Laser Based Headspace Analysis for CCIT

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Overview

Part 1: Laser based headspace analysis

- Technology overview
- Application to CCI testing of sterile products

Part 2: Theoretical background

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

Part 3: Case studies and examples

- Process optimization
- Typical use

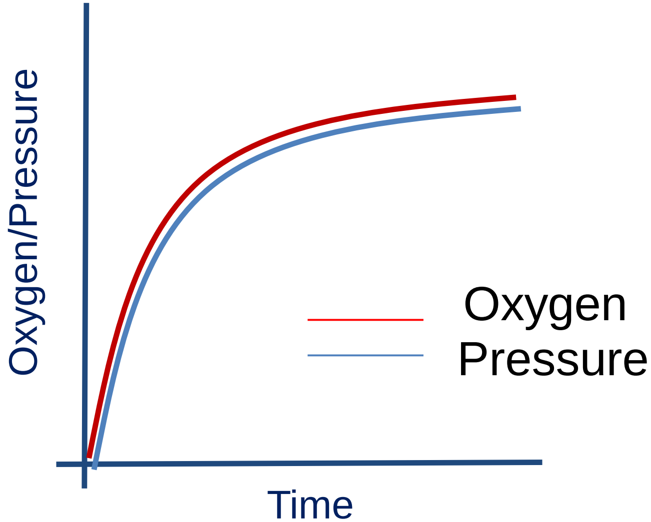
Characterizing the headspace non-destructively

Nondestructive

What gases can be measured?

- Headspace oxygen
- Headspace carbon dioxide
- Headspace moisture (water vapor)
- Headspace total pressure levels

Application to CCI testing-Products packaged under a modified atmosphere



Product
Stoppered under a modified atmosphere

Lyophilized product:
Partial vacuum with nitrogen or full vacuum

Oxygen sensitive liquids:
Purged with nitrogen

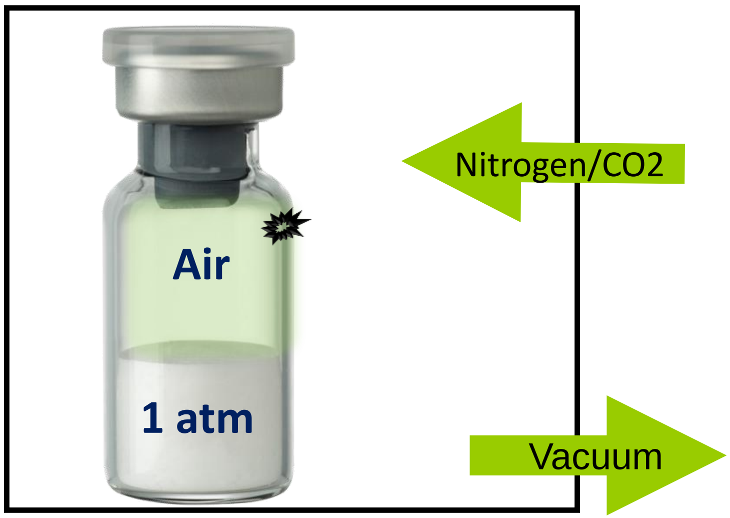
Storage Condition
Ambient air

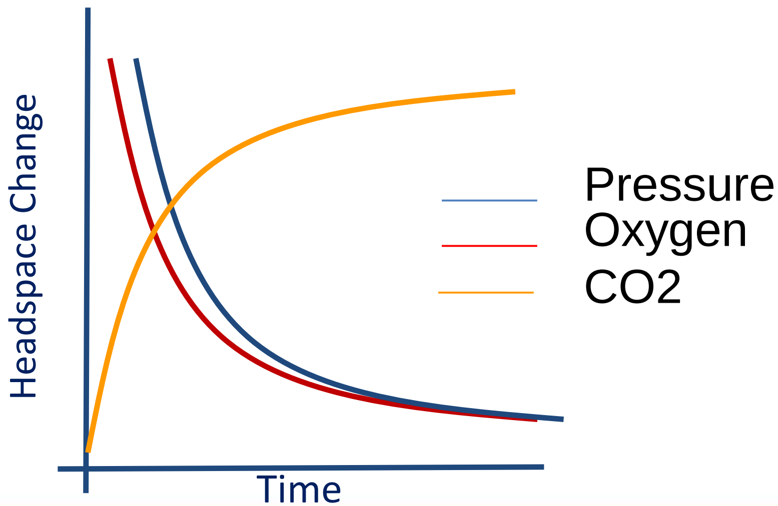
Leak Indicating Measurement
Increase in oxygen level and/or increase in pressure.

Application
Laboratory instruments or fully automated inspection

Application to CCI testing-Products packaged under a non-modified atmosphere

Chamber that can be purged or evacuated





Product

Stoppered under a non-modified atmosphere.
Headspace is air at 1 atm
Typical of many liquids

Storage Conditions

Must put container in a chamber to drive a headspace change (similar to Blue Dye testing, but HSA is more sensitive and doesn't involve dye). After a pre-determined conditioning time then remove and test in a headspace analyzer.

Leak Indicating Measurement

Decrease in oxygen level/increase in CO2/ decrease in pressure level.

Application

Laboratory instruments

What type of product-packages?

- Clear or amber glass
- Transparent plastics
- Liquid, lyophilized or powder filled
- Vials, syringes, ampoules, cartridges
- Nominal volume ranging from 0.2mL to 250mL

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Parenteral Drug Association

Headspace Analysis Systems

Laboratory and At-line Instruments and accessories

Automated Inspection Machines

BOSCH
Invented for life

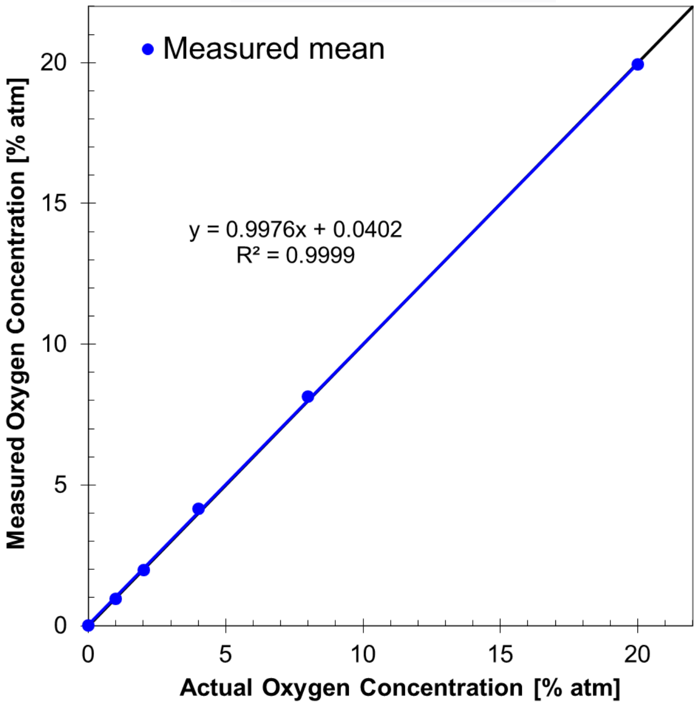
Strategic partnership with Bosch for CCI machines with Lighthouse laser measurement technology inside.

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	0.000	0.01	0.01	0.02
1.0	1.005	0.96	-0.04	0.03
2.0	2.004	1.98	-0.03	0.03
4.0	3.998	4.02	0.02	0.04
8.0	7.999	8.13	0.13	0.03
20.0	20.00	19.93	-0.06	0.04

↑ Accuracy (Error) ↑ Precision (St. Dev.)



For every delivered system:

- Full validation package:
  Functional Requirements (FR)
  Design Specification (DS)
  Traceability Matrix (TM)
  Installation Qualification (IQ)
  Operational Qualification (OQ)

- 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

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Part 2

Gas diffusion theory

Gas ingress for CCI testing

In general, there are two different ways by which gas can flow through a defect in and out of a pharmaceutical container:

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

CCI testing: Gas diffusion theory

$$\vec{J} = -D\vec{\nabla}n$$ **Fick's 1st Law**

$$\frac{\partial P_i(t)}{\partial t} = \frac{-D \cdot A_0}{V}\frac{\partial P_i(z,t)}{\partial z}$$

New USP <1207> states:

"Mathematical models appropriate to leak flow dynamics may be used to predict the time required for detecting leaks of various sizes or rates."

$$\%Oxygen(t) = 20.9\% \cdot \left[1 - \exp\left(-\frac{\alpha_{Diff}}{V}t\right)\right]$$

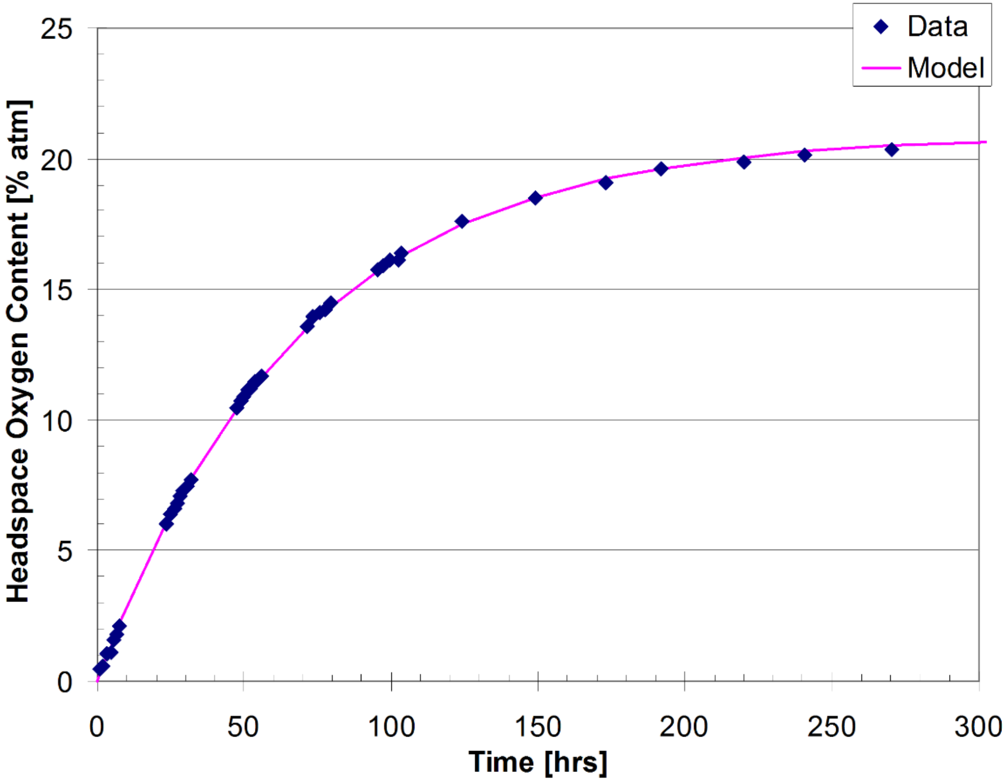
The change in oxygen concentration will be exponential with respect to time

Diffusion Parameter

$$\alpha_{Diff}\left[\frac{cm^3}{s}\right] = \frac{D \cdot A_0}{L}$$

The Diffusion Parameter is a function of the Diffusion Coefficient, *D*, the defect cross-sectional Area, A_0, and Depth, *L*.

Validation of Oxygen Ingress Model



With fixed values for:

$D = 0.22\ cm^2/s$
$A_0 = 20\mu m^2\ (5\mu m\ ø)$
$V = 18cc \quad (15R)$

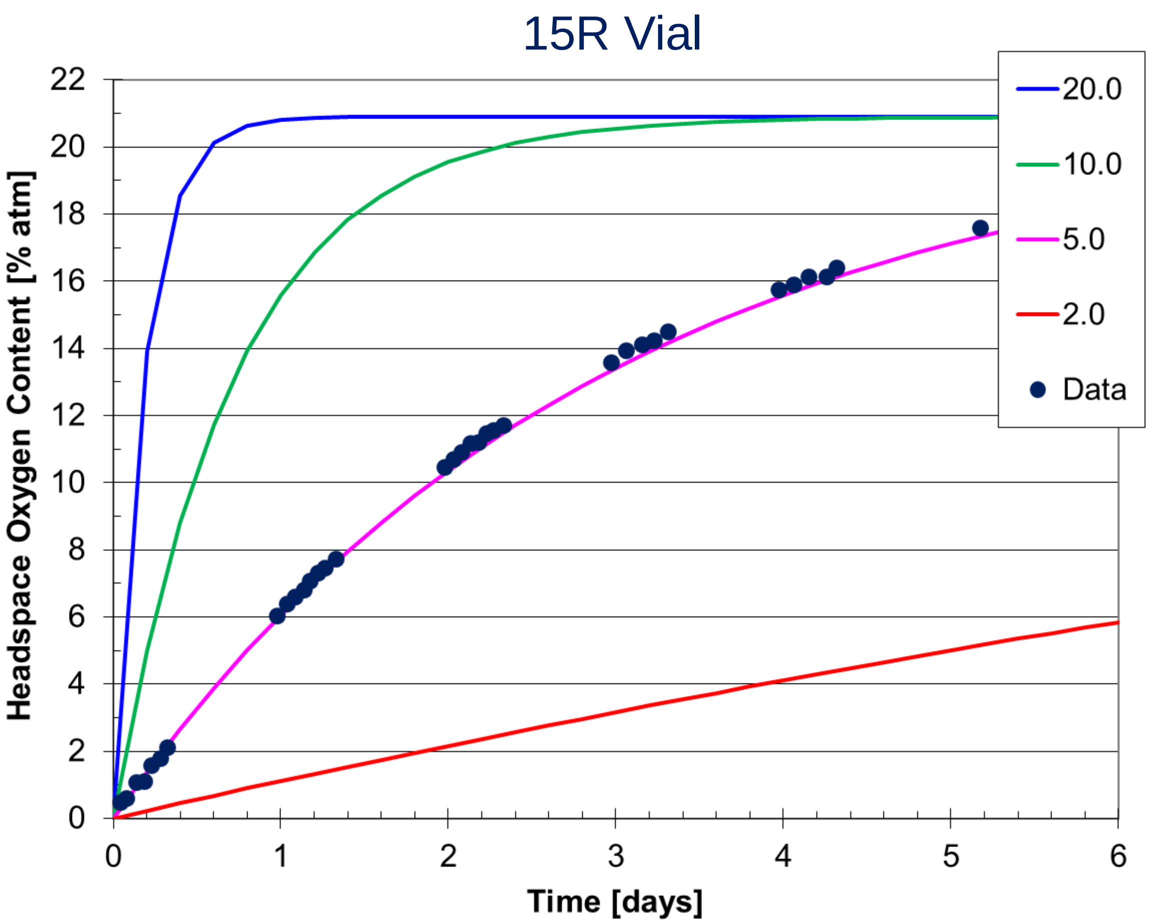
Obtain an empirical depth parameter value:

$L = 6\ \mu m$

Model matches the data ±0.3 %-atm oxygen at every point

Oxygen Ingress Model Example

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



Defect diameter [μm]

Accepted for publication PDA Journal Nov-Dec 2017 issue: Method Development for CCI Evaluation via Gas Ingress by Using Frequency Modulation Spectroscopy [K. Victor]. Pre-publication published on July 20, 2017.

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Part 3
Case studies and examples

Overview Case studies

1. Filling line CCI qualification
2. Method development
3. Package development syringe CCI and permeation
4. Cold Storage CCI Study
5. 100% inspection of lyophilized product

Case Study 1:
Filling line CCI qualification

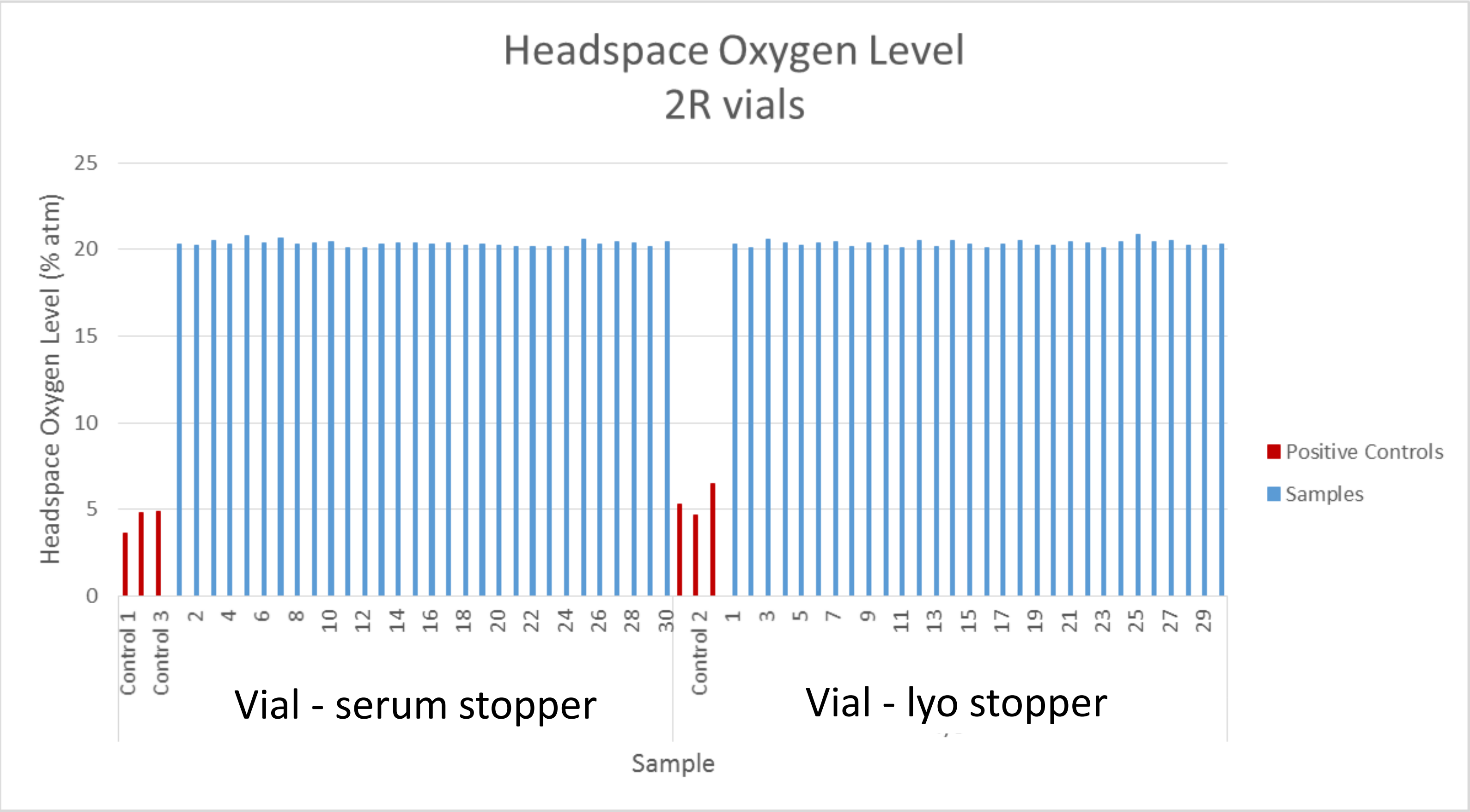
- **Objective: Generate data demonstrating that the filling process produces good CCI for a specific vial-stopper combination**

- CCI Study:
  - Produce empty stoppered & crimped vials with the process. Initial headspace is 1 atm of air (20.9% oxygen).
  - Use headspace gas ingress model to design a sample chamber evacuation, nitrogen backfill, and sample hold cycle.
  - Measure samples for changes in headspace composition. Include positive controls having a 10 µm micro-capillary through the stopper.

	Headspace Oxygen Level after defined evacuation, backfill, and storage cycle [% atm]		
Sample Vial	**1 µm ideal defect**	**0.6 µm ideal defect**	**0.5 µm ideal defect**
2R	**1**	**4.1**	**7.1**
6R	**3.4**	**12.1**	**15.0**
20R	**11.1**	**18.8**	**19.5**

Case Study 1:
Filling line CCI qualification

Results headspace CCI test



Example: Gas ingress measurements straightforwardly produced robust CCI data

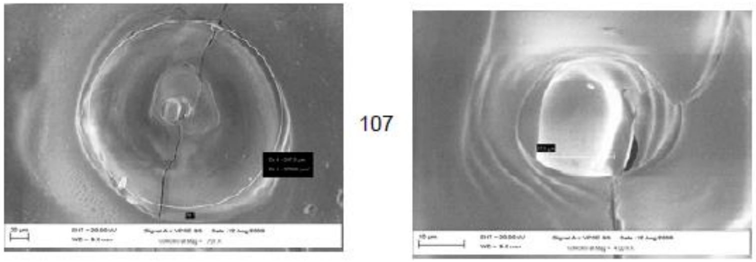
Case Study 2: Method development

Objective

Detection of 5 micron leak within 30 minutes

Sample set

- 6R DIN clear tubing vial – 1.5mL product
- Positive controls: 2µm, 5µm,10µm and 15µm laser drilled defects
  - Glass defects
  - Metal plate defects



Nominal hole size 5 µm

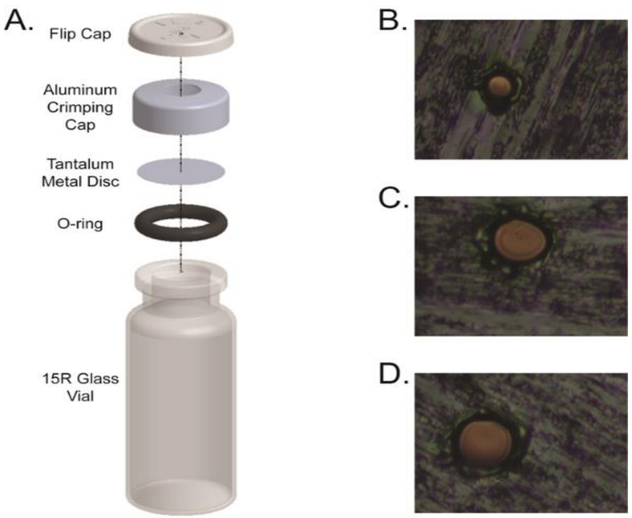


Image provided by Lenox Laser

Study 1: Manufacturing conditions

- Determine purge quality

Study 2: API reactivity

- Oxidation rate

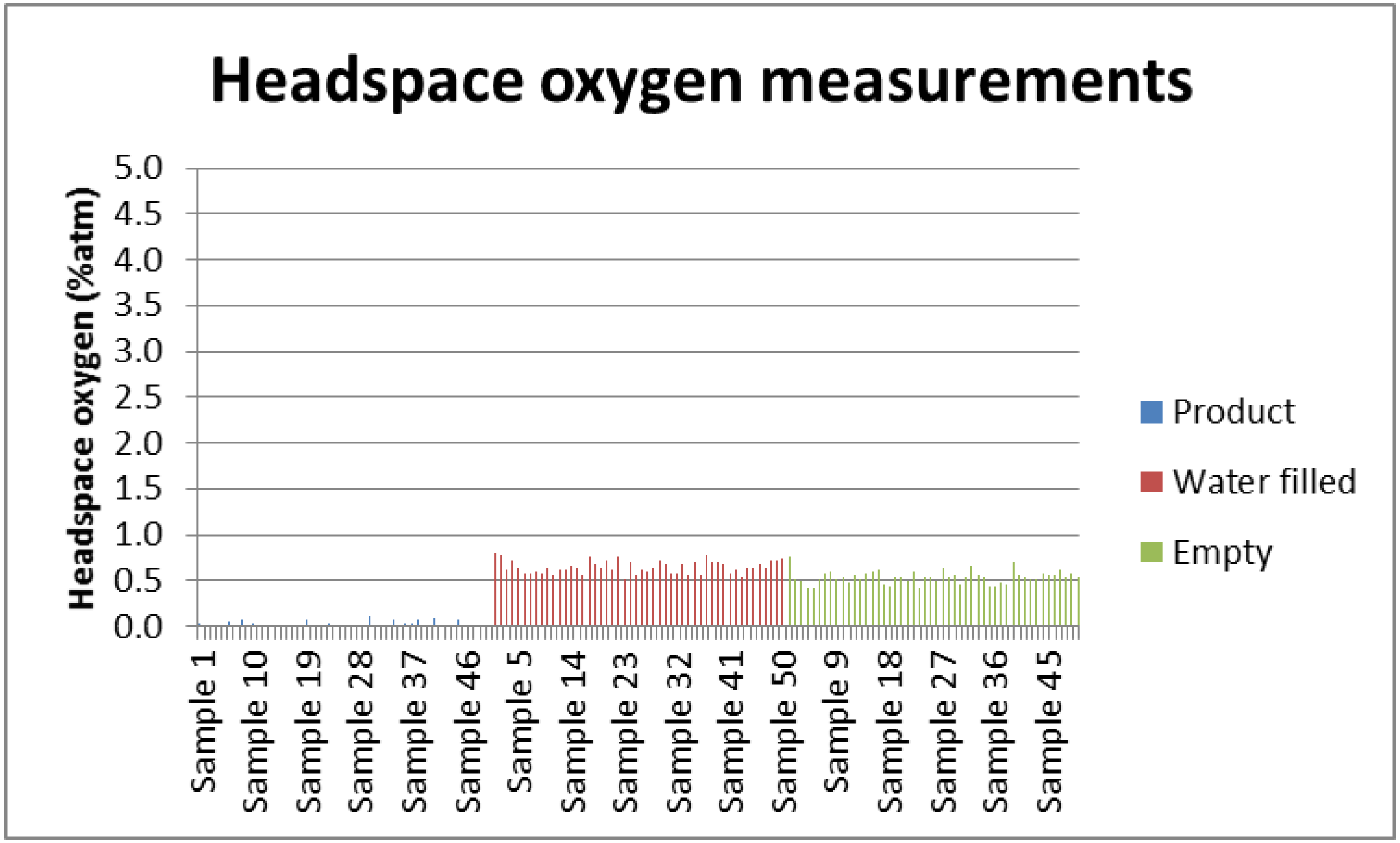
Study 3: CCI method development

- Diffusion tests with vials with known defects
- Effusion test with vials with known defects
- Method protocol

Case Study 2:
Method development

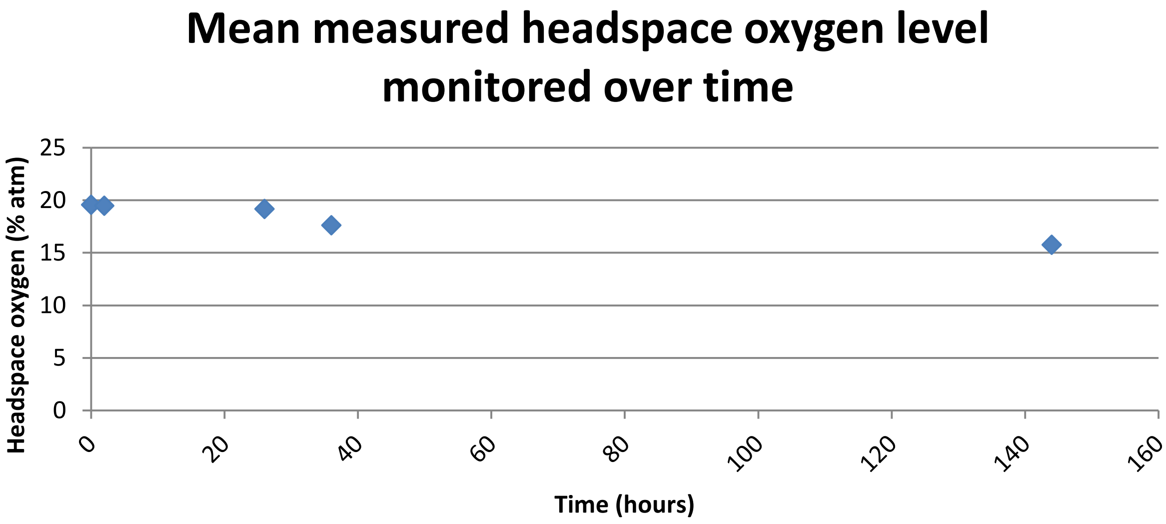
Study 1: Manufacturing conditions

- 50 product, water-filled and empty samples



Study 2: API reactivity

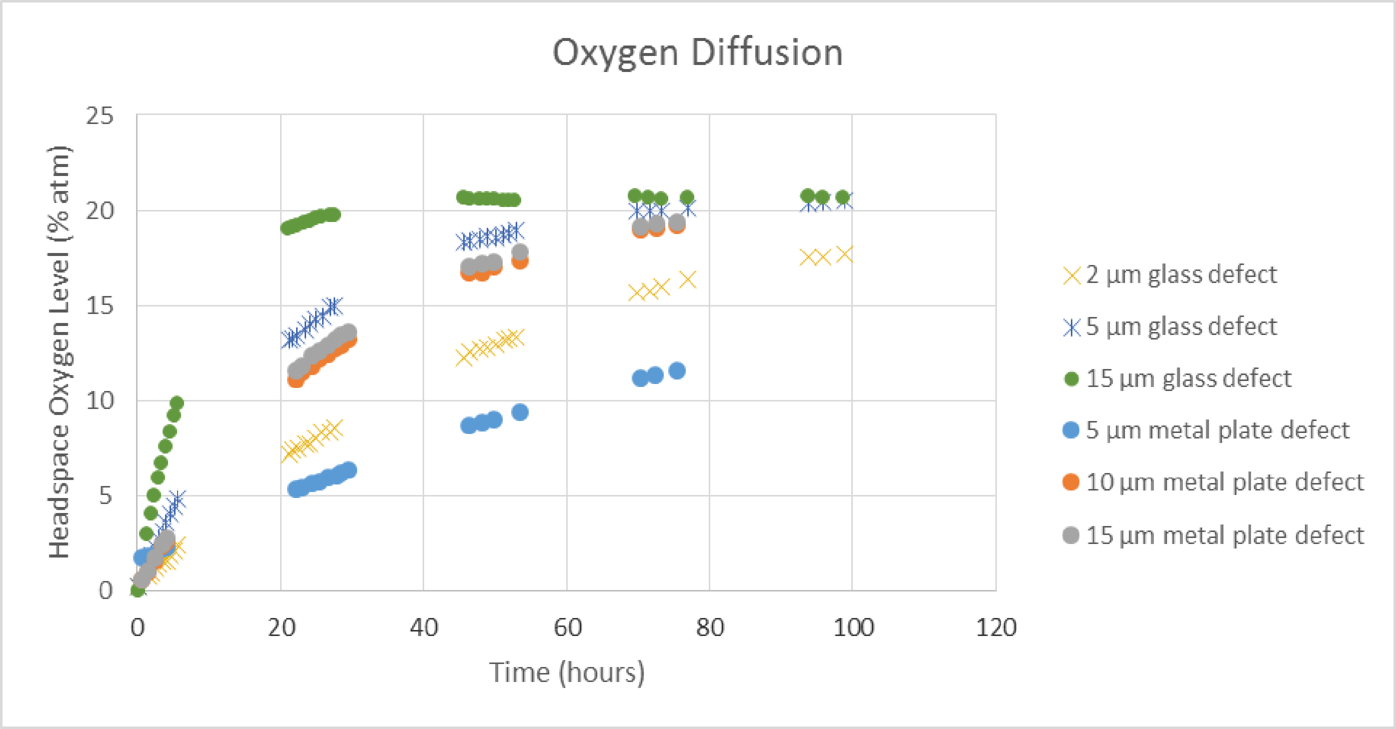
- 50 product samples opened to air and followed over time



	Oxygen (% atm)
Start	19.59
2 hours	19.50
26 hours	19.18
36 hours	17.63
144 hours	15.76

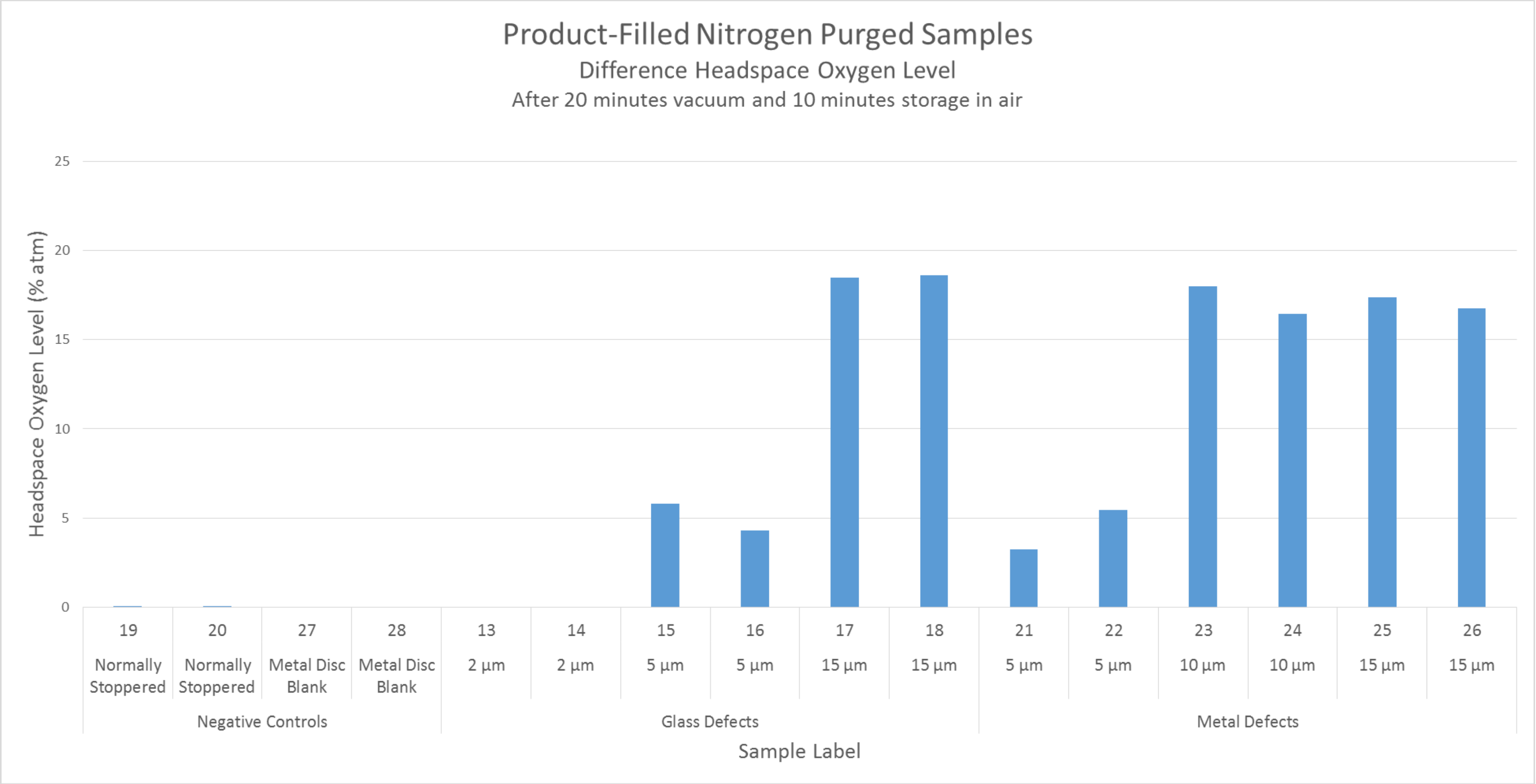
Study 3: CCI method development

- Diffusion tests with vials with known defects



Study 3: CCI method development

- Effusion tests with vials with known defects

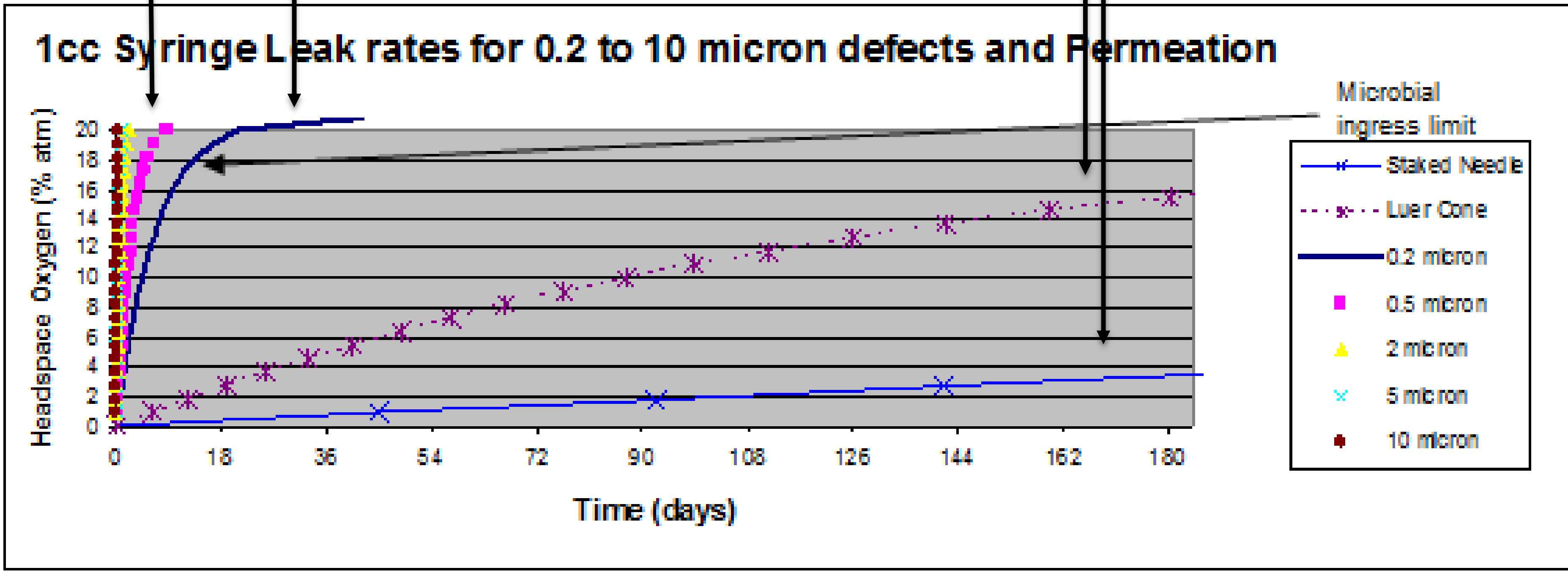


Case Study 3: Package Development Syringe CCI and Permeation

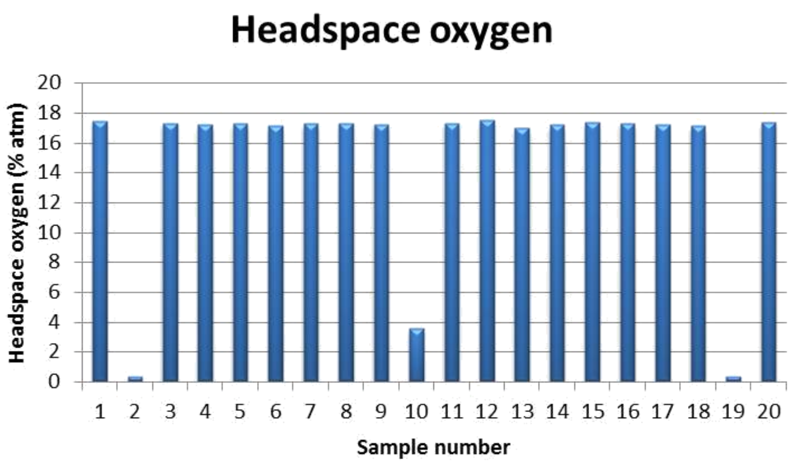
Sample set

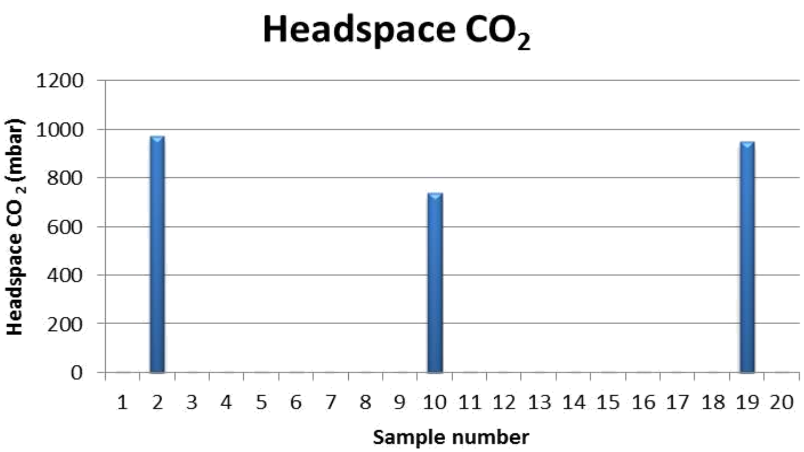
- Two syringe types: Staked needle and Luer cone
- Positive controls: 2µm, 5µm,10µm laser drilled glass defects

Step 1: Establishing the inherent leak rate of a package.
Step 2: Determine leak rate for positive controls
Step 3: Model MALL (0.2 µm for sterility assurance)



Case Study 4:
CCI testing for vials stored on dry ice (CO_2)





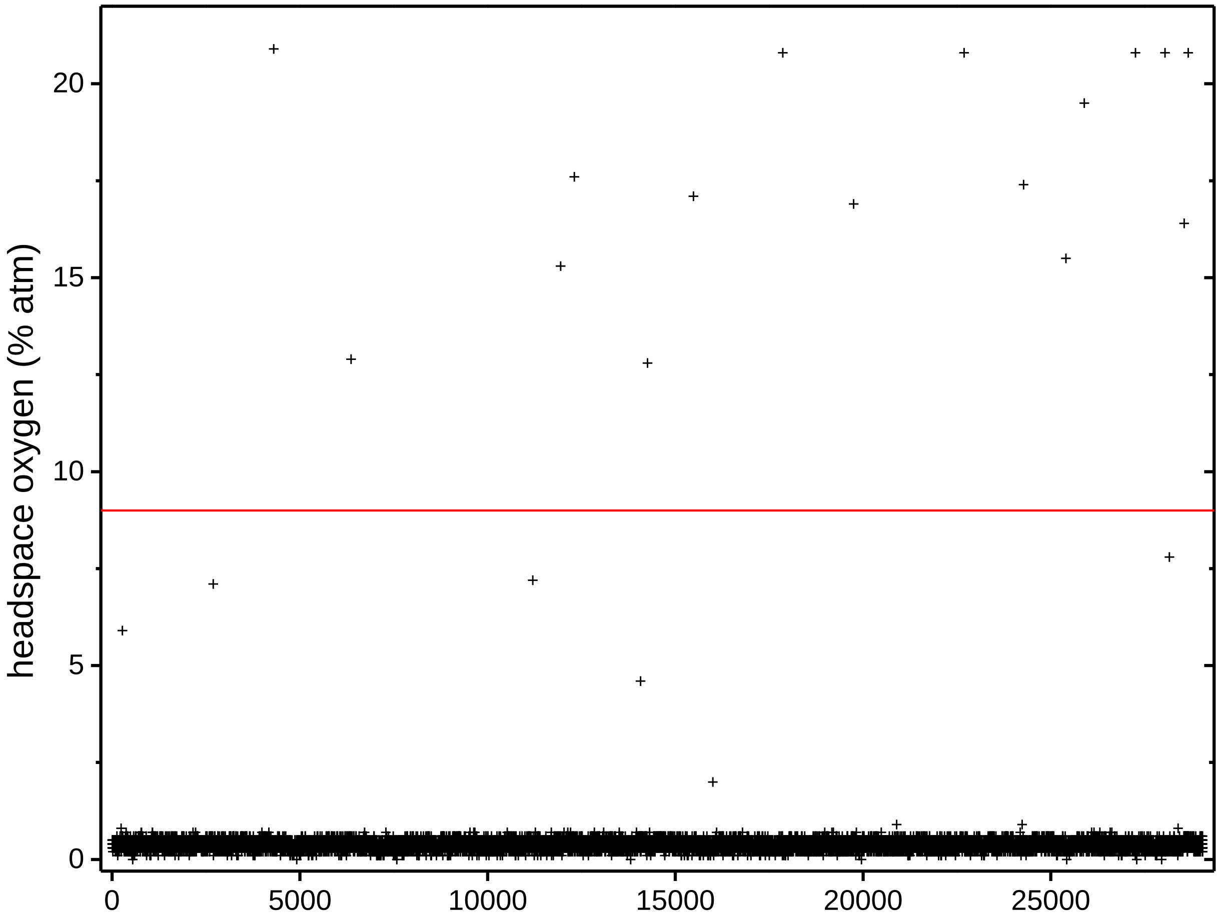
Case

- Air headspace vials stored on dry ice (CO_2)
- Storage on dry ice increases risk of container closure integrity loss,
- Conventional rubber stoppers lose elasticity at -80°C risking CO_2 ingress

Result

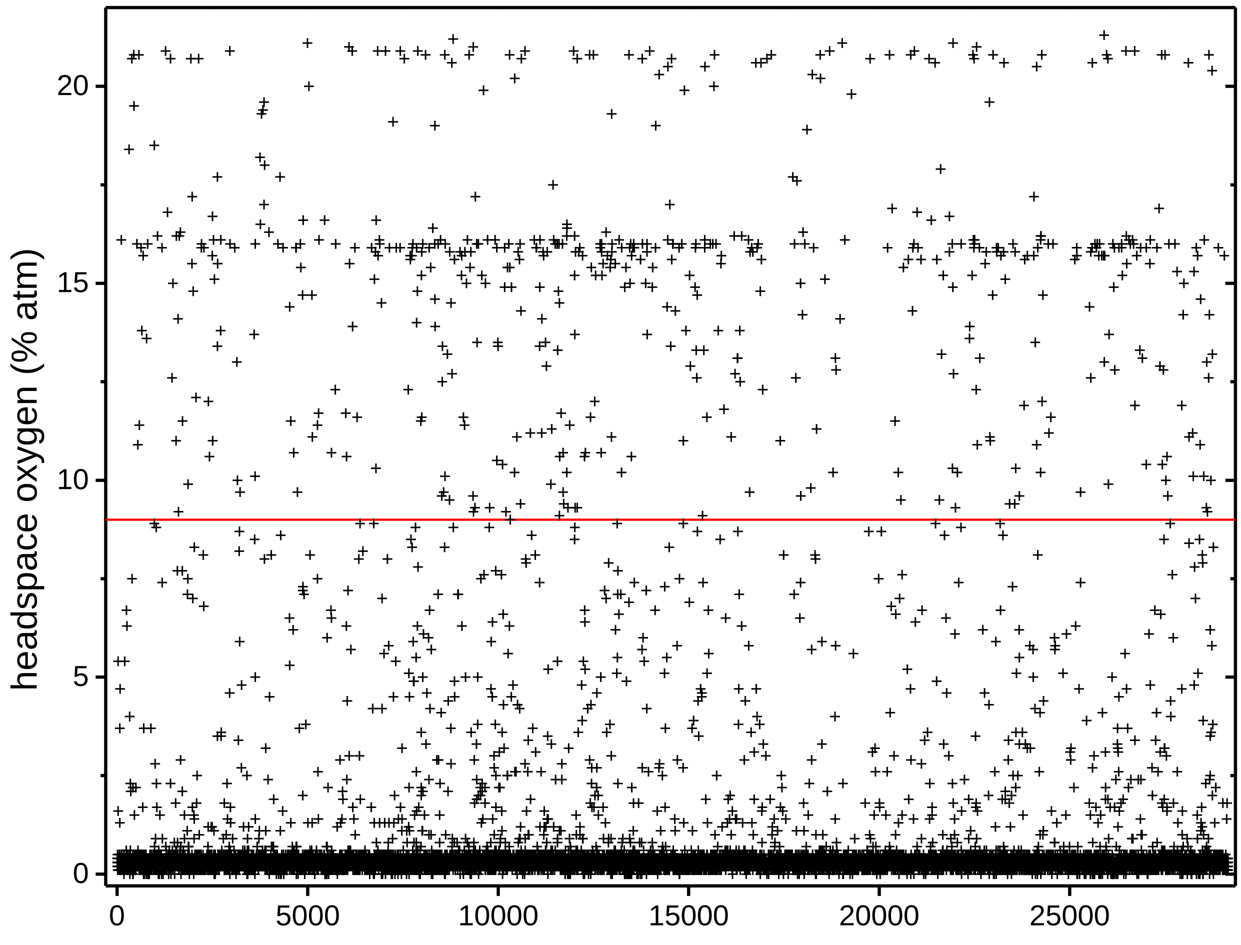
- 3 containers revealed decreased oxygen levels
- Same vials revealed increased CO_2 levels

Case Study 5:
100% Inspection of lyo product



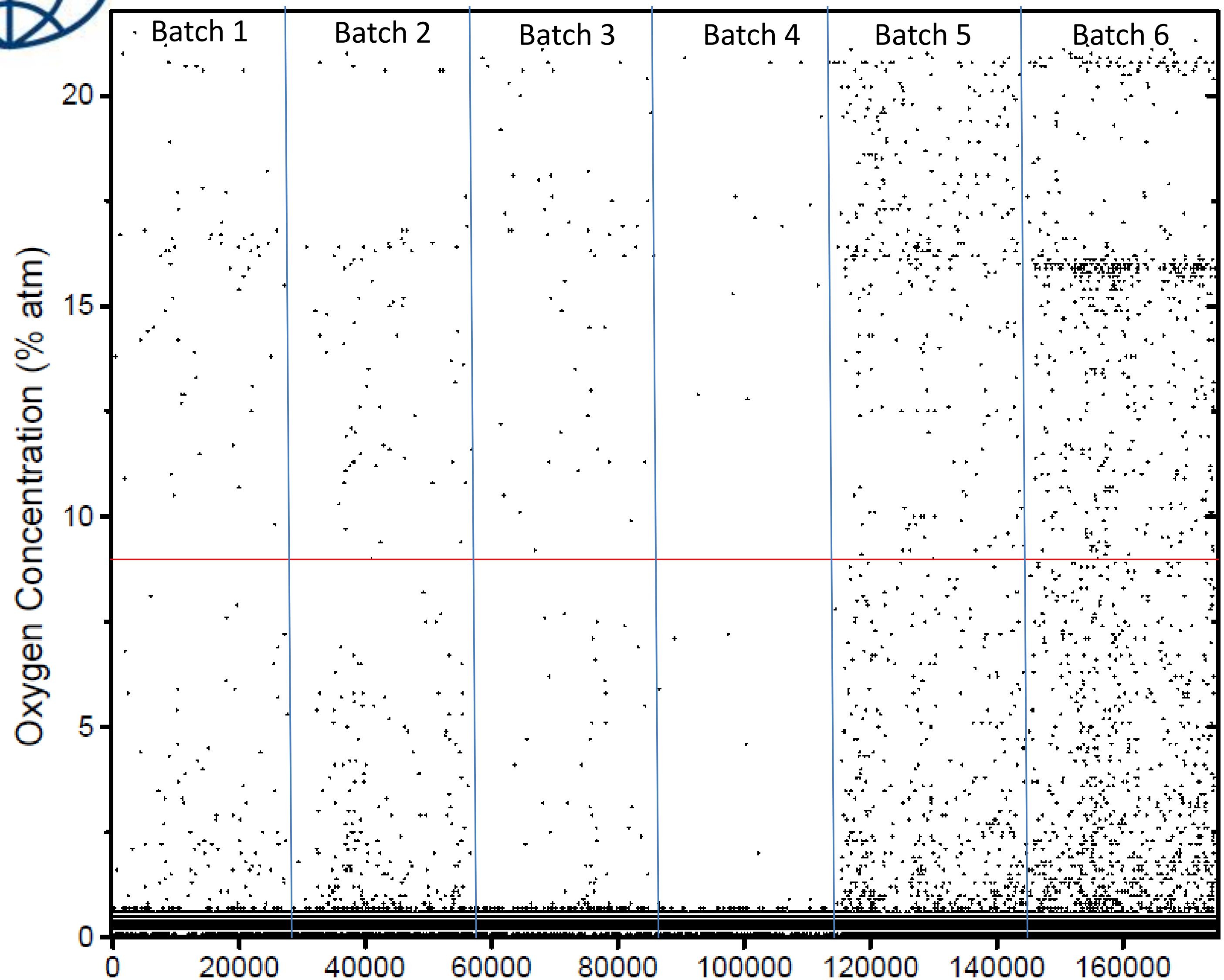
Total batch size: 29048
Number rejected: 16
Reject rate: 0.06%

Case Study 5:
100% Inspection of lyo product



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

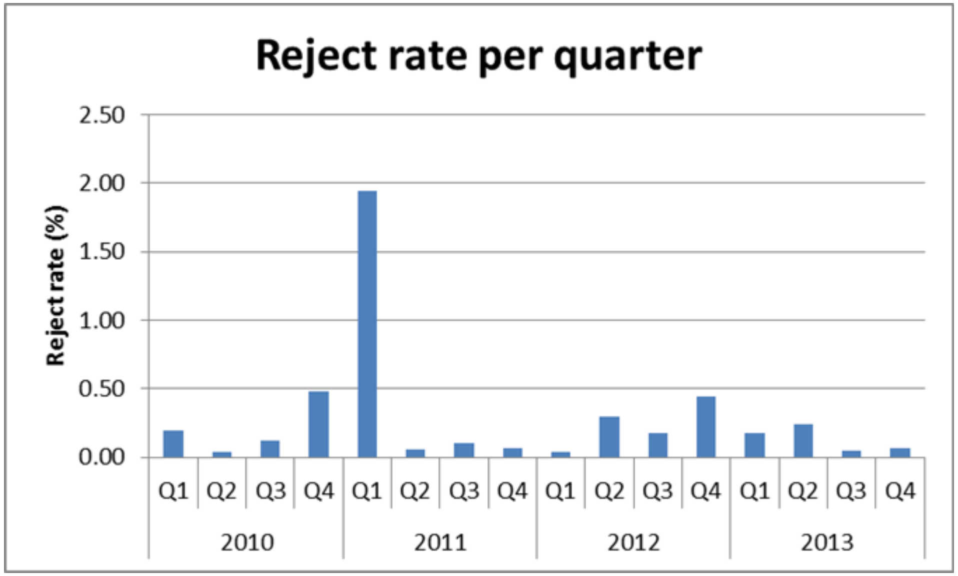
Case Study 5:
100% Inspection of lyo product



Results of 6 chronological batches

Not a robust process

Case Study 5:
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

Advantages and disadvantages

Pro's	Con's
• Non-destructive • Rapid • Quantitative results • Deterministic method • Operator independent • Applicable over whole leak range • Permanent & temporary leaks detectable	• Not all fill levels • Sample needs to be transparent to laser • Inline production inspection needs modified headspace

Thank you!