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# Laser-Based Headspace Inspection

## Packaging Development Applications

PDA Container Closure Workshop
29th of April, 2009
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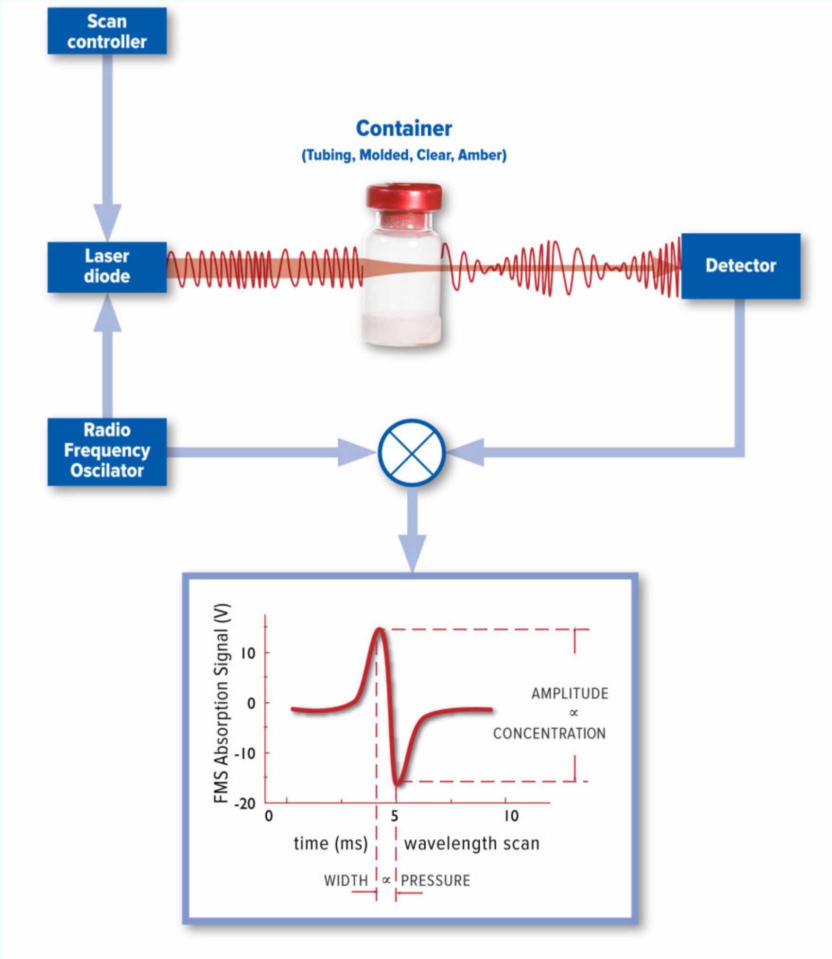
LIGHTHOUSE

The Science of Pharmaceutical Manufacturing

# Agenda

- ✓ **Introduction**
  - Method principle
- ✓ **Headspace Leak Rate Model**
  - Modeling headspace dynamics of a leaking container
- ✓ **Container Closure Studies**
- ✓ **Packaging Component Studies**

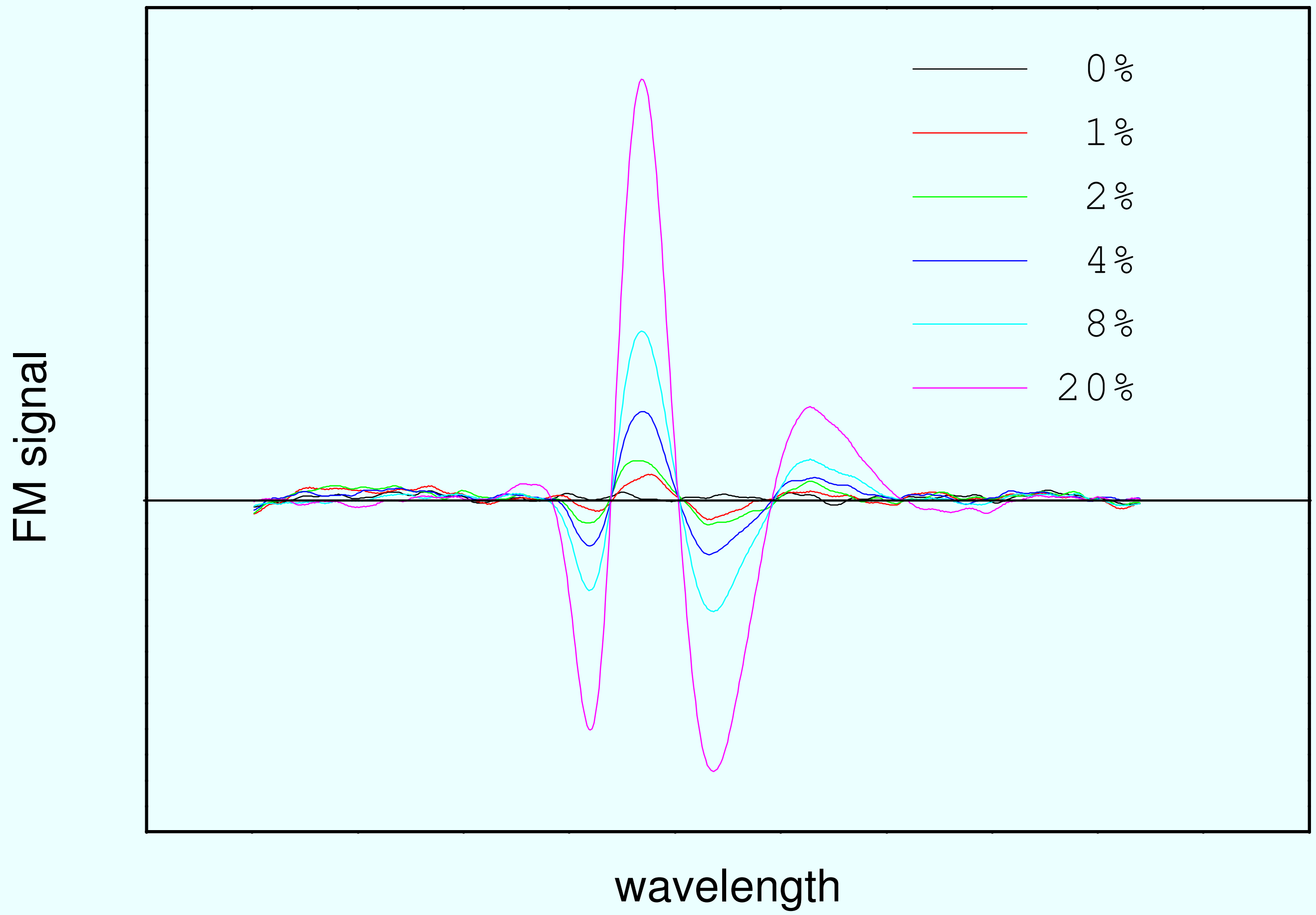
# Frequency Modulation Spectroscopy



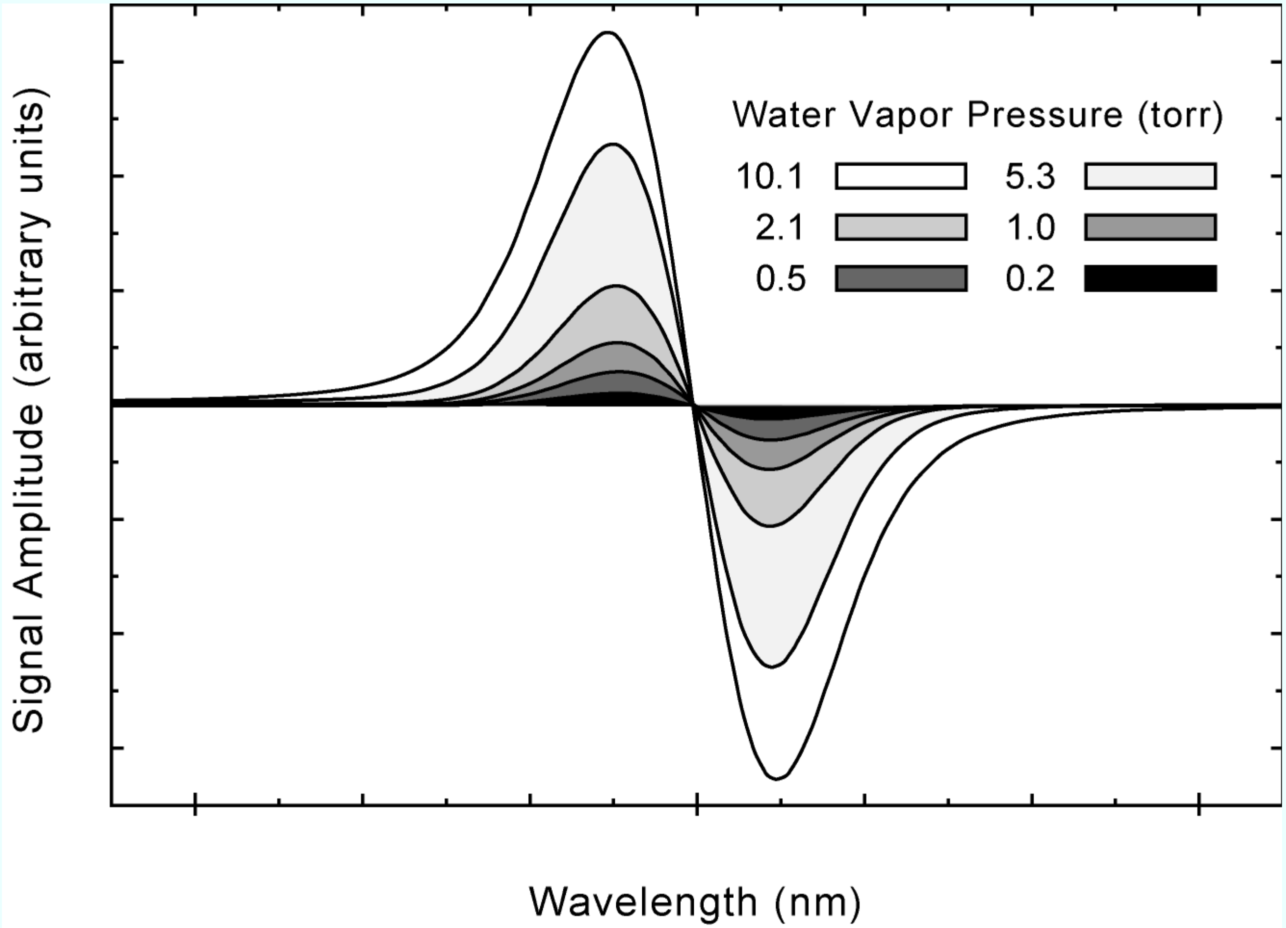

**Headspace Method**

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

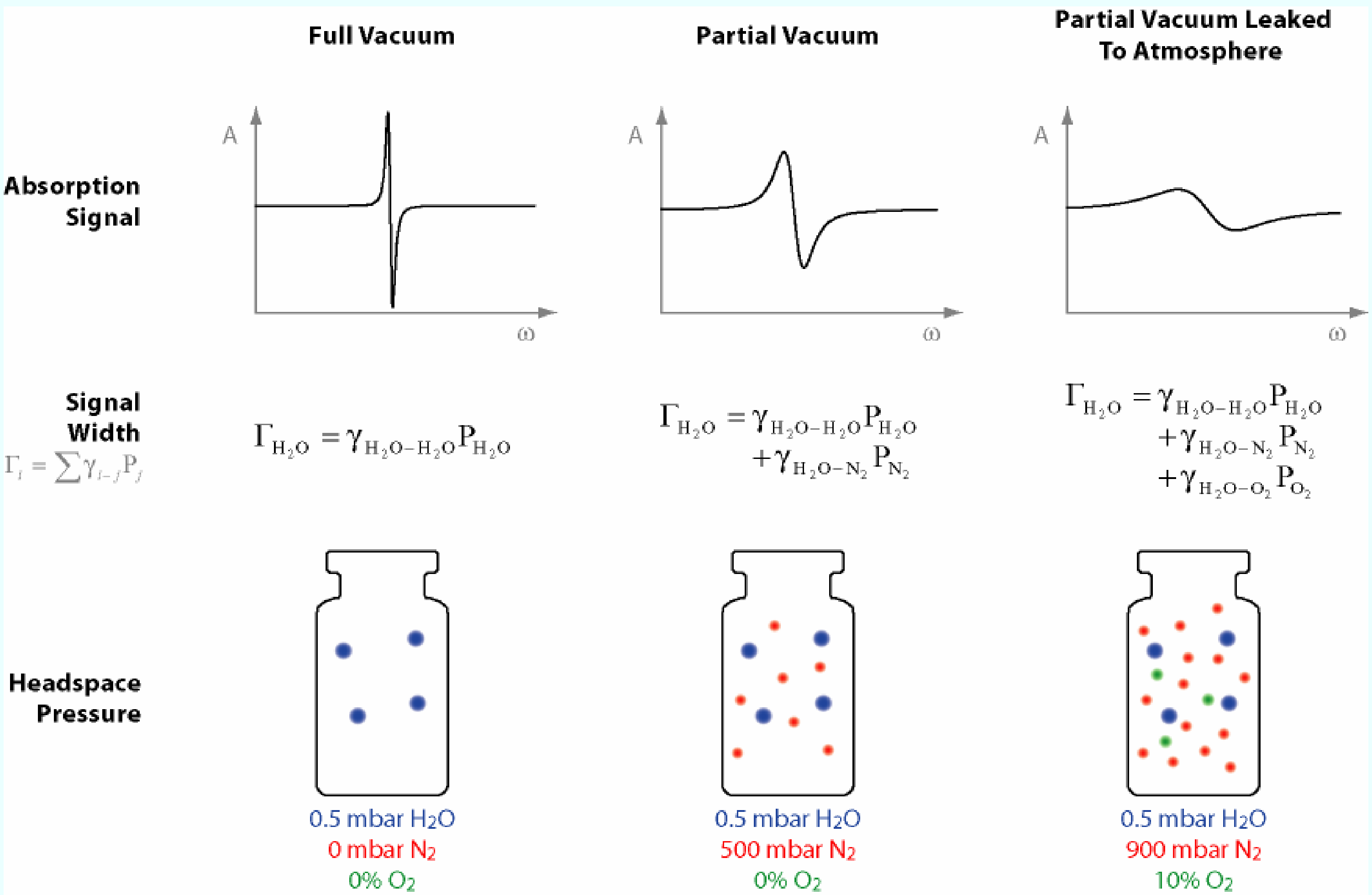
# Headspace Oxygen Signal



# Headspace Moisture Signal



# Headspace Pressure Signal



# LIGHTHOUSE Headspace Inspection Platforms

## Initially developed with FDA funding

Automated systems:

VISTA/THC:  Oxygen, pressure, moisture

VISTA/O:  Oxygen

VISTA/P:  Pressure, moisture

At-/Off-line systems:

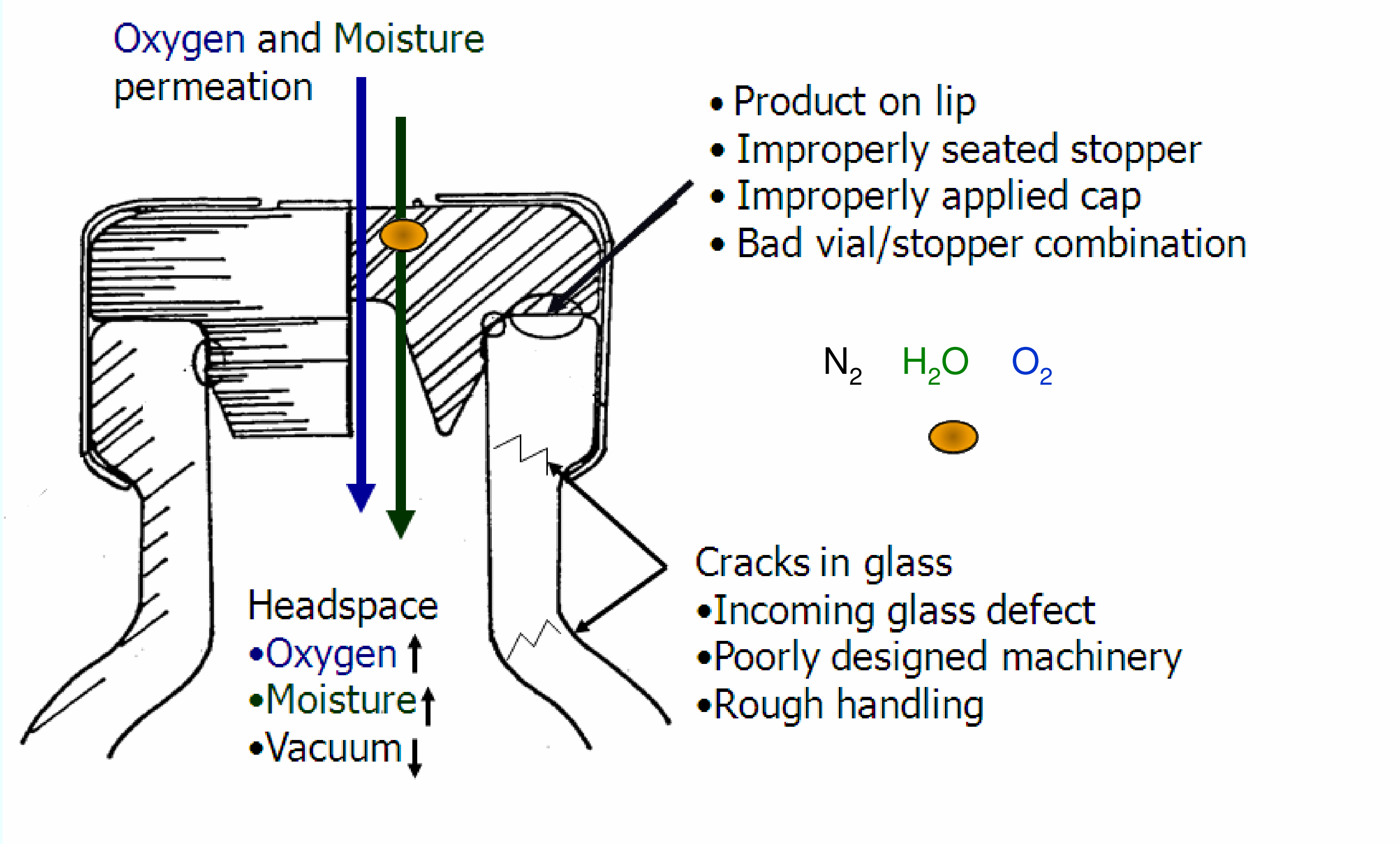
FMS-760:  Oxygen

FMS-1400:  Pressure/Moisture

# Headspace Leak Rate Model

## Calculating Headspace Dynamics for a Leaking Container

# CCI failures result in gas exchange for modified headspace conditions

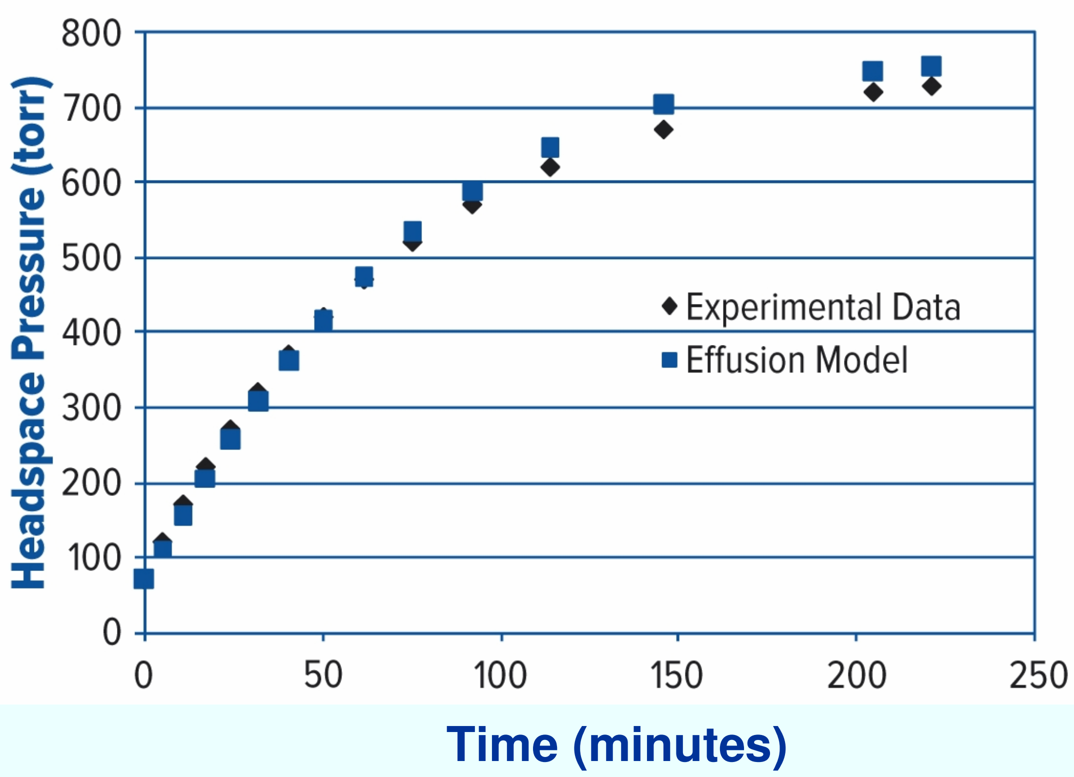


# Pressure rise resulting from a 5 micron hole

Effusion

*Initial headspace Conditions at 100mbar of nitrogen*

- LIGHTHOUSE 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.



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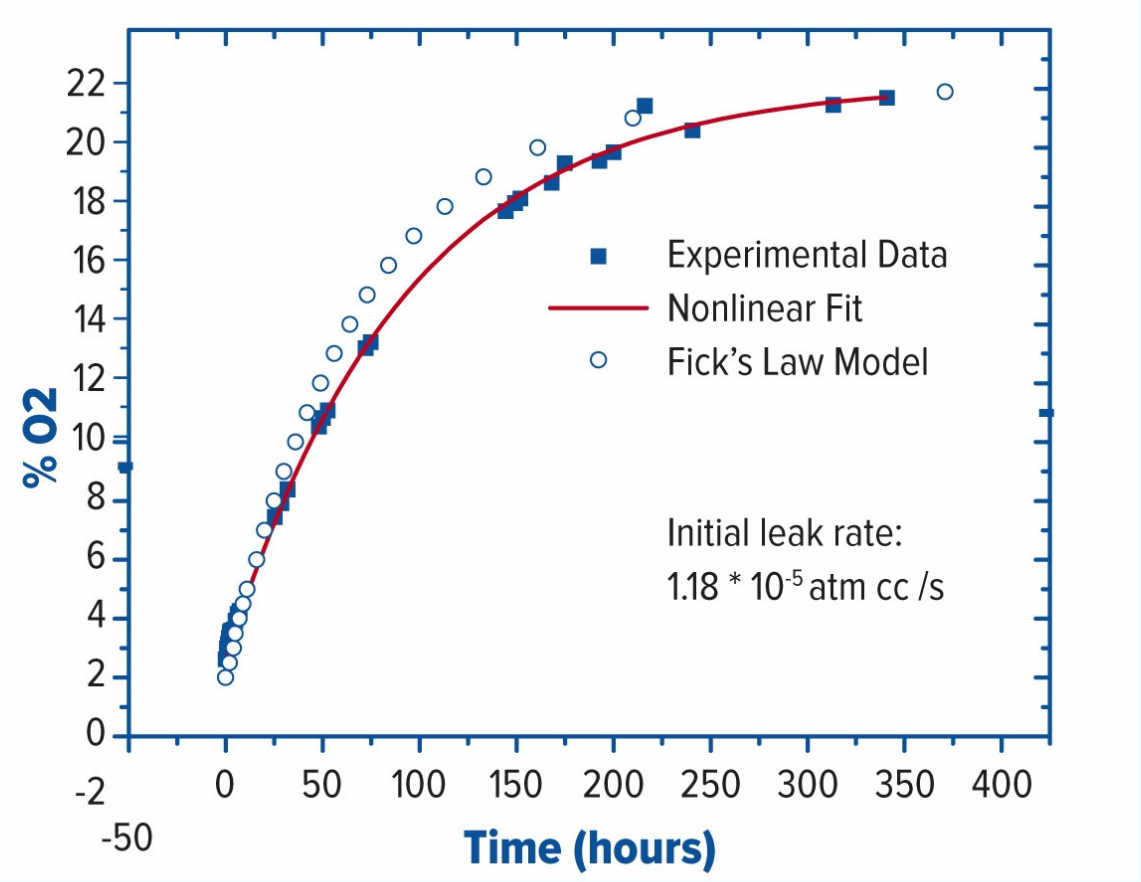
# $O_2$ ingress through a 50 micron hole

Diffusion

*Initial headspace Conditions of 1atm of nitrogen*

- LIGHTHOUSE 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.




# Container Closure Studies

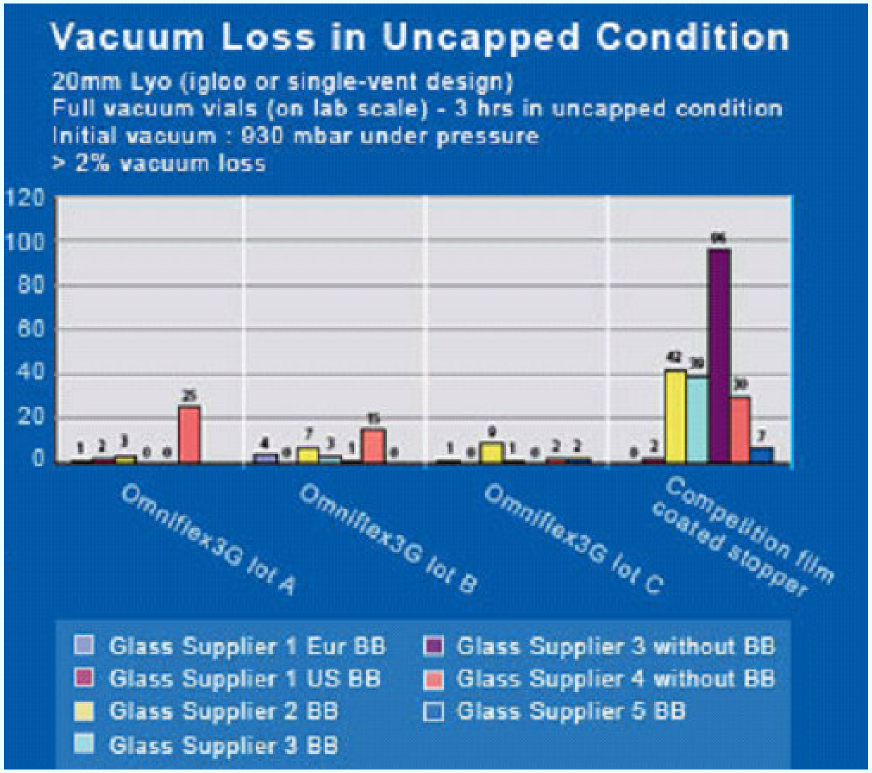
# "Stopper Pop-Up" Study in Uncapped Vials Using Barrier-coated Stoppers

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

# Container Closure Study:
## 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

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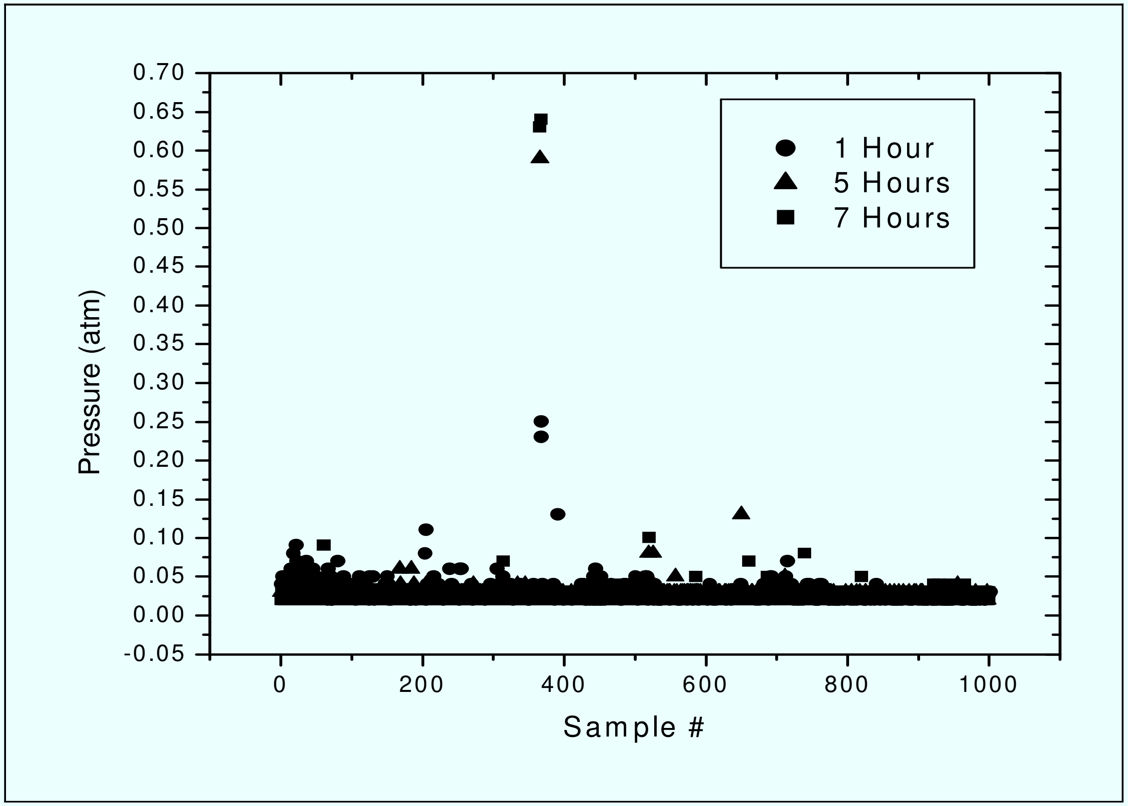
# Case Study Results




**The Results:**

Only one vial found to be leaking (0.10%)

# Container Closure Case Study:
## Lyophilized Product Under Vacuum

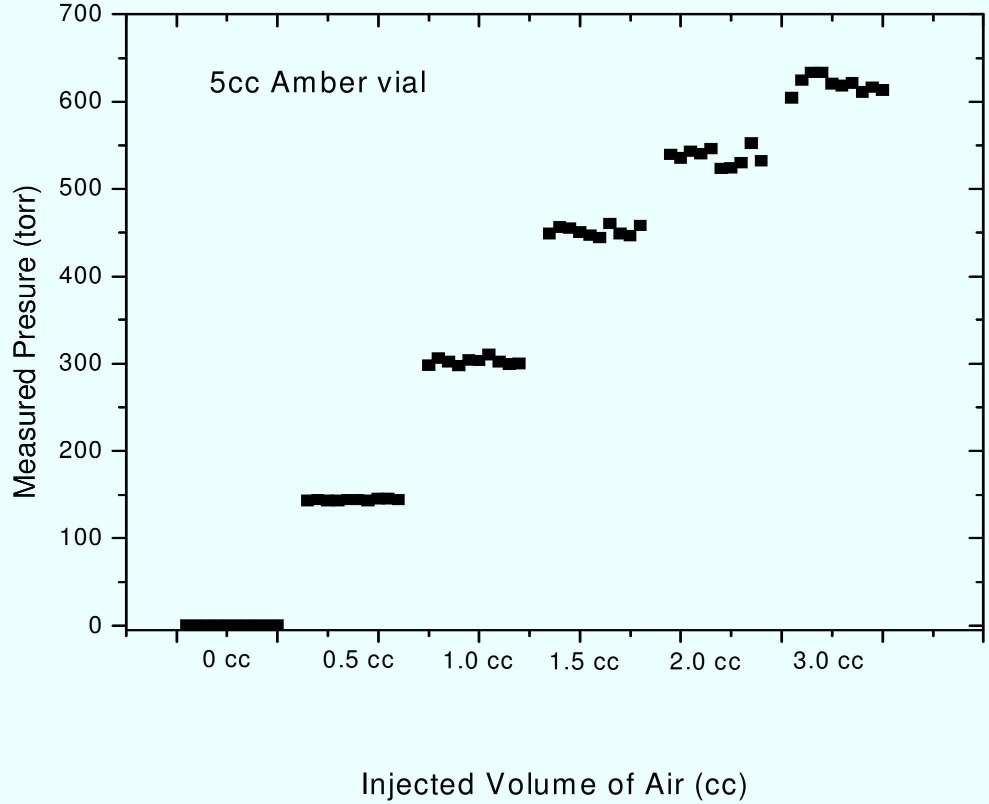
✓ **The Problem:**

- Assess headspace pressure measurement for detecting leaks in lyophilized product

✓ **The Experiment:**

- Lyophilized product sealed under vacuum in 5cc amber glass vial
- Injected increasing volumes of air to simulate leak
- Measured pressure 10 times for each injected volume

# Case Study Results




**The Results:**

Pressure measurement able to discriminate over wide pressure range

# Case Study: Correlating Container Closure Measurements to Microbial Ingress

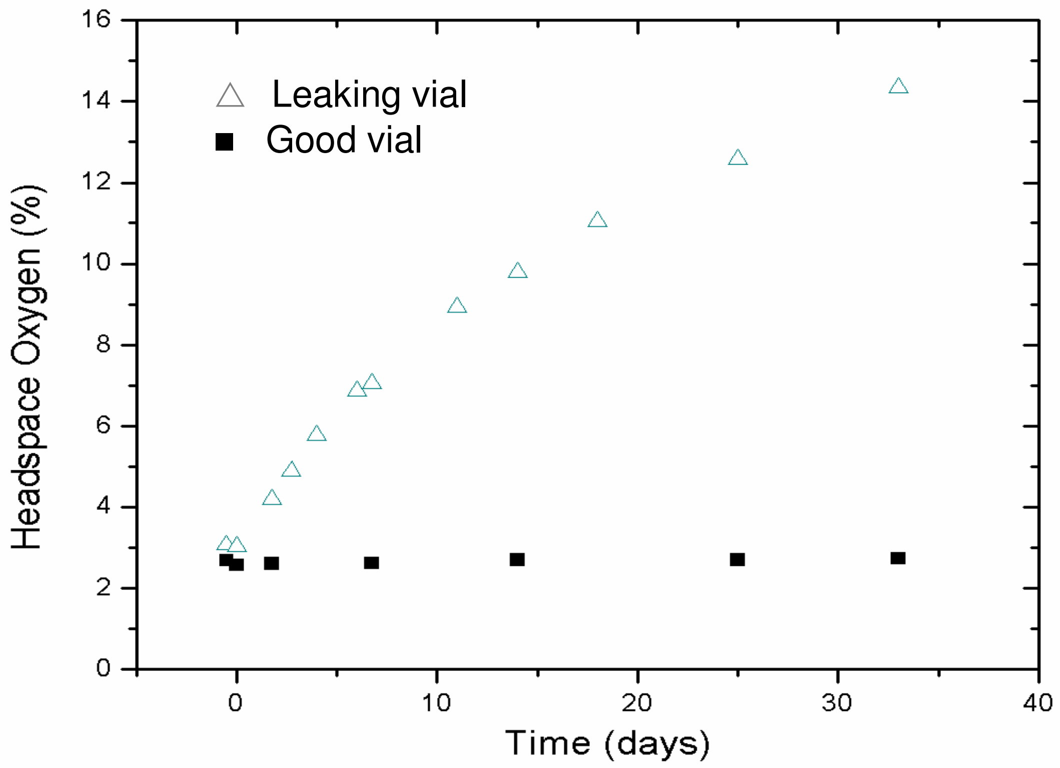
## ✓ The Problem:

- Assess leak rate in a parenteral container
- Correlate container closure measurements to probability of microbial ingress
- Goal: Streamline current microbial testing methods

## ✓ 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

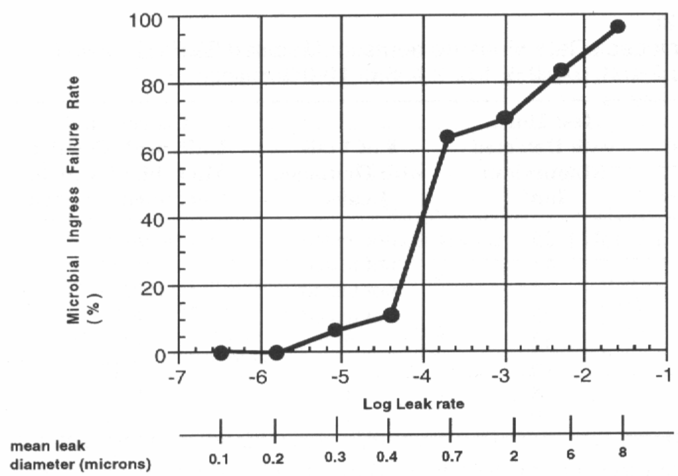



Figure 2—The correlation of microbial failure rate (%) and the mean logarithm of the absolute leak rate and nominal leak diameter for modified SVPs. The absolute leak rate (standard cubic centimeters per second) was determined by mass spectrometry-based helium leak rate detection. Microbial failure was 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: Headspace oxygen container closure study

- ✓ LIGHTHOUSE non-destructive oxygen platform enabled monitoring of headspace oxygen in a parenteral container over time to determine leak rates.
- ✓ Analysis showed that an increase in headspace oxygen levels is readily observed even for a small leak.
- ✓ The observation of elevated headspace oxygen levels is indicative of a container closure failure for product packaged under a modified headspace.

# Conclusions: Container Closure and Microbial Testing

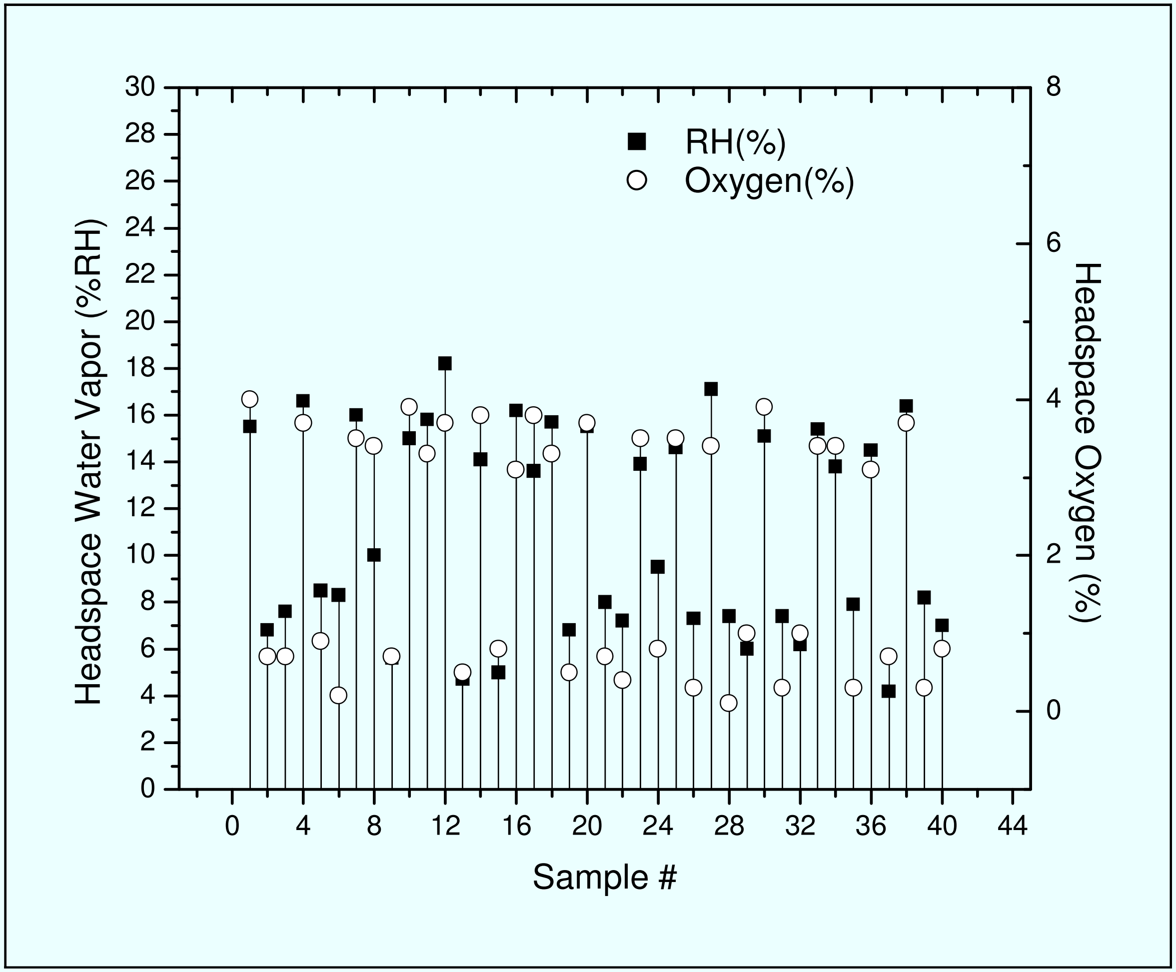
- ✓ **Potential for streamlining microbial testing using container closure measurements - see FDA guidance "Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products"**
- ✓ **Validation experiments need to be done correlating container closure measurements to microbial ingress.**
- ✓ **Another potential application:**
  - Aerobic media fills to demonstrate sterility of the filling process.
  - Monitoring headspace oxygen levels in the media fill may quickly identify the presence of aerobic microbes


# 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℃ | 24 hours at 100℃ |
| Pre-treatment of the stopper at 100℃ | 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℃ | 24 hours at 100℃ |
| Pre-treatment of the stopper at 100℃ | 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 % |

# 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.
- Application of LIGHTHOUSE rapid non-destructive measurement enables efficient stopper studies.
- What is the effect on the stability of lyophilized product? See reference on following slide.

# Full 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

# 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

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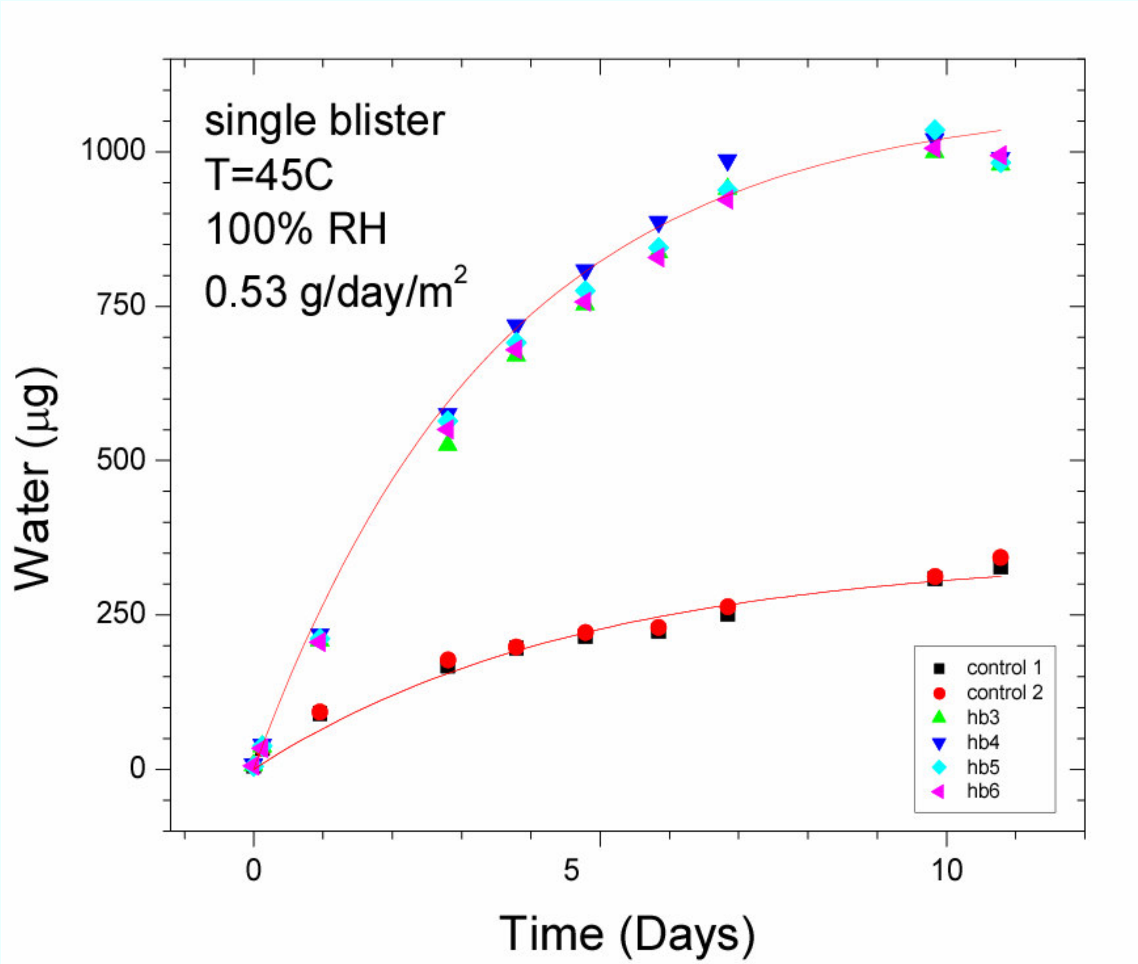
# Results: Moisture Permeation in Blisters



# Conclusions: Moisture Permeation in Blisters

✓ **Conclusions:**

- Monitoring increase of headspace moisture over time with LIGHTHOUSE method enables measurement of the blister packaging system moisture permeation 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.

# Key Benefits of Rapid Non-Destructive Headspace Method for Packaging Development Activities

- **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.
  - No waste disposal issues.
- **Ability to rapidly perform 100% inspection.**
  - Gives science-based insight into process variability, enables optimisation.
  - Quality of finished product guaranteed

Laser-based Headspace Inspection

# Thank you!