Laser-Based Headspace Inspection

Container Closure Applications

PDA Container Closure Workshop
27th of April, 2010
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LIGHTHOUSE

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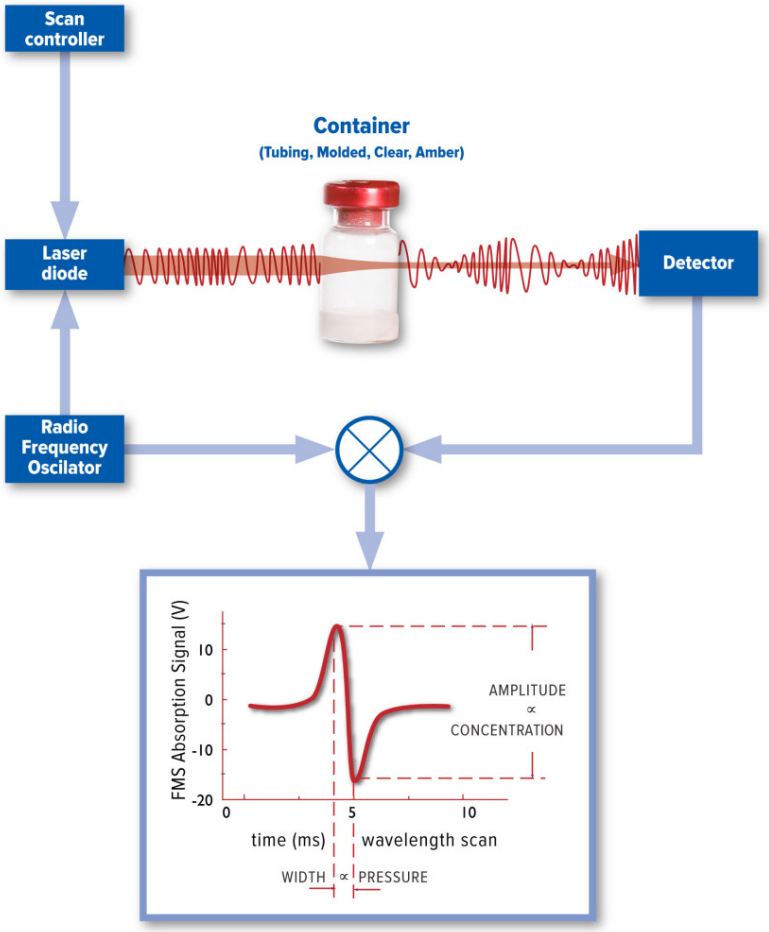
The Science of Pharmaceutical Manufacturing

Agenda

- **Introduction**
  - Method principles for using laser-based headspace analysis to determine container closure
- **Headspace Leak Rate Model**
  - Modeling and understanding headspace dynamics of a leaking container
- **Container Closure Studies**
  - Optimising packaging components and processes
- **Scale up to Manufacturing Inspection Applications**
  - Guaranteeing closure quality for 100% of finished product

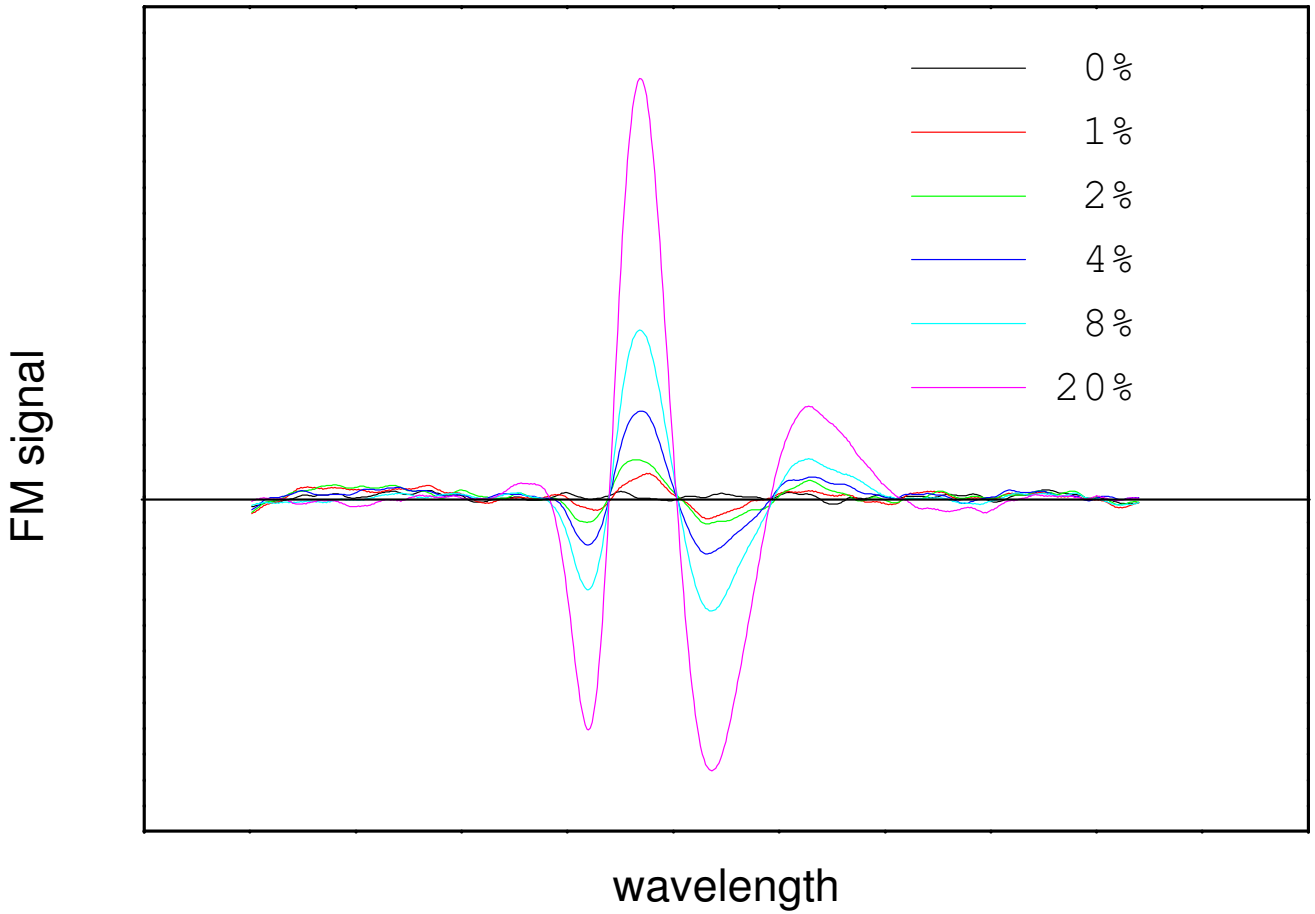
Frequency Modulation Spectroscopy



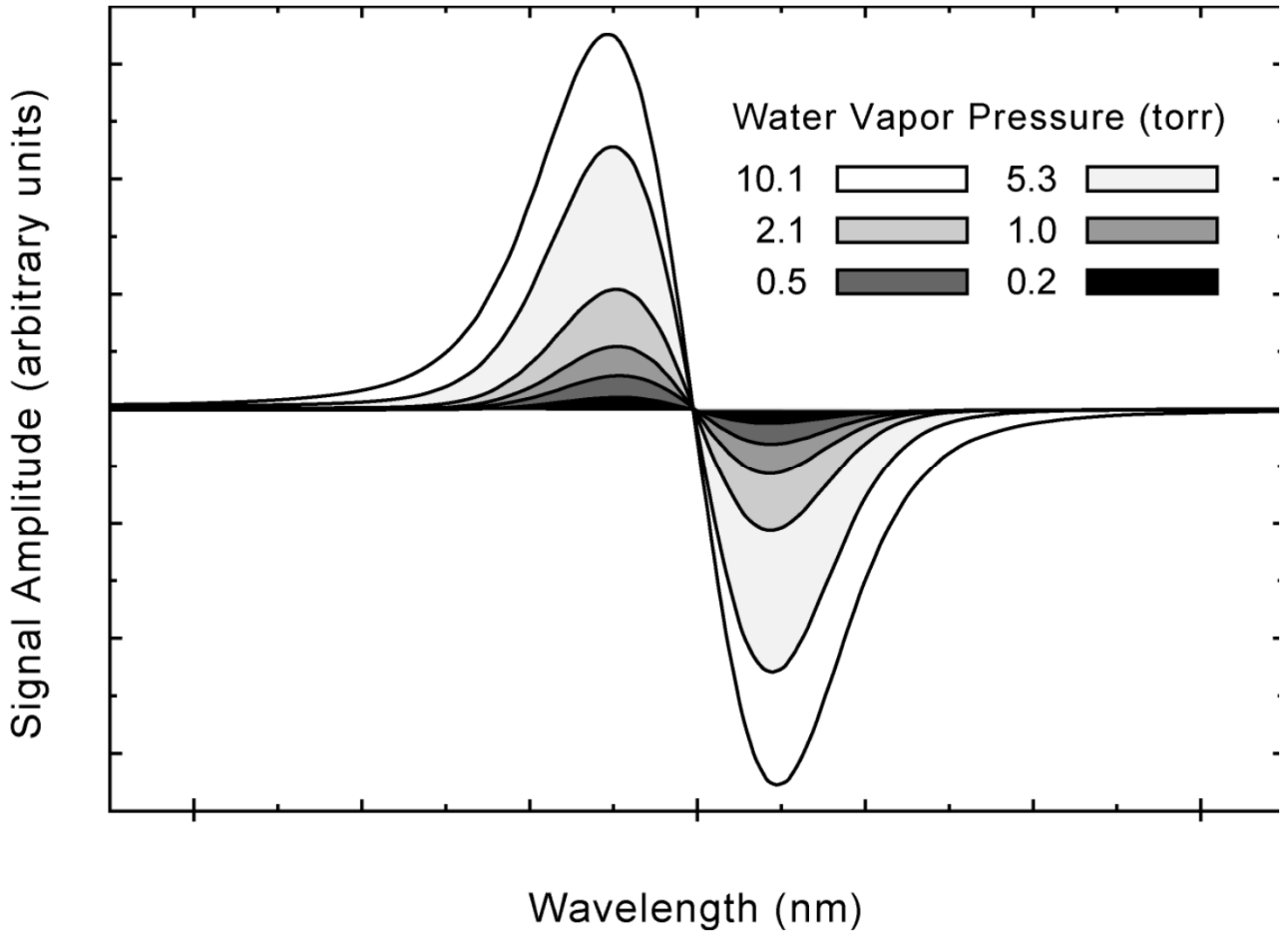
Headspace Method

Modulation techniques result in 10,000x increase in sensitivity compared to first order absorption techniques such as NIR

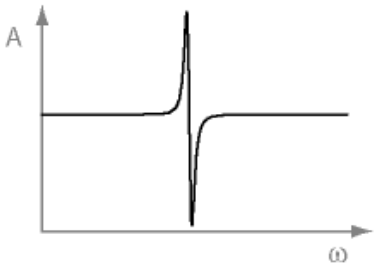
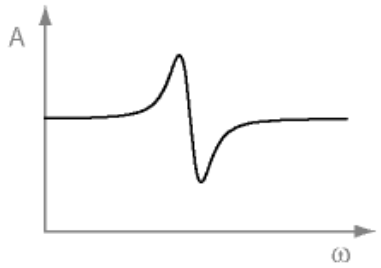
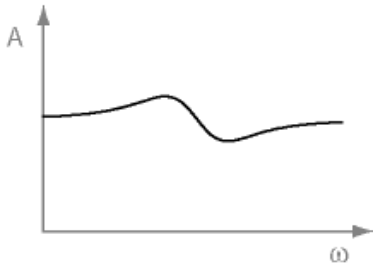
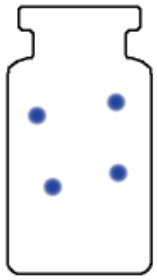
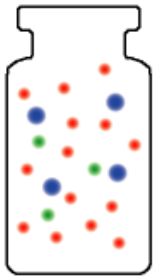
Headspace Oxygen Signal



Headspace Moisture Signal



Headspace Pressure Signal

	Full Vacuum	Partial Vacuum	Partial Vacuum Leaked To Atmosphere
Absorption Signal			
Signal Width $\Gamma_i = \sum \gamma_{i-j} P_j$	$\Gamma_{H_2O} = \gamma_{H_2O-H_2O} P_{H_2O}$	$\Gamma_{H_2O} = \gamma_{H_2O-H_2O} P_{H_2O} + \gamma_{H_2O-N_2} P_{N_2}$	$\Gamma_{H_2O} = \gamma_{H_2O-H_2O} P_{H_2O} + \gamma_{H_2O-N_2} P_{N_2} + \gamma_{H_2O-O_2} P_{O_2}$
Headspace Pressure	 0.5 mbar H_2O 0 mbar N_2 0% O_2	 0.5 mbar H_2O 500 mbar N_2 0% O_2	 0.5 mbar H_2O 900 mbar N_2 10% O_2

Headspace Inspection Platforms

Initially developed with FDA funding

<u>Automated systems:</u>

VISTA/THC: Oxygen, pressure, moisture

VISTA/O: Oxygen

VISTA/P: Pressure, moisture

<u>At-/Off-line systems:</u>

FMS-760: Oxygen

FMS-1400: Pressure/Moisture

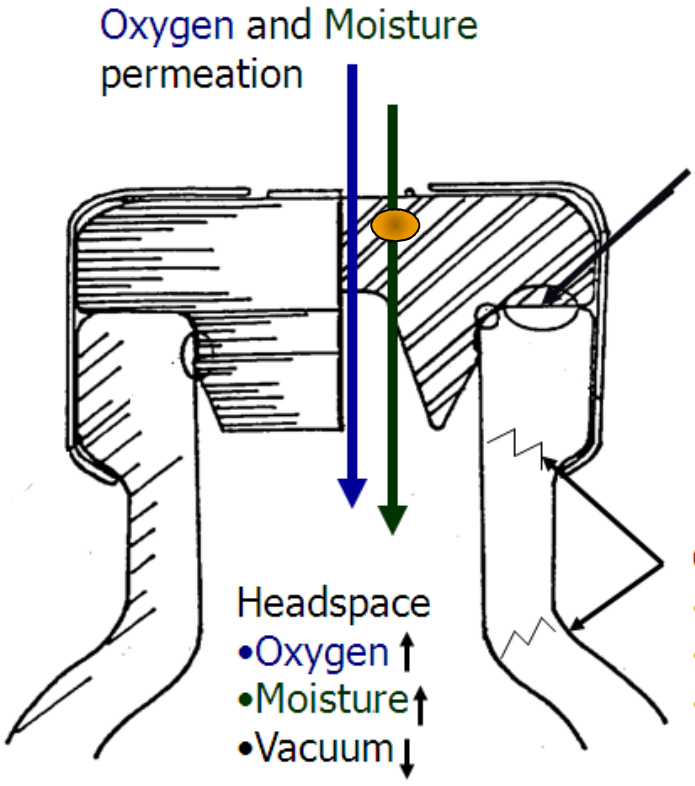
Calibration with traceable standards

- Certified gas mixtures of oxygen and nitrogen
- Certified vacuum levels
- Certified moisture levels
- Patented configuration for continuous machine calibration

Headspace Leak Rate Model

Calculating Headspace Dynamics for a Leaking Container

CCI failures result in gas exchange for modified headspace conditions



- Product on lip
- Improperly seated stopper
- Improperly applied cap
- Bad vial/stopper combination

N_2 H_2O O_2

Cracks in glass
- Incoming glass defect
- Poorly designed machinery
- Rough handling

Headspace Leak Rate Model

- **Allows you to model headspace dynamics due to leaks of all different sizes in product configurations having every kind of initial headspace condition and headspace volume.**

Book Chapter Reference:
"New Inspection Techniques For Aseptic Processing"
by James Veale

Practical Aseptic Processing, Vol 1
Edited by
Jack Lysfjord

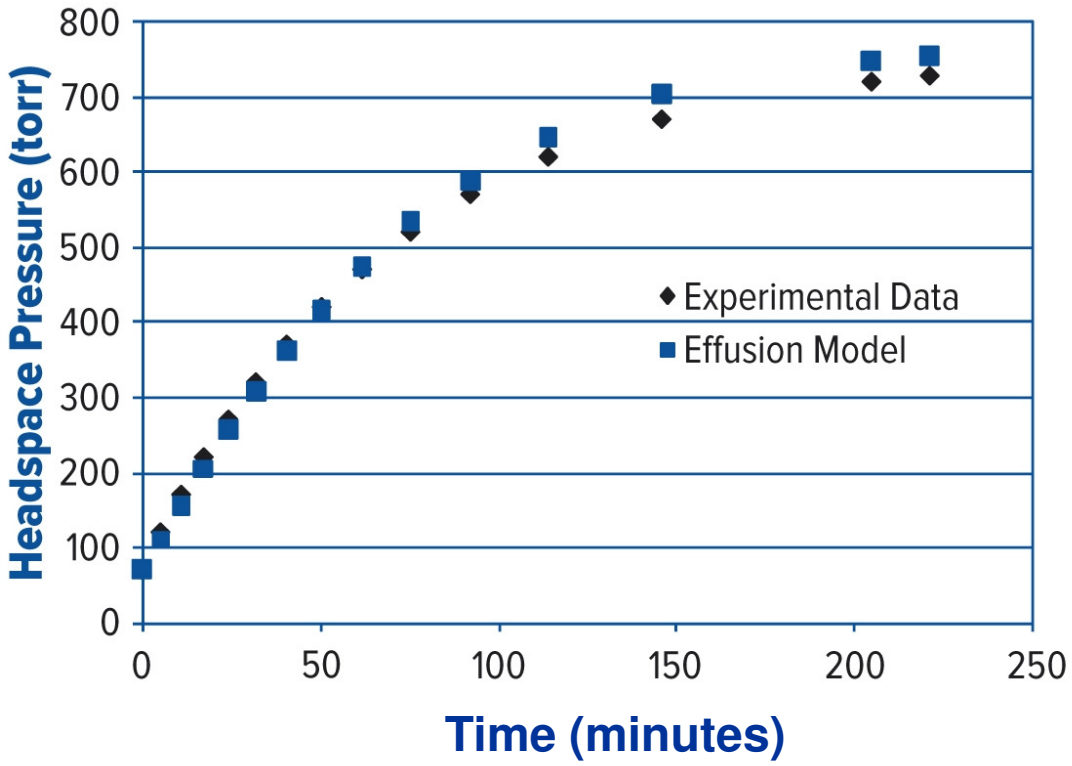
Available at the PDA Bookstore

Pressure rise resulting from a 5 micron hole

Effusion

Initial headspace Conditions at 100mbar of nitrogen

- Headspace leak rate model predicts change in headspace conditions as result of effusion. Model can be run for different container sizes, hole sizes, and initial headspace conditions.

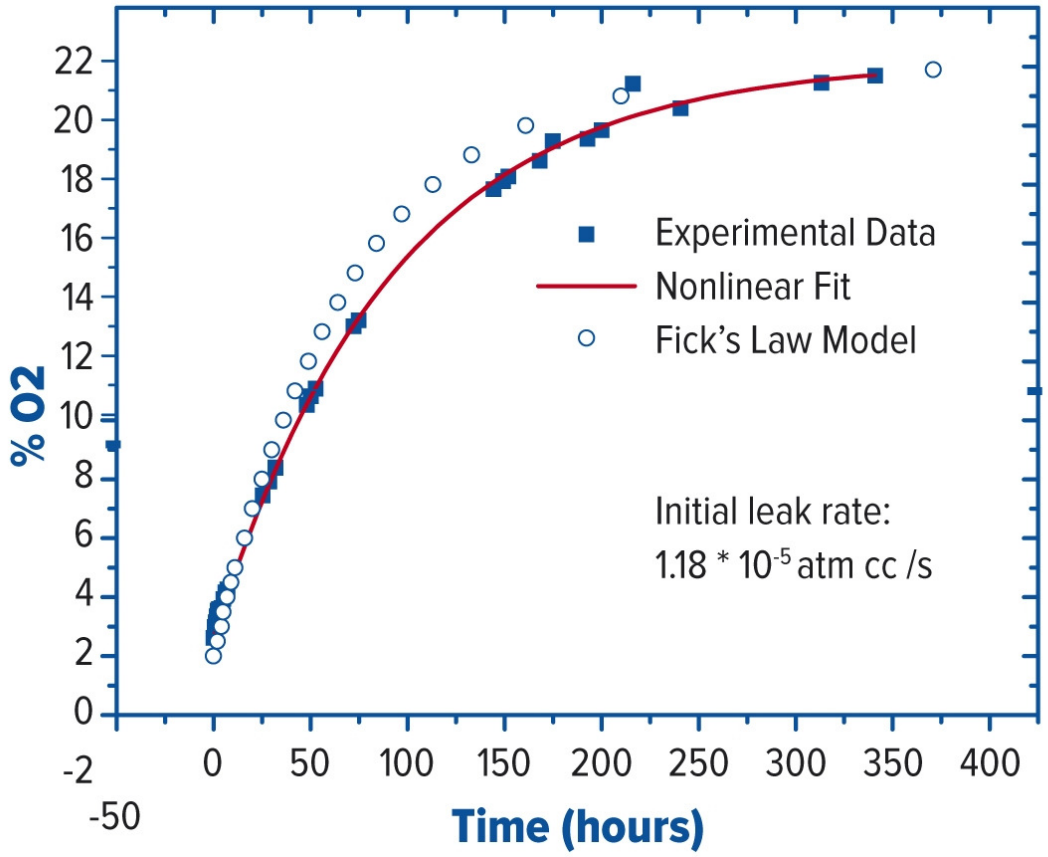


O_2 ingress through a 5 micron hole

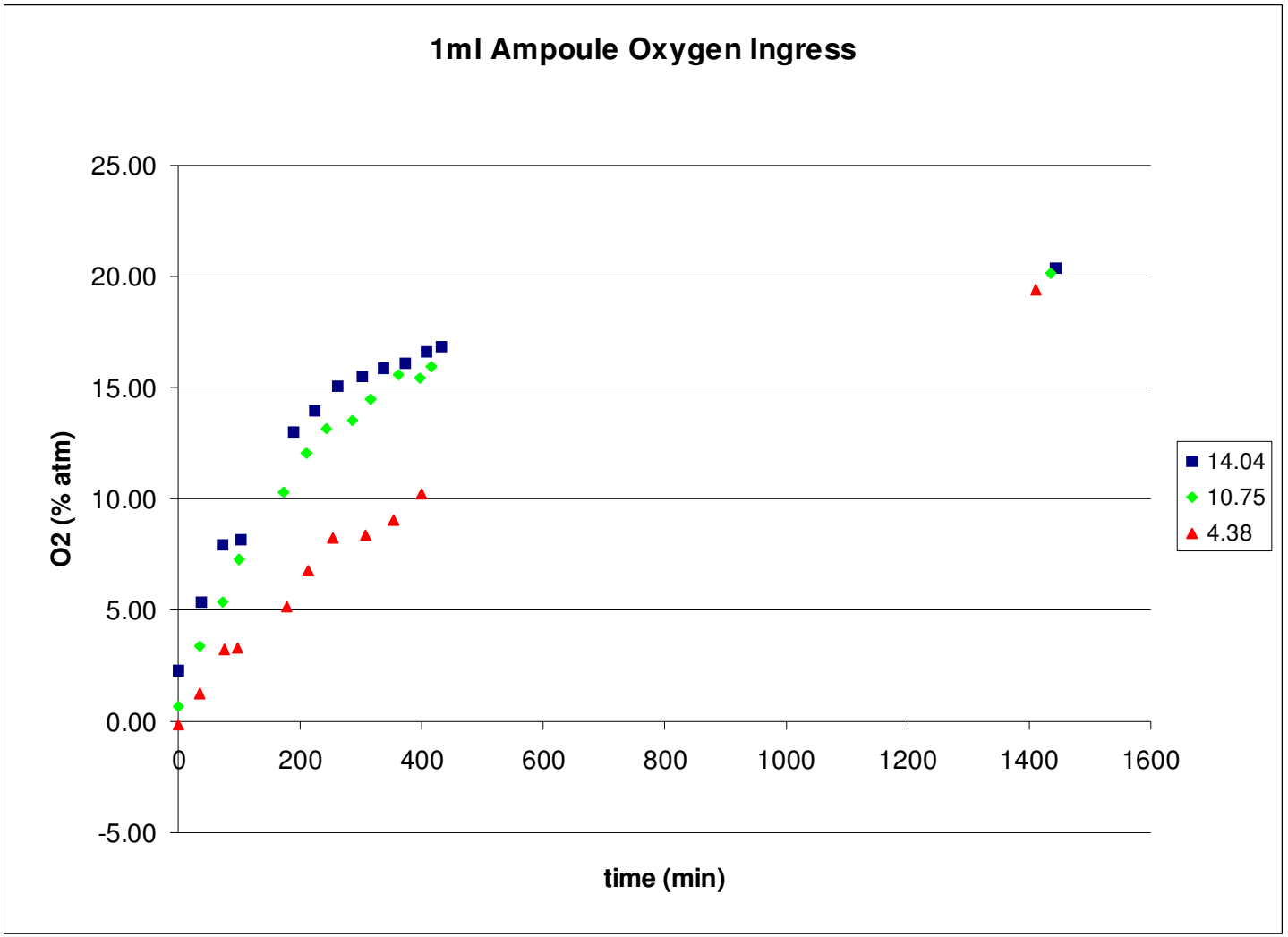
Diffusion

Initial headspace Conditions of 1atm of nitrogen

- Headspace leak rate model predicts change in headspace conditions as result of diffusion. Model can be run for different container sizes, hole sizes, and initial headspace conditions.

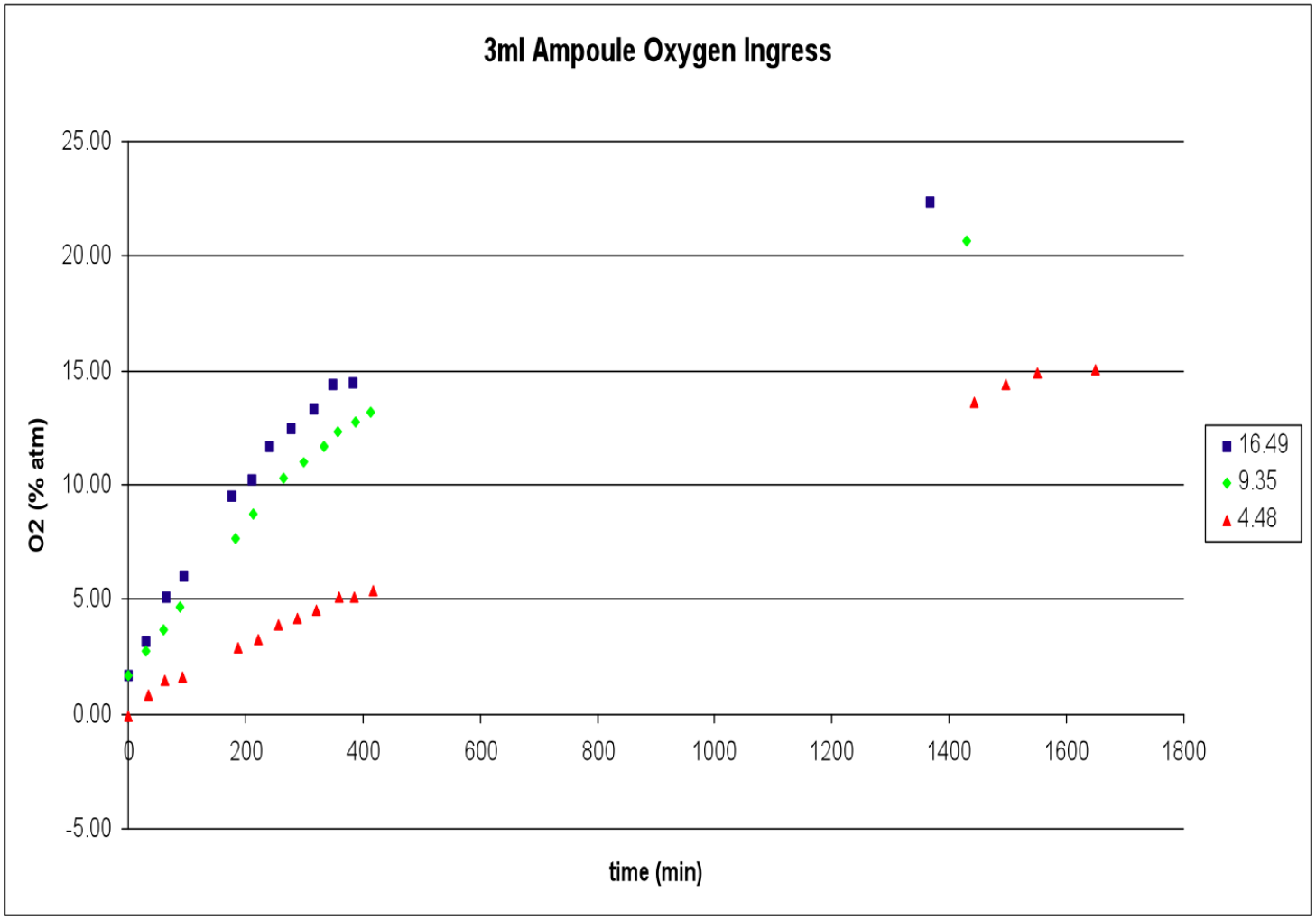


O_2 ingress by diffusion through laser drilled defects



Defect sizes (microns)

O_2 ingress by diffusion through laser drilled defects



Defect sizes (microns)

Experimental data compared to headspace model predictions

Volume (ml)	Hole Size (microns)	Measured vs Theoretical Oxygen Concentration					
		Initial (% atm)		8 hours (% atm)		24 hours (% atm)	
1	4.38	0	0	10.19	10	19.44	18.2
	10.75	0.69	0.69	15.93	17.4	20.12	20.9
	14.04	2.25	2.25	16.85	18.47	20.33	20.9
3	4.48	0	0	5.41	6.36	13.62	14.54
	9.35	1.71	1.71	13.17	11.72	20.63	19.23
	16.49	1.7	1.7	14.45	15.06	22.34	20.9

Comparing different container closure methods for detecting 5, 10, 15 micron leaks

Reference: Dana Guazzo, 'Nondestructive Container Closure Integrity Tests For Prefilled Syringes', PDA conference October, 2008

1. **Vacuum Decay Leak Detection**
2. **High Voltage Leak Detection**
3. **Dye Ingress**
4. **Microbial Ingress**

- **Methods 1 and 2 sensitive down to 5 microns, lower limit for method 2 not defined in this study.**
- **Method 3 reliable down to 10 um.**
- **Method 4 most sensitive but not as reliable as methods 1 and 2.**

Headspace Analysis

⇨ **Sensitive to all leak sizes with the appropriate waiting period.**

⇨ **Identifies permanent and temporary leaks.**

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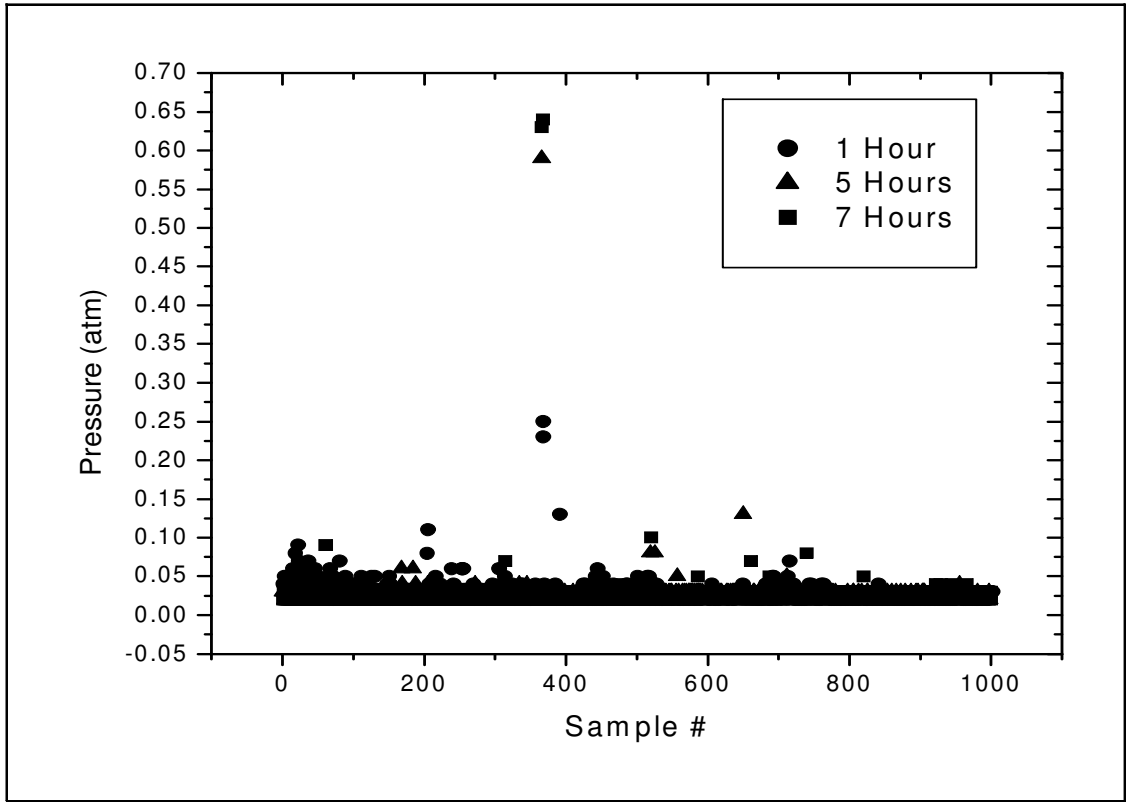
Container Closure Studies

Container Closure Study:
Vacuum Retention Butyl Rubber Stoppers

- **The Problem:**
  - Gain insight into failure rate of packaging components used for lyophilized products

- **The Experiment:**
  - Evacuated 1,000 15cc vials to 0.5 torr
  - Stoppered and removed from chamber
  - Measured pressure at 1, 5 and 7 hour intervals

Vacuum Retention Results



The Results:

One vial found to be leaking (0.10%)

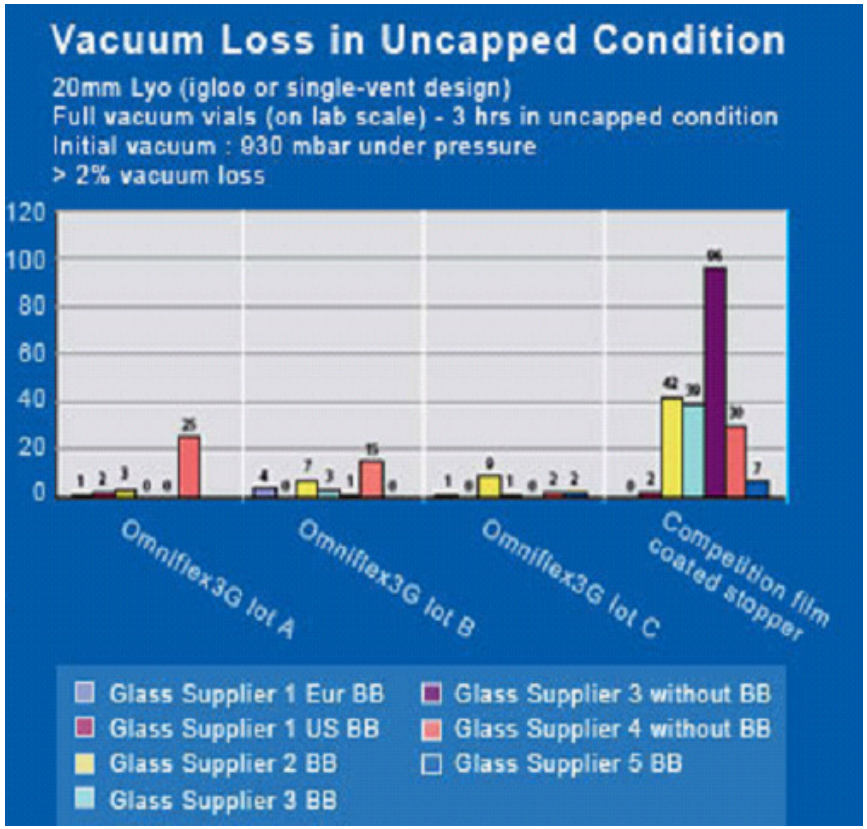
"Stopper Pop-Up" Study in Uncapped Vials Using Barrier-coated Stoppers

Graph shows percentage of vials suffering from vacuum loss after 3 hrs in the uncapped condition.

Why does vacuum loss happen?

Hypothesis:

In the uncapped situation there can be a slight force upwards exerted on the stopper. This causes the stopper to "pop up" resulting in loss of closure and therefore loss of vacuum.



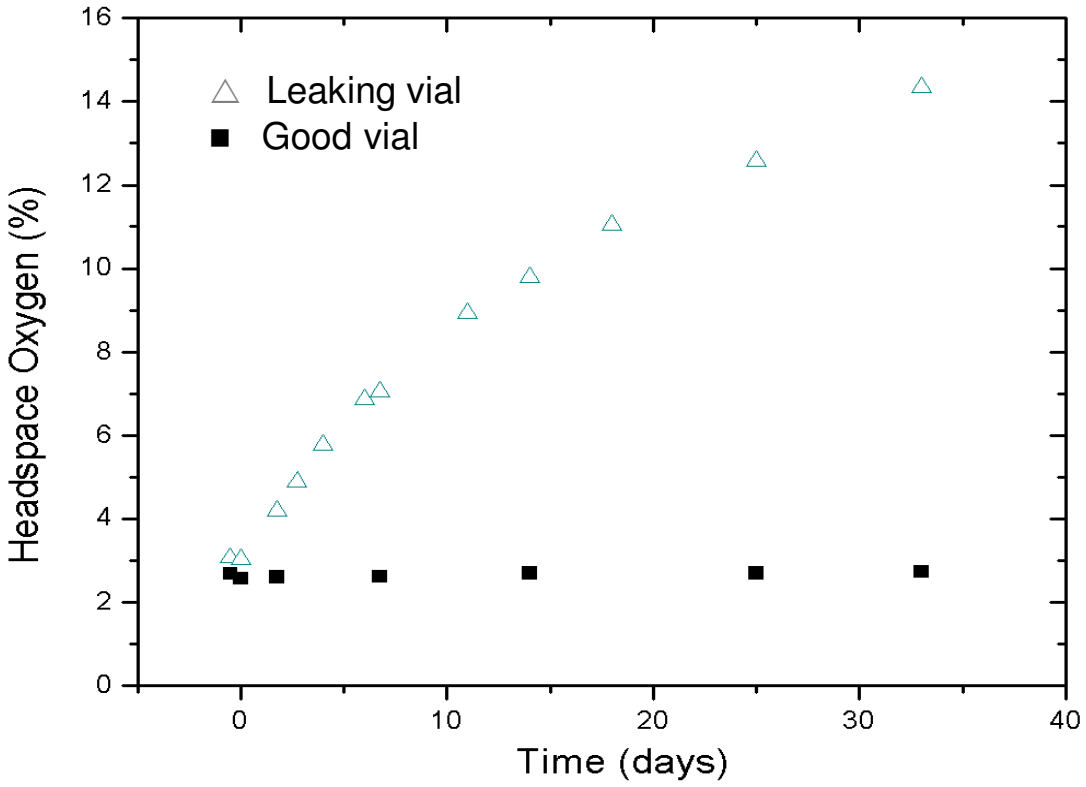
Graph courtesy of Helvoet Pharma Omniflex3G website

Leak detection: Product packaged under one atmosphere of nitrogen

- **The Problem:**
  - Identify leak in a one atm purged headspace container
  - Quantitatively determine the leak rate

- **The Experiment:**
  - Initial 1 atm headspace of 2% oxygen & 98% nitrogen
  - Puncture 10cc vial 5 times with 18G needle
  - Measure oxygen ingress over days

Leak detection: Product packaged under one atmosphere of nitrogen



Results:

Leak rate of $3x10^{-6}$ sccs; correlates to hole size < 0.2 microns

Correlating Leak Rate To Microbial Ingress Probability

Microbial Ingress Probability Function

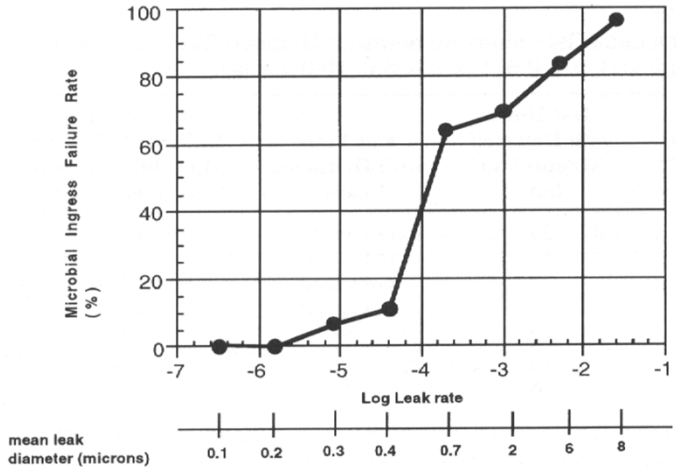


Figure 2—The correlation of microbial failure rate (%) and the mean logarithm of the absolute leak rate and nominal leak diameter for modified SVPs. The absolute leak rate (standard cubic centimeters per second) was determined by mass spectrometry-based helium leak rate detection. Microbial failure was measured by microbial ingress after 24 hour immersion in a bath (37°C) containing 10^8 to 10^{10} *P. diminuta* and *E. coli* organisms/mL and a 13 day, 35°C incubation.

Kirsch, et al, *PDA J Pharm Sci & Technol* 51, 5, 1997 p. 200

Conclusions: Container Closure and Microbial Testing

- **Potential for streamlining microbial testing using container closure measurements - see FDA guidance "Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products"**

- **Validation experiments need to be done correlating headspace container closure measurements to microbial ingress.**

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Packaging Component Studies

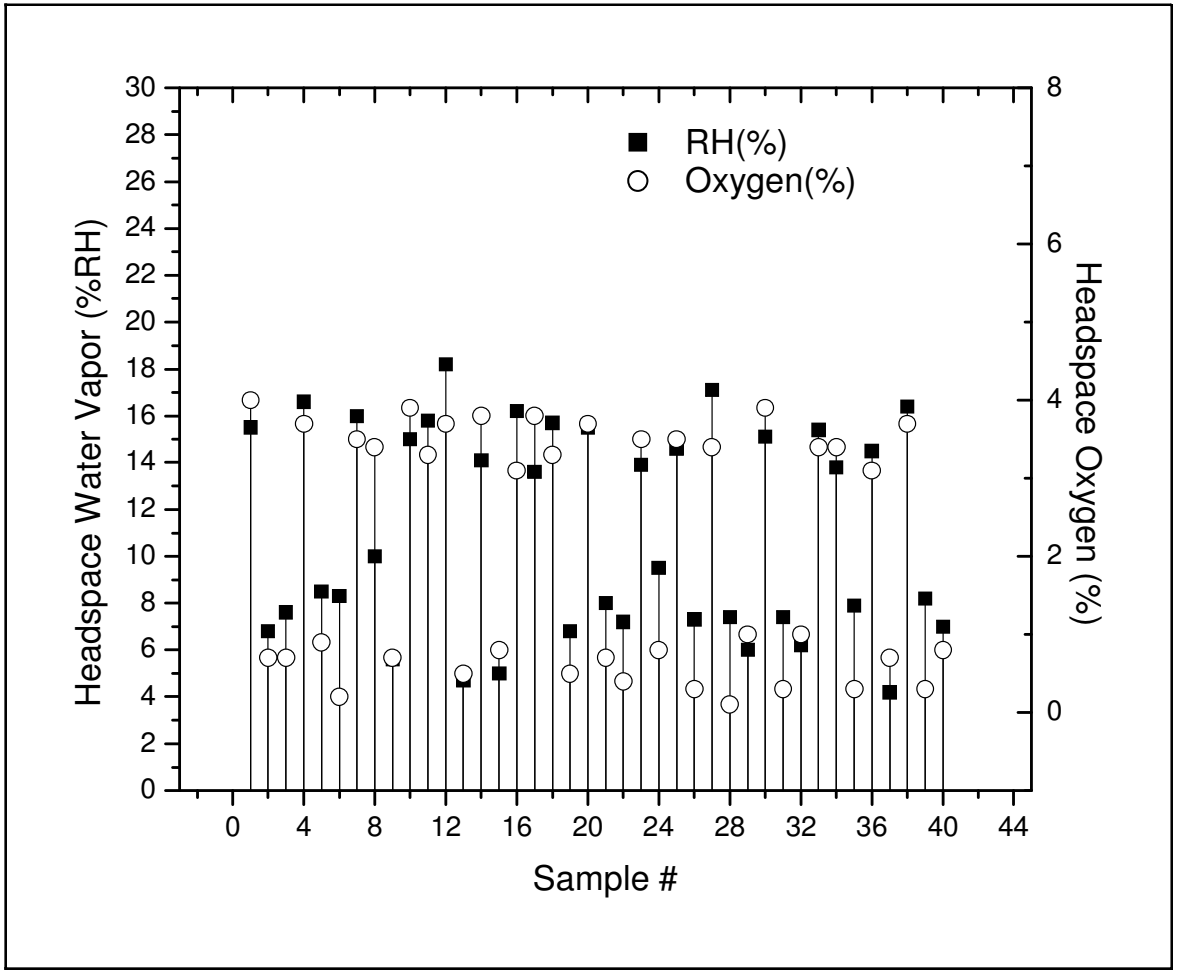
Case Study: End of Shelf Life Stability Study

- **The Objective:**
  - Assess headspace moisture & oxygen levels in lyo formulation samples for end of shelf life stability study application.

✓ **The Experiment:**

- Two blind sets of lyophilized product (recently manufactured and past shelf life) delivered for analysis.
- Measure moisture and oxygen in headspace.

End of Shelf Life Results



Conclusions: End of Shelf Life Stability Study

- **Conclusions:**
  - Old & new lyo product easily distinguishable with headspace measurement.
  - 4x increase of oxygen: permeation through stopper
  - 2x increase of moisture: permeation & desorption of stopper
  - Knowledge of headspace dynamics contributes to better assessment of shelf life
  - LIGHTHOUSE non-destructive measurement enables headspace monitoring over the full shelf life in a single vial

Case Study: Rubber Stopper Processing

- **The Problem:**
  - Assess the effects of temperature conditioning on rubber stoppers for their moisture retention
- **The Experiment:**
  - Vary the baking time for 225 rubber stoppers (9 groups of 25) and closed vials
  - Measure headspace moisture to determine optimum pretreatment conditioning time
- **The Results:**
  - Increased pretreatment time of stoppers resulted in less headspace moisture
  - Storage of vials in elevated temperature environment increased the headspace moisture content

Rubber Stopper Sample Sets

Each sample set represents 25 vials

		Conditioning of Closed Vial		
		Ambient Condition	8 hours at 100°C	24 hours at 100°C
Pre-treatment of the stopper at 100°C	t = 0	Sample A	Sample B	Sample C
	t = 45 min	Sample D	Sample E	Sample F
	t = 90 min	Sample G	Sample H	Sample I

Rubber Stopper Processing Results

		Conditioning of Closed Vial		
		Ambient Condition	8 hours at 100°C	24 hours at 100°C
Pre-treatment of the stopper at 100°C	t = 0	67.1 %	89.0 %	92.0 %
	t = 45 min	31.8 %	72.5 %	83.8 %
	t = 90 min	19.4 %	52.5 %	68.1 %

- Increased pretreatment time of stoppers resulted in less headspace moisture
  - Storage of vials in elevated temperature environment increased the headspace moisture content

Case Study: Rubber Stopper Processing

- **Conclusions:**
  - Longer stopper drying cycles results in less moisture available to outgas into the headspace.
  - Storage of stoppered vials at elevated temperature results in increased headspace moisture levels.
  - What is the effect on the stability of lyophilized product?

Rubber stopper / lyo product study reference

- **"Determination of the Moisture Content of Bromobutyl Rubber Stoppers as a Function of Processing: Implications for the Stability of Lyophilized Products"**

by Merck Research Laboratories, PDA Journal March/April 2003

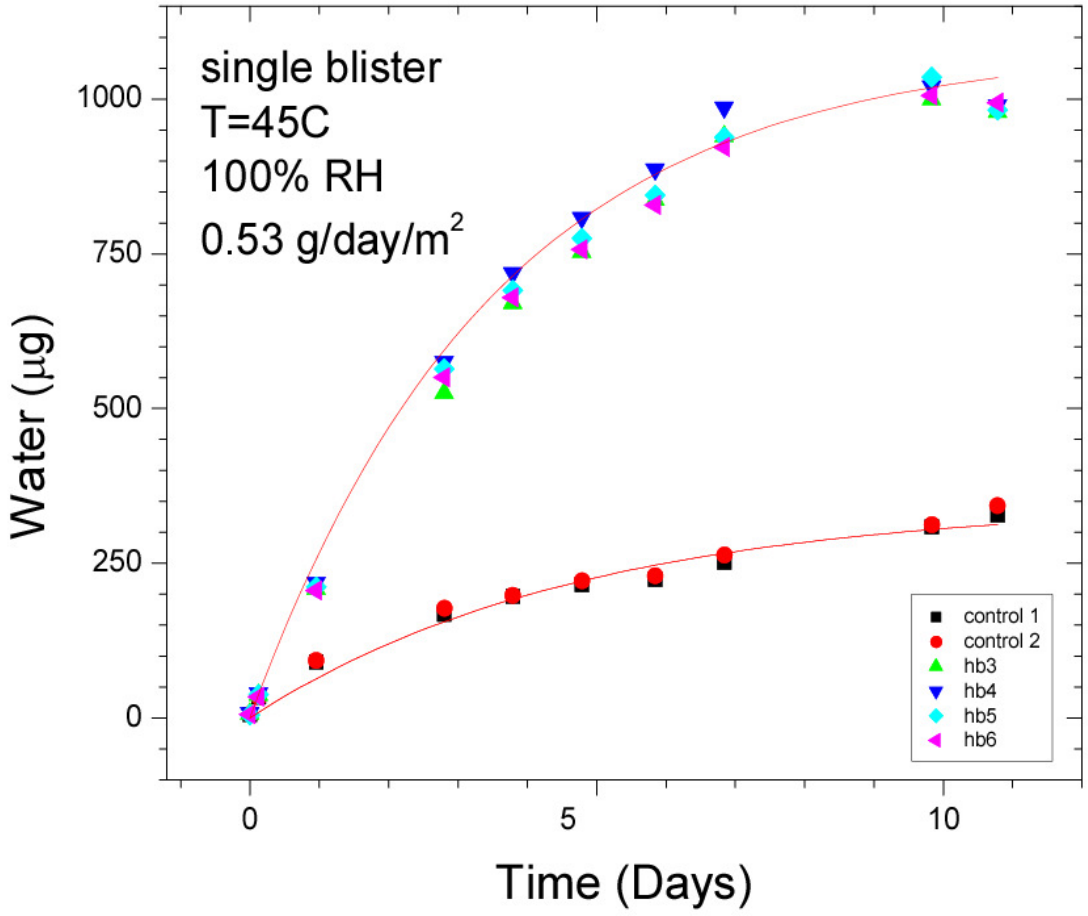
- **"Stoppers for Freeze Drying", presentation by Dr. Wolfgang Dirk, West Pharmaceutical Services**

PDA Stoppers & Elastomers Workshop, 24th of March, 2010

Case Study: Moisture Permeation in a Blister Package System

- **The Problem:**
  - Measure the moisture permeability rate of a blister package system.
- **The Experiment:**
  - Seal a drop of water in a blister package
  - Insert the blister in a dry purged vial and seal the vial
  - Non-destructively measure headspace moisture permeating out of blister into vial headspace

Results: Moisture Permeation in Blisters



Conclusions: Moisture Permeation in Blisters

- **Conclusions:**
  - Monitoring headspace moisture over time with a non-destructive measurement method enables accurate and efficient measurement of the blister water vapor transmission rate.
  - This permeation rate of the real system is more accurate than the permeation rate of the sheet material provided by supplier.
  - Efficient moisture stability studies of oral solid dosage product can be performed as a function of water activity.

Benefits of Rapid Non-Destructive Headspace Method for Container Closure Studies

It is a quantitative physical test for container closure integrity calibrated with traceable standards

- **Ability for multiple measurements on same container.**
  - Trends over time, under different storage conditions.
  - Reduction in sample preparation time & material.
  - Increased accuracy: no sample-to-sample variability.
- **Ability to rapidly perform 100% inspection.**
  - Gives science-based insight into process and component variability, enabling efficient optimisation and validation.
  - Not only identifies sterility risk by identifying leaking containers but also identifies product stability risk in cases of oxygen/moisture sensitivity

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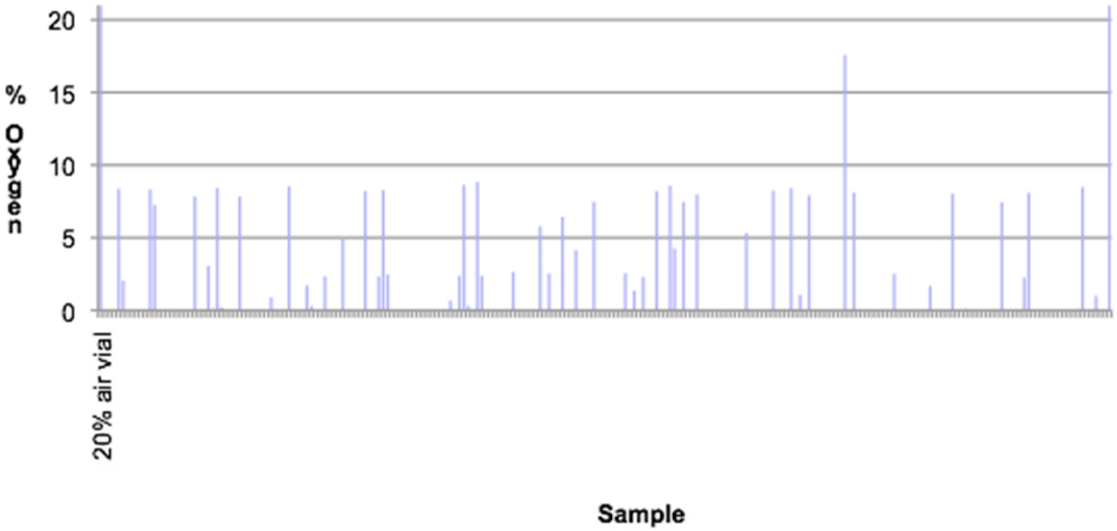
Automated 100% Container Closure Inspection in Manufacturing

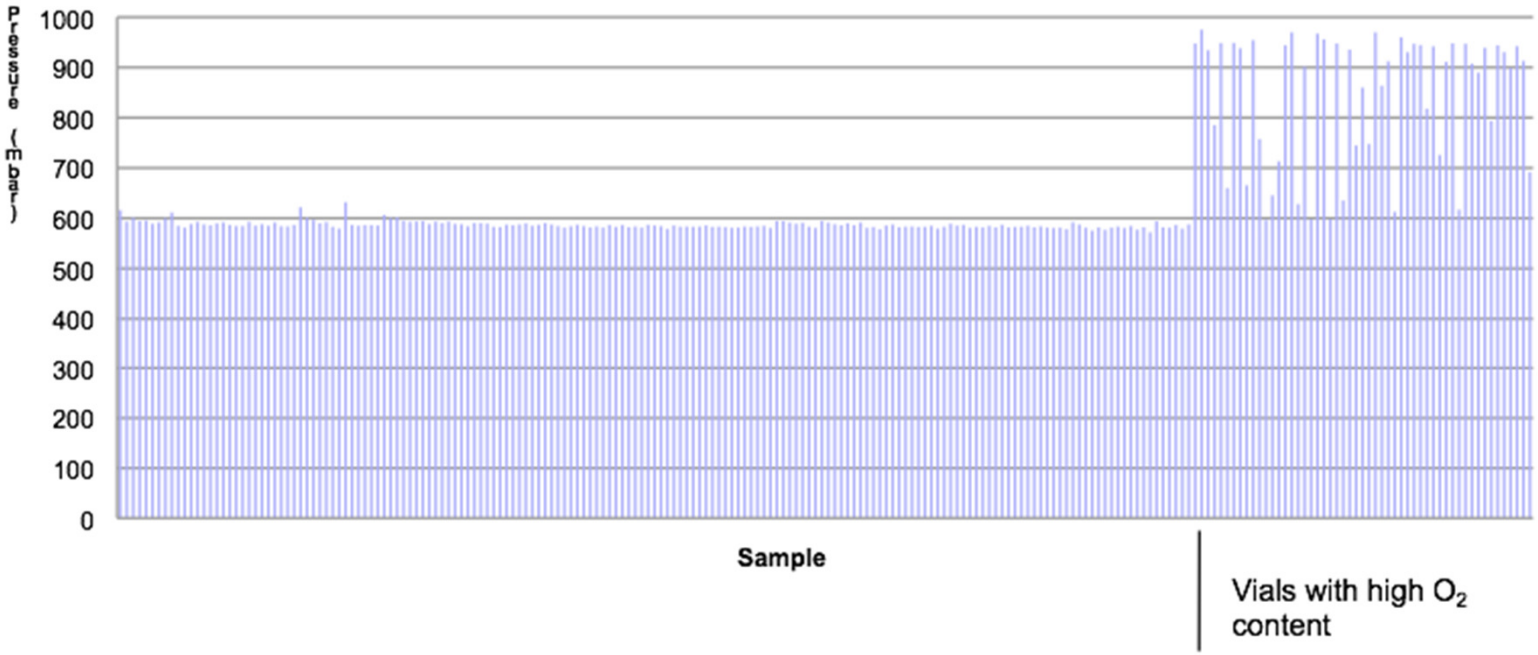
Manufacturing Inspection Case study: Raised stopper issue commercial batch of cytotoxic lyo

- Troubleshoot a lyophilized product batch of 11,000 vials packaged at 600mbar
- A suspected raised stopper issue motivated 100% inspection
- Total Headspace Characterization™ was performed.



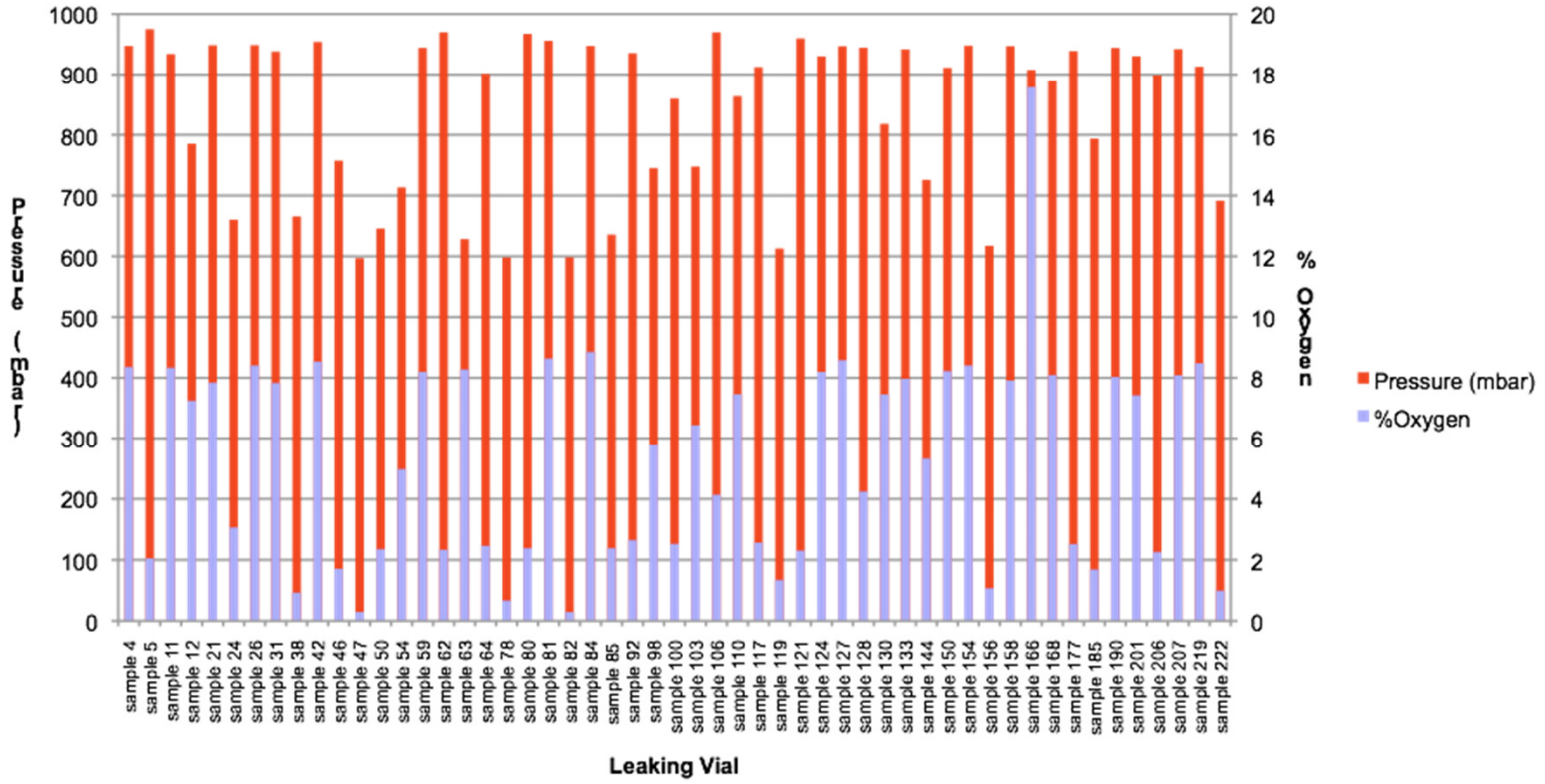
Headspace oxygen analysis showed ~25% of the vials had raised Oxygen levels due to a leak occurring in air

Manufacturing Inspection Case study:
Raised stopper issue commercial batch of cytotoxic lyo



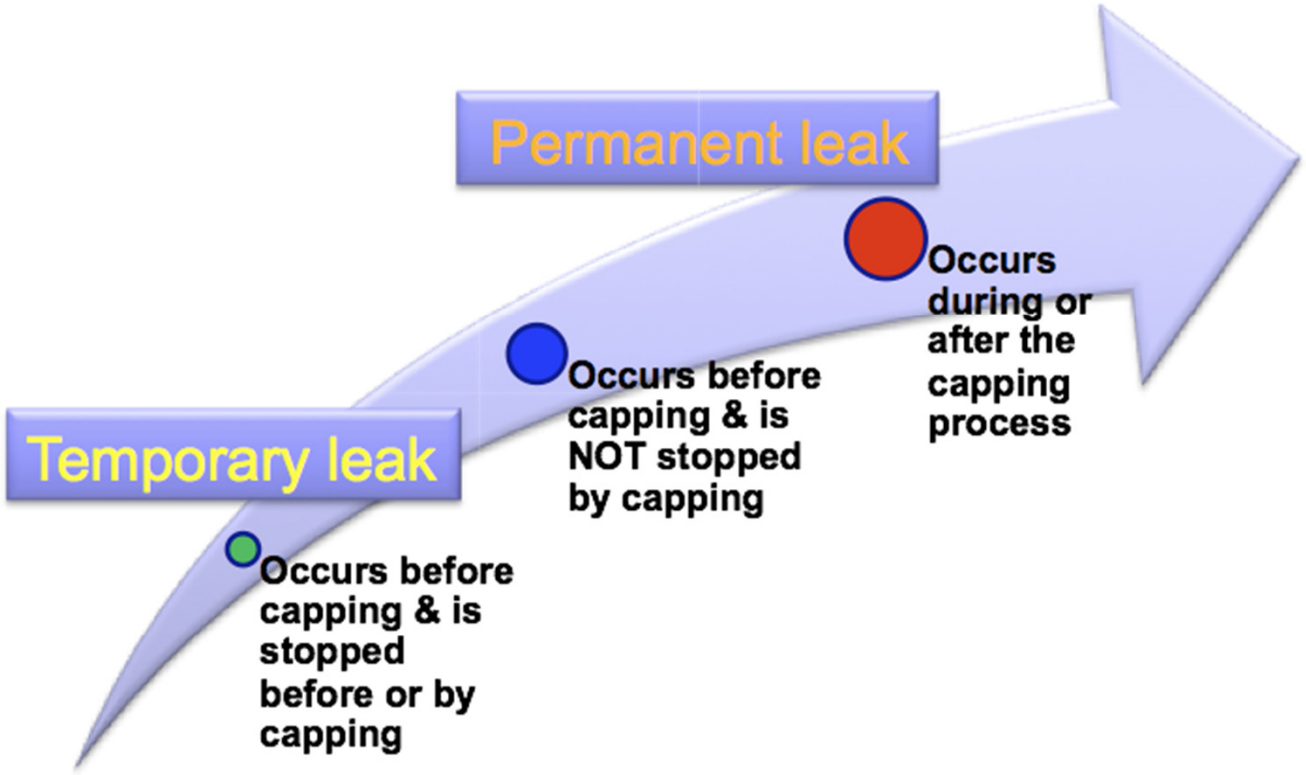
Vials with raised O_2 levels showed partial or full vacuum loss

Manufacturing Inspection Case study: Raised stopper issue commercial batch of cytotoxic lyo



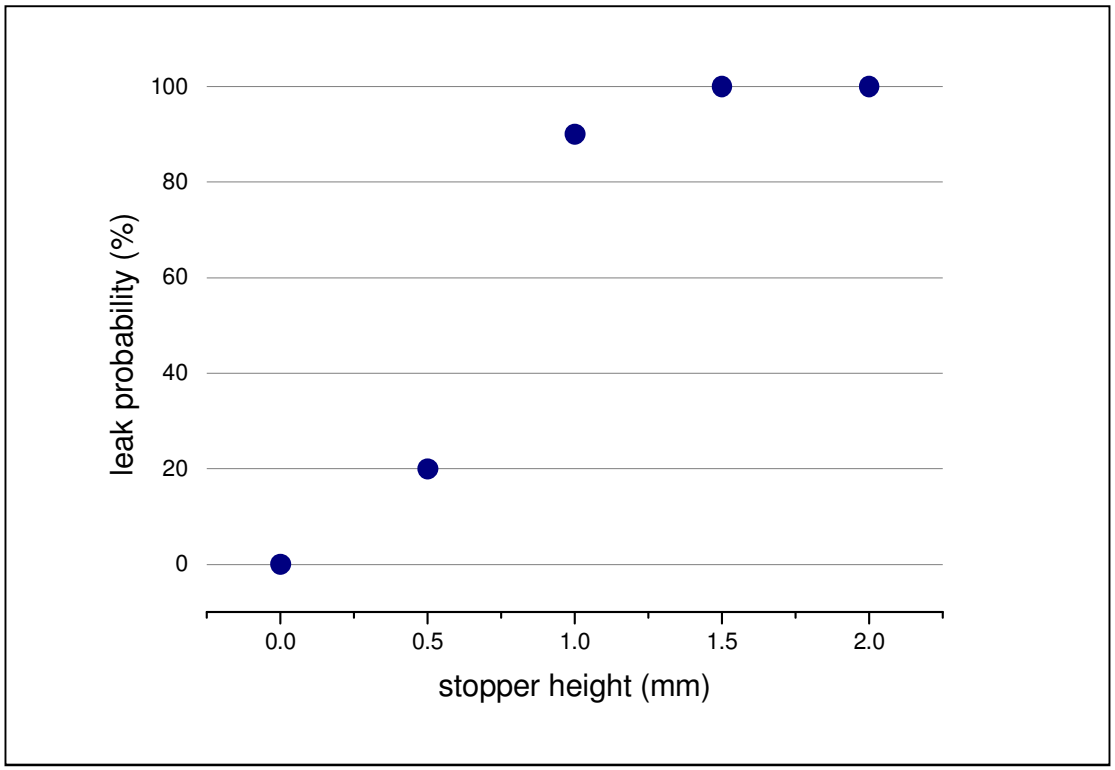
Correlating O2 and pressure measurements identified the general process issue (raised stopper coming out of the freeze dryer) and individual types of leak (temporary or permanent)

Container leak scenarios



Headspace inspection at a later stage (after capping) will identify all containers which have lost of integrity

Probability of gas ingress as a function of raised stopper height



- Even slightly raised stoppers (0.5 mm) have some probability of leaking
- Headspace inspection identifies leaks at all raised stopper heights.

Case Study Conclusions

- 100% laser-based headspace inspection after capping identified all vials suffering from container closure issues due to raised stoppers in the capping area.
- In contrast to visual methods, headspace inspection directly measures loss of closure.
- Such an inspection process robustly accomplishes the objectives of the Revised Annex 1 with respect to ensuring good container closure and therefore maintenance of sterility.

Headspace analysis…

- …can be a powerful analytical tool for investigating container closure.
- ……uses rapid non-destructive measurements enabling efficient development studies in terms of time and material.
- …physically characterises the headspace gases which not only identifies leaks but also gives insight into stability risks to the formulation.
- …scales for automated 100% container closure inspection in manufacturing guaranteeing closure quality of finished product.

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Thank you!