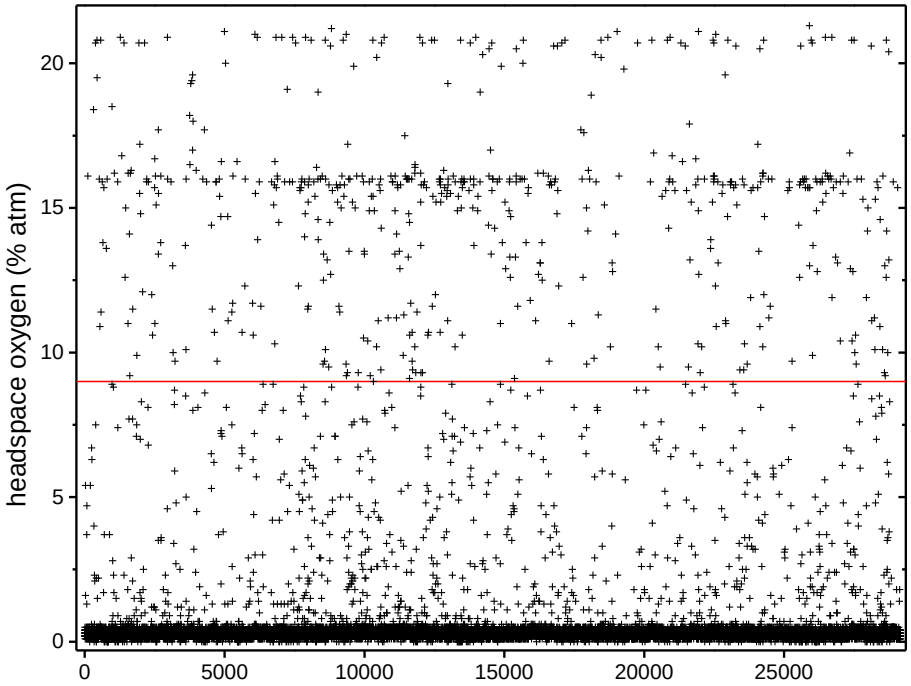
→ Run 100% inspection

100% inspection of lyo product



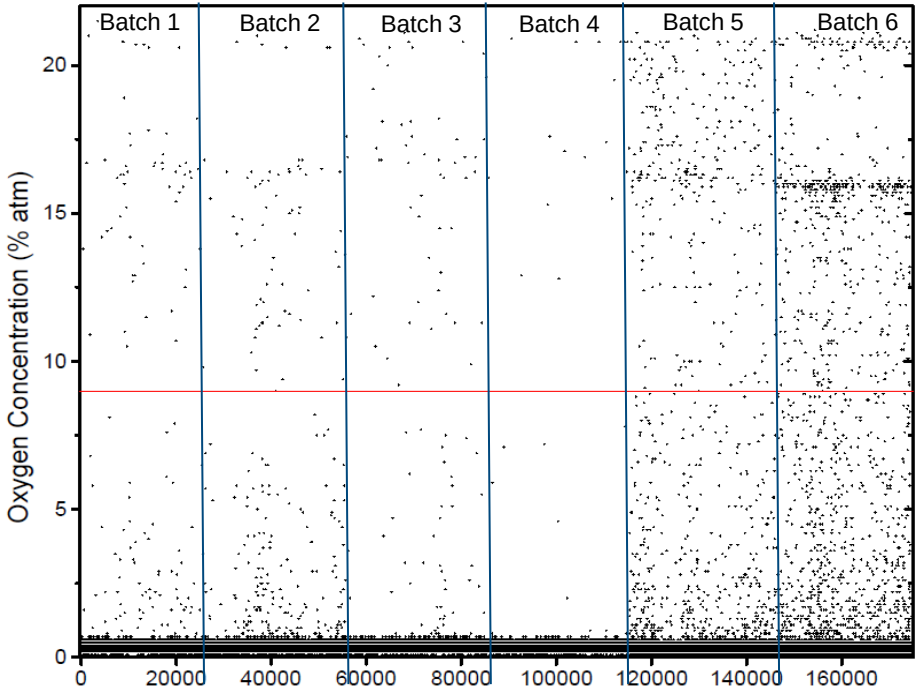
- Total batch size: 29048
- Number rejected: 16
- Reject rate: 0.06%

100% inspection of lyo product



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

100% inspection of lyo product

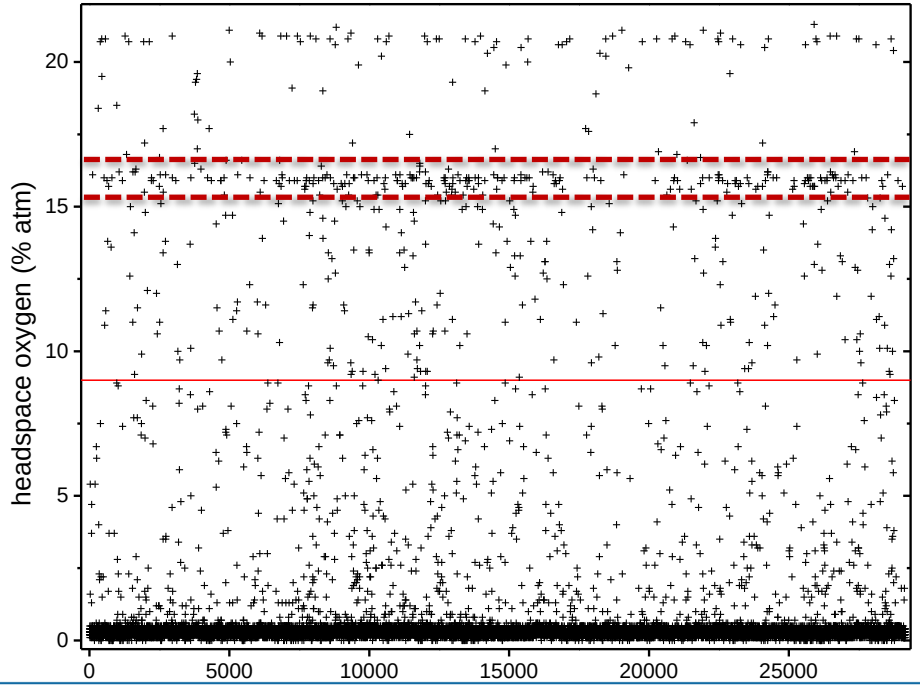


Results of 6 chronological batches

Not a robust process

→ When would you discover this?

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

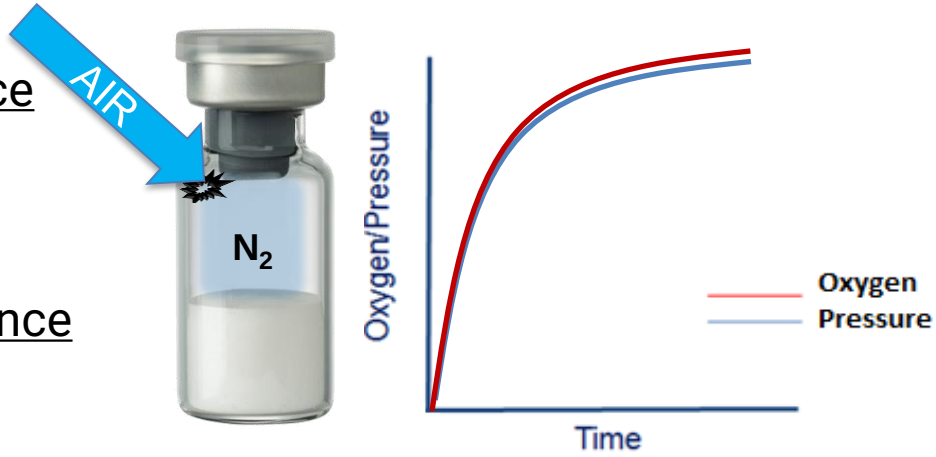
Theoretical background

Gas flow dynamics

Two ways gas can flow

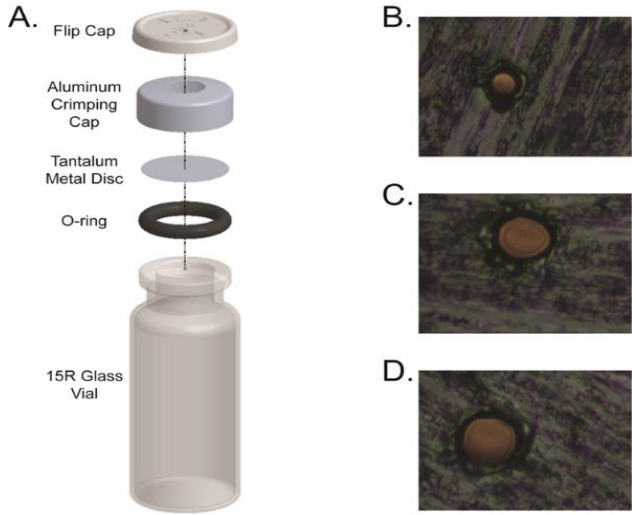
Effusion
Gas flow driven by a total pressure difference across the defect

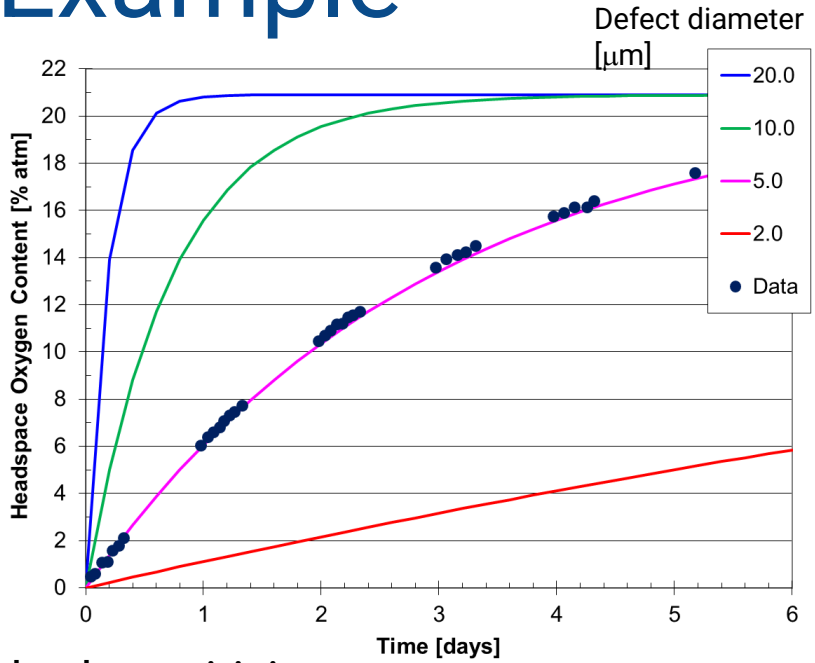
Diffusion
Gas flow driven by a partial pressure difference of that gas across the defect



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

Oxygen Diffusion Example

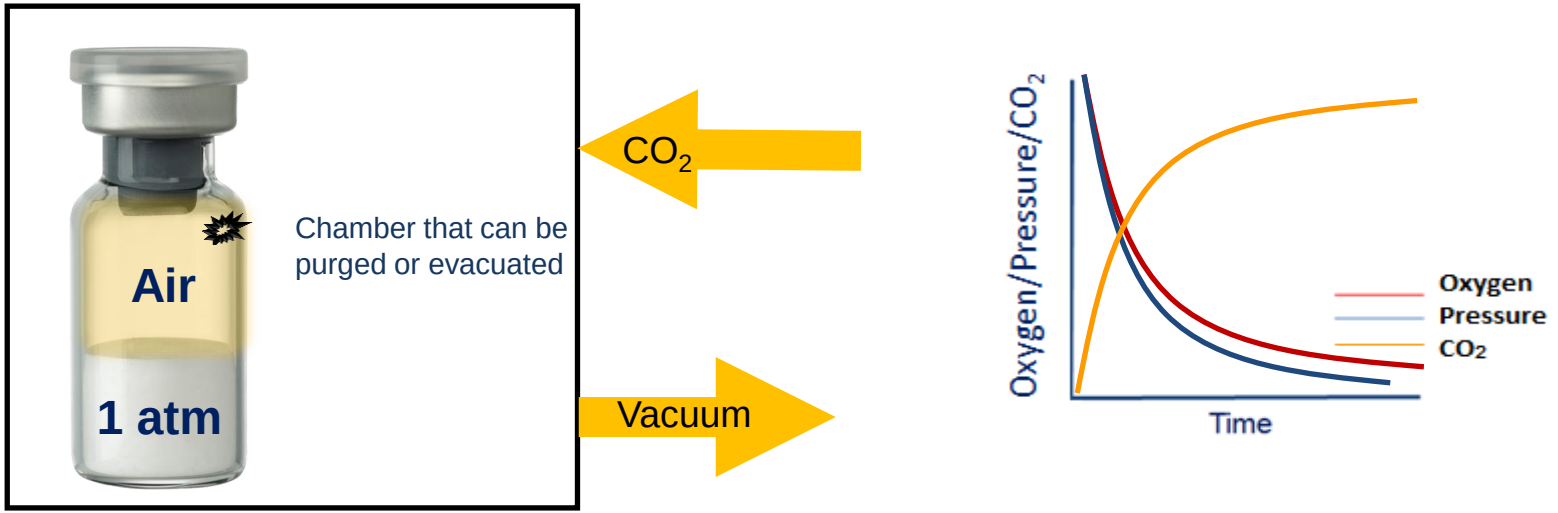




Theoretical model enables calculation of method sensitivity

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.

What if the headspace is *unmodified*?



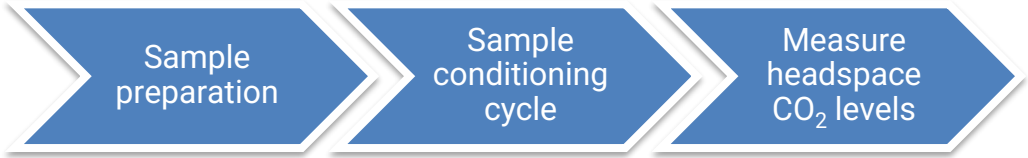
Use the same approach but change the ***outside*** environment

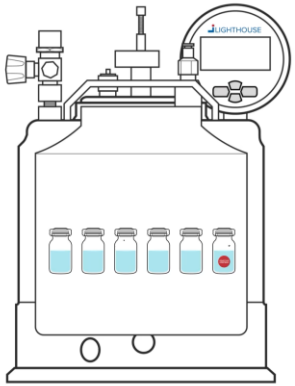
Case study 2
CCIT method development and validation

Gas Ingress Testing for CCI

Objective

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





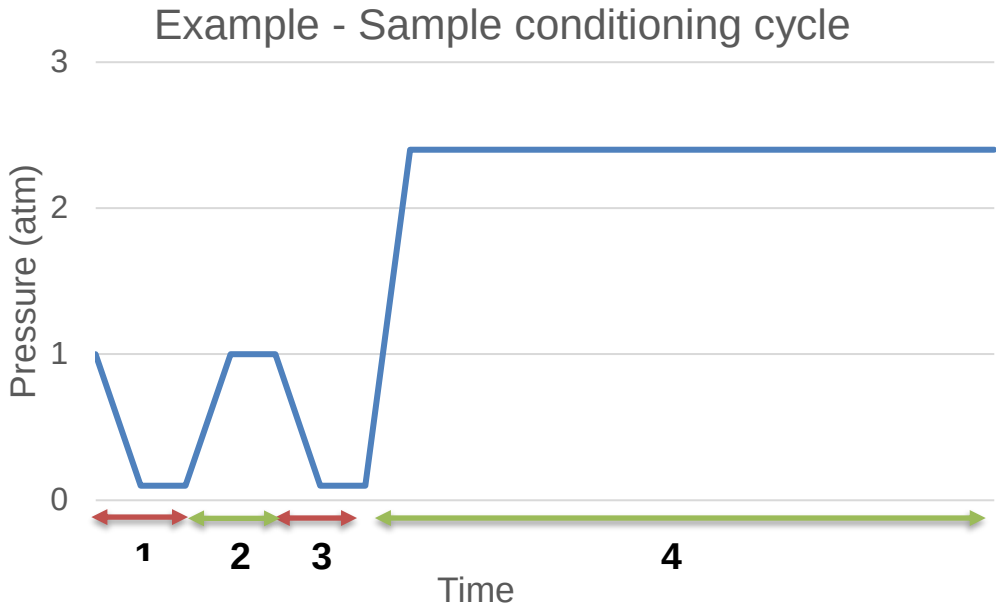
Method Development

1: Vacuum

2: CO_2 (1 atm)

3: Vacuum

4:CO_2 (2.4 atm)



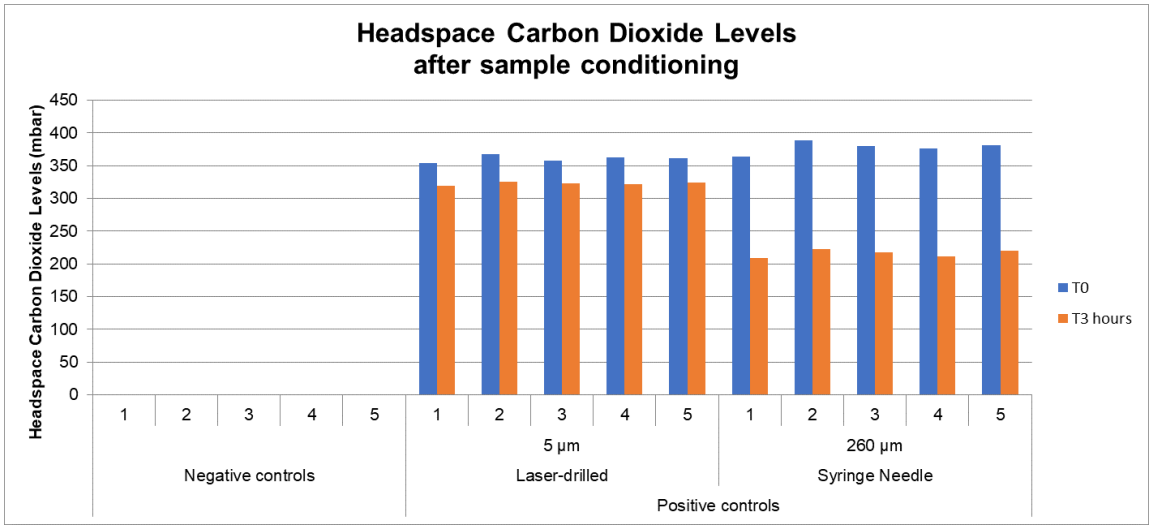
Method Development: Vials

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	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

Method Development: Syringes



Method parameters based on results:

- Overpressure CO_2
- Time in vessel: 60 min
- Wait time after vessel:15 min
- Acceptance criteria: defect between 5µm and 260µm

Case study 3
CCIT in Package Development

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!**

CCI testing for syringes stored on dry ice

Objective

Determine optimal PFS packaging components to prevent loss of CCI during ultra cold storage and transport

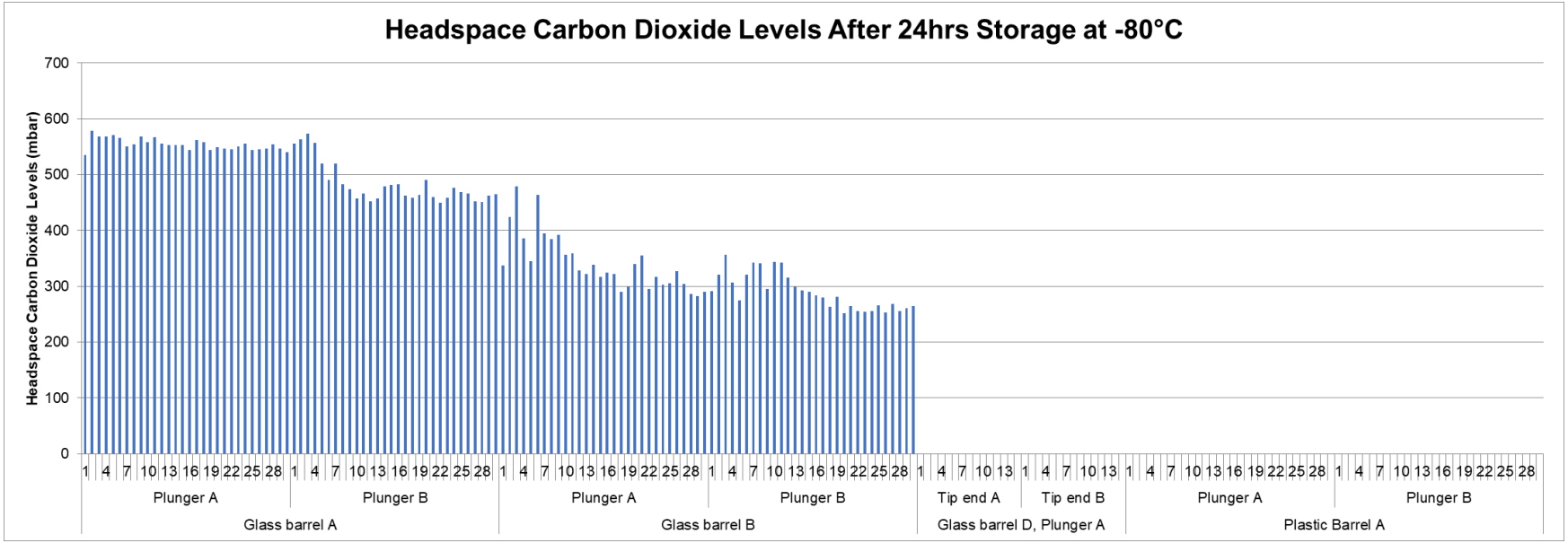
Study setup

Investigate multiple barrel, plunger and tip-end types

Store on dry ice for at least 24 hours

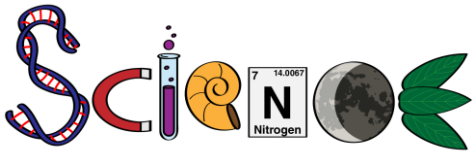
Measure headspace CO_2 levels

Packaging Component Selection



Lighthouse Offerings

Generate data for safer drugs



Headspace Analysis

Analytical services

Benchtop instruments

Automated inspection machines

Headspace gas ingress for CCIT

- 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

Thank you!

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