Container Closure Integrity Testing

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In This Presentation

We will be discussing

- USP <1207> and different probabilistic and deterministic methods within
- Dye ingress testing
- Oxygen headspace testing

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Container Closure Integrity Testing (CCIT) Background

Sterility is required at release and at each 12-month time point by ICH for parenteral drug products.

In 2008, FDA issued guidance that allowed CCIT in lieu of sterility after release. However, there was minimal guidance about how to actually implement testing.

Container Closure Integrity Testing Background

Leaks of Concern	Product Quality Risks Posed by Leaks
Capable of allowing entry of microorganisms	Failure of product sterility quality attribute
Capable of allowing escape of product dosage form or allowing entry of external liquid or solid matter	Failure of relevant product physicochemical quality attributes
Capable of allowing a change in gas headspace. For example, loss of headspace inert gases (e.g. nitrogen), loss of headspace vacuum, and/or entry of gases (e.g. oxygen water vapor, air)	Failure of relevant product physicochemical quality attributes and/or hindrance of product access by the end-user

Container Closure Integrity Testing Background

In 2016, the updated USP <1207> came out with new guidance listing the following technologies:

Deterministic CCIT Technologies	Probabilistic CCIT Technologies
High-voltage leak detection	Bubble emission
Laser-based headspace analysis	Microbial challenge
Mass extraction	Tracer gas detection, sniffer mode
Pressure decay	Tracer liquid/dye ingress
Tracer gas detection, vacuum mode	
Vacuum decay	

Probabilistic CCIT Technologies

Per USP <1207>, Probabilistic Technologies

Technology	Non-destructive	Works with			Requires	
		Rigid containers	Flexible containers	Product at leak site	Submersion	Headspace
Bubble emission	X	√	*	X	√	√
Microbial challenge	X	√	*	√	√	X
Tracer liquid	X	√	*	√	√	X
Tracer gas detection, sniffer mode	*	√	*	√	X	X

√ = yes; * = Case-dependent; X = no

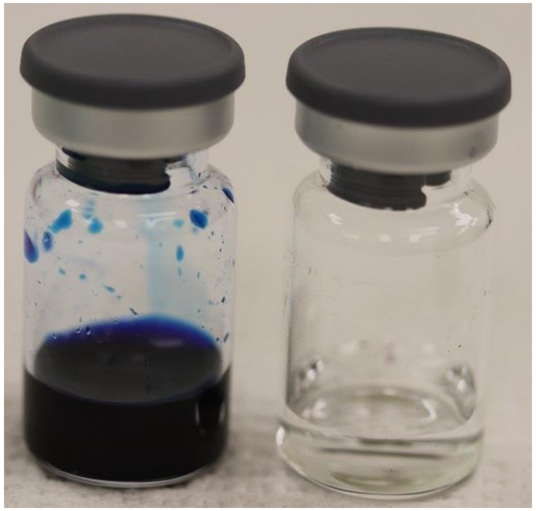
Probabilistic CCIT Technologies

Technology	Considered Probabilistic Because
Bubble emission	Escaping gas can be entrapped within or between package components; false-leak out-gassing events; small leaks may solubilize; test sample setup inadequate
Microbial challenge	Multiple events needed to occur: microorganism at leak, liquid path through leak and microorganism flowing through liquid path
Tracer liquid	Needs combination of tracer solution wicking, tracer solution effusion and tracer element diffusion through liquid filled leak path
Tracer gas detection, sniffer mode	Concentrated tracer gas at leak site is not a well-defined or predicable event; sniffer scanning prone to variability

Probabilistic CCIT Technologies: Dye Ingress

Dye Ingress CCI Testing

- Procedure
  - Place samples and positive controls in dye
  - Apply vacuum, overpressure
  - Remove samples and positive controls from dye, rinse, wipe dry and inspect for dye ingress
- Made more robust by the use of positive controls ≤20 micron diameter defects in every test



Dye Ingress Validation Challenges: System Suitability Controls

- **Updated guidance**: Need ≤ 20 micron defects at qualification and each routine test
- **Options**: Laser drilled containers or capillaries/micro pipettes
- **Capillaries**: Technique dependent, long defect
- **Laser drilled vial**: Expire in 6 months, continually needing to be reordered throughout the lifetime of a stability study

- **Potential Solution**: Include a "standard" system suitability control (10mL vial or 1mL syringe) in validation and then include it at each routine time point to demonstrate dye ingress through 20 micron defects

Dye Ingress Validation Challenges

- **Challenge 1:** Pressure or vacuum can move syringe stopper
- **Solutions:**
  - Tooling to hold plunger in place
  - Change pressure and vacuum challenge conditions to still detect desired defects, but not move stoppers

- **Challenge 2:** Labels flaking off and blocking defects
- **Solution:** Removal of labels prone to disintegration in liquid prior to testing

- **Challenge 3:** Pressure/Vacuum vessel not maintaining vacuum
- **Solutions:**
  - Monitor for leaking immediately after sealing
  - Upgrade vessel to more robust design

Deterministic CCIT Technologies

Per USP <1207>, Deterministic Technologies:

Technology	Non-destructive	Works with: Rigid containers	Flexible containers	Product at leak site	Requires: Product at leak site	Headspace	Conductive product	Optically transparent
High-voltage leak detection	*	√	√	√	√	X	√	X
Laser-based headspace analysis	√	√	*	*	X	√	X	√
Mass extraction	√	√	*	*	X	√	X	X
Pressure decay	*	√	*	X	X	*	X	X
Tracer gas detection, vacuum mode	*	√	*	*	X	√	X	X
Vacuum decay	√	√	*	*	X	√	X	X

√ = yes; * = Case-dependent; X = no

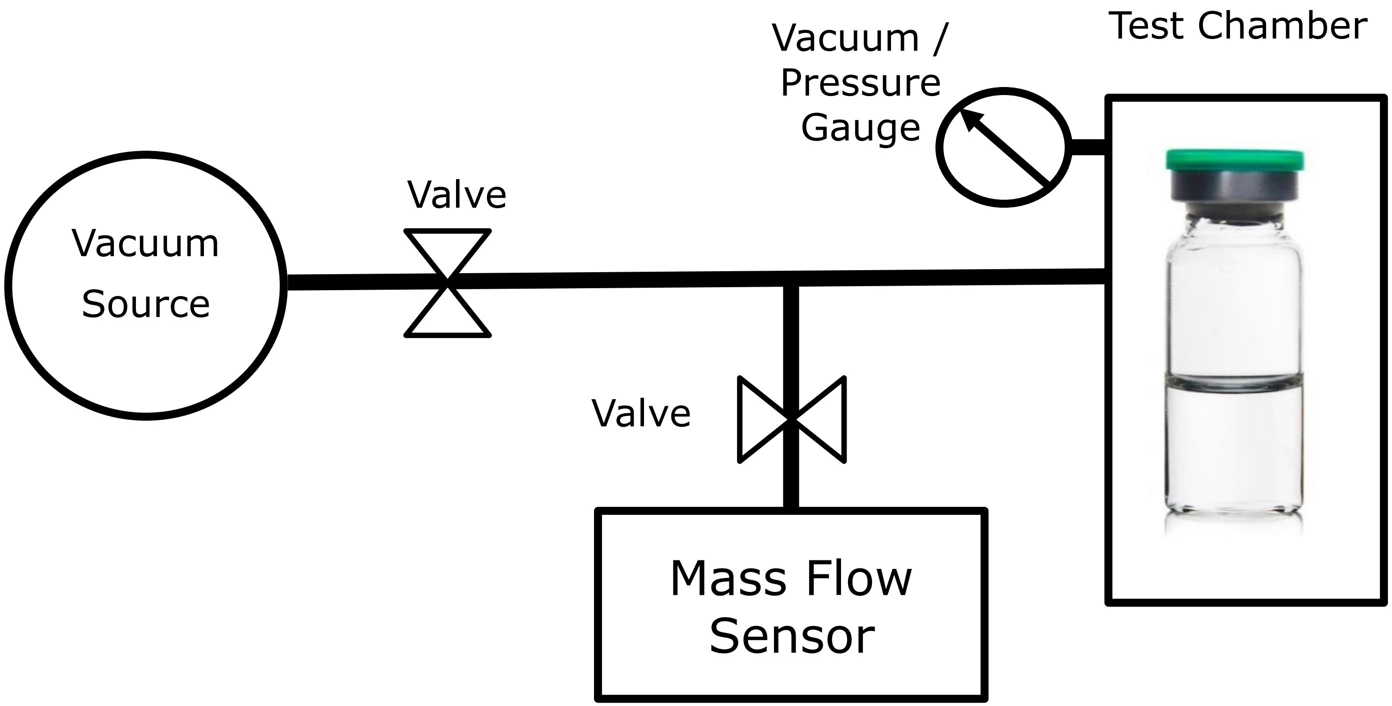
The Different Deterministic Tests

+ Many of the tests rely on applying a pressure differential (absolute or partial pressure of a tracer gas) and monitoring for change.

+ All methods generate a quantitative result which is compared with positive and negative controls at validation to establish limits above which container closure integrity is considered to have failed.

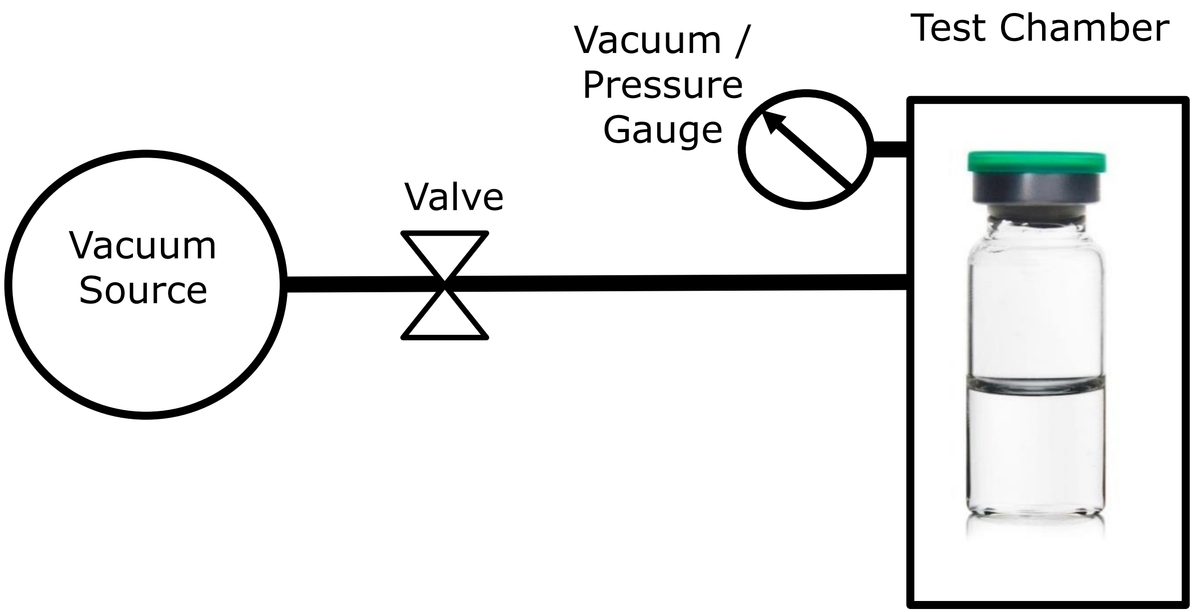
The Different Deterministic Tests: Mass Extraction

Pull a vacuum below the pressure inside the test sample and monitor absolutes pressure, pressure decay rate and/or mass flow for gas or product vapor escaping the test sample



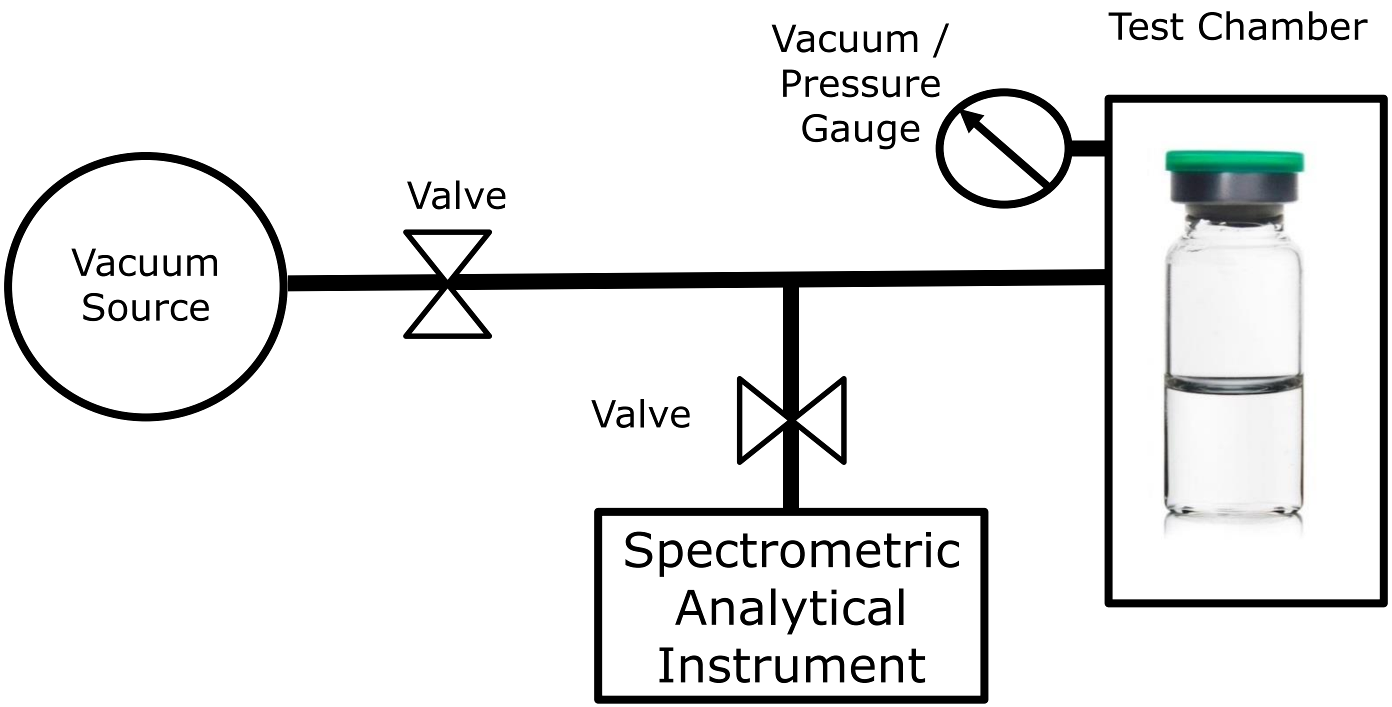
The Different Deterministic Tests: Vacuum Decay

Pull a vacuum below the pressure inside the test sample and monitor vacuum decay for gas or product vapor escaping the test sample



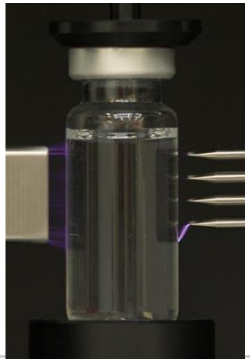
The Different Deterministic Tests: Tracer Gas Detection, Vacuum Mode

Fill test sample with tracer gas (e.g. Helium) and pull a vacuum around it, monitoring for helium escaping the package.



The Different Deterministic Tests: (continued)

+ **Pressure decay:** over-pressuring the test samples and monitoring for decrease in pressure within the test sample due to gas escaping.
+ **Laser-based headspace analysis**: Measures a gas concentration or total pressure and compares for change over time.
+ **High-voltage leak detection:** Uses a difference in resistance between the product and packaging to generate a different voltage if there is a defect with product nearby.



Deterministic Technologies: Laser-based Headspace Analysis

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Laser-based Oxygen Headspace Analysis

Laser-based headspace analysis using LIGHTHOUSE Instruments Headspace Oxygen Analyzer

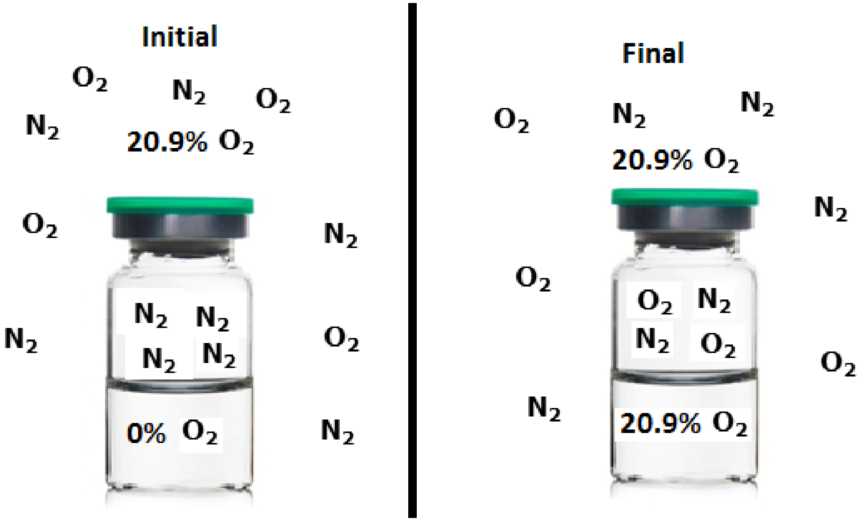
- Non-destructive
- Fast
- Detects wide range of defect sizes

Limitations

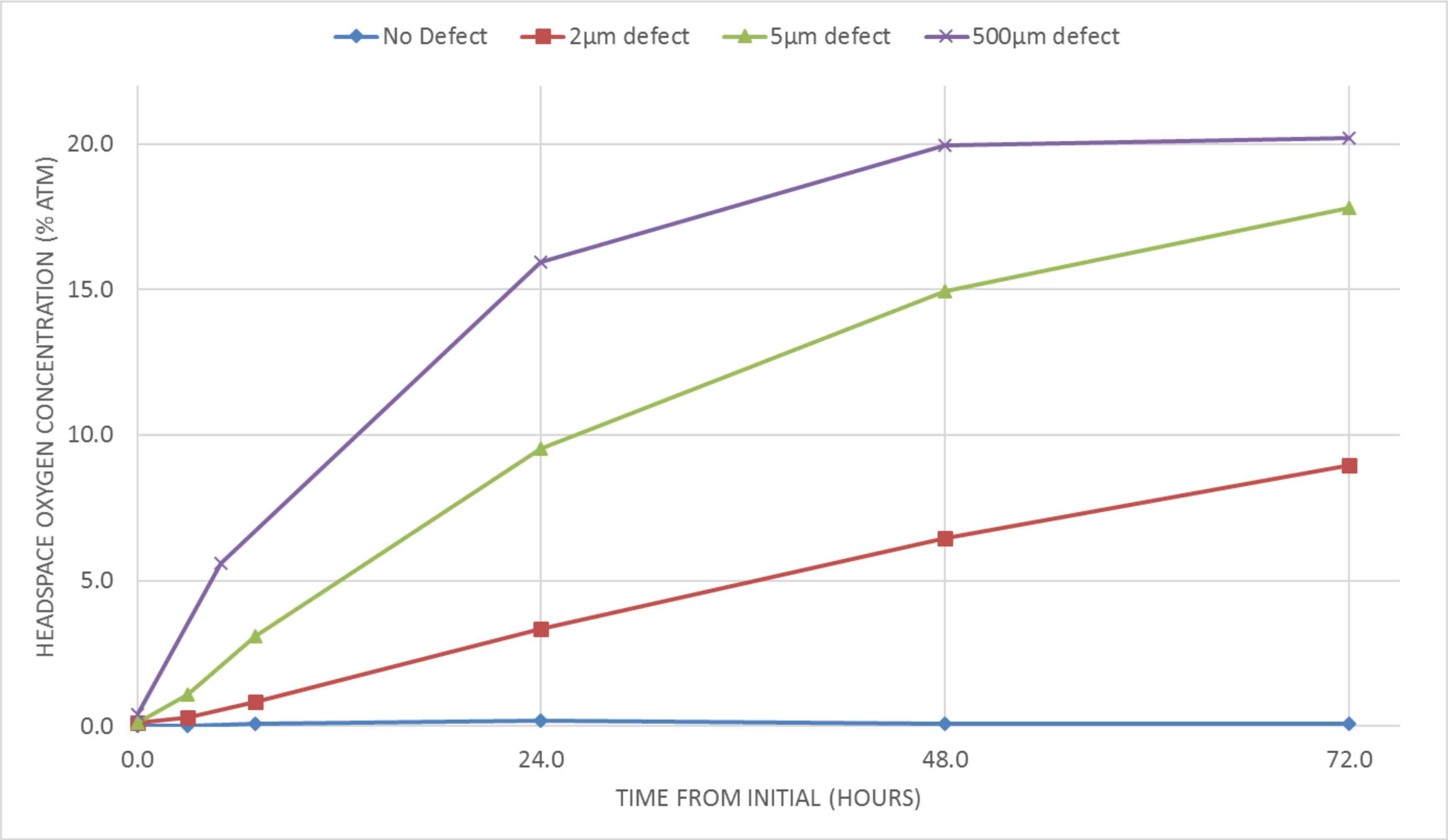
- Need an optically transparent container
- Need a gas headspace
- Rigid container

Oxygen CCIT Method Outline

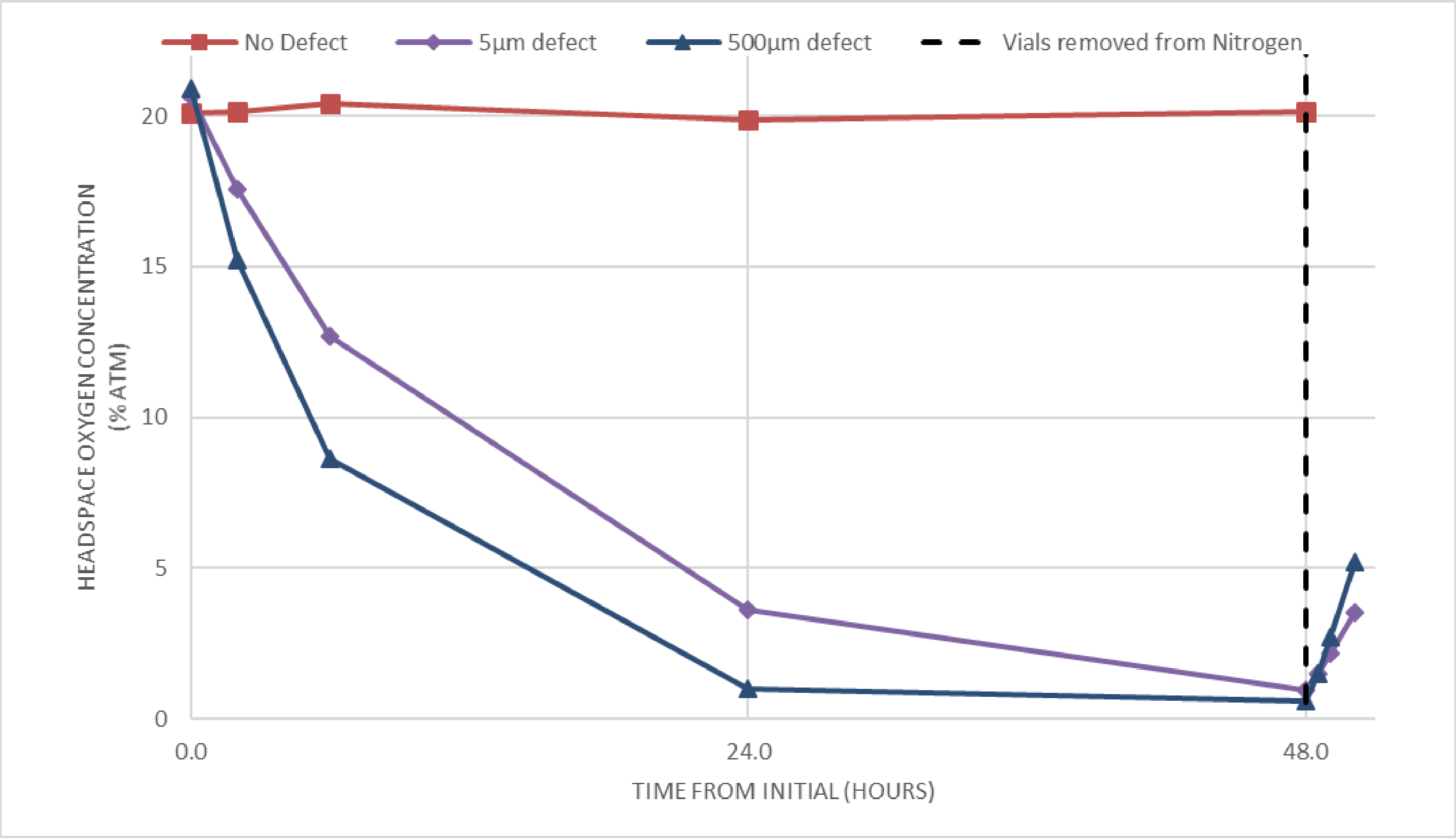
+ Measure initial headspace oxygen concentration
+ Store in challenge conditions (different oxygen concentration than in vial) for a set time
+ Measure final headspace oxygen concentration
+ Compare the change in headspace oxygen for each vial with the maximum allowable oxygen change over the challenge time



Example Data: 10 mL Vial Starting with No Oxygen in Headspace and Stored in Air



Example Data: 2mL Vial Starting with Air Headspace and Stored in Nitrogen



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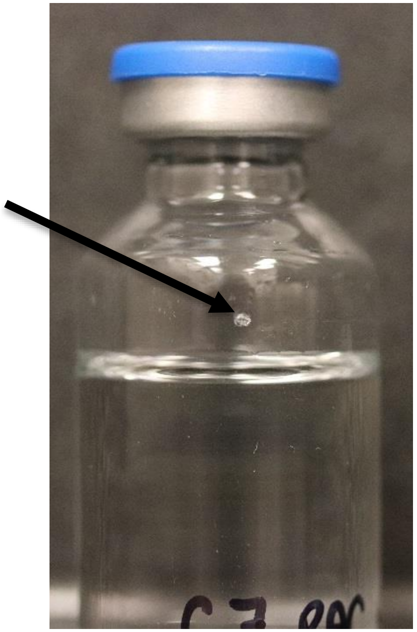
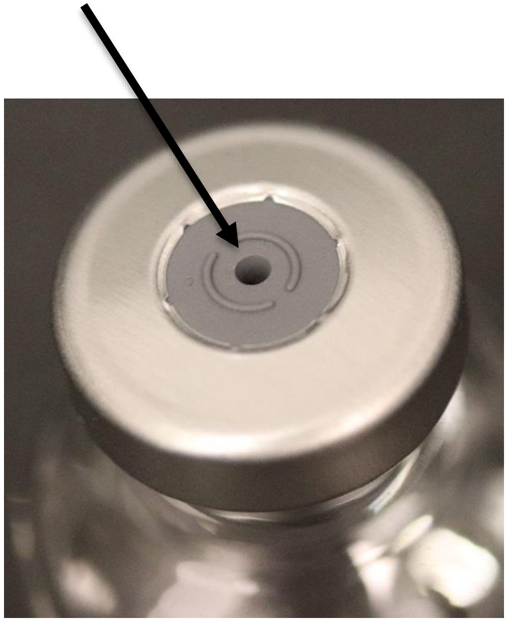
Method Validation of Headspace Oxygen CCIT

- Perform repeated measurements of oxygen standards and test samples for calculating analytical parameters
- Evaluate method with multiple runs by multiple analysts at the minimum and maximum challenge time





Powder on Vial Walls – Low-power Error

Challenge: Some vials, such as lyopholized products, can have powder on the walls that can block the laser

- For one example only approximately half of vials could be measured initially

Solution 1: A "high power seeking" mode

- This allowed about two thirds of the vials to be measured

Solution 2: Use an electrostatic device to shock powder off the sides of the vials combined with the "high power seeking" mode

- 95% of vials could be measured

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Large Defects Positive Controls

Challenge 1: Used 21 gauge needles without luer locks for positive controls. However, when developing a method for a liquid product, found that if the vials tipped over, liquid could block the needle slowing the gas diffusion rate.

Solution 1: Switched to boring stoppers with a 2mm punch for a larger, more robust positive control

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Challenge 2: However for a small container with a small air headspace, the 2mm bored defect changes from low oxygen to 20% oxygen in <30 minutes.

Solution 2: Tested and confirmed 21 gauge no luer lock needle defect remained detectable for > 30 min.

Summary

- USP <1207> outlines multiple different test methods, broken into deterministic and probabilistic categories
- No one test method works for all situations. All methods have different strengths and weaknesses
- Methods continually evolve, with new challenges and expectations

Questions?