# Artificial Leaks / Positive Controls

# Artificial Leaks

- Artificial leaks are required in order to assess CCIT method capability to detect a leak
- Artificial leaks are require din order to act as positive controls
- Artificial leaks do not necessarily simulate actual defects due to the irregular shapes and pathways found in container closure systems
- High variability among artificial leaks based on method used to create leaks
- Difficulty relating artificial leaks to leak size
- No gold standard – each approach has advantages and disadvantages
  - Laser drilling
  - Mircon wire
  - Micropipettes
  - Capillaries

| Leak Type | Advantages | Disadvantages | Experiences |
|---|---|---|---|
| Mirco-pipettes, ≥0.1 µm ID (e.g. glass) | Easy sample preparation | • Fragile & broken tips may not be detected<br>• Difficult to determine hole size<br>• Difficult to handle | • Too fragile for routine use<br>• High risk of false sensitivity<br>• Need complete seal around micropipette<br>• Silicone oil can clog<br>• Pinhole type defect<br>• Material matches primary container if glass is used |
| Laser-drilled holes, ≥0.5 µm ID | • Wide range of sizes<br>• Better resembles natural defects (cracks in glass; pinholes in polymer)<br>• Newer techniques allow for defined holes; fewer cracks | • Cost<br>• Size of laser-drilled void needs to be calibrated and represents defined path<br>• Small hole can clog (silicone, viscous liq)<br>• Holes can increase in size (temp changes, tension)<br>• Variability in sizes depending on material/ wall thickness<br>• Irregular shapes<br>• Cannot be prepared on product | • Risk of alteration post manufacture/calibration<br>• Specialized external supplier<br>• Many material can be drilled<br>• Closer to real world defects<br>• May reuse positive controls<br>• Dirt or particulates could impact quality of holes |

"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, ≥0.2 µm ID (e.g. fused silica) | • Robust<br>• Easy preparation at testing location<br>• Possible to prepare controls in specific packaging format and for multiple products<br>• Prepared in flexible way (e.g. may contact liq and headspace) | • Length of microtube defects is usually longer than real world defects<br>• Typically nominal diameters > 2µm available & uncertainty of actual diameter<br>• Capillary diameter and hold diameter not comparable with regard to flow rate<br>• Glue can create blockage | • Robust, wide size range & different materials available<br>• Leakage rates can be fine-tuned through length of capillaries; not only using IDs<br>• Consistent dimensions/leaks<br>• Defined dimensions mean don't have to calibrate each lead |
| Micron wires, ≥10 µm ID (e.g. uncoated copper) | • Low cost<br>• Robust | • Handling of micron wires can be difficult and size of void needs to be calibrated and represent undefined path<br>• Holes can close up over time depending on material relaxation<br>• No direct measurement of hole size | • Reproducible leak size with defined capping parameter and wire size<br>• Leak size only defined when measured relative to physical phenomenon<br>• Need to consider copper wire diameter and elastomer behavior for consistency<br>• Actual size depends on many parameters |

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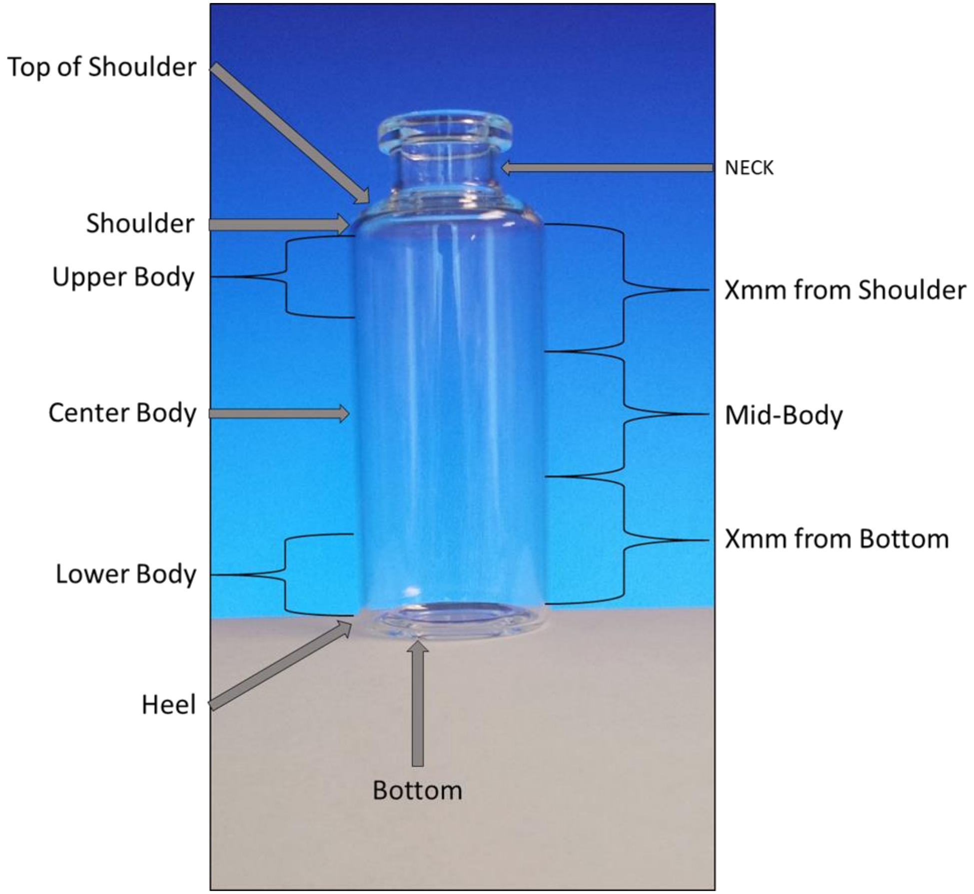
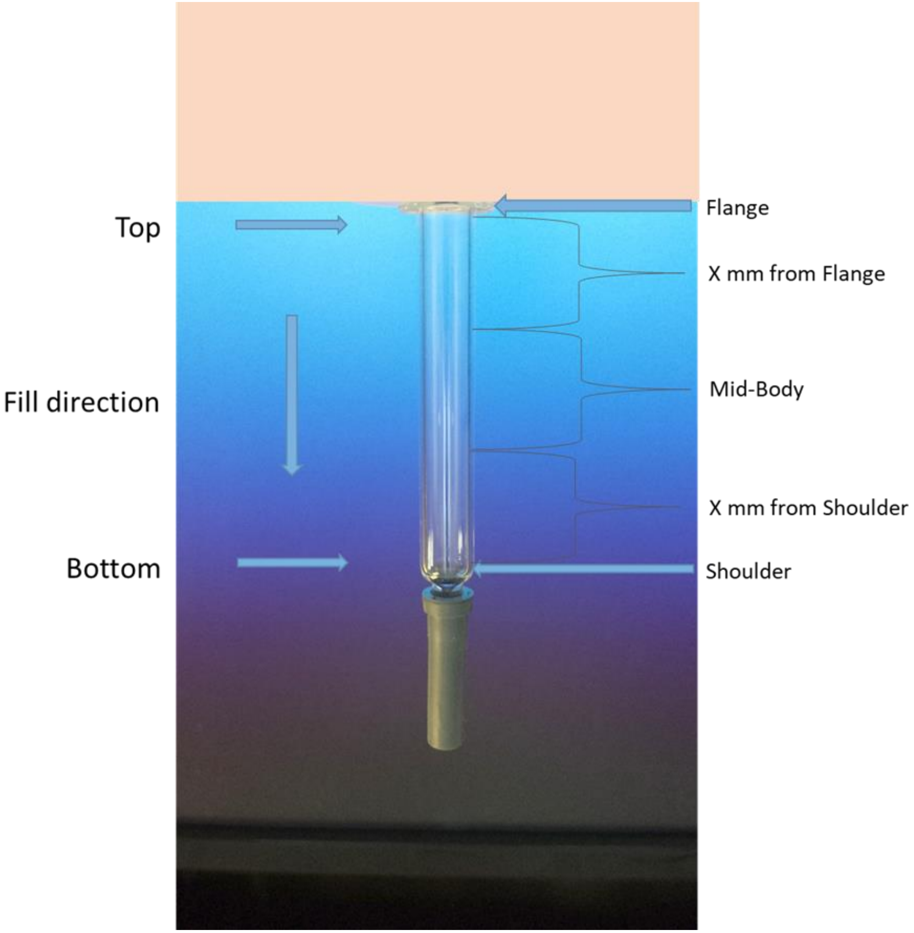
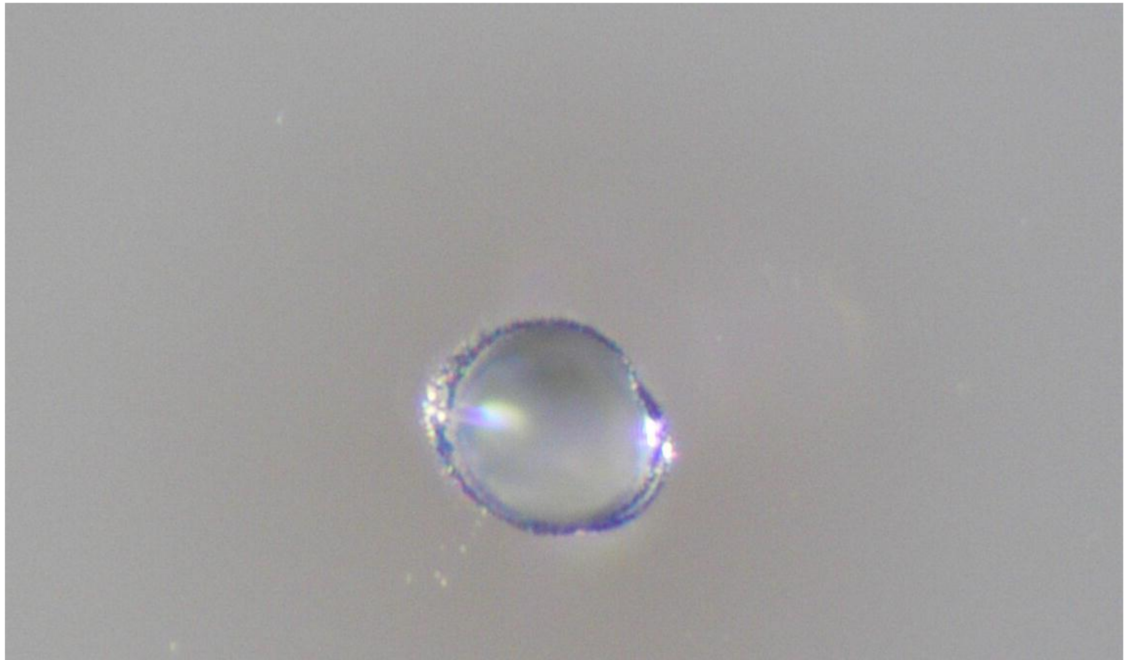
# Common Hole Locations in Glass Vials



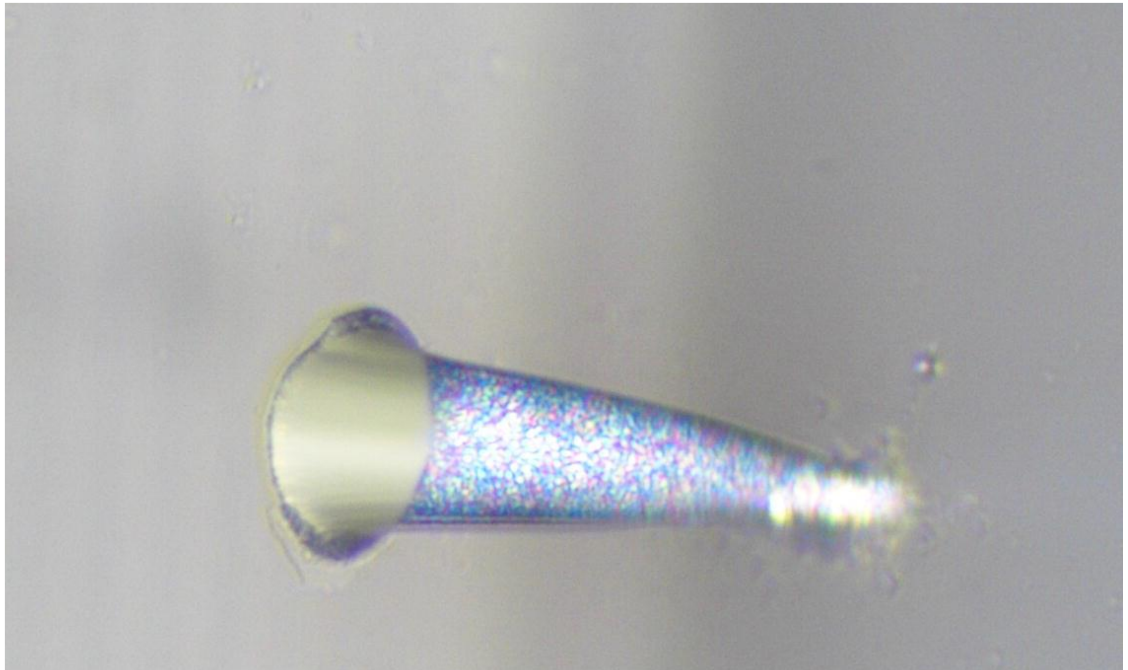
# Common Hole Locations in Syringes



# Micro hole leak: light microscope images of laser drilled



micro hole (60 µm nominal diameter) in vial wall
frontal



micro hole (60 µm nominal diameter) in vial wall
lateral

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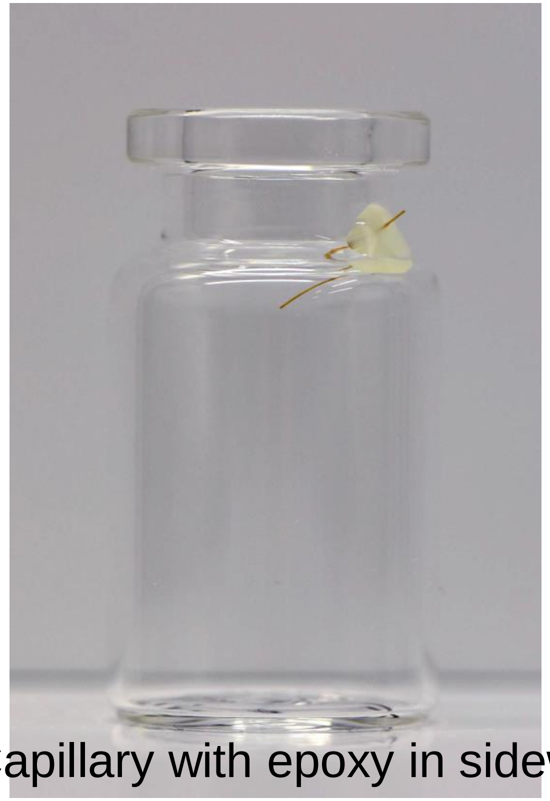
“Comparing Physical Container Closure Integrity Test Methods and Artificial Leak Methodologies.”

# Capillary & Microfibers



Capillary with epoxy in sidewall

Copper wire between stopper and vial





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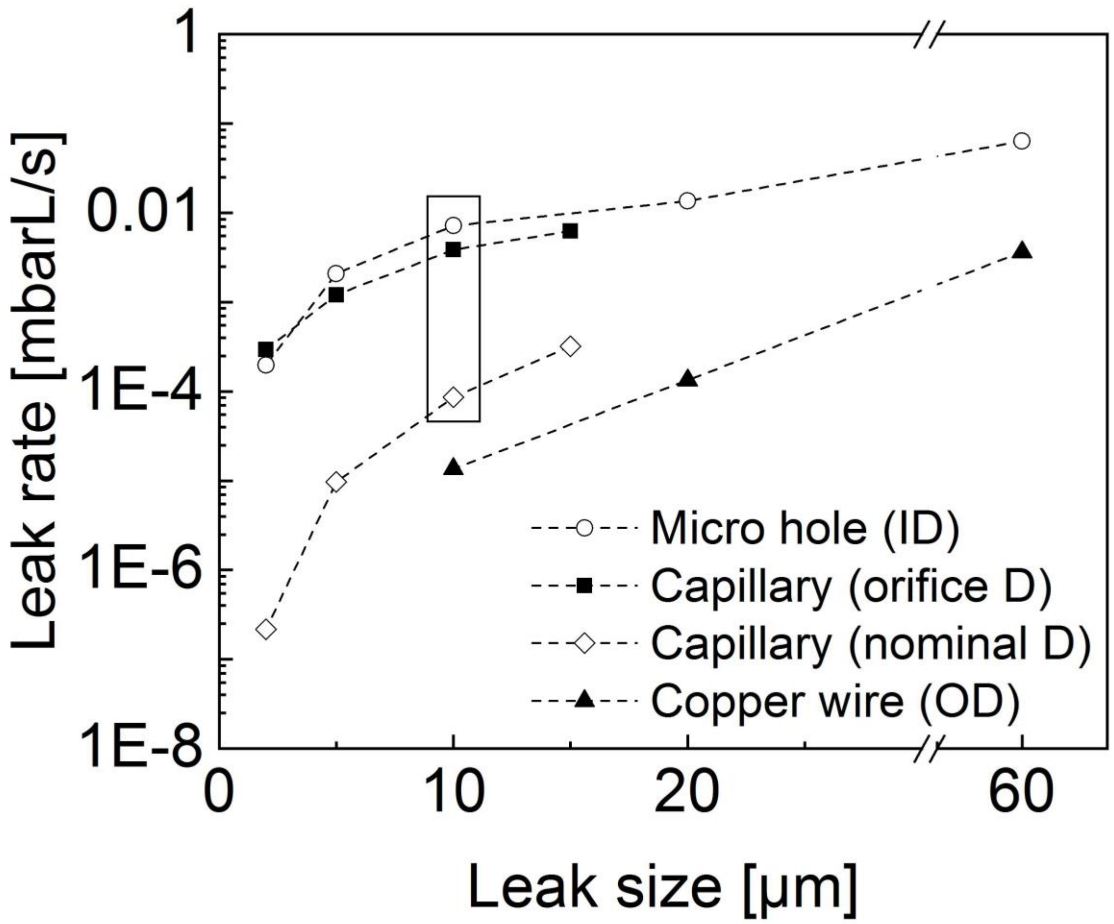
# Percentage of detected leaks (n=10) for CCIT Methods



| Artificial Leak | Leak Size | He Leak | Vacuum Decay | HSA | Dye Ingress |
|---|---|---|---|---|---|
| Negative Control | | 0% | 0% | 0% | 0% |
| Micro hole (ID) | 60 µm | 100% | 100% | 100% | 100% |
| | 20 µm | 100% | 100% | 100% | 100% |
| | 10 µm | 100% | 100% | 100% | 100% |
| | 5 µm | 100% | 100% | 100% | 60% |
| | 2 µm | 100% | 0% | 0% | 0% |
| Capillary (orifice diamer) | 15 µm | 100% | 100% | 100% | 90% |
| | 10 µm | 100% | 100% | 100% | 100% |
| | 5 µm | 100% | 100% | 100% | 50 |
| | 2 µm | 100% | 10% | 100% | 0% |
| Capillary (nominal diameter) | 15 µm | 100% | 20% | 100% | 0% |
| | 10 µm | 100% | 0% | 0% | 0% |
| | 5 µm | 100% | 0% | 0% | 0% |
| | 2 µm | 100% | 0% | 0% | 0% |
| Copper wire (OD) | 60 µm | 100% | 100% | 100% | 100% |
| | 20 µm | 100% | 20% | 0% | 0% |
| | 10 µm | 100% | 40% | 0% | 0% |

# 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 mirco hole = capillary leak (orifice diameter) > capillary leaks (nominal diameter) > copper wire
- Strong dependence of glass flow rate on leak path length

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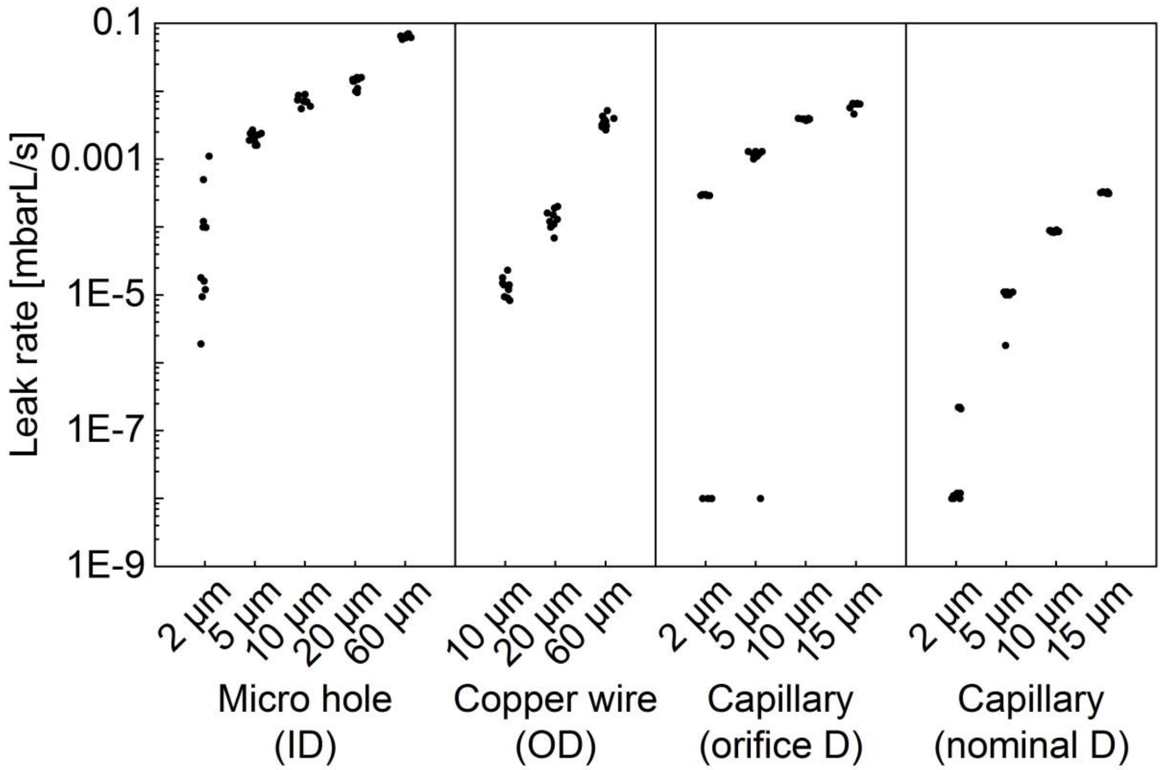
# Variability of Leak Rates of Artificial Leaks




- 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

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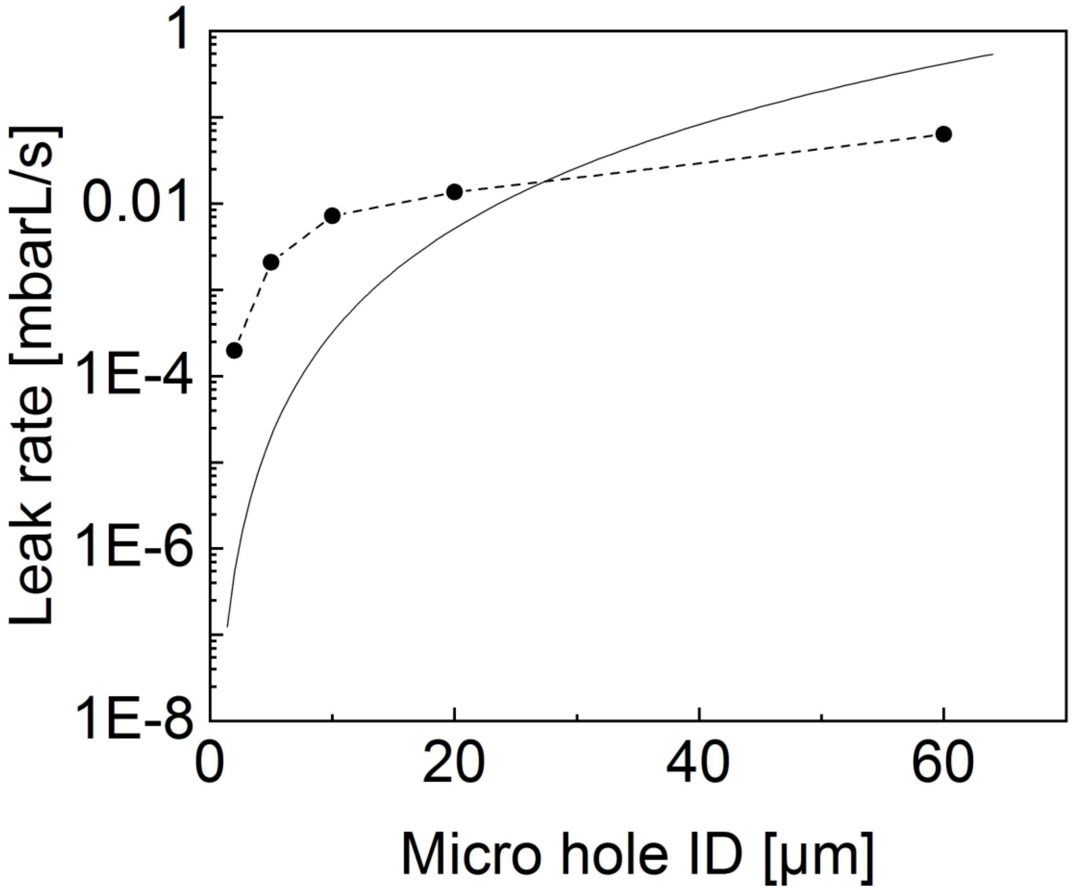
# He Leak Rates with Micro Holes vs Theoretical




- Actual leak rates vs theoretical leak rates
- Small micro holes were much larger than expected and declared by supplier – defect could increase in size during shipping or handling

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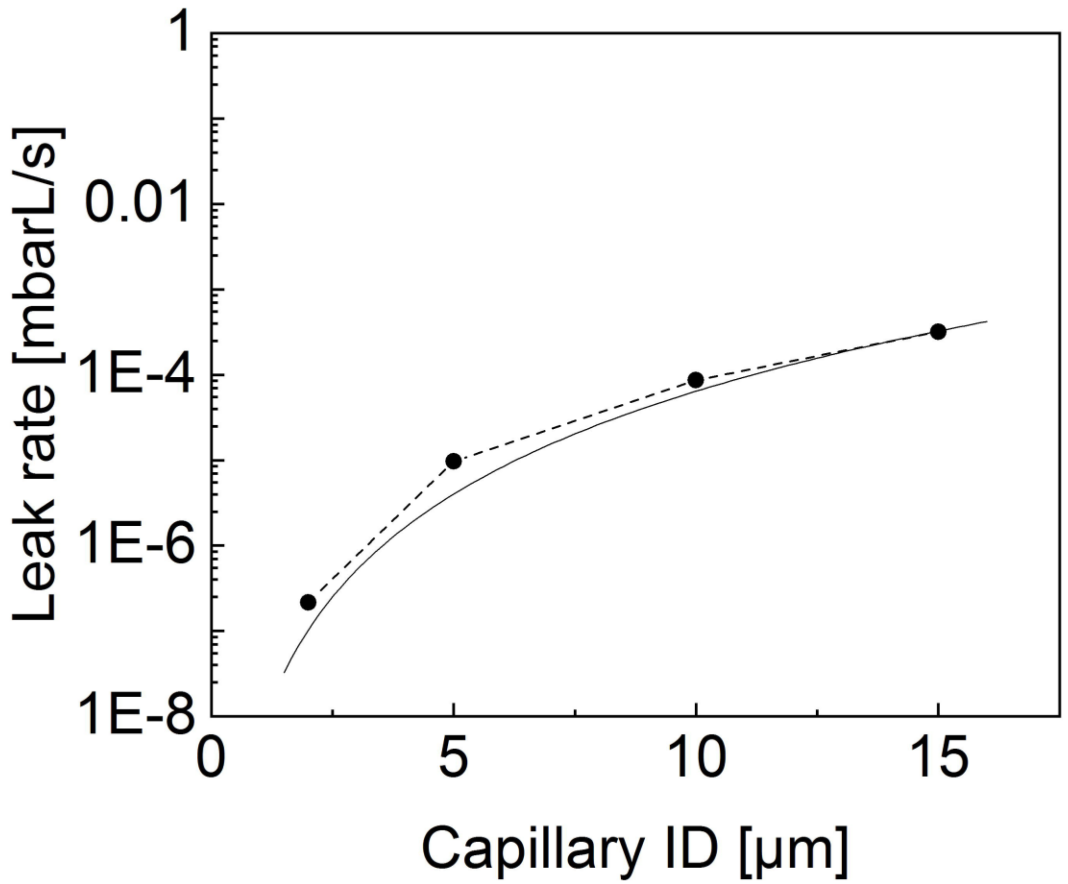
# He Leak Rates with Capillaries vs Theoretical




- Actual leak rates vs theoretical leak rates
- Capillaries with nominal diameters show good correlation to estimated theoretical leak rate at all sizes





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# Comparing Capillary Leaks with Nominal Diameter and Orifice Diameter

- Orifice diameter prepared by adjusting length and ID of capillary according to calculated leak rate
- Nominal diameter prepared with consistent length and varying ID of capillary
- Orifice sizes higher He leak rates for all sizes compared to nominal diameter
- Nominal diameter He leak rats were lower because of the negative proportional relation of the path length to the leak rate

***<u>Importance of capillary diameter and path length</u>***