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

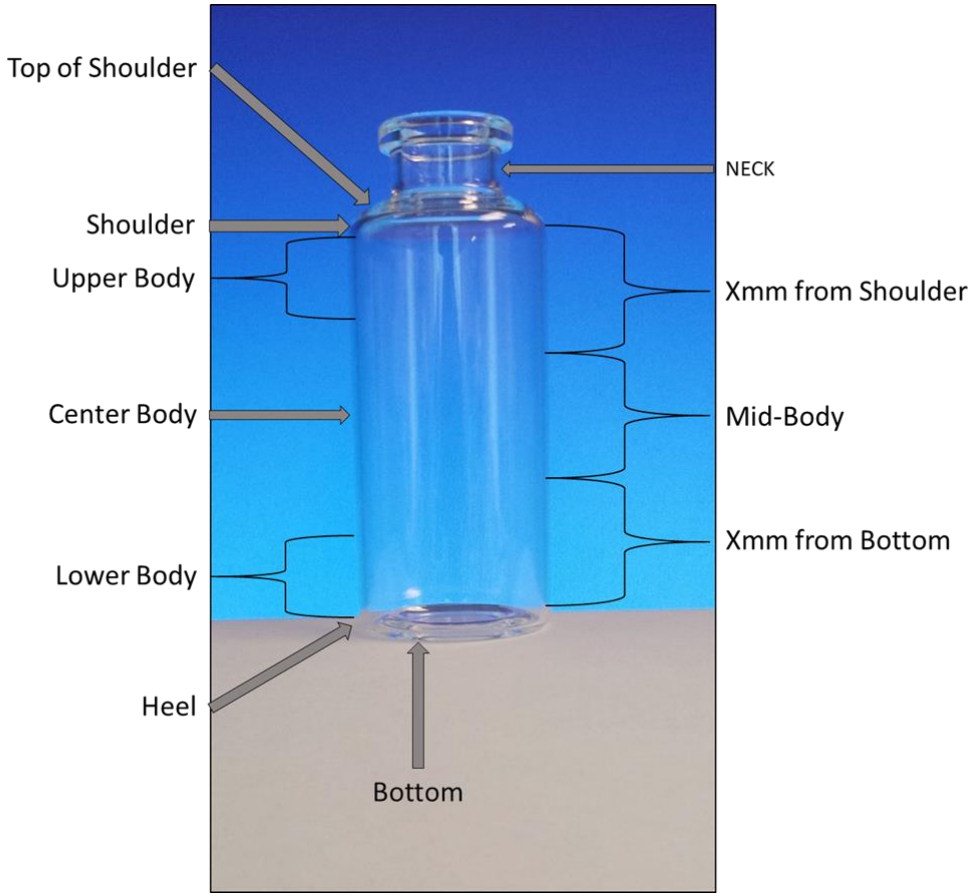
Leak Type	Advantages	Disadvantages	Experiences
Mirco-pipettes, ≥0.1 µm ID (e.g. glass)	Easy sample preparation	• Fragile & broken tips may not be detected • Difficult to determine hole size • Difficult to handle	• Too fragile for routine use • High risk of false sensitivity • Need complete seal around 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

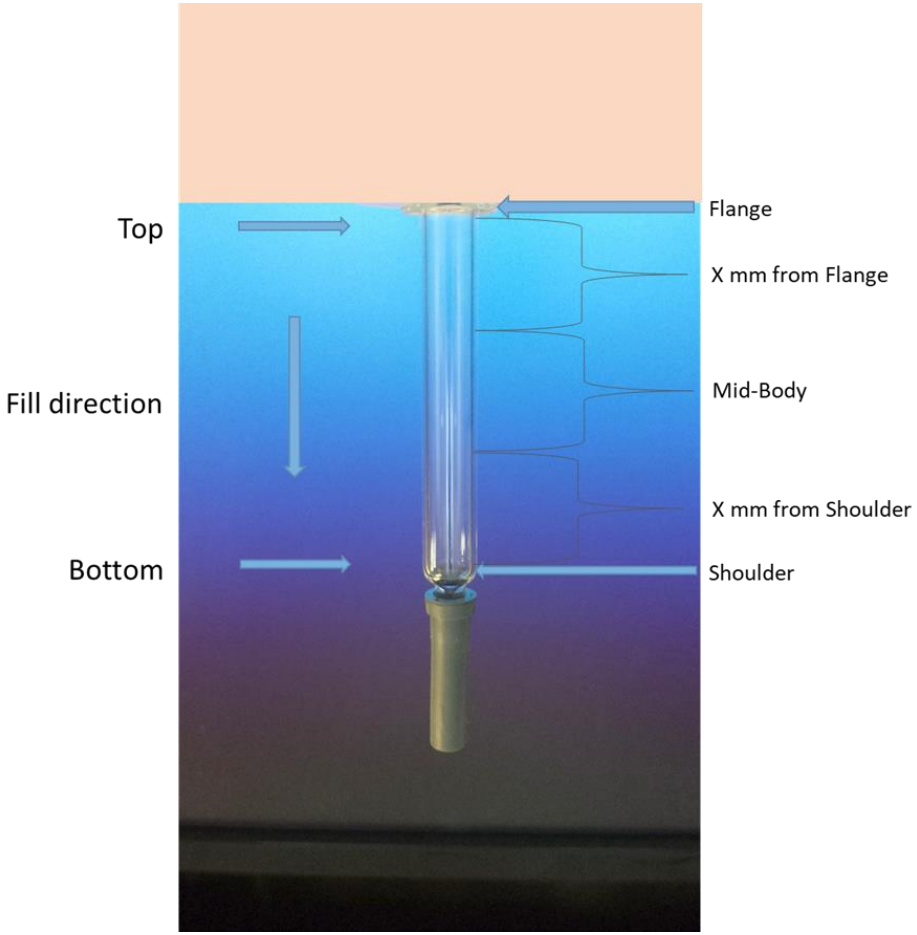
Leak Type	Advantages	Disadvantages	Experiences
Capillaries, ≥0.2 µm ID (e.g. fused silica)	• Robust • Easy preparation at testing location • Possible to prepare controls in specific packaging format and for multiple products • Prepared in flexible way (e.g. may contact liq and headspace)	• Length of 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

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

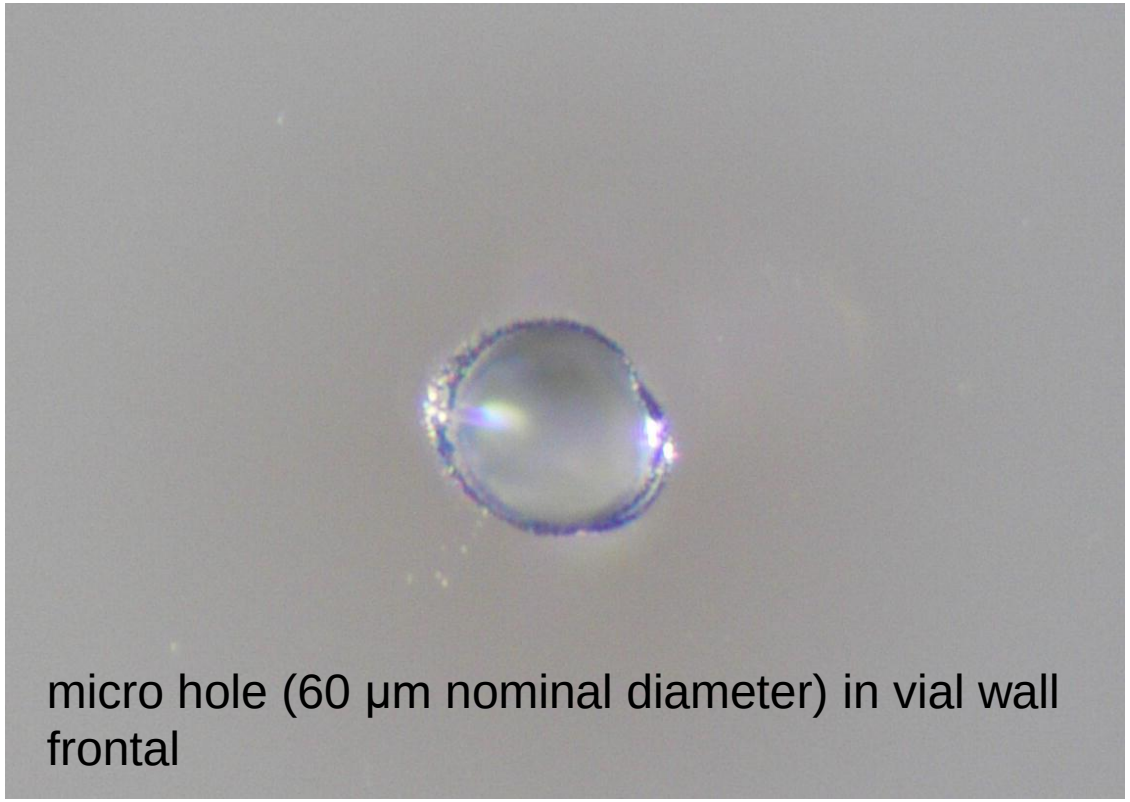
Common Hole Locations in Glass Vials



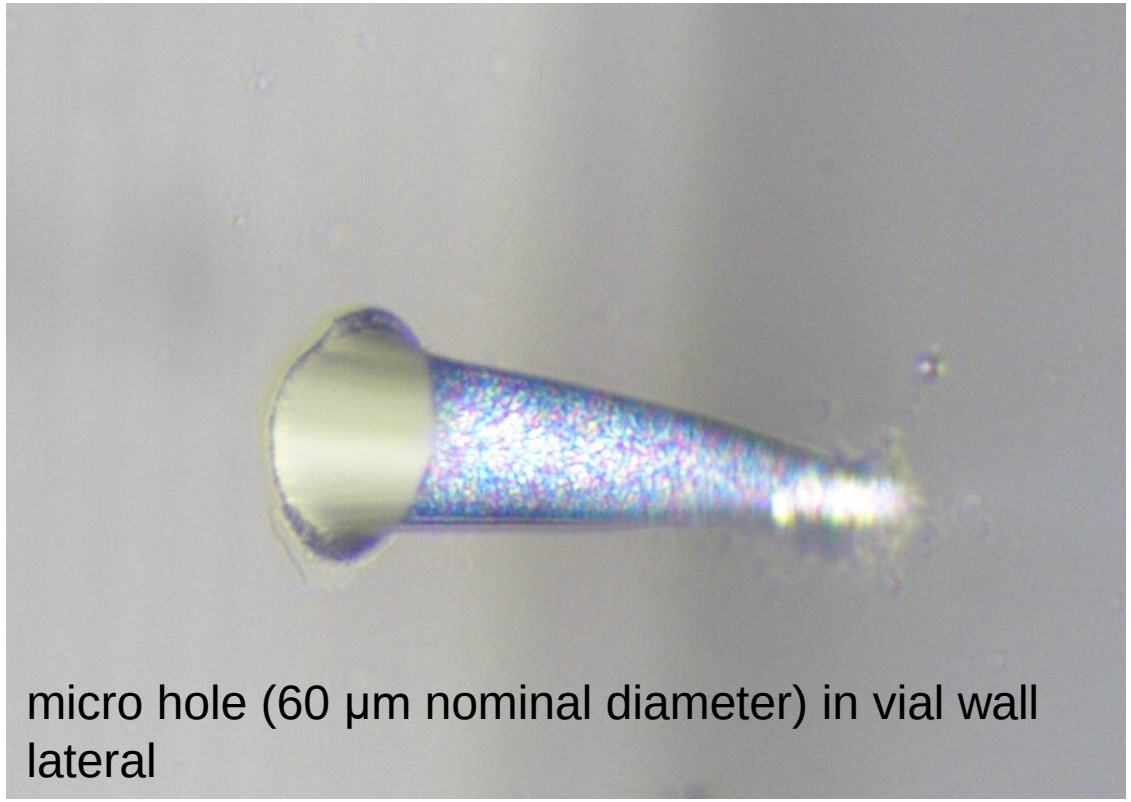
Common Hole Locations in Syringes



Micro hole leak: light microscope images of laser drilled



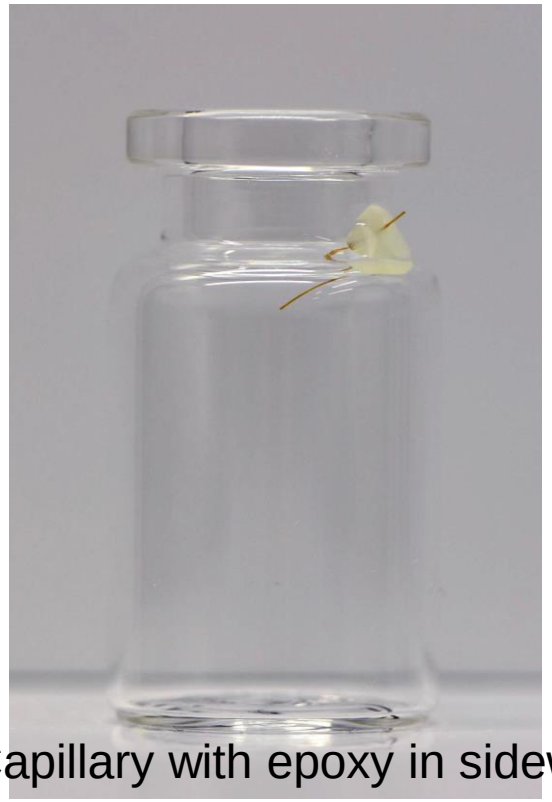
micro hole (60 µm nominal diameter) in vial wall frontal



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

Sarah S Peláez, Hanns-Christian Mahler, Christoph Herdlitschka, et al. PDA Journal of Pharmaceutical Science and Technology 2019. "Comparing Physical Container Closure Integrity Test Methods and Artificial Leak Methodologies."

Capillary & Microfibers



Capillary with epoxy in sidewall

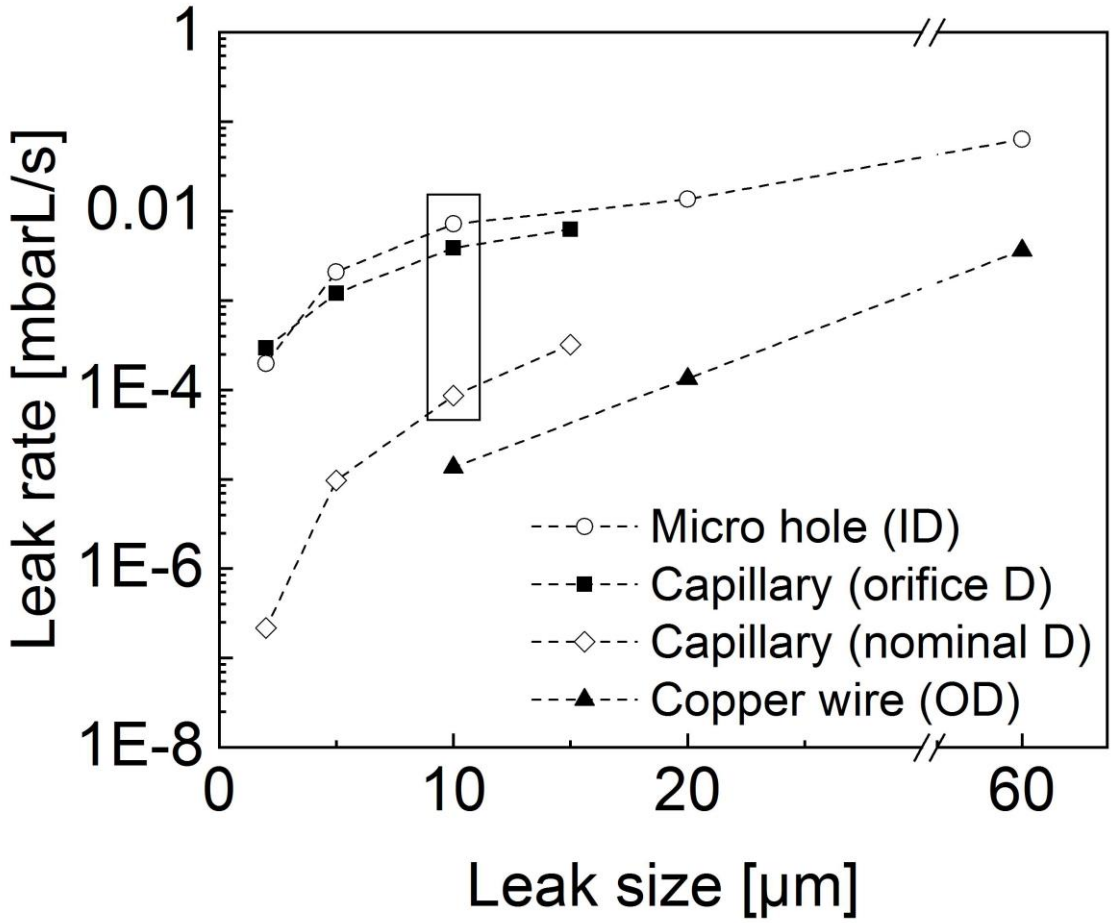
Copper wire between stopper and vial

Sarah S Peláez, Hanns-Christian Mahler, Christoph Herdlitschka, et al. PDA Journal of Pharmaceutical Science and Technology 2019. "Comparing Physical Container Closure Integrity Test Methods and Artificial Leak Methodologies."

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%

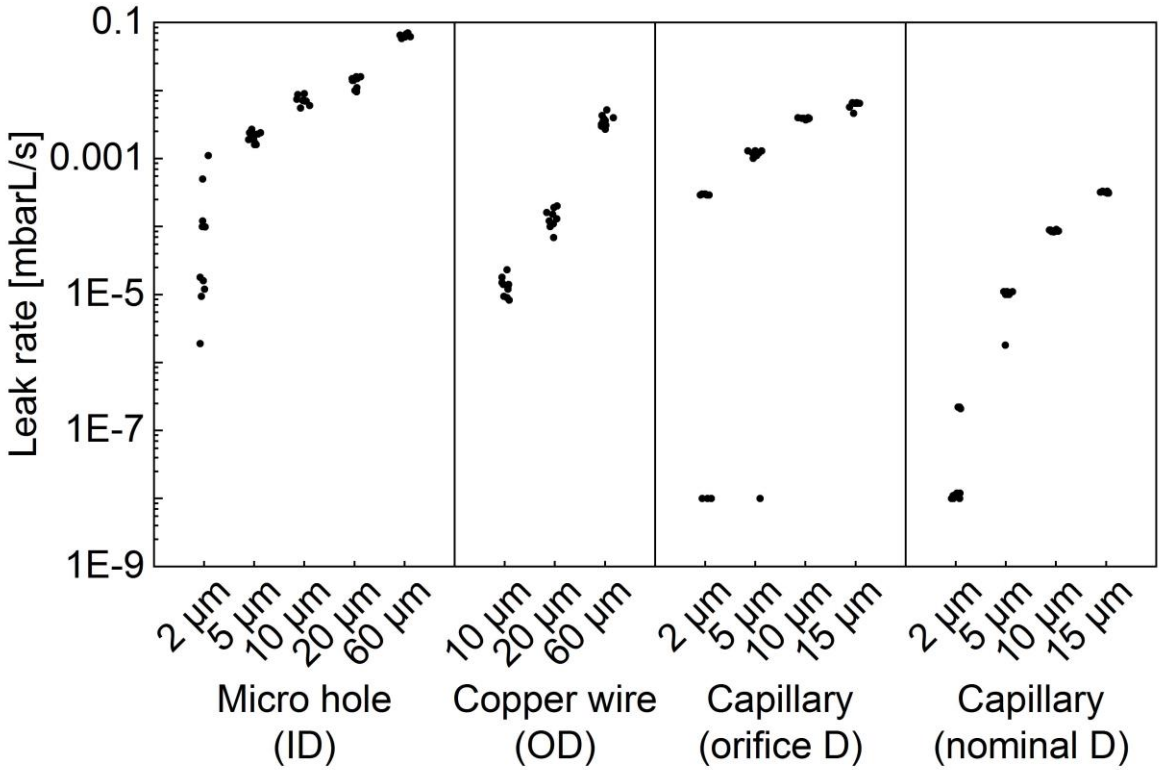
He Leak Rates for Artificial Leaks



- 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

Sarah S Peláez, Hanns-Christian Mahler, Christoph Herdlitschka, et al. PDA Journal of Pharmaceutical Science and Technology 2019. "Comparing Physical Container Closure Integrity Test Methods and Artificial Leak Methodologies."

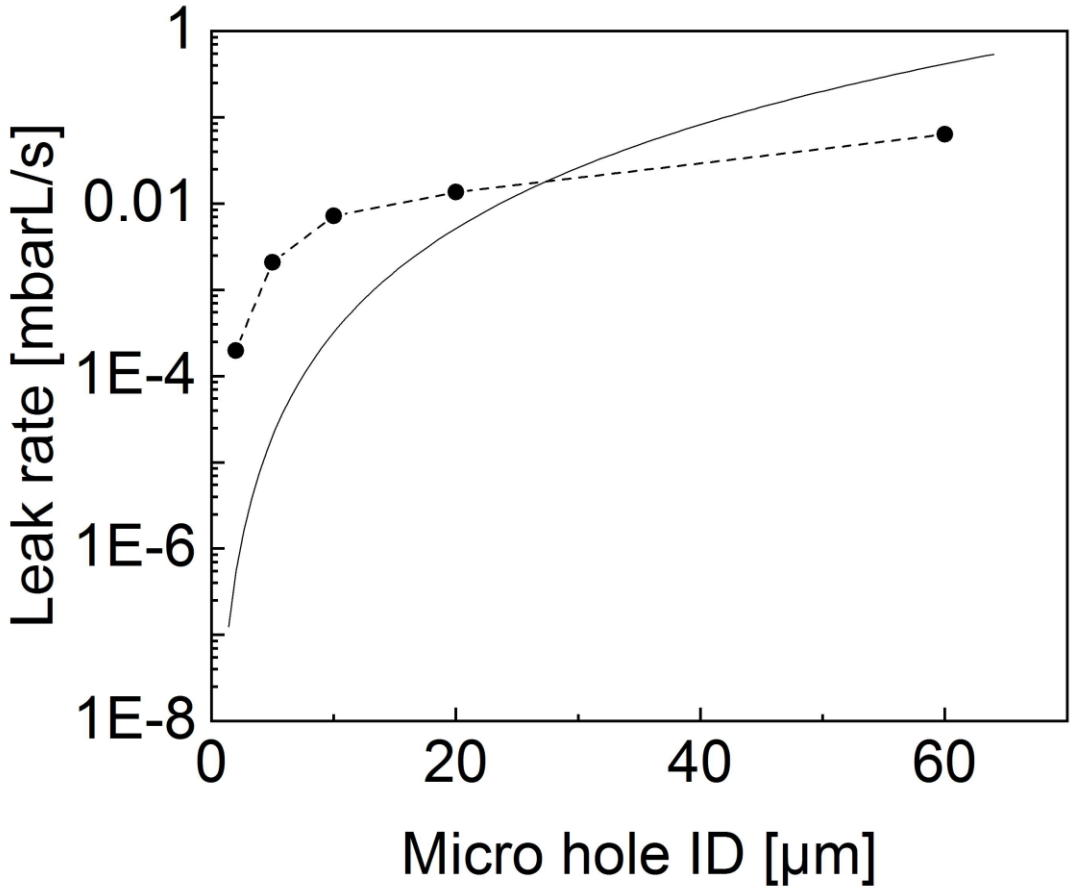
Variability of Leak Rates of Artificial Leaks



- 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

Sarah S Peláez, Hanns-Christian Mahler, Christoph Herdlitschka, et al. PDA Journal of Pharmaceutical Science and Technology 2019. "Comparing Physical Container Closure Integrity Test Methods and Artificial Leak Methodologies."

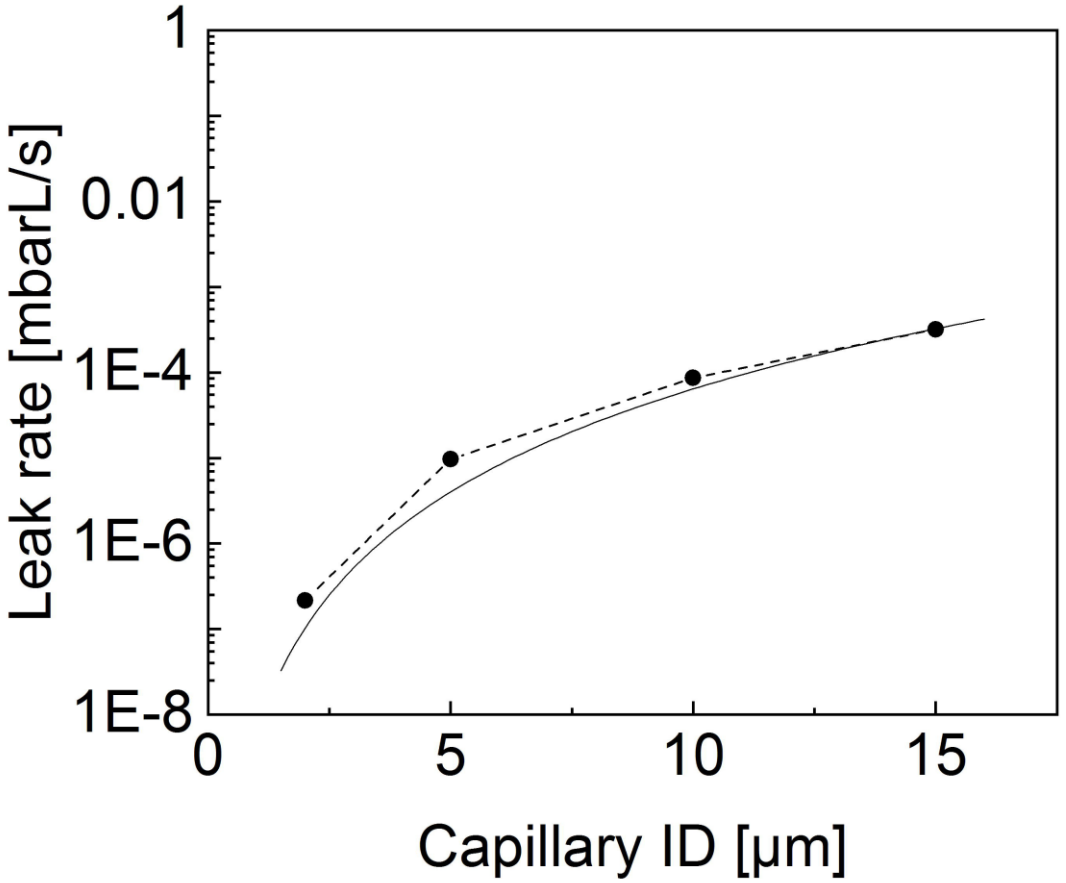
He Leak Rates with Micro Holes vs Theoretical



- 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

Sarah S Peláez, Hanns-Christian Mahler, Christoph Herdlitschka, et al. PDA Journal of Pharmaceutical Science and Technology 2019. "Comparing Physical Container Closure Integrity Test Methods and Artificial Leak Methodologies."

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

Sarah S Peláez, Hanns-Christian Mahler, Christoph Herdlitschka, et al. PDA Journal of Pharmaceutical Science and Technology 2019. "Comparing Physical Container Closure Integrity Test Methods and Artificial Leak Methodologies."

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