Laser Based Headspace Analysis for CCIT

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Overview – Case Studies

Part 1:

Application to CCI testing - products packaged under a **non-modified** atmosphere

- Filling line CCI qualification
- Cold storage CCI study

Part 2:

Application to CCI testing - products packaged under a **modified** atmosphere

- Method development and validation lyo products
- Method development liquid product
- 100% inspection of lyophilized product

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.

Part 2
Case studies – non-modified headspace

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:

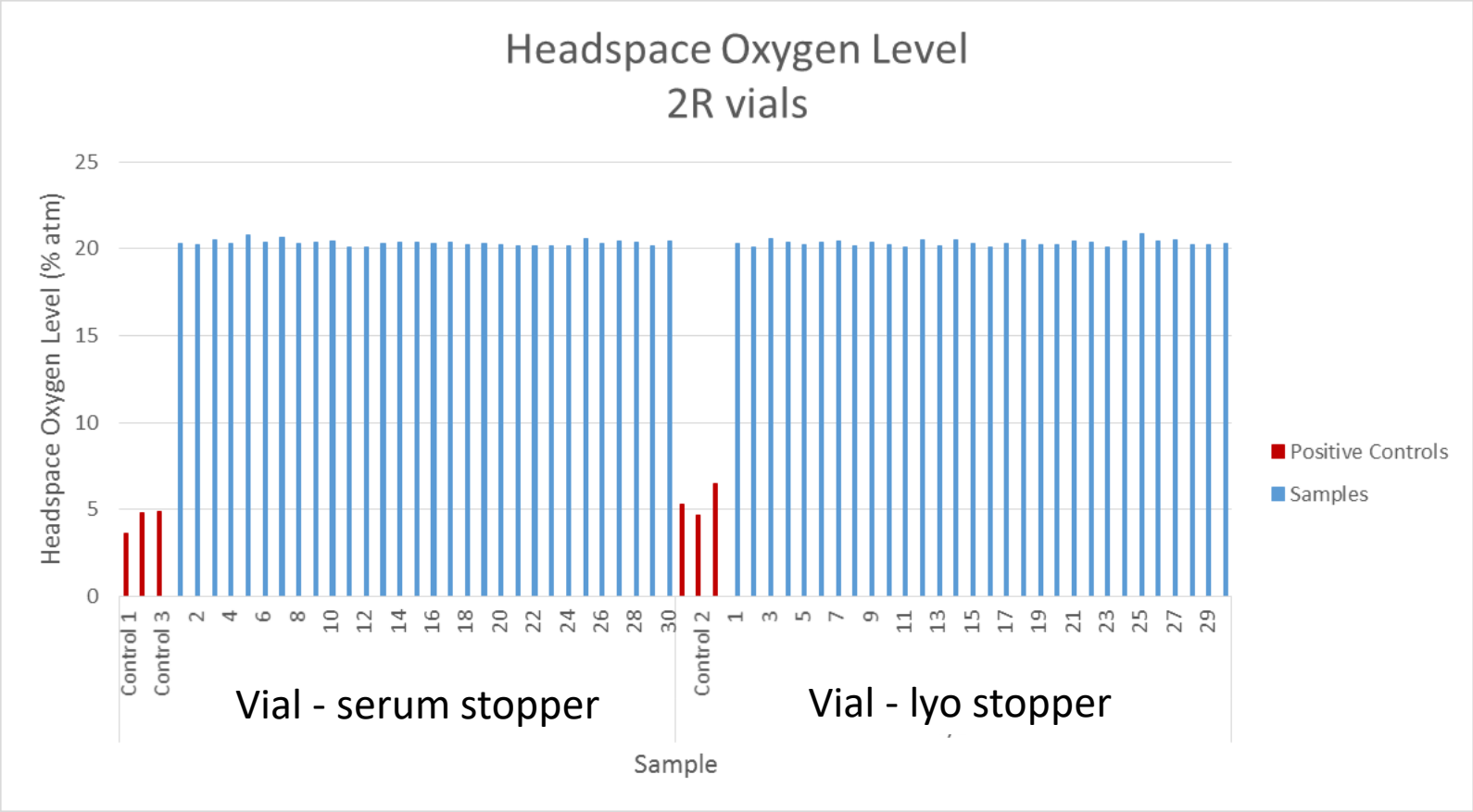
- Produce empty stoppered & crimped vials with the process. Initial headspace is 1 atm of air (20.9% oxygen).
- Use headspace gas ingress model to design a sample chamber evacuation, nitrogen backfill, and sample hold cycle.
- Measure samples for changes in headspace composition. Include positive controls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

Headspace gas flow model can be used to calculate oxygen levels as a function of vial size, sample preparation cycle, and defect size.

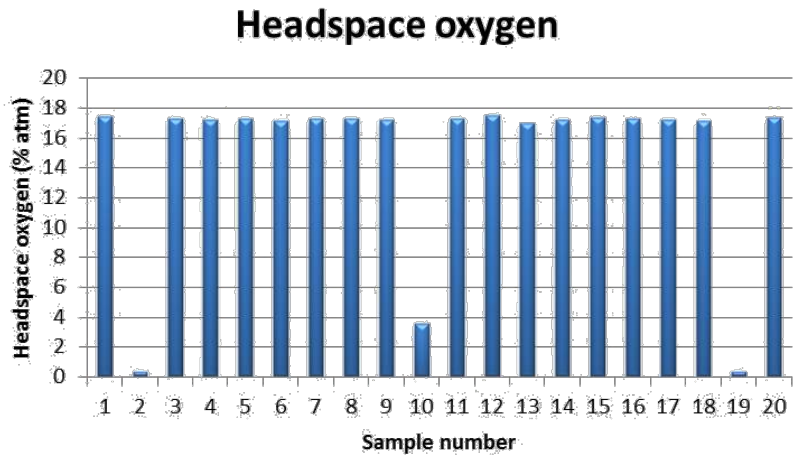
Case Study 1:
Filling line CCI qualification

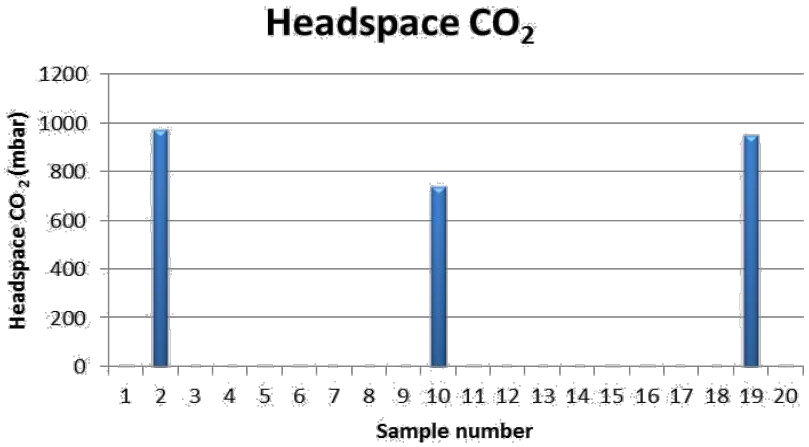
Results headspace CCI test



Example: Gas ingress measurements straightforwardly produced robust CCI data

Case Study 2:
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

Part 3
Case studies – modified headspace

Case Study 3:
Method development and validation – lyo product

- Headspace analysis CCI method development and validation based on UPS<1207>
- Data & reports reviewed and approved by FDA

Overview of Projects

1) Information gathering

- Product picture, feasibility assessment, type and size vial, headspace composition and pressure, # and sizes positive controls, etc.

2) Method Development project at Lighthouse

- Verify initial headspace conditions, predict headspace changes using validated leak rate model, design protocol, perform tests

3) On-site system and Method Validation

- Lighthouse system IQ/OQ & 21-CFR-11
- Provide Method Validation Protocol according to USP<1207> and ICH Q2/R1 guidelines

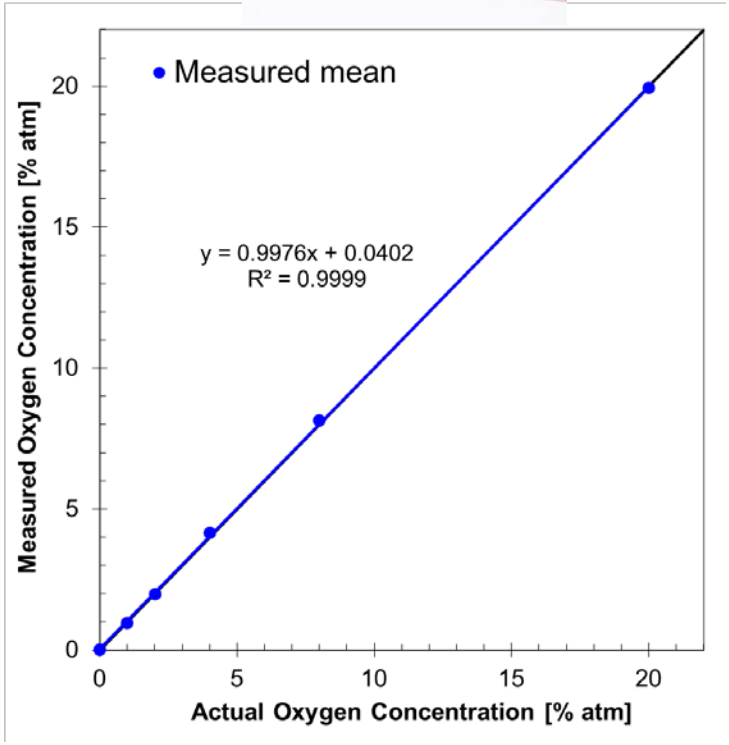
Case Study 3:
Method development and validation – lyo product

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 Precision



Case Study 3:
Method development and validation – lyo product

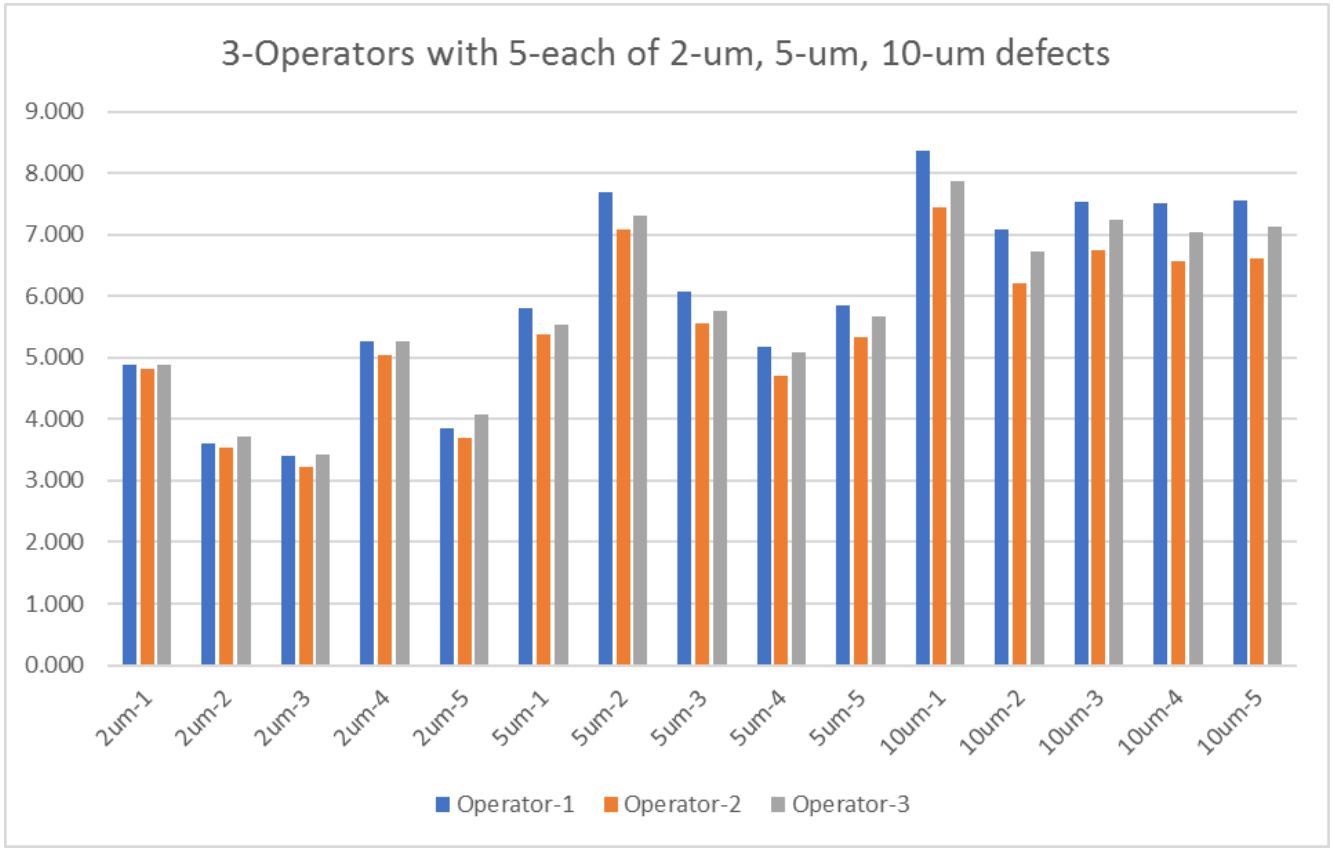
ICH Q2/R1: Validation of analytical procedures

2R vial – 10 replicate measurements

- Accuracy (% Recovery): 90-110%
- Precision (% RSD): <10%
- Linearity
- Limit of detection
- Limit of quantitation
- Range

Case Study 3:
Method development and validation – lyo product

Example of results



Each operator tested all 15 positive controls

100% of defective vials were detected

Intermediate precision <10% RSD

Case Study 3:
Method development and validation – lyo product

CCI Validation Overview of Results

	Operator-1	Operator-2	Operator-3
2um Defect 5-vials	5 of 5 100%	5 of 5 100%	5 of 5 100%
10um Defect 5-vials	5 of 5 100%	5 of 5 100%	5 of 5 100%
20um Defect 5-vials	5 of 5 100%	5 of 5 100%	5 of 5 100%
Gross Defect 5-vials	5 of 5 100%	5 of 5 100%	5 of 5 100%
No Defect	0 of 5 100%	0 of 5 100%	0 of 5 100%

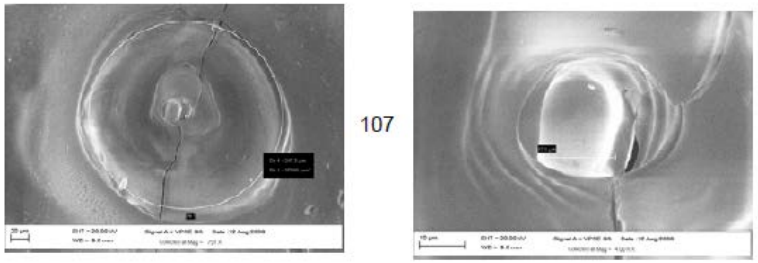
Case Study 4:
Method development – liquid product

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

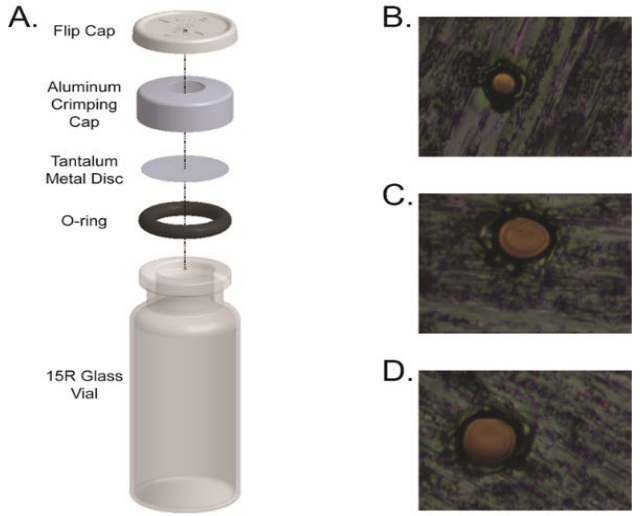


Image provided by Lenox Laser

Case Study 4:
Method development – liquid product

Study 1: Manufacturing conditions

- Determine purge quality

Study 2: API reactivity

- Oxidation rate

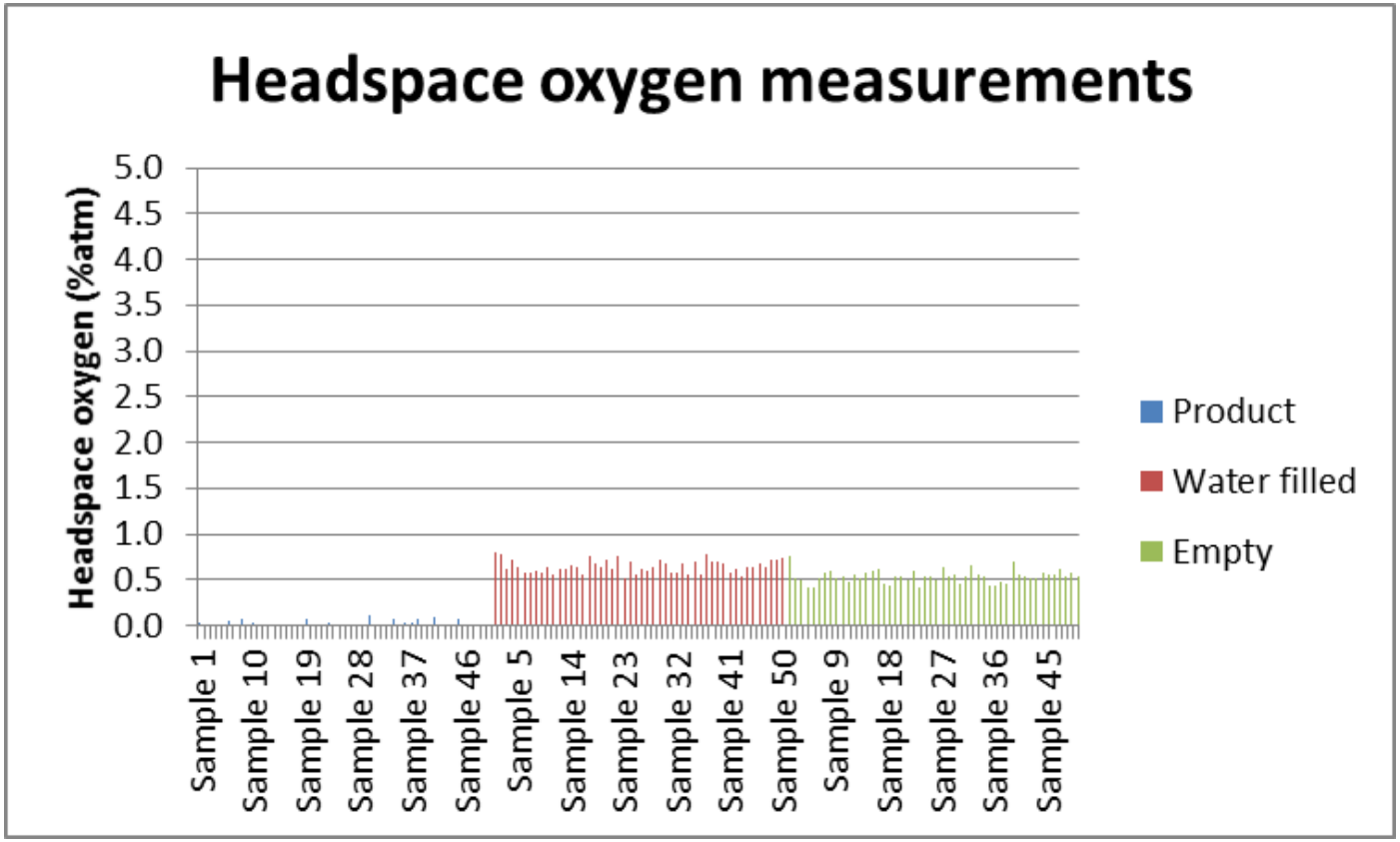
Study 3: CCI method development

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

Case Study 4:
Method development – liquid product

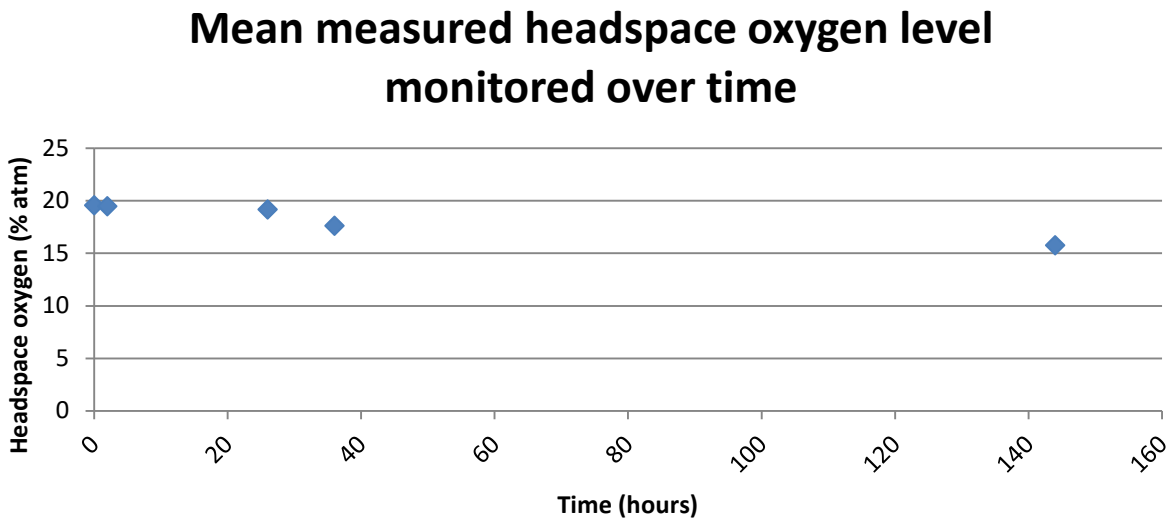
Study 1: Manufacturing conditions

- 50 product, water-filled and empty samples



Study 2: API reactivity

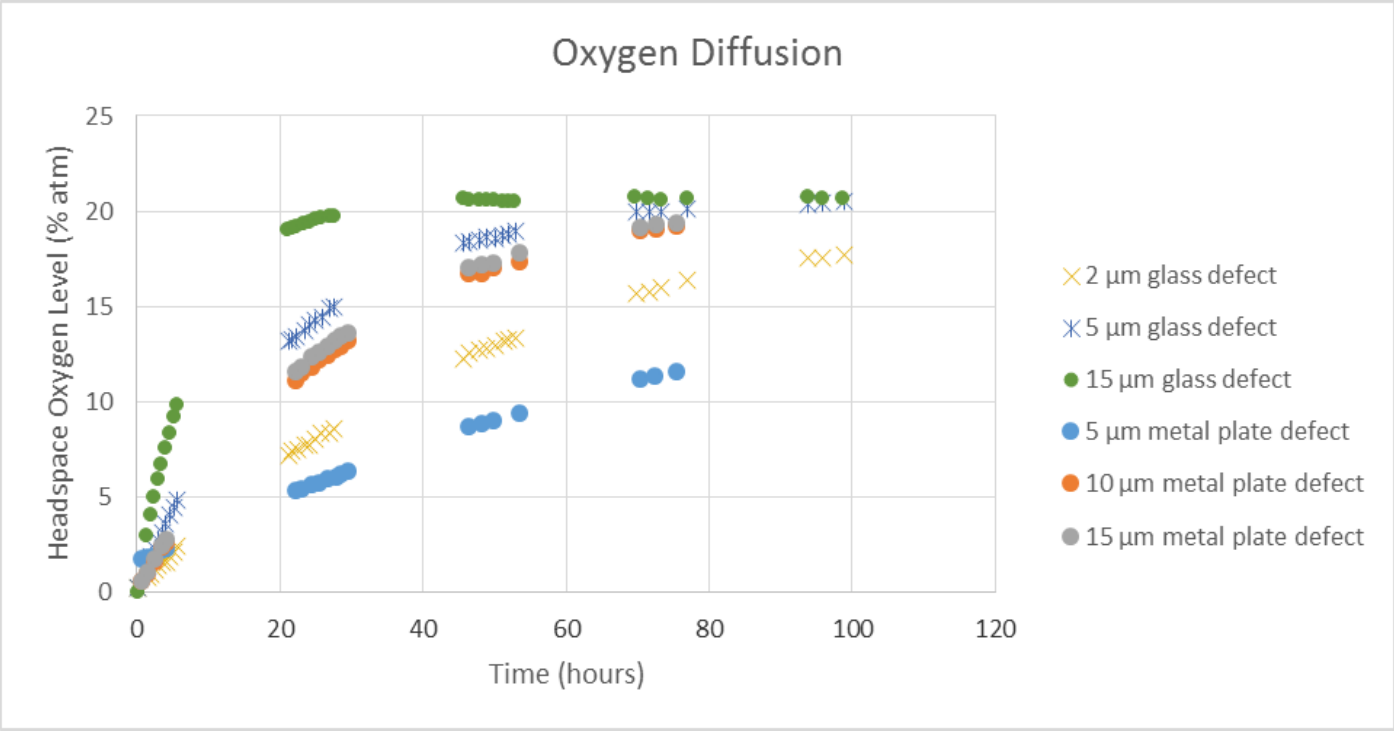
- 50 product samples opened to air and followed over time



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

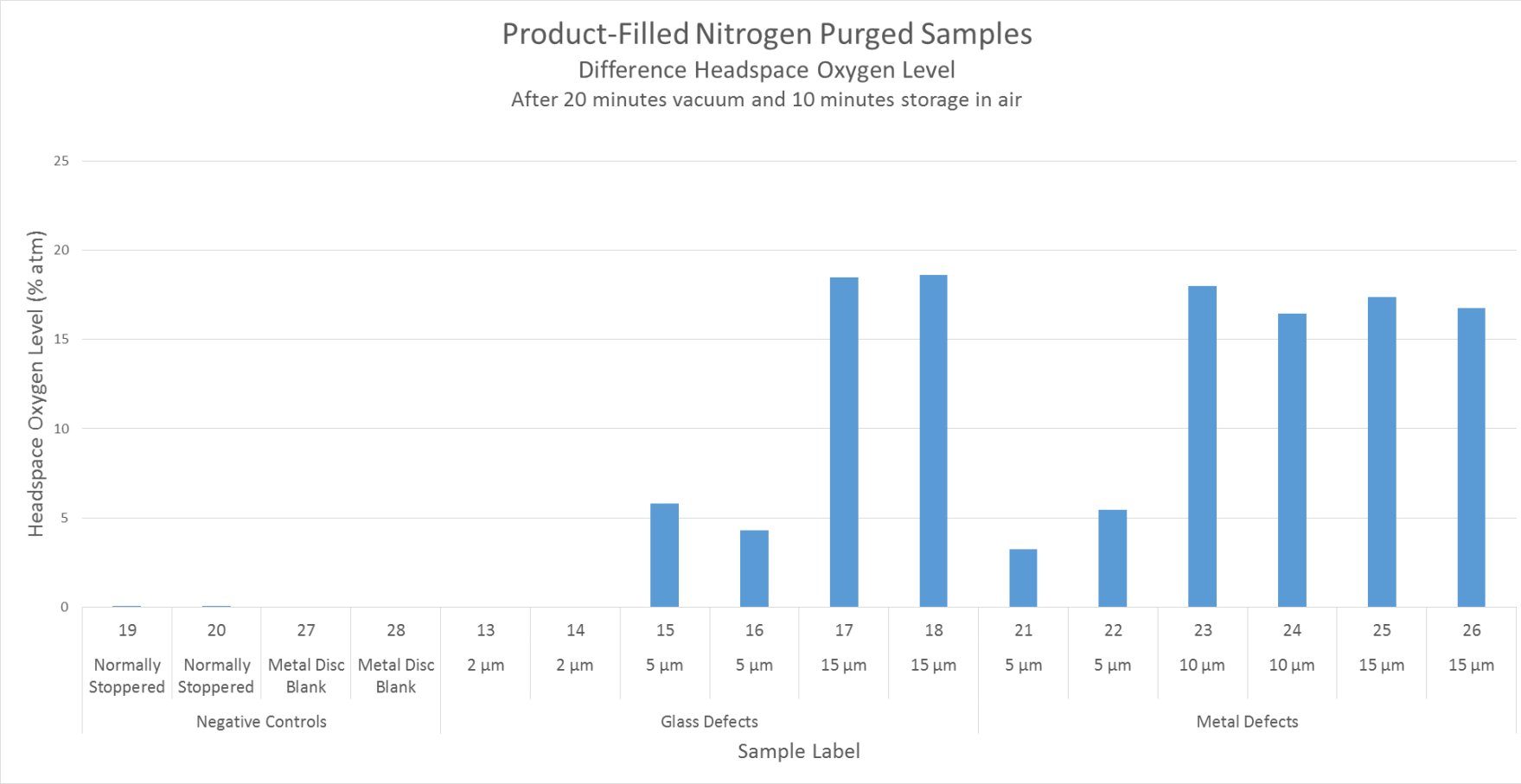
Study 3: CCI method development

- Diffusion tests with vials with known defects



Study 3: CCI method development

- Effusion tests with vials with known defects

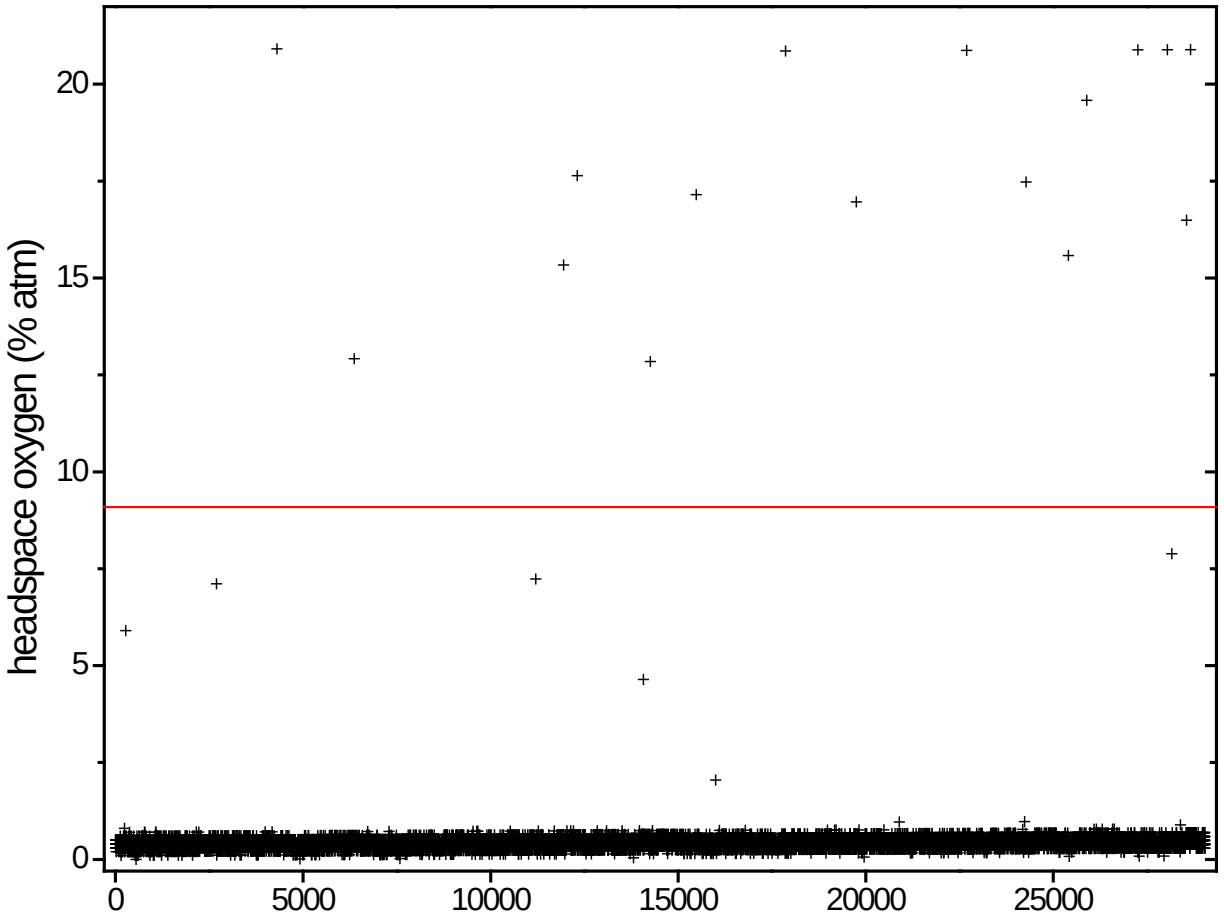


Case Study 5:
100% Inspection of lyo product

- QC vials showed loss of vacuum (spec 200 mbar N_2)
- Client decided to perform 100% CCI inspection of suspect batches

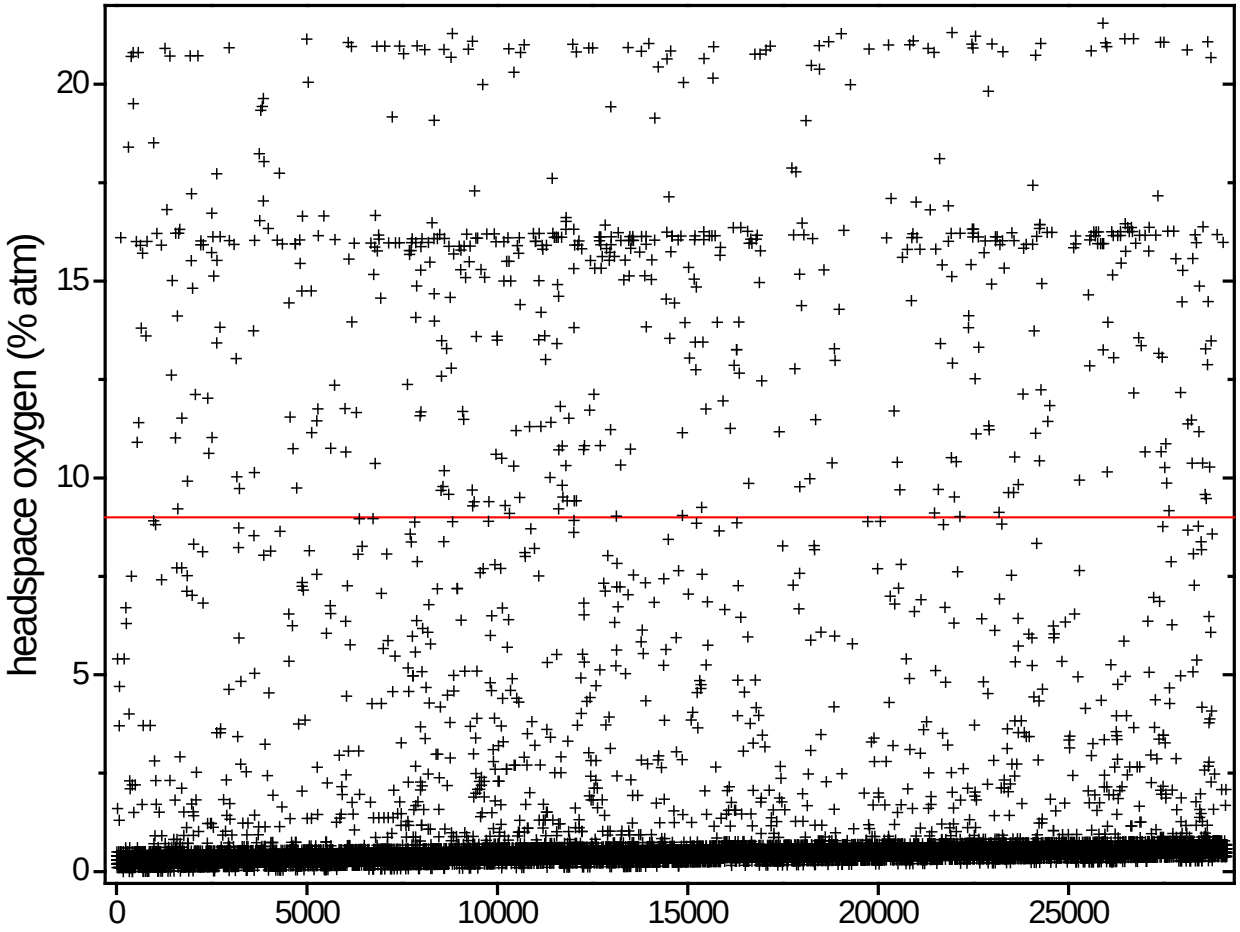
Headspace inspection machine configured for 100% oxygen inspection to identify lyo product vials with high oxygen content and reject them as leaking vials

Case Study 5:
100% Inspection of lyo product



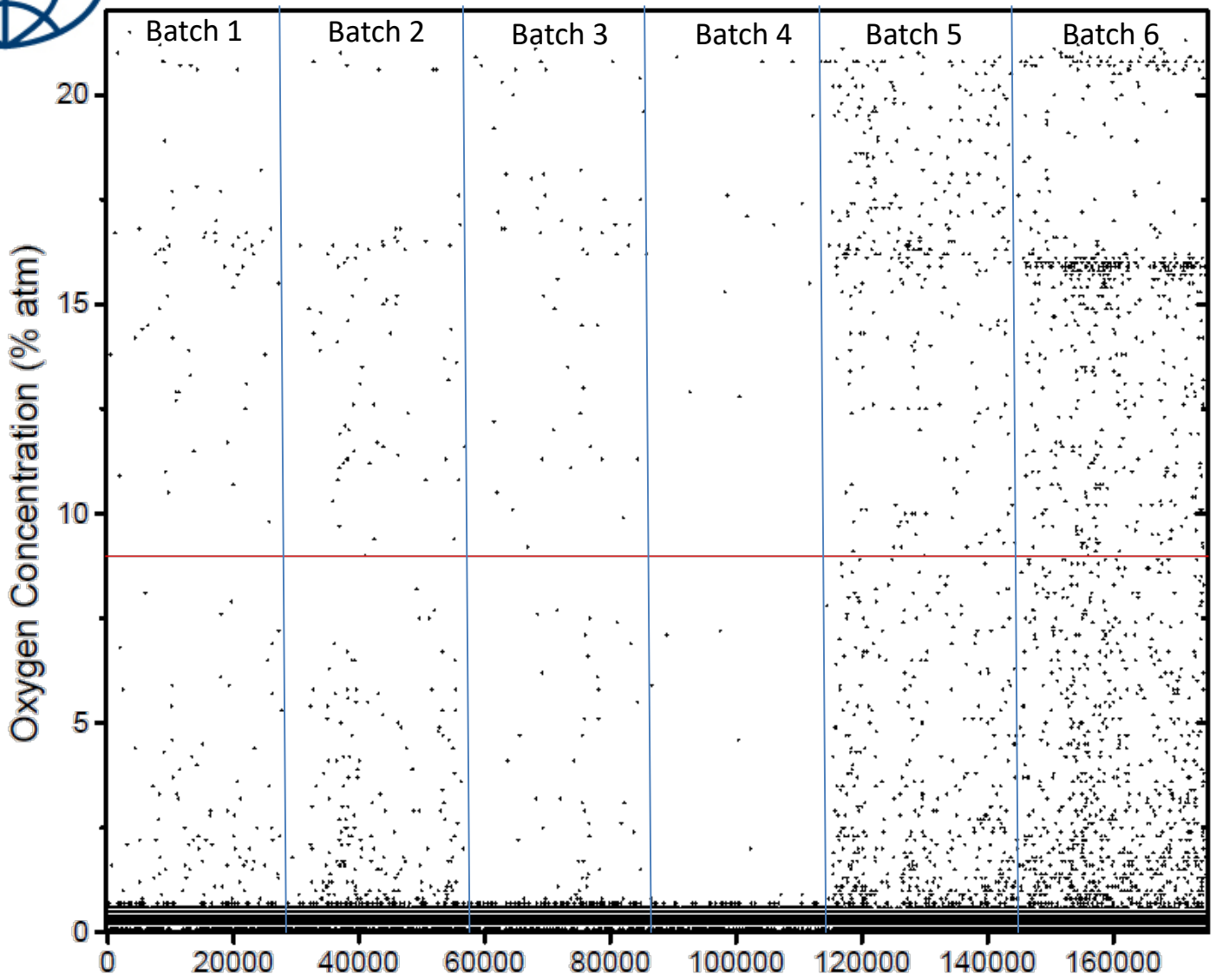
Total batch size: 29048
Number rejected: 16
Reject rate: 0.06%

Case Study 5:
100% Inspection of lyo product



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

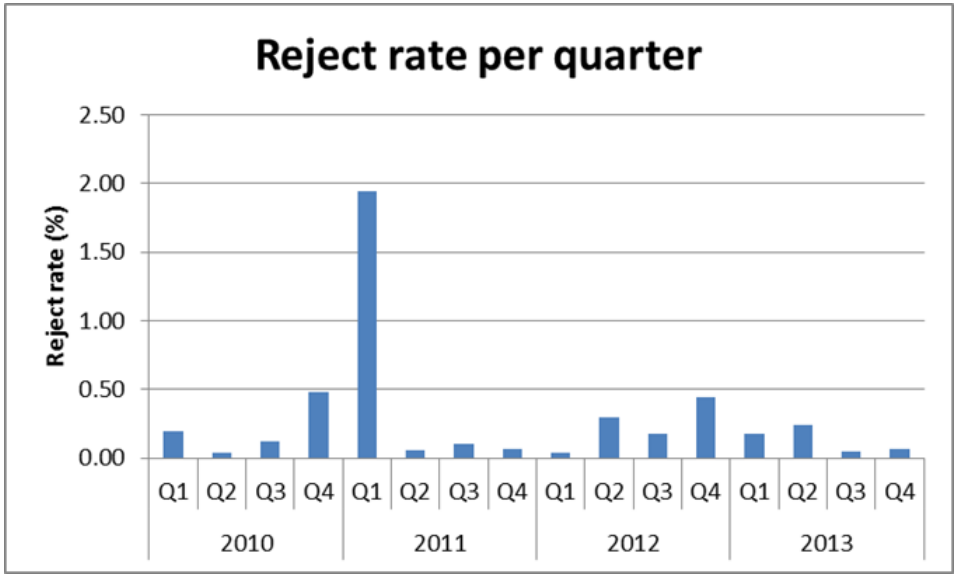
Case Study 5:
100% Inspection of lyo product



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

Thank you for your attention!

For more information about Headspace Applications and how LIGHTHOUSE can support you with equipment and measurement services, please speak to the expert(s) around the room:

- Container closure integrity method development
- Container closure integrity testing
- Headspace oxygen stability studies
- Nitrogen purge optimization and validation
- Lyo cycle optimization
- Lyo chamber moisture mapping
- Packaging permeation studies