



# CCI: Regulations, Test Methods, Application Test Methods: Fundamentals



# OUTLINE - Test Method Fundamentals

1

CCI Testing Principles

2

Leak & Positive Controls

3

Gas flow: Flow Rate & Leak  
Size

4

“Sizing” : Correlation between  
leak size & flow rate

# RECAP

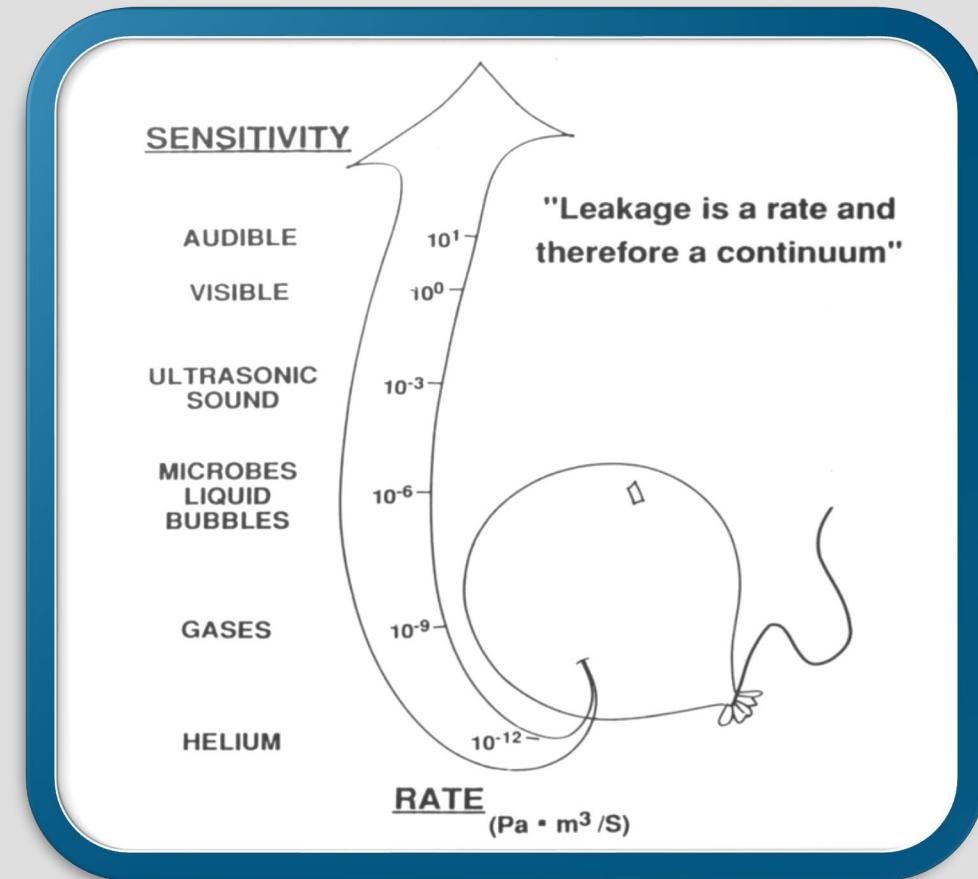
**Most advanced CCIT technologies rely on gas flow:**

- ❑ More reliable (for micron-size leaks)
- ❑ More predictable, some are quantitative

**Smallest leaks only  
allow**

**Larger leaks may also  
allow**

**Largest leaks may also  
allow**



# CCI Testing Technology Overview

Most CCIT technologies do not detect leak (defects) directly.

Instead, they detect presence of leak by monitoring the **biological and/or physiochemical responses** caused by a medium passing through the leaking path, typically driven by certain challenge conditions.

Technology detection performance depends on:

1. Test medium: Liquid (with microbe/dye tracer) vs. gas
2. Challenge conditions: Pressure differential, high voltage
3. Response detection methods

# CCI Testing Technology Overview

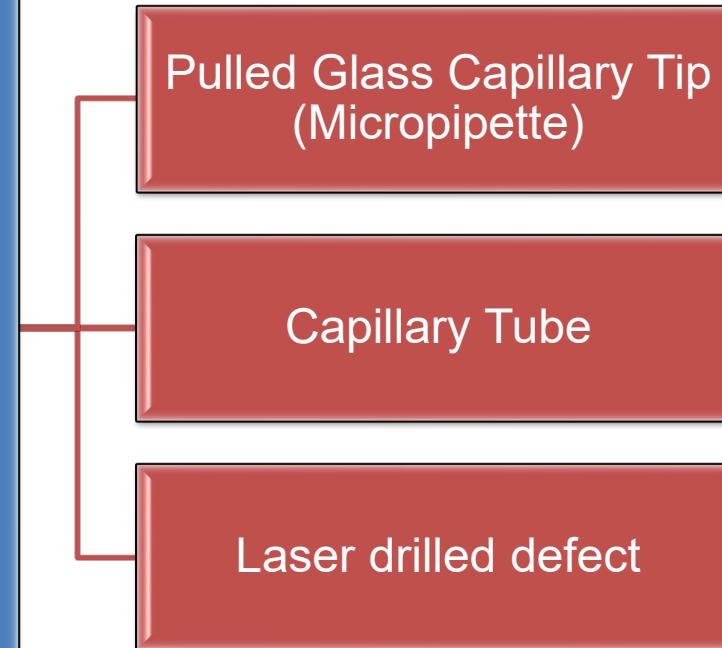
Technology	Test Medium	Typical Challenge Condition	Response	Detection
Microbial Challenge	Liquid flow (Microbial species)	Pressure differential	Turbidity due to microbe growth	Visual
Dye ingress	Liquid flow (Dye solution)	Pressure differential	Dye presence	Visual or spectrophotometer
Vacuum Decay	Gas flow	Pressure differential	Pressure change	Pressure transducer
Mass Extraction	Gas flow	Pressure differential	Mass flow	Mass flow sensor
Headspace (e.g., oxygen) Analyzer	Gas flow (e.g., O <sub>2</sub> )	Partial pressure differential (e.g., O <sub>2</sub> )	Oxygen	Laser absorption spectroscopy
Helium Leak Detection	Gas flow (Helium)	Pressure differential	Helium	Mass spectrometer
Optical Emission Spectrometry	Gas Flow (e.g., N <sub>2</sub> , CO <sub>2</sub> , Ar, H <sub>2</sub> O)	Pressure differential	Air Leakage	OES
High Voltage Leak detection	Electron flow (Current)	High voltage	Current (electron flow)	Current to voltage converter

## Artificial Standards (Positive Controls)

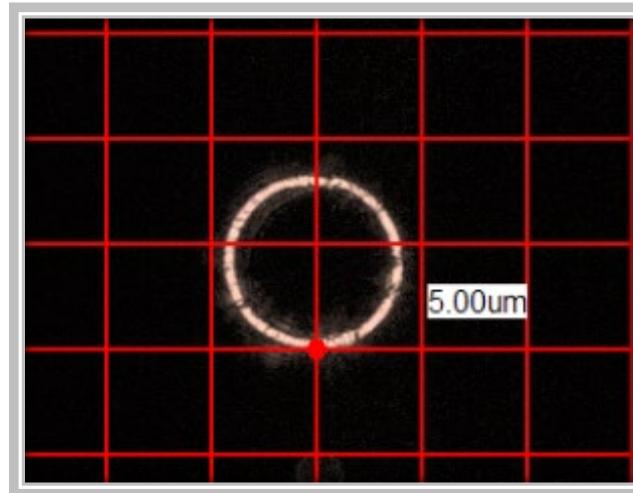
### Leak

- ❑ A gap or breach in the container capable of permitting the passage of liquid or gas (Syn. "Leak path").
- ❑ Real world leaks are usually complex, featuring various shapes, length, forms; some are transient and can change over time.

### Common Leak Standards (Positive Controls)



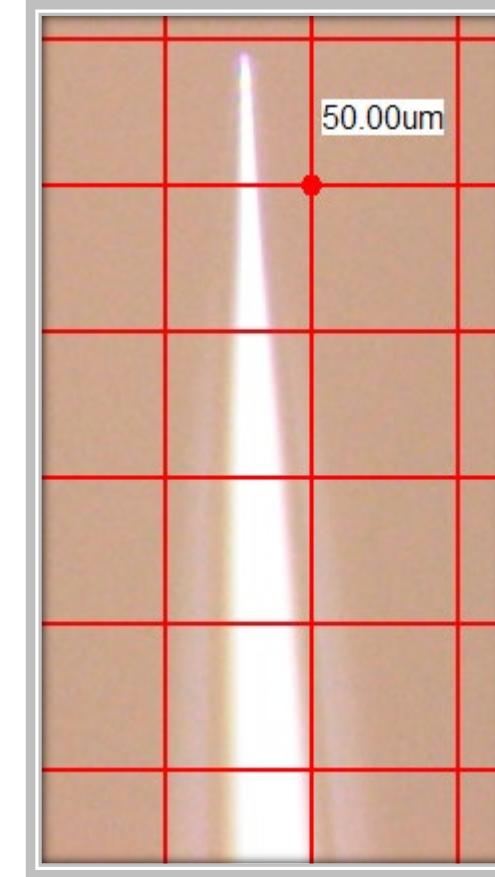
## Pulled Glass Capillary Tip (Micropipette)



Top view showing the tip orifice



Side view showing approximate length



**Glass tube with the tip pulled into micron size capillary**

## Capillary Tubes / Wires

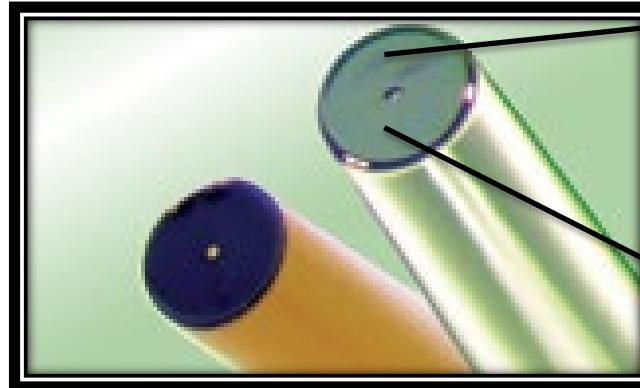
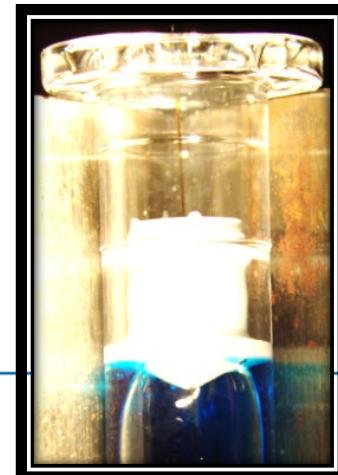
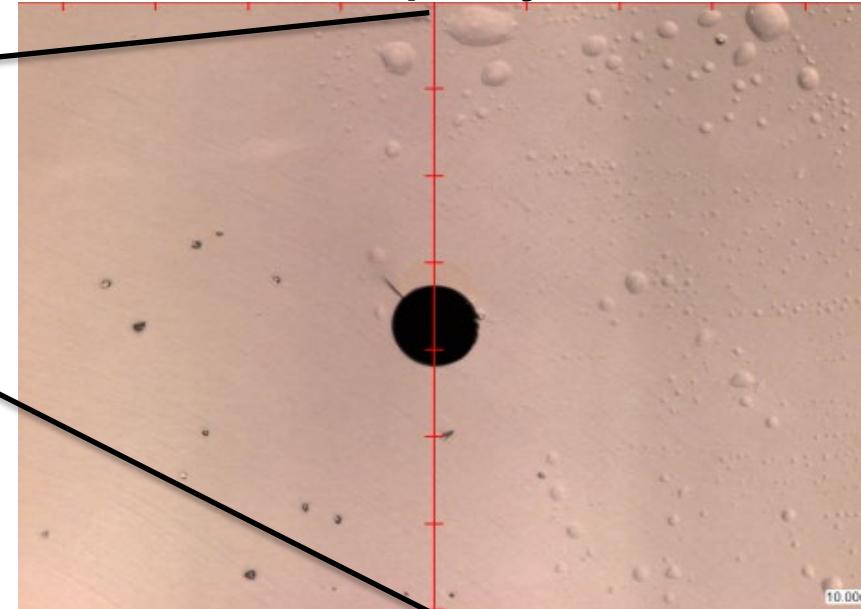
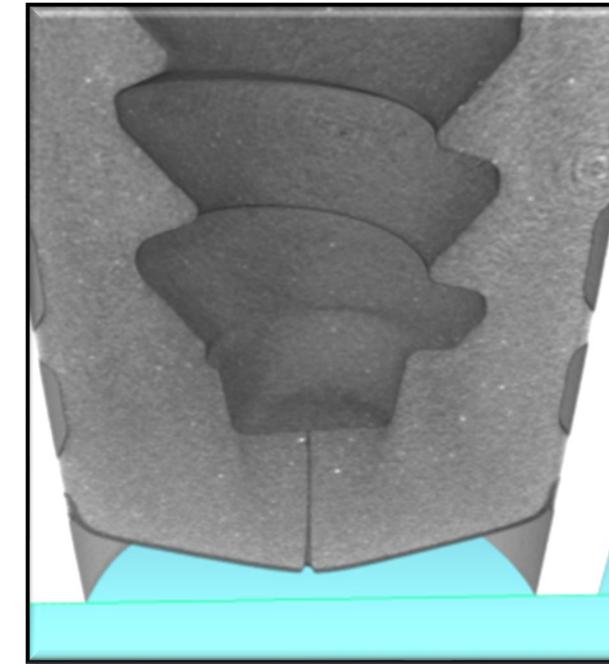
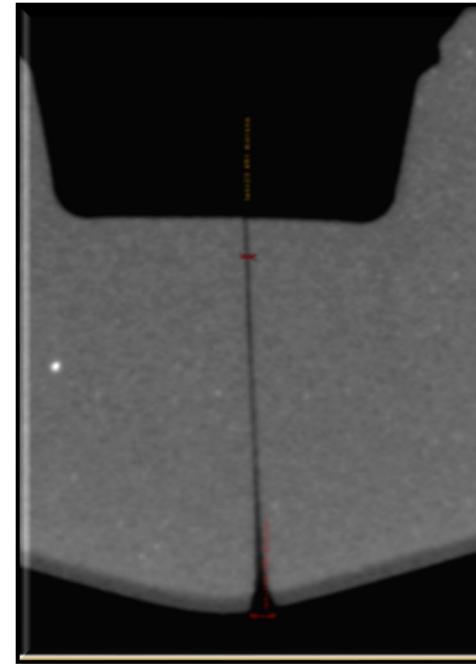
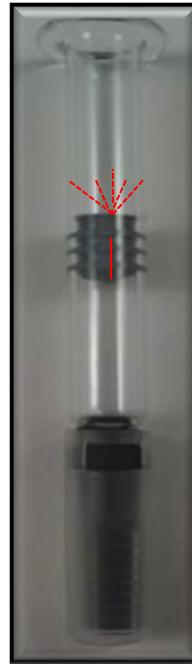


Image courtesy: Polymicro Technologies by Molex®

**Uniform size through the length of the capillary tube**



## Laser Drilled Defect (Elastomer/Plastics)

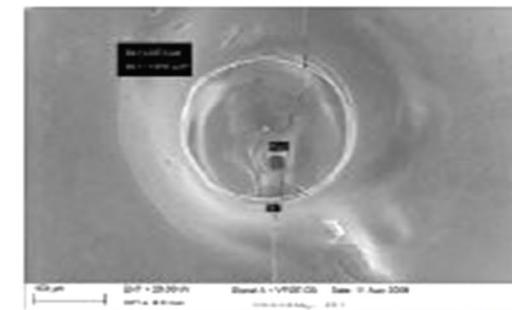
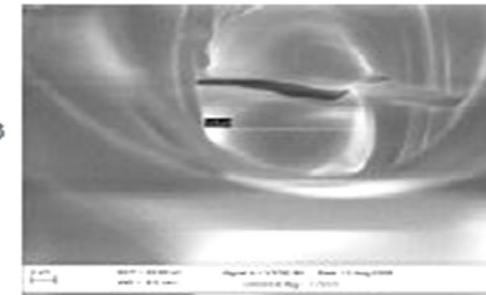
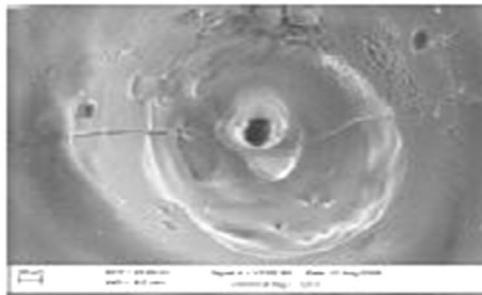


- Laser drilled defect can be readily created in plastics or elastomer materials
- Defect size may change upon applying stress on elastomer materials (e.g., insertion in syringe barrel)

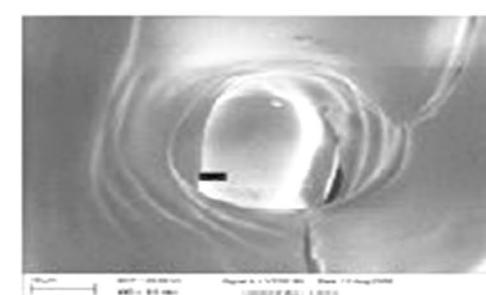
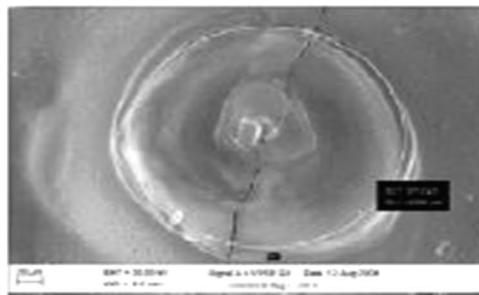
## Laser Drilled Defects in Glass

The laser-drilled defects in glass are not 'ideal' defects but realistic 'tortuous path' defects

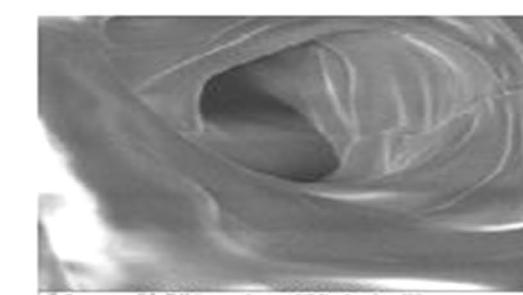
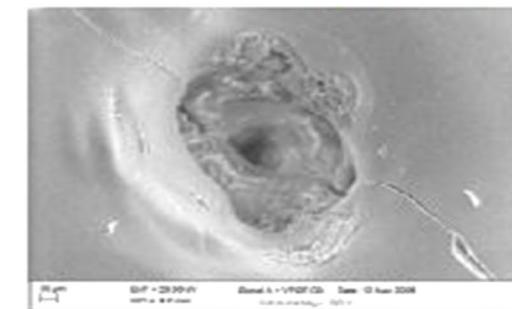
### Glass Syringe Defects by Lenox Laser



**Nominal hole size 10 μm**



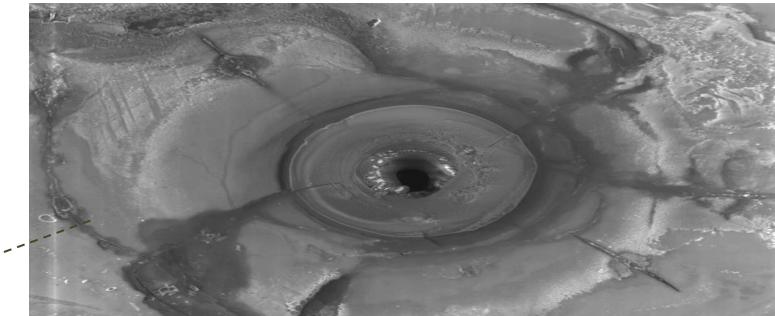
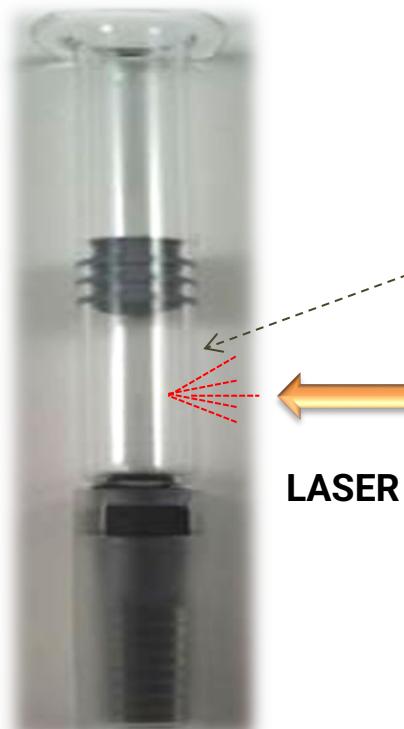
**Nominal hole size 5 μm**



**Nominal hole size 15 μm**

## Laser Drilled Defects in Glass

Example image of a laser drilled defect on the laser exit (i.e., glass interior surface)



Example image of a laser drilled defect on the laser entrance side (i.e., glass exterior surface)

- Laser drilled defects in glass are not well-defined holes of a uniform size.
- Some may be made to approximate “holes” while others may resemble a network of cracks – both are valuable as they represent specific types of “real-world” defects.
- Know the laser drill processes and the defect characteristics.

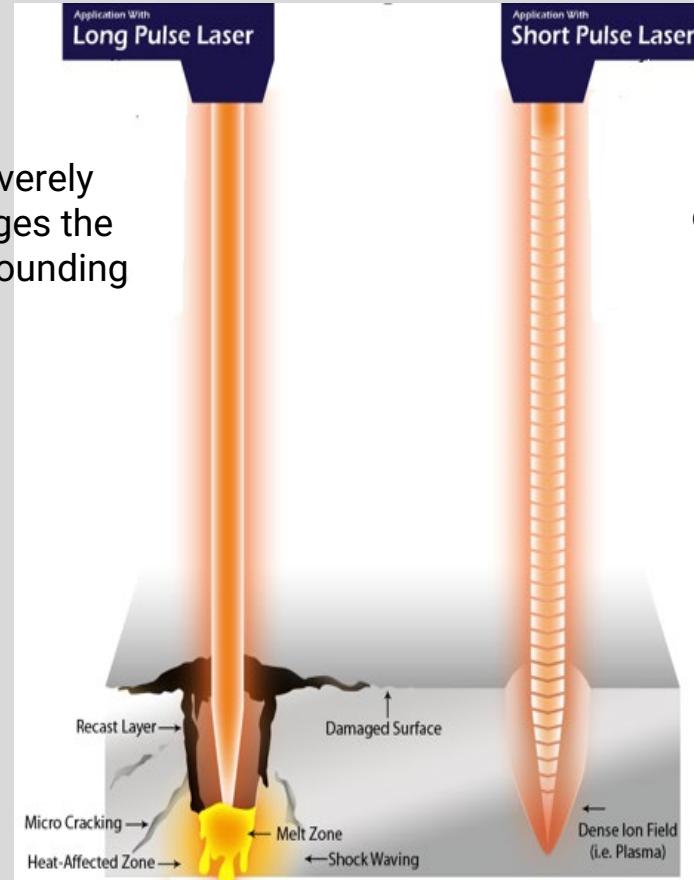
## What is a “Calibrated Leak”?

**Definition for CCIT case:** Calibrated leak is the opening in wall of a container in a shape of orifice or crack that gives a specific flow rate for a given gas or liquid at given pressures applied to both sides of the material wall where the leak is made.

Slide courtesy of Greg Soylar, Lenox Laser

## What is a “Calibrated Leak”?

This style of laser drilling severely damages the piece and changes the properties of the material surrounding the drilled hole.



This style of laser drilling with minimal damage to the piece. This is possible due to the creation of plasma in a technique called cold ablation.

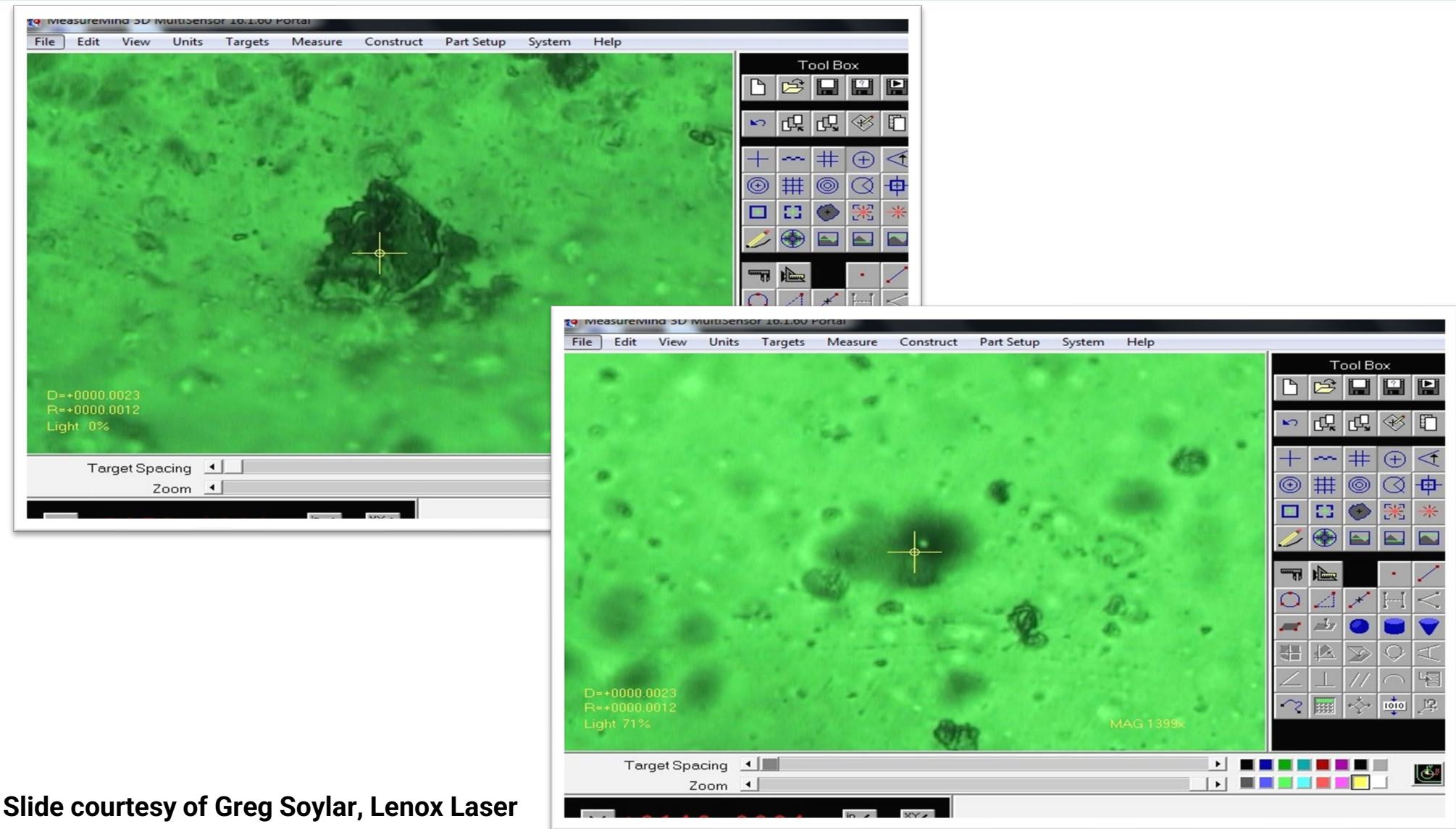
Slide courtesy of Greg Soylar, Lenox Laser



Slide courtesy of Greg Soylar, Lenox Laser

## Interwoven Plastic Bag



Plastic Bag (20  $\mu\text{m}$  Thick)

Slide courtesy of Greg Soylar, Lenox Laser

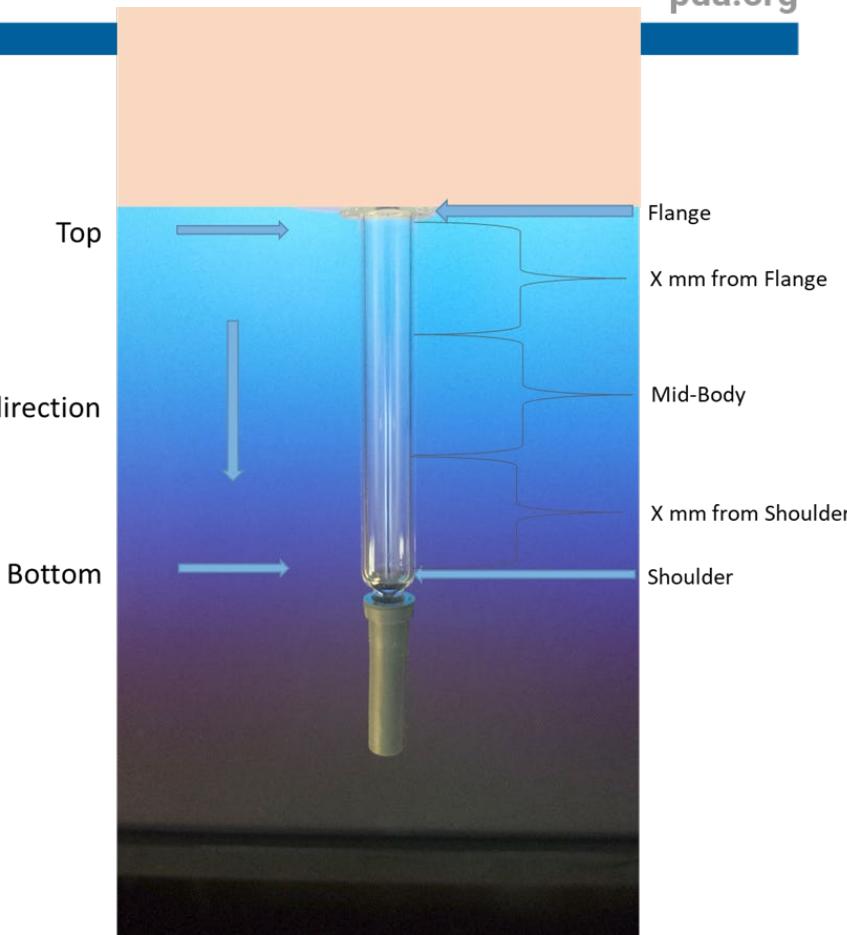
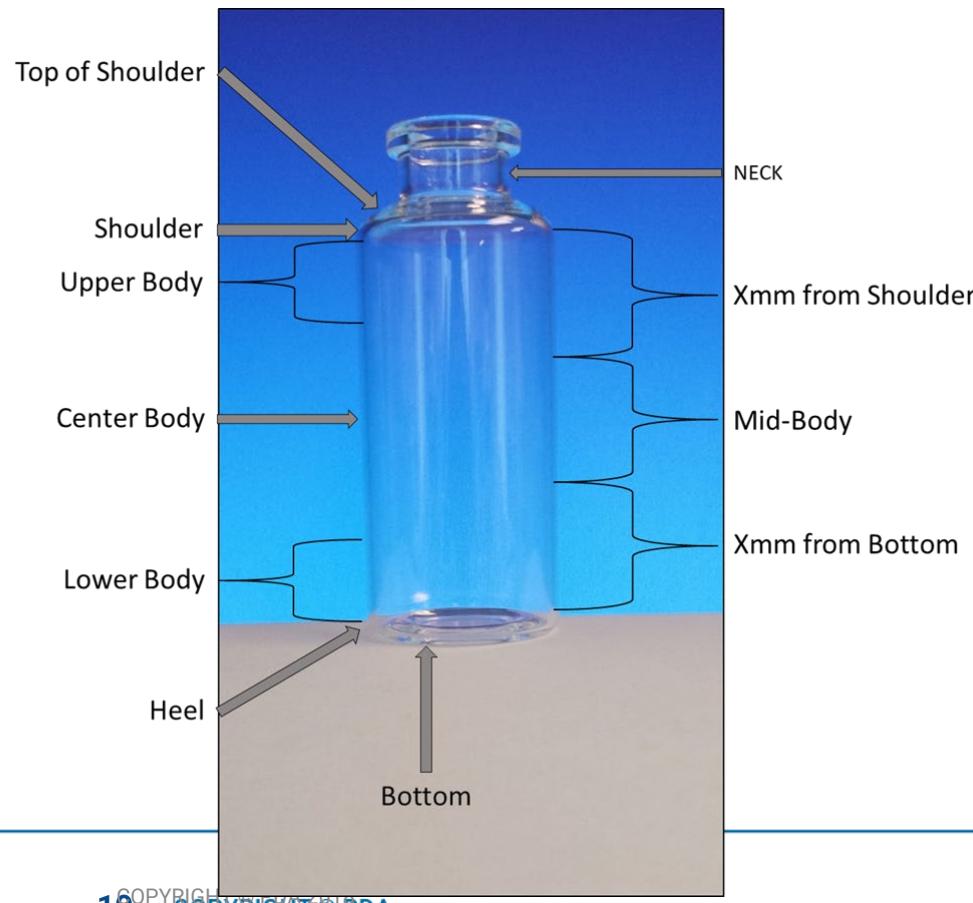
Leak Type	Advantages	Disadvantages	Experiences
Micro-pipettes, $\geq 0.1 \mu\text{m}$ ID (e.g. glass)	Easy sample preparation	<ul style="list-style-type: none"> <li>Fragile &amp; broken tips may not be detected</li> <li>Difficult to determine hole size</li> <li>Difficult to handle</li> </ul>	<ul style="list-style-type: none"> <li>Too fragile for routine use</li> <li>High risk of false sensitivity</li> <li>Need complete seal around micropipette</li> <li>Silicone oil can clog</li> <li>Pinhole type defect</li> <li>Material matches primary container if glass is used</li> </ul>
Laser-drilled holes, $\geq 0.5 \mu\text{m}$ ID	<ul style="list-style-type: none"> <li>Wide range of sizes</li> <li>Better resembles natural defects (cracks in glass; pinholes in polymer)</li> <li>Newer techniques allow for defined holes; fewer cracks</li> </ul>	<ul style="list-style-type: none"> <li>Cost</li> <li>Size of laser-drilled void needs to be calibrated and represents defined path</li> <li>Small hole can clog (silicone, viscous liq)</li> <li>Holes can increase in size (temp changes, tension)</li> <li>Variability in sizes depending on material/ wall thickness</li> <li>Irregular shapes</li> <li>Cannot be prepared on product</li> </ul>	<ul style="list-style-type: none"> <li>Risk of alteration post manufacture/calibration</li> <li>Specialized external supplier</li> <li>Many material can be drilled</li> <li>Closer to real world defects</li> <li>May reuse positive controls (??)</li> <li>Dirt or particulates could impact quality of holes</li> </ul>

"Container Closure Integrity Testing – Practical Aspects and Approaches in the Pharmaceutical Industry" PDA J. Pharma. Sci. Technol. 2017 Mar-Apr;71(2):147-162

Leak Type	Advantages	Disadvantages	Experiences
Capillaries, $\geq 0.2 \mu\text{m}$ ID (e.g. fused silica)	<ul style="list-style-type: none"> <li>• Robust</li> <li>• Easy preparation at testing location</li> <li>• Possible to prepare controls in specific packaging format and for multiple products</li> <li>• Prepared in flexible way (e.g. may contact liq and headspace)</li> </ul>	<ul style="list-style-type: none"> <li>• Length of microtube defects is usually longer than real world defects</li> <li>• Typically nominal diameters <math>&gt; 2\mu\text{m}</math> available &amp; uncertainty of actual diameter</li> <li>• Capillary diameter and hold diameter not comparable with regard to flow rate</li> <li>• Glue can create blockage</li> </ul>	<ul style="list-style-type: none"> <li>• Robust, wide size range &amp; different materials available</li> <li>• Leakage rates can be fine-tuned through length of capillaries; not only using IDs</li> <li>• Consistent dimensions/leaks</li> <li>• Defined dimensions mean don't have to calibrate each lead</li> </ul>
Micron wires, $\geq 10 \mu\text{m}$ ID (e.g. uncoated copper)	<ul style="list-style-type: none"> <li>• Low cost</li> <li>• Robust</li> </ul>	<ul style="list-style-type: none"> <li>• Handling of micron wires can be difficult and size of void needs to be calibrated and represent undefined path</li> <li>• Holes can close up over time depending on material relaxation</li> <li>• No direct measurement of hole size</li> </ul>	<ul style="list-style-type: none"> <li>• Reproducible leak size with defined capping parameter and wire size</li> <li>• Leak size only defined when measured relative to physical phenomenon</li> <li>• Need to consider copper wire diameter and elastomer behavior for consistency</li> <li>• Actual size depends on many parameters</li> </ul>

"Container Closure Integrity Testing – Practical Aspects and Approaches in the Pharmaceutical Industry" PDA J. Pharma. Sci. Technol. 2017 Mar-Apr;71(2):147-162

# Common Hole Locations in Glass Vials



# Common Hole Locations in Syringes

## Which Type of Defect Should I Use?

- ❑ Use positive controls that best resemble “real-world” defects of interest to demonstrate method effectiveness.
- ❑ **Examples:** To demonstrate the method is capable of detecting 10um defects.

Defect Type of interest	Positive Controls (10um)
IV bag leaks caused by punctures/ abrasion	Laser drilled pinhole on the bag film with ~10um ID (measured by microscopic imaging)
Poor seals or micro-channels on the IV bag seams	10um capillary tube of similar length glued into the seam (the 10um ID can be microscopically verified)
Cracks in a vial glass wall (~2mm thick)	Laser drilled irregular glass defects, calibrated to be ~10um using gas flow rate per USP method

## Characterization of Leaks

- Most industries uses leak flow rate to characterize a leak
  - ✓ Leak flow rate directly correlated to the material loss through the leak (e.g., compressed natural gas pipeline leaks)
  - ✓ Leakage Flow Rate is a measure of the rate of gas flow (mass or volume units) which passes through a leak path under defined conditions of temperature and/or absolute or partial pressure gradient of leaking matter that exists across the package barrier
- Gas leak flow rates are usually expressed in standard cubic centimeter per second (sccs) under standard conditions (temperature 273K, pressure 760 torr)
  - ✓ Other units are also widely used



Jackson CN, Sherlock CN, Moore PO, Nondestructive Testing Handbook, 3<sup>rd</sup> ed. Vol 1 Leak Testing, American Society for Nondestructive Testing, Inc. 1998

## Characterization of Leaks

Pascal Cubic Meter Per Second	Standard Cubic Centimeter Per Second	Millibar Liter Per second	Torr Liter Per Second
$\text{Pa} \cdot \text{m}^3 \cdot \text{s}^{-1}$	$\text{Std cm}^3 \cdot \text{s}^{-1}$ (Alternatively, sccs)	$\text{mb} \cdot \text{L} \cdot \text{s}^{-1}$	$\text{torr} \cdot \text{L} \cdot \text{s}^{-1}$
1	9.87 ( $\approx 10$ )	$1.00 \times 10^1$	7.50



Jackson CN, Sherlock CN, Moore PO, Nondestructive Testing Handbook, 3<sup>rd</sup> ed. Vol 1 Leak Testing, American Society for Nondestructive Testing, Inc. 1998

## “Sizing” Leaks

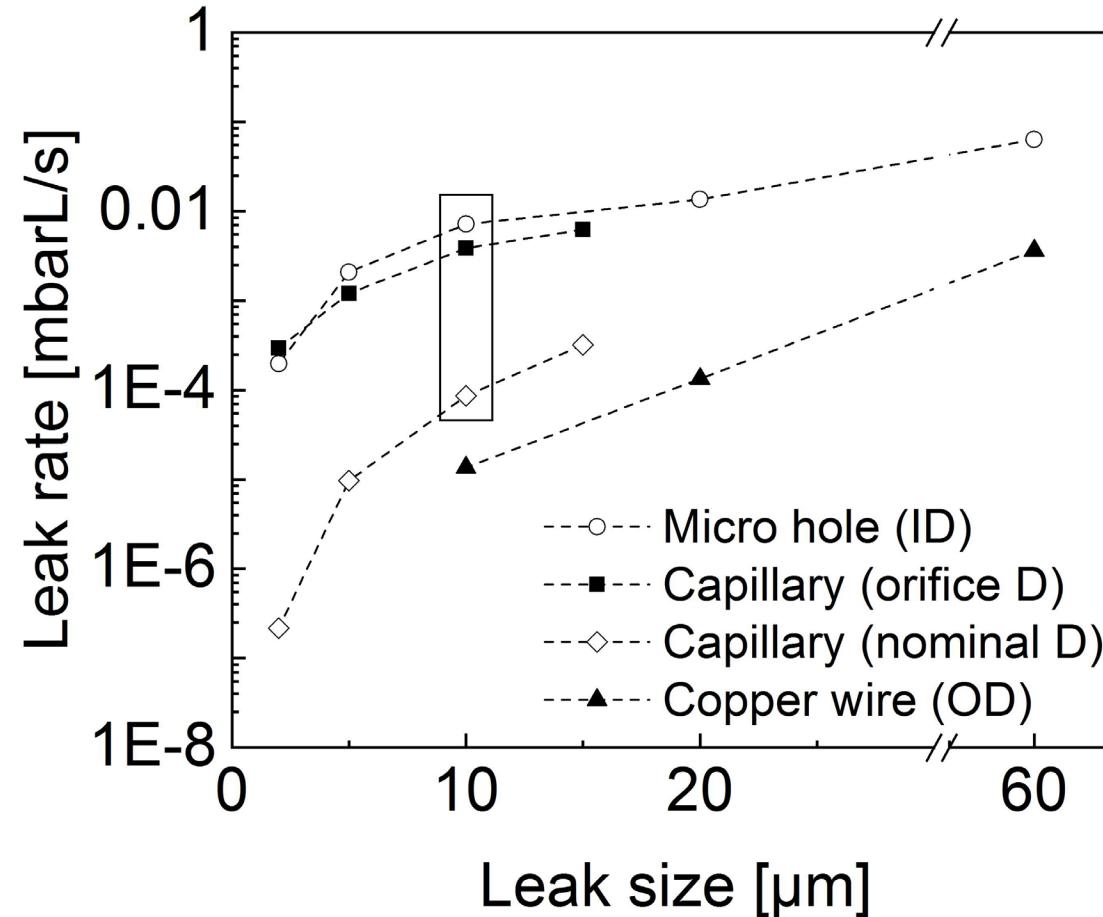
### Flow vs Size?



**“Leak size” is widely used in pharmaceutical industry as a key characteristic for leaks largely due to its close association with microbial ingress risk.**

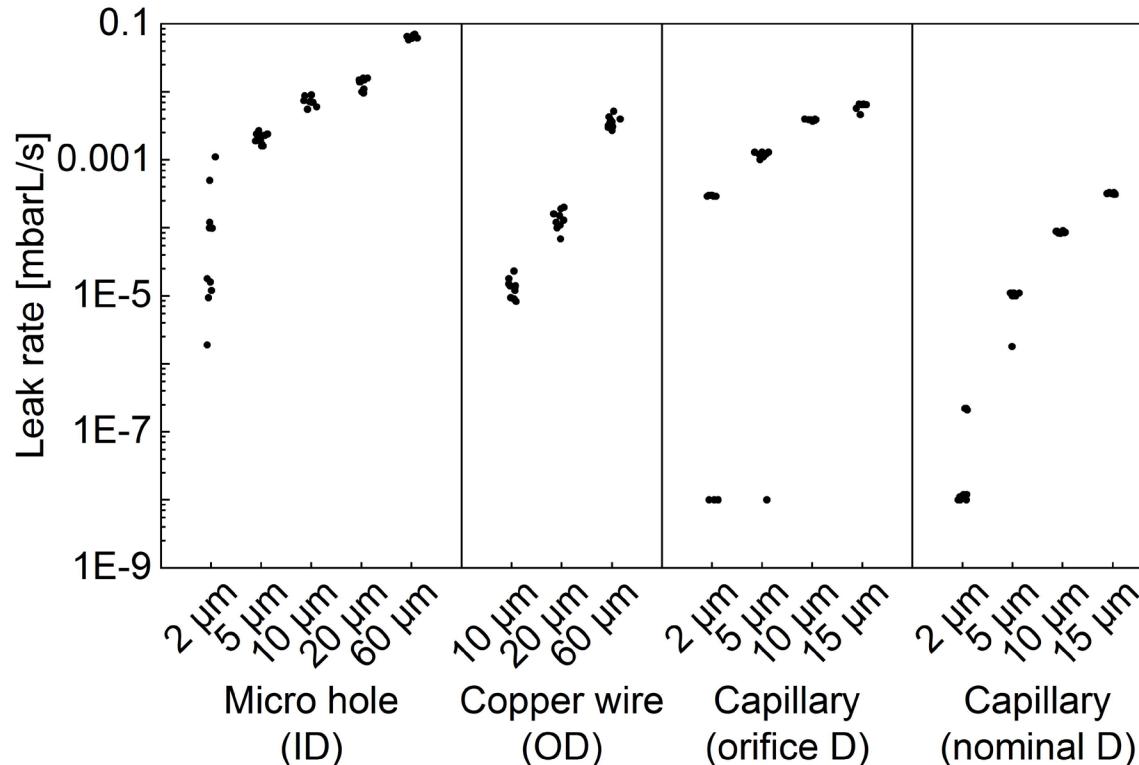
- Dimensionally sizing natural “real-world” leaks is not always practical nor precise.
  - Leaks are commonly thought of as HOLES or CHANNELS. But natural leaks are complex, multi-cavity, tortuous paths (rarely uniform)
  - Size alone does not fully define a “real-world” natural defect
- “Sizing”, although not a comprehensive and precise characterization of a defect, is still useful because it allows for a rough and simplified assessment of microbial ingress risks

# He Leak Rates for Artificial Leaks



- He leak rates increase with larger leak sizes
- Leak types show specific leak rates according to leak geometries
- 3 leak types at 10 μm significant differences in He flow rates
- Theoretical leak rates from equation  $\text{micro hole} = \text{capillary leak (orifice diameter)} > \text{capillary leaks (nominal diameter)} > \text{copper wire}$
- Strong dependence of glass flow rate on leak path length

# Variability of Leak Rates of Artificial Leaks



- Variability increased for smaller leaks
- Artificial leaks can have significant variability in actual leak size and deviation from target
- Micro holes highest variability, especially at smallest diameter (complex and irregular shapes of micro hole channels contributes)
- Capillary leaks are consistent channels with know ID, but are quite different than real-life leaks
- Capillary leaks of very small ID can become clogged or defective (see very low leak rates), capillary leaks must be prepared with care and handled with care
- Copper wire can have kinks in the wire, become entrapped in rubber stopper wrinkles, breakage of wire; path length may vary based on stopper, leak channel size cannot be defined

## Methods for “Sizing” Defects Characterization

### Direct microscopic dimensional measurement

- Usually applies to simple “regular” natural defects (e.g., pin holes on an IV bag film) or positive control defects (e.g., capillary tubes)

### Calibration via gas diffusion rate (or headspace changes) measurement

- Gas diffusion and headspace composition modeling are usually acceptable

## Methods for “Sizing” Defects Characterization

### Calibration via gas leak flow rate measurement

- Usually for complex “real-world” defects (e.g., glass cracks)
- A “*nominal*” size can be obtained by comparing the gas flow rate of the defect against known leak standards (e.g., NIST-traceable leak standards)
- Two types of leak standards are commonly used – Need to specify
  - ✓ Orifice (a pin-hole of known size with essentially no depth)
  - ✓ Capillary (with known uniform ID and Length)



## Sizing Based on Gas Leak Flow Rate – Calibration using Orifice Leak Standards

For orifice leaks (i.e., leaks with essentially no “depth”, a.k.a. sharp edge defects)

$$\text{Flow Rate} \propto d^2$$

- Flow rate usually measured at a fully “chocked” conditions to simplify the calculation.
- Methodology is included in USP<1207>.
- Nominal sizes can be easily calculated using the flow rate equation or online calculators

### Calculator Examples:

<https://lenoxlaser.com/resources/calculators/orifice-calculator/>



Gas Flow Calculator

Orifice Diameter: DISABLED

Missing: Inlet Pressure, Outlet Pressure, Temperature and Flow Rate  
All pressure values are assumed to be absolute value (except psig).

Inlet Pressure: psig

Outlet Pressure: psig

Gas Type\*: Air

Molecular Weight\*: 28.96

Temperature: Fahrenheit

Flow Rate: std cubic cm/min

Orifice Diameter: Micron

Calculate

\* Please register to unlock these options. Register here.  
See our calculator app on the Google Play Store.



## Gas Leak Flow Rate vs. Orifice Size

Row	Air Leakage Rate <sup>a</sup> (stdcm <sup>3</sup> /s)	Orifice Leak Size <sup>b</sup> (μm)
1	<1.4 x E-6	<0.1
2	1.4 x E-6 to 1.4 x E-4	0.1 to 1.0
3	>1.4 x E-4 to 3.6 x E-3	>1.0 to 5.0
4	>3.6 x E-3 to 1.4 x E-2	>5.0 to 10.0
5	>1.4 x E-2 to 0.36	>10.0 to 50.0
6	>0.36	>50.0

<sup>A</sup> Dry air leakage rate measured at 1 atm differential pressure across an orifice leak (i.e., leak inlet pressure of 1 atm versus outlet pressure of approximately 1 Torr) at 25°. The theoretical correlations of orifice sizes to air leakage rates were provided by Lenox Laser, Glen Arm, MD. Leakage rates are approximation ranges.

<sup>B</sup> Nominal diameter orifice sizes assume a leak path of negligible length. Orifice sizes are approximation ranges.

## Sizing Based on Gas Flow Rate – Calibration using Capillary Leak Standards

*For defects with significant length (L)*

### Gas Flow Model EXAMPLES

- Hagen-Poiseuille viscous flow (barometric, shallow vacuum)

$$Q = \frac{128}{\pi} \frac{d^4}{L} \times \frac{P^2_{IN} - P^2_{OUT}}{\mu}$$



- Knudsen model for molecular flow (small defects, hard vacuum)

$$\dot{m} = \frac{\pi d^3}{\sqrt{2RT}} * \frac{P^2_{IN} - P^2_{OUT}}{L}$$



$P_{in}$  - pressure inside package;

$P_{out}$  - pressure inside chamber;

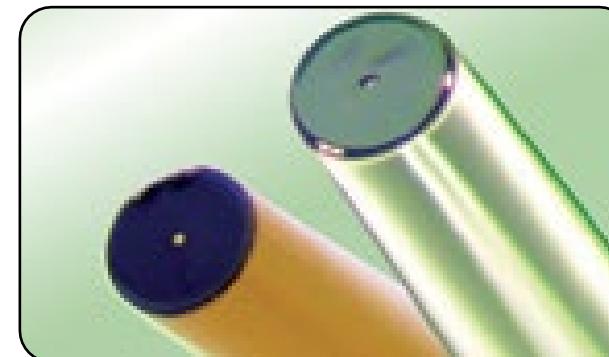
$\mu$  - Viscosity;  $T$  - Temperature;  $R$  - Specific Gas Constant

**Flow (Q-volumetric flow, mass flow)**

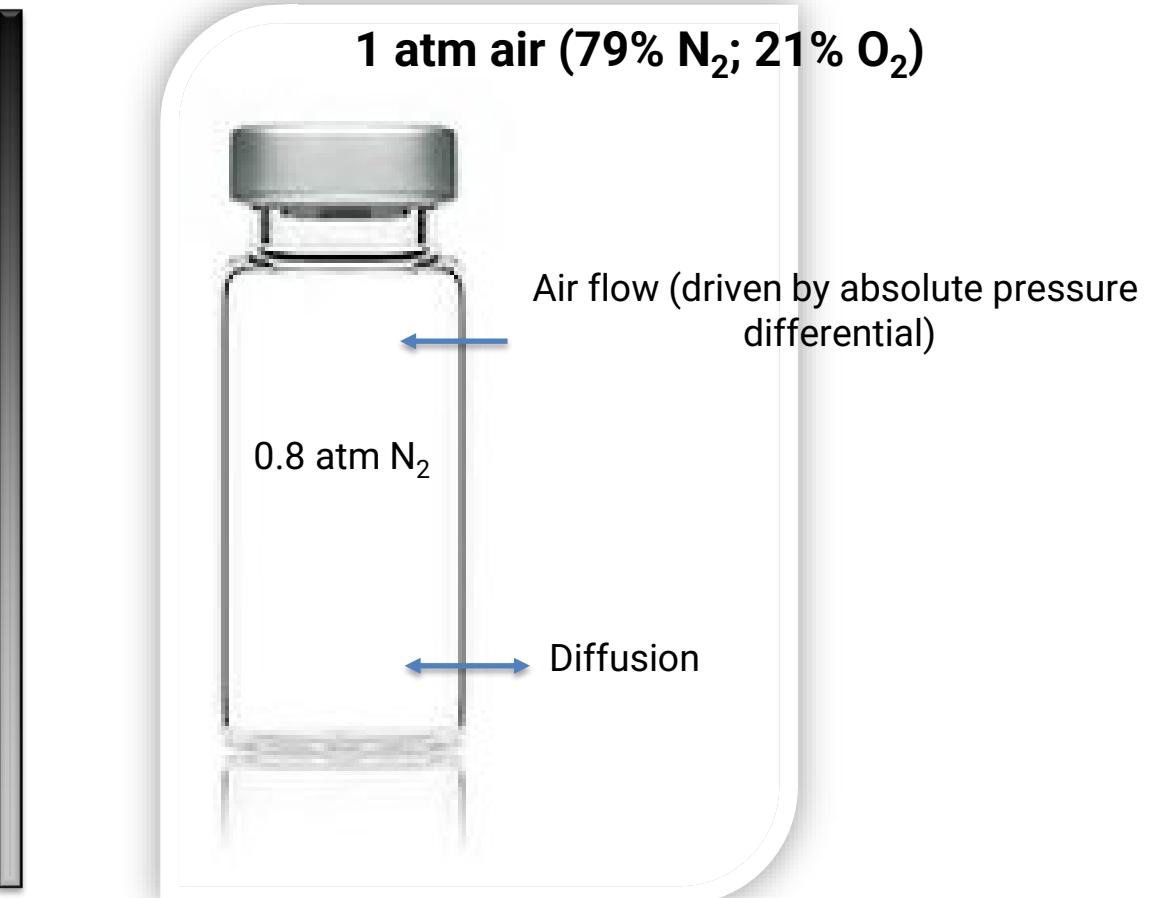
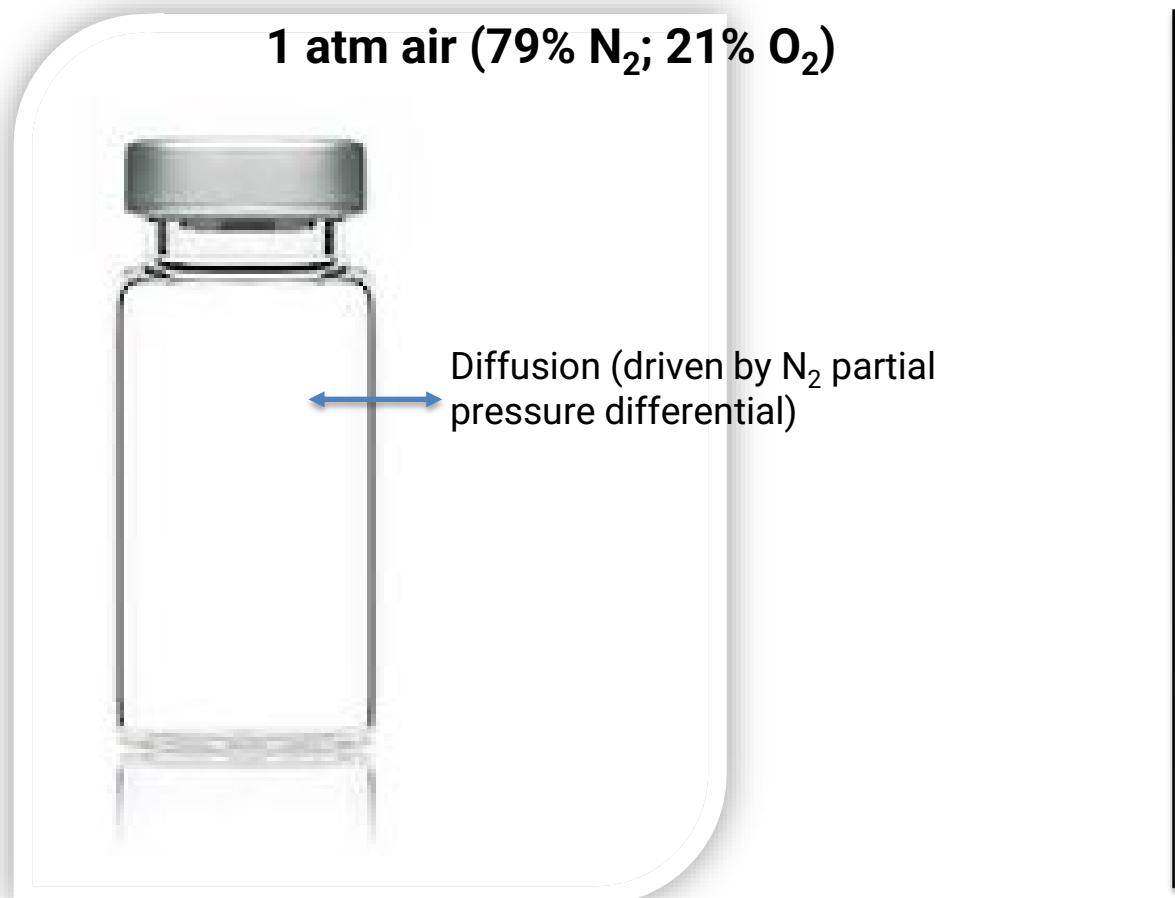
$$= f (d, \text{Length}, P_{in}, P_{out}, T)$$

Kept constant

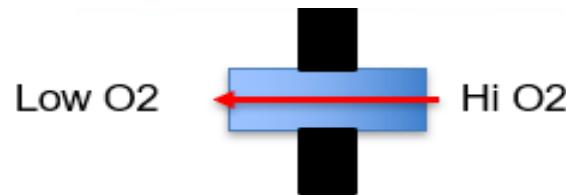
- Nominal sizes can be readily obtained experimentally by comparing flow rates of samples against those of known capillary standards (preferably of similar length L)



## Sizing Based on Headspace Changes



## Sizing Based on Gas Diffusion Rate (or Headspace Gas Concentration Change)



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

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

$$P_{oxygen}(t) = 20.9\% (1 - \exp(-\alpha t))$$

Ingress Rate

$$\alpha = \frac{D \cdot A_0}{l \cdot V} \quad [s^{-1}]$$

**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."

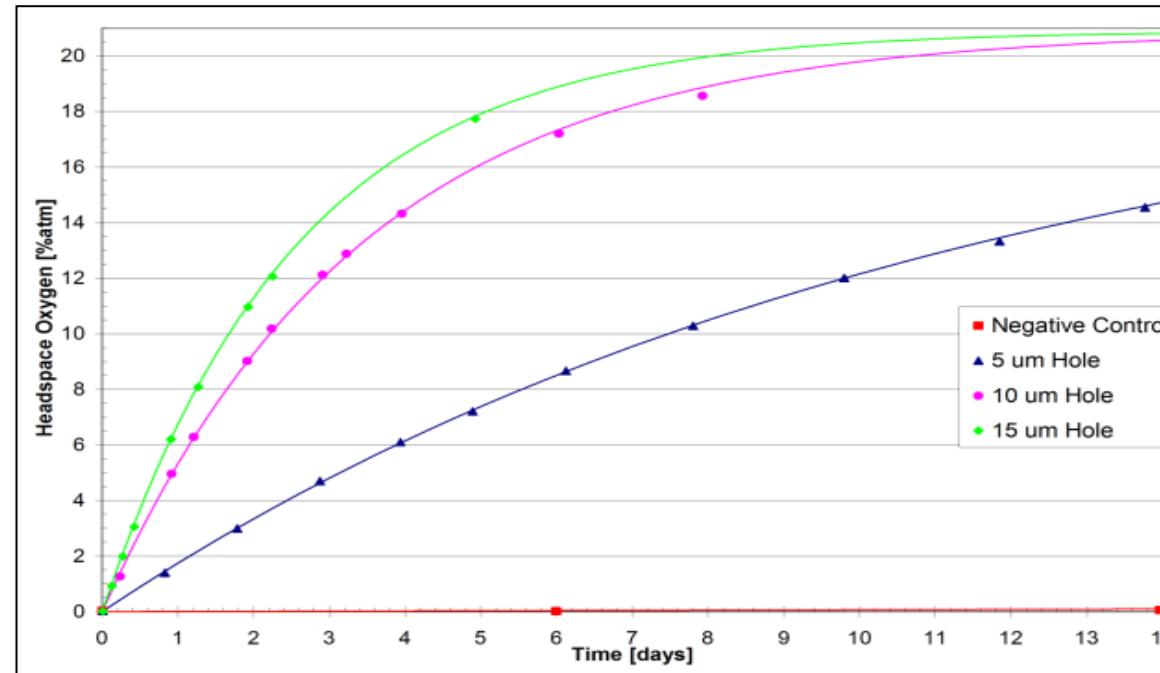
The change in oxygen will be exponential with respect to time

The Ingress Rate is a function of the Diffusion Coefficient, the container Volume and the defect cross-sectional Area and Depth

D. Duncan, Lighthouse Instruments

## Example: Headspace Oxygen % vs. Leak Size

The linear regression fit (RSQ) for each line was 0.99 or higher for each set of data.



Laser-drilled holes in thin metal plates are well-defined defects. They can therefore be used to generate 'calibration data' for gas ingress dynamics through a defect into a container.

D. Duncan, Lighthouse Instruments

## Reporting Leak Size

- ❑ “Nominal” size – a useful tool for communication with key stakeholders (e.g., business leaders, regulatory agency microbiology reviewers)
- ❑ Many methodologies can be used to “size” a leak – the resultant nominal sizes may not in full agreement
- ❑ No consensus methodologies haven been established yet
- ❑ When stating leak sizes (or reporting package integrity), it is important to **define the measurement approach – Be transparent!**



## Reporting Leak Size - Examples

### Example 1. An intentional leak size-certified in gas flow rate terms.

A laser-drilled hole = 10.3  $\mu\text{m}$ , certified that the air flow rate through this defect matches that of a same diameter pre-drilled hole in a thin metal plate measured at defined pressure and temperature conditions.

- *Comment: This statement indicates that the intentional leak sample is characterized using USP 1207 methodology and therefore is suitable for use as a positive control in method development and validation studies*

## Reporting Leak Size - Examples

### **Example 2. Unintentional leak(s) directly sized in gas flow rate terms.**

A test package containing 100% helium (flooded prior to closure) demonstrated a helium leak rate of  $1 \times 10^{-7}$  mbarL/s, when tested using a helium mass spectrometer, at 1 atmosphere differential pressure and ambient temperature.

- *Comment: This statement indicates that resultant helium leak rate is obtained using the identical methodology by Lee Kirsch as referenced in USP 1207. Therefore, the measured leak rate can be directly compared against the MALL to demonstrate container integrity.*