A science- and risk-based strategy to qualify sterilised prefilled syringes as primary packaging material in a hospital pharmacy

K.H.M. Larmené- Beld[1,2], A. Kuiper[1], S. van Berkel[1], H. Robben[1], R.W. Wijnsma[1], K. Taxis [2], H.W. Frijlink[3]

[1] Isala, Department of Clinical Pharmacy, Zwolle, The Netherlands.
[2] University of Groningen, Unit of PharmacoTherapy, -Epidemiology & PharmacoEconomics (PTE2), Groningen Research Institute of Pharmacy, Groningen, The Netherlands
[3] University of Groningen, Department of Pharmaceutical Technology and Biopharmacy, Groningen, The Netherlands.

Introduction

To improve medication safety in hospitals, The Joint Commission International standard recommend implementation of ready to administer (RTA) drugs. Many hospital pharmacies facilitate this in aseptic filling of polypropylene single use syringes. One of the main disadvantages of this product, though the container is not meant for storage, is the aseptic process, the short shelf life and the refrigerator capacity. The solution was found in a cyclic olefin polymer (COP) syringe, which can be terminally sterilized. All individual components of the syringe comply with the regulatory demands but to ensure that the new product do not adversely affect patient safety or product quality qualification is needed.

Purpose

A science- and risk based strategy to qualify COP syringes as primary packaging material for production of terminally sterilized ready to administer syringes with an high speed (semi-) automatic filling and closing machine in hospital pharmacy.

Material and methods

Component	5ml	50ml
Syringe barrel	BD Crystal Clear Polymer (polycycloolefine) Lubrication: silicone coating	BD Crystal Clear Polymer (polycycloolefine) Lubrication: silicone coating
Plunger stopper	SBR rubber - Silicon coating: DC 360	FM457 butyl rubber - Silicon coating: Rhodia 70047
Tip cap	Luer lok: Thermoplastic elastomer blend	S-Lok; plastic part: Polypropylene Rubber part: Butyl rubber.

→ pH and polarity are decisive for the egress of possible extractables and leachables from the syringe.[1,2]

→ Validation batches were produced:
- → NaCl 0.9%
- → Na_2HPO_4 / NaH_2PO_4 buffer with pH 2, 5.8, 8 and 11
- → IPA 5% in water
- → Water for Injections (WFI)

Following tests were performed
- Clarity and degree of opalescence of the solution (Ph. Eur. 2.2.1.)
- Degree of coloration of the solution (Ph. Eur. 2.2.2)
- pH of the solution
- Absorbance (Ph. Eur 3.2.2.1)
- Reducing substances (Ph. Eur. 3.2.2.1)
- Transparancy (Ph. Eur 3.2.2.1),
- Weight loss
- Subvisible particles (Ph. Eur. 2.9.19)
- Silicium
- Closure integrity (related to Ph. Eur. 3.2.9)
- Sterility (Ph. Eur. 2.6.1).

Analyses were performed at t=0, 1, 2, 3, 4, 5, 6, 9, 12, 18 and 24 months

Results

All performed tests comply with acceptance criteria according to the Ph. Eur. Monographs.

Solvent	Minimum- maximum level measured during 0-24 months				
	pH	Clarity (Clear)	Colour (≤ BY7)	Weight loss (≤2.0%)	Absorbance (≤0.20)
Phosphate buffer pH 2.0	2.2 - 2.3	Clear	< BY7	0 - 0.3%	<0.01 - 0.01
Phosphate buffer pH 5.8	5.7 - 5.9	Clear	< BY7	0 - 0.5%	<0.01 - 0.02
Phosphate buffer pH 8.0	7.8 - 7.9	Clear	< BY7	0 - 0.3%	<0.01 - 0.01
Phosphate buffer pH 11.4	11.4 - 11.5	Clear	< BY7	0 - 0.3%	0.02 - 0.05
NaCl 0.9%	5.0 - 10.0	Clear	< BY7	0 - 0.3%	<0.01 - 0.02
IPA 5%	NA	Clear	< BY7	0 - 0.3%	<0.01 - 0.03

Table 1: *Results general chemistry tests syringe 5ml*

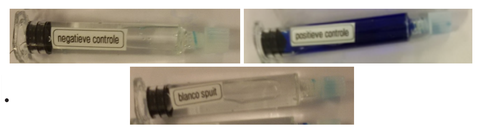
Solvent	Minimum- maximum level measured during 0-24 months				
	pH	Clarity (Clear)	Colour (≤ BY7)	Weight loss (≤2.0%)	Absorbance (≤0.20)
Phosphate buffer pH 2.0	2.2 - 2.3	Clear	< BY7	0 - 0.1%	<0.01 - 0.03
Phosphate buffer pH 5.8	5.4 - 5.9	Clear	< BY7	0 - 0.1%	<0.01 - 0.02
Phosphate buffer pH 8.0	7.8 - 7.9	Clear	< BY7	0 - 0.1%	<0.01 - 0.02
Phosphate buffer pH 11.4	11.4 - 11.6	Clear	< BY7	0 - 0.1%	<0.01 - 0.06
NaCl 0.9%	5.5 – 8.9	Clear	< BY7	0 - 0.3%	<0.01 - 0.02
IPA 5%	NA	Clear	< BY7	0 - 0.1%	0.01 - 0.03

Table 2: *Results general chemistry tests syringe 50ml*

High pH value (11.4) shows higher absorbance, indicating more extractables and leachables (maximum 0.06 at t=24 months) than neutral pH ranges (5-8), maximum 0.02. This effect was also seen for the silicum concentrations in the syringes, with higher concentration silicium at pH 11.4 and pH 2.

The solutions were sterile and the amount of particles was within limits (≤6000 particles/ syringe for particles ≥10µm and ≤600 particles/ syringe for particles ≥25µm).

All syringes passed the closure integrity test. Test has been validated with a positive control.



Conclusion

The syringes are suitable as primary packaging material for producing ready to administer products in hospital pharmacy.

Already 20 products (17 API's) are qualified in the container.

References

[1] Extractables Characterization for Five Materials of Construction Representative of Packaging Systems Used for Parenteral and Ophthalmic Drug Products. D. Jenke, J.Castner, T. Egert, et al. PDA J Pharm Sci and Tech 2013, 67 448-511

[2] Evaluation of the General Solution Compatibility of Polymer Materials Used in Medical Devices such as Syringes. D. Jenke, A. Odufu, T. Couch, et al. PDA J Pharm Sci and Tech 2012, 66 286-306

university of groningen

isala