SWITCHING TO SILICONE OIL FREE SYRINGES FOR INTRAVITREAL APPLICATION: DESIGN OF A REGULATORY COMPLIANT CONTAINER CLOSURE INTEGRITY TEST REALIZABLE IN A HOSPITAL PHARMACY

Simon Decker, Karin Nemec
Hospital pharmacy, Clinic Donaustadt, Vienna, Austria

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Background and importance

- Aseptic compounding of medicinal products for intravitreal application (IVOM) into ready-to-use syringes
- Commonly used lubricant silicone oil can elicit adverse reactions[1,2]
- Silicone-oil free syringes with minimal dead space are available
- Container closure integrity test (CCIT) required before switching primary packaging container

Aim and objectives

- **Design of CCIT:** Demonstrate the design of CCIT in compliance with EU GMP Annex 1
- **Cost-Effective Methods:** Employ only economical devices that are widely accessible to hospital pharmacies.
- **Syringe Testing:** Evaluate all locally available, silicone oil-free syringes suitable for intravitreal application.

	SJJ	Braun	Ocuject
product	Zero Residual 0.2ml	Inject F Luer Solo	Vitreject Syringe LDS
manufacturer	SJJ Solutions B.V.	B. Braun Melsungen AG	Ocuject LLC
maximum volume	0.2 mL	1.0 mL	1.0 mL

Table 1: Comparison of all tested syringes

Materials and methods

- EU GMP Annex 1 8.23 & 8.25 demand validated methods that include environmental parameters which can negatively impact packaging integrity (i.e. decompression during transport)

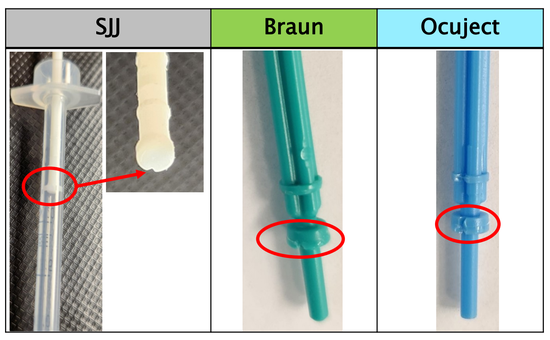

Fig. 1: Positive controls are made by cutting a small opening into the seal of the plunger using pliers. Visualized with red circles. Representative pictures shown for each product tested.

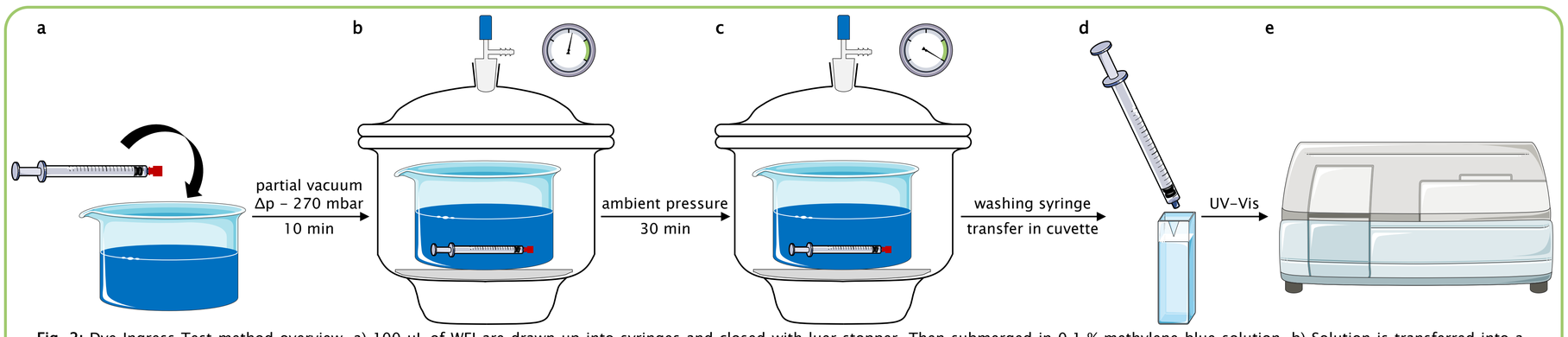

Fig. 2: Dye Ingress Test method overview. a) 100 µL of WFI are drawn up into syringes and closed with luer stopper. Then submerged in 0.1 % methylene blue solution. b) Solution is transferred into a desiccator and partial vacuum applied (– 270 mbar relative to ambient pressure) for 10 minutes c) Desiccator is re-pressurized to ambient pressure and syringes left in dye solution for 30 minutes d) Syringes are washed 5 times, visually checked for coloring and solutions transferred into cuvettes e) Dye ingress is quantified via absorption at 633 nm

Results

- ✓ All syringes passed CCIT
- ✓ Standard curve of methylene blue dye 0.05 – 5 µg/mL
- ✓ Luer lock and luer slip fittings showed no difference
- ✓ Positive controls showed strong signal (blue coloring)

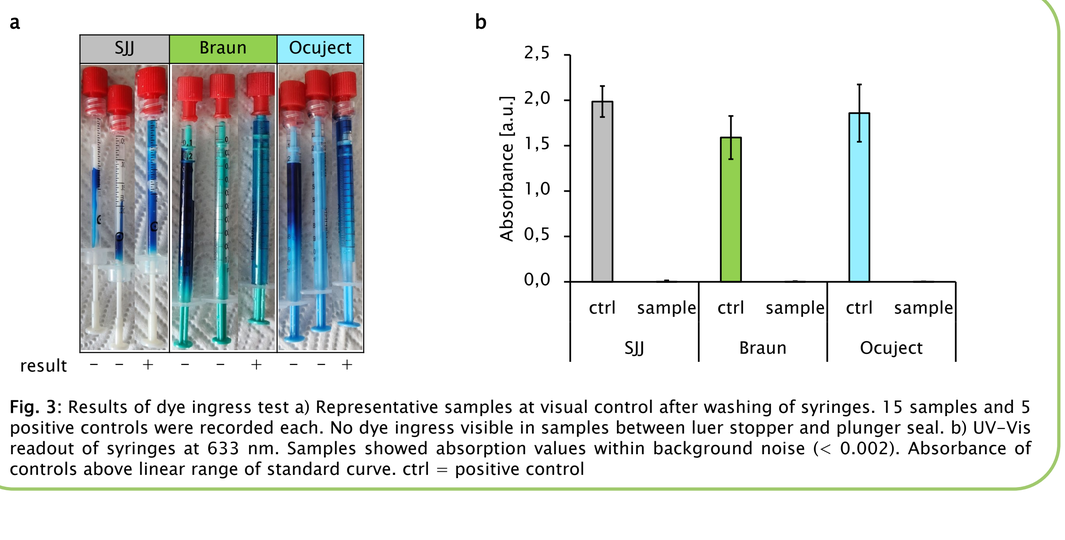

Fig. 3: Results of dye ingress test a) Representative samples at visual control after washing of syringes. 15 samples and 5 positive controls were recorded each. No dye ingress visible in samples between luer stopper and plunger seal. b) UV-Vis readout of syringes at 633 nm. Samples showed absorption values within background noise (< 0.002). Absorbance of controls above linear range of standard curve. ctrl = positive control

Conclusion and relevance

- **Duration:** The entire test procedure can be completed in approximately 2 hours
- **Simplicity:** Requires minimal prerequisites for administration
- **Cost-effectiveness:** Low-cost solution
- **Purpose:** Enable hospital pharmacies with limited budget to design GMP compliant CCIT
  - The test displayed is designed for validation off-line on representative syringe samples and is not suitable for online testing

References

1. John T. Thompson, Prospective Study of Silicone Oil Microdroplets in Eyes Receiving Intravitreal Anti-Vascular Endothelial Growth Factor Therapy in 3 Different Syringes. Ophthalmol Ret. 2021;5(3):234-240. https://doi.org/10.1016/j.oret.2020.07.021.
2. Lu Liu et al., Silicone Oil Microdroplets and Protein Aggregates in Repackaged Bevacizumab and Ranibizumab: Effects of Long-term Storage and Product Mishandling. Invest. Ophthalmol. Vis. Sci. 2011;52(2):1023-1034. https://doi.org/10.1167/iovs.10-6431.

Wiener Gesundheitsverbund
Klinik Donaustadt

Für die Stadt Wien

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Contact information: Simon Decker, simon.decker@gesundheitsverbund.at