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 • Difficult to determine hole size • Difficult to handle	• Too fragile for routine use • High risk of false sensitivity • Need complete seal around micropipette • Silicone oil can clog • Pinhole type defect • Material matches primary container if glass is used
Laser-drilled holes, ≥0.5 µm ID	• Wide range of sizes • Better resembles natural defects (cracks in glass; pinholes in polymer) • Newer techniques allow for defined holes; fewer cracks	• Cost • Size of laser-drilled void needs to be calibrated and represents defined path • Small hole can clog (silicone, viscous liq) • Holes can increase in size (temp changes, tension) • Variability in sizes depending on material/ wall thickness • Irregular shapes • Cannot be prepared on product	• Risk of alteration post manufacture/calibration • Specialized external supplier • Many material can be drilled • Closer to real world defects • May reuse positive controls • 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 • Easy preparation at testing location • Possible to prepare controls in specific packaging format and for multiple products • Prepared in flexible way (e.g. may contact liq and headspace)	• Length of microtube defects is usually longer than real world defects • Typically nominal diameters > 2µm available & uncertainty of actual diameter • Capillary diameter and hold diameter not comparable with regard to flow rate • Glue can create blockage	• Robust, wide size range & different materials available • Leakage rates can be fine-tuned through length of capillaries; not only using IDs • Consistent dimensions/leaks • Defined dimensions mean don't have to calibrate each lead
Micron wires, ≥10 µm ID (e.g. uncoated copper)	• Low cost • Robust	• Handling of micron wires can be difficult and size of void needs to be calibrated and represent undefined path • Holes can close up over time depending on material relaxation • No direct measurement of hole size	• Reproducible leak size with defined capping parameter and wire size • Leak size only defined when measured relative to physical phenomenon • Need to consider copper wire diameter and elastomer behavior for consistency • Actual size depends on many parameters

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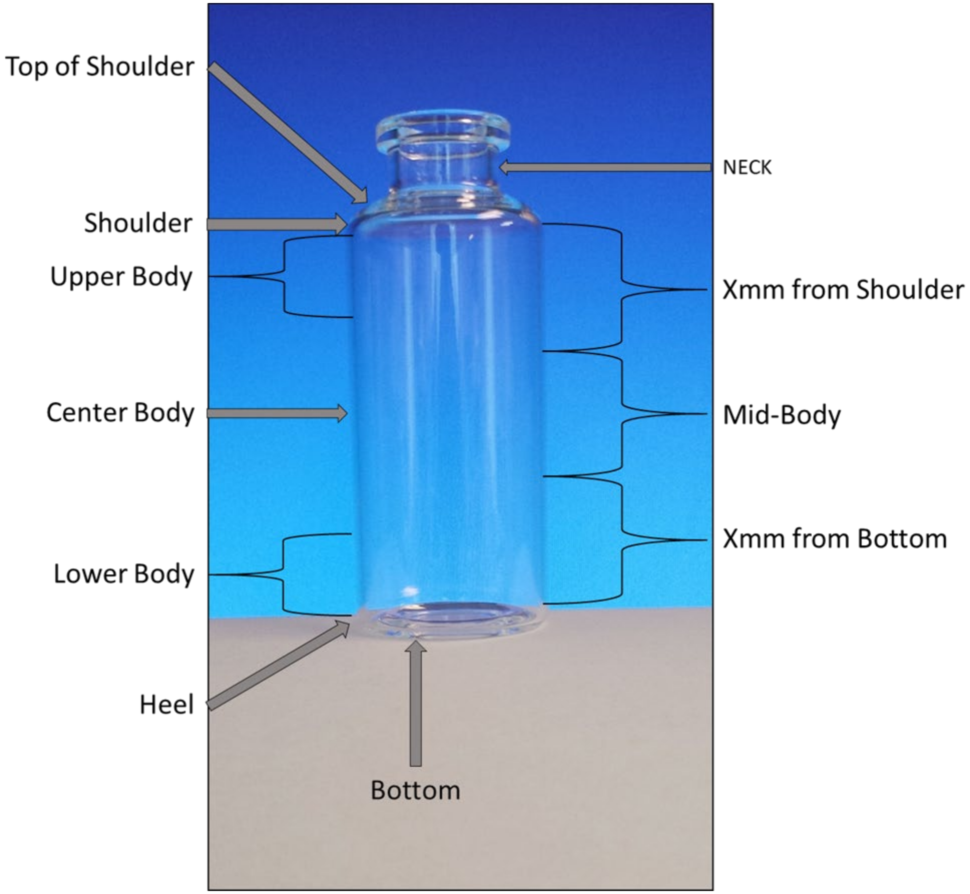
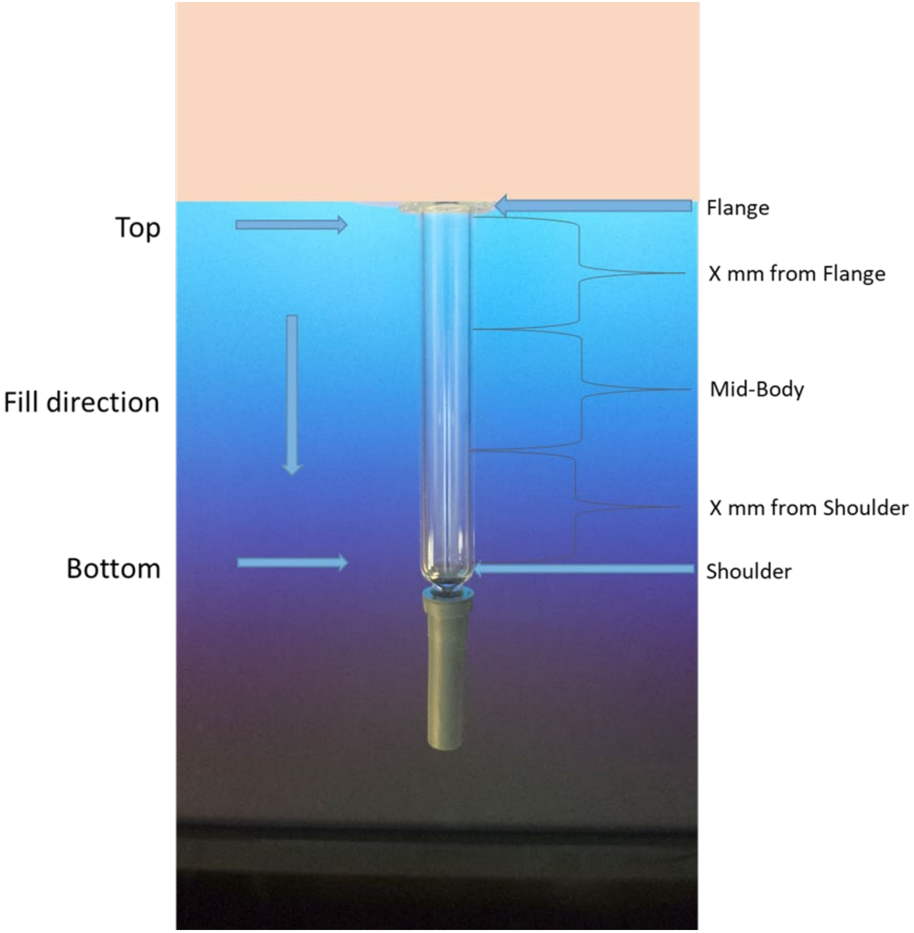
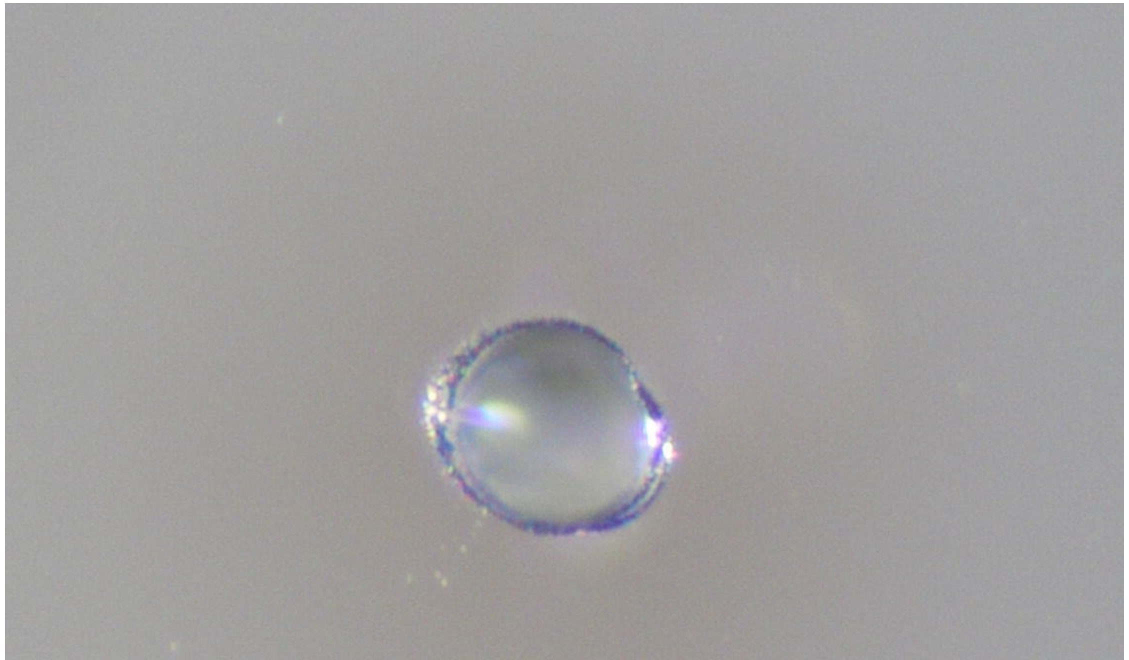
Common Hole Locations in Glass Vials



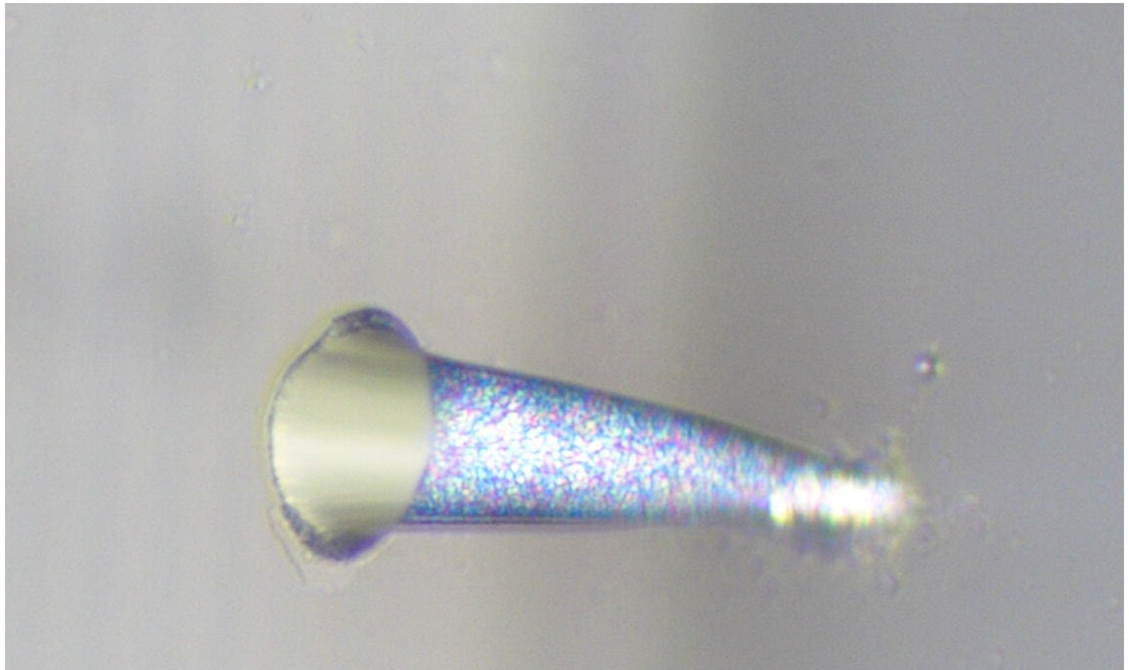
Common Hole Locations in Syringes



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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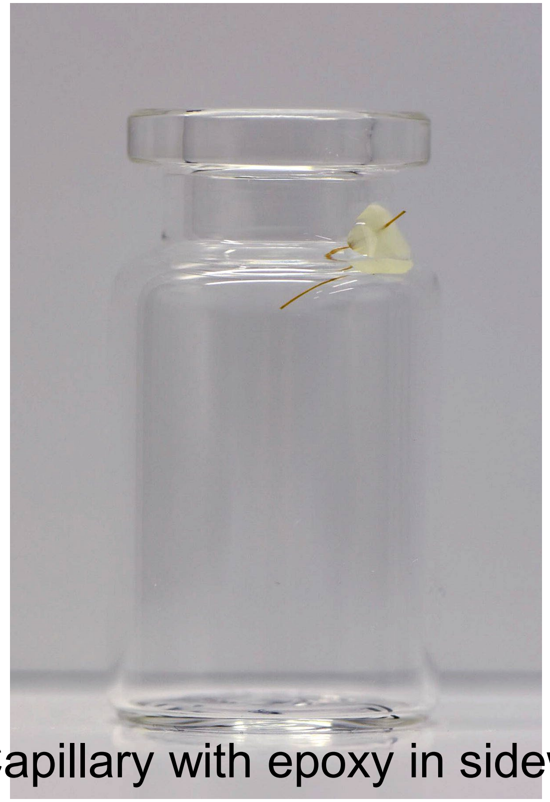
Capillary & Microfibers



Capillary with epoxy in sidewall

Copper wire between stopper and vial

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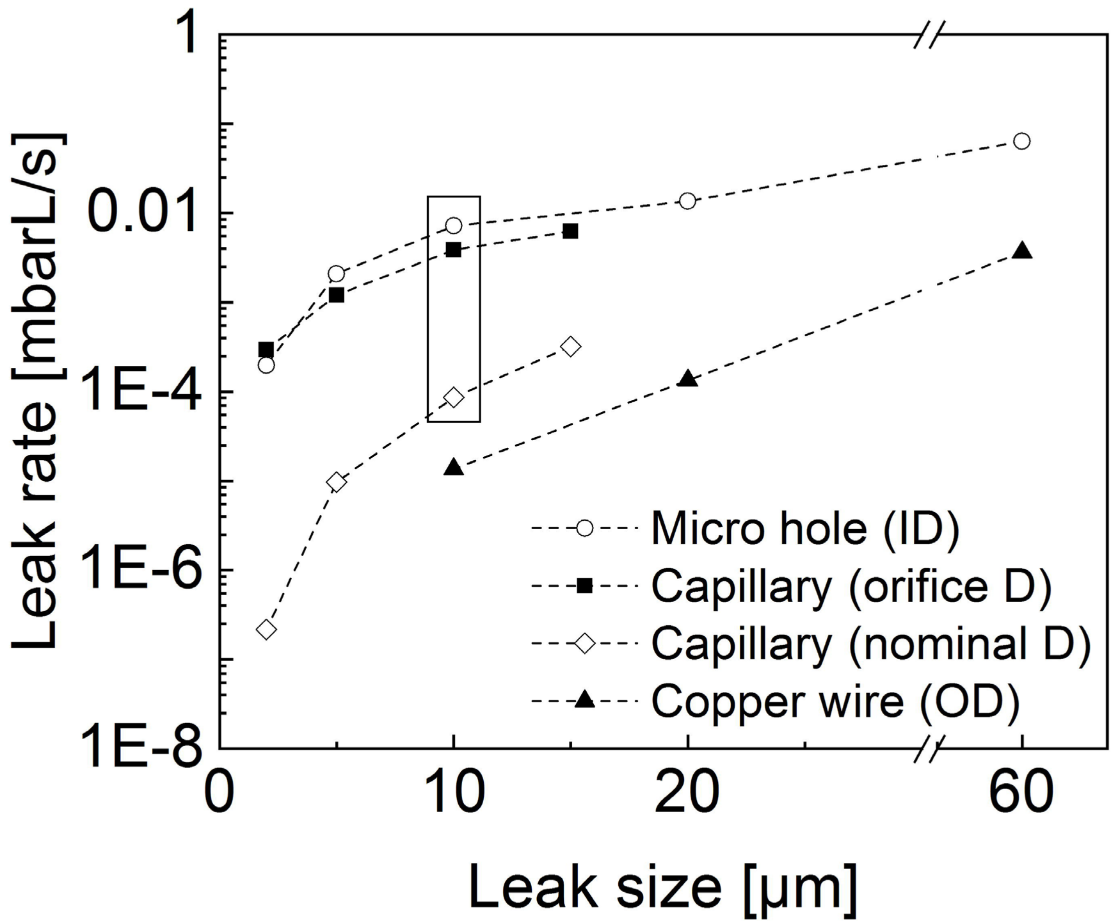
Percentage of detected leaks (n=10) for CCIT Methods

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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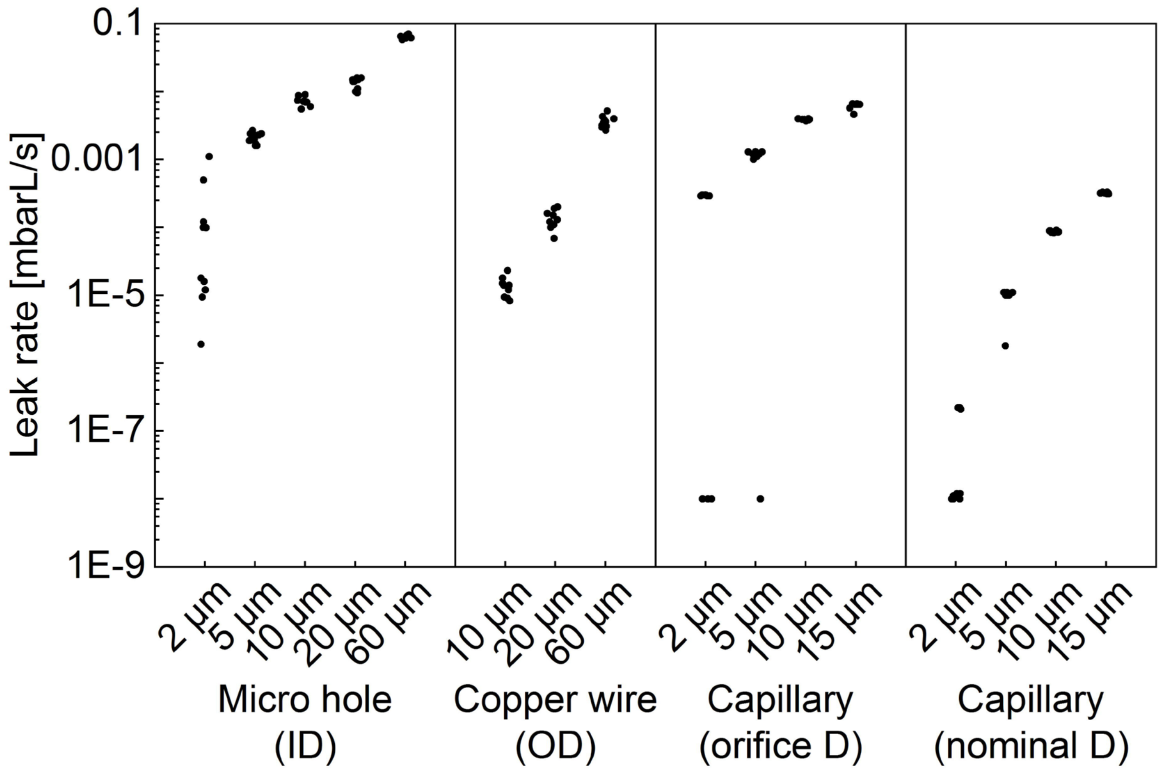
Variability of Leak Rates of Artificial Leaks



- 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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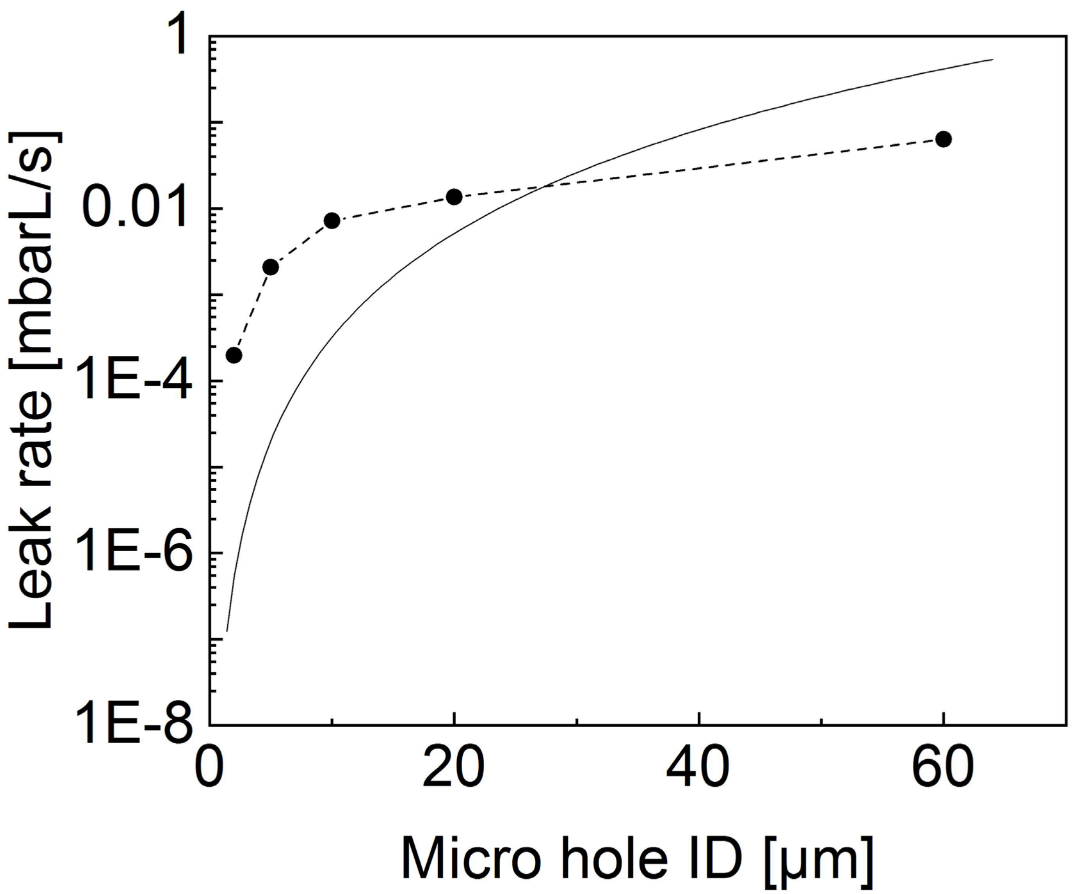
He Leak Rates with Micro Holes vs Theoretical



- 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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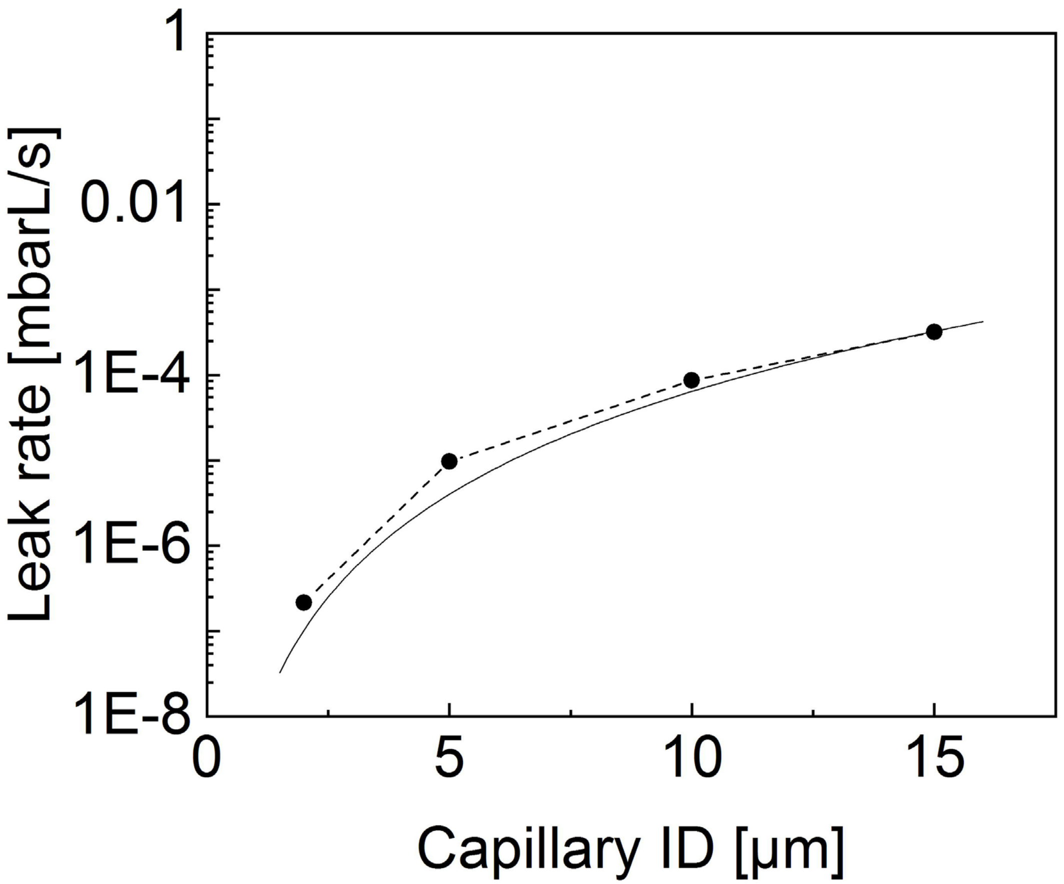
He Leak Rates with Capillaries vs Theoretical



- 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

Importance of capillary diameter and path length