Sterilized RTA syringes produced by the hospital pharmacy; a field report from The Netherlands

8 February 2023
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Hospital pharmacist, Isala Zwolle, The Netherlands

Introduction

2016- present : Head of production facility , Isala

2014- present : Hospital pharmacist, Isala

2014-2020 : PhD thesis “Ready to administer parenteral medication produced by the hospital pharmacy: cost, labelling, and quality” University of Groningen, promotors: prof. dr. K. Taxis, prof. dr. M. J. Postma, prof. dr. H.W. Frijlink

2010- 2013 : Trainee hospital Pharmacist Isala

Isala hospital

Teaching hospital, two locations:

Isala Zwolle

Isala Diaconessenhuis Meppel

- 1224 beds
- Nursing days 211.113
- Employees: 6.490 (4843 fte)

Department of Clinical pharmacy- production

- ✓ GMP
- ✓ Manufacturings licence (small volume parenterals)

Stock preparation:

- Aseptic preparation
- Non sterile
- Sterile
  - Infusion bags
  - Syringes

Individual preparation:

- Aseptic (infliximab, antibiotics, pain medication)
- Cytostatics
- Parenteral nutrition
- Capsules, liquids

Hospital pharmacy in The Netherlands

12-15 hospital pharmacies with a production facility (clean room)

According to the Dutch medicine law

small scale, own patients

Dutch Healthcare Inspectorate:

Hospital pharmacies are allowed to produce unlicensed medicinal products

under strict condition of the circular letter

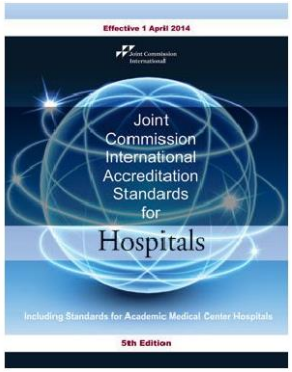
→ Set of conditions (rationale, product dossier, GMP)

Preparing parenteral drugs is high risk process

- Wrong drug
- Wrong dosage
- Calculation errors
- Microbial contamination

Guidelines

- European Resolution CM/Res(2016)1 and 2
- Dutch Guideline High risk medication
- JCI standards

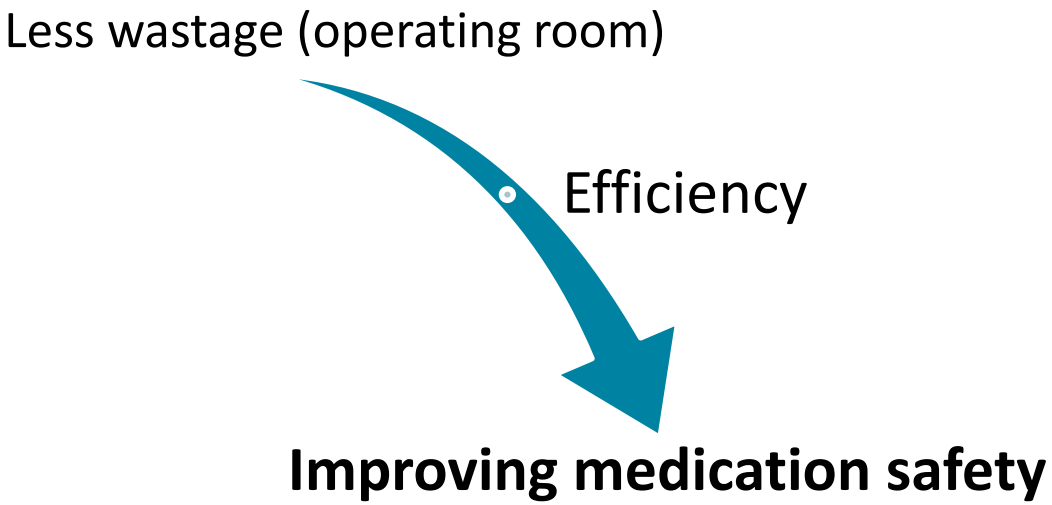


→ Delivering medications in the most ready to administer form to the wards

Advantages preparation ready to use medication by hospital pharmacy

Savings

- Time preparation nurses of medication
- Reducing medication errors
- Less microbial contamination
- Less usage needles, syringes on the ward



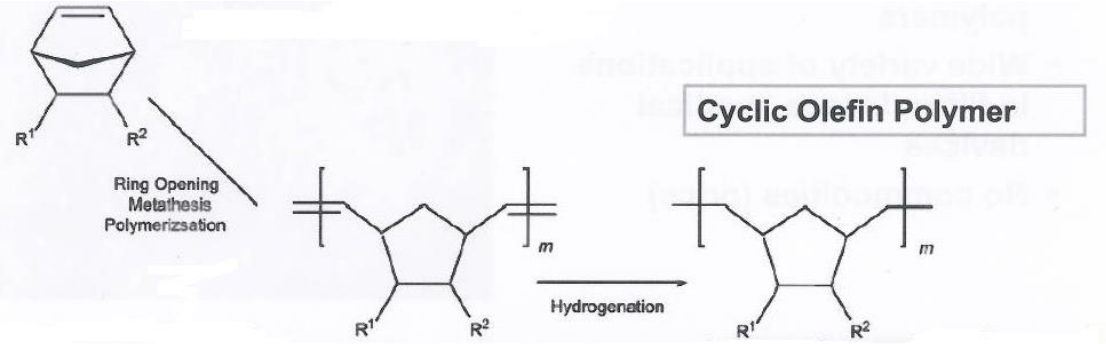
Aseptic syringes (polypropylene)

Disadvantages:

- Shelf life 1 month in the refrigerator
- Small batches
- Logistics (cold chain)
- Refrigerator capacity on the wards.

COP- syringe

COP: Cyclic olefin polymer



- High mechanical resistance, reducing breakages during processing and use
- Transparancy (like glass)
- Low extractables/ leachables
- High chemical resistance
- Resistance to autoclaving
- High barrier properties with minimal mooisure vapor transmission rate

Cost analysis

Clinical Therapeutics/Volume 41, Number 6, 2019

A Cost Minimization Analysis of Ready-to-Administer Prefilled Sterilized Syringes in a Dutch Hospital

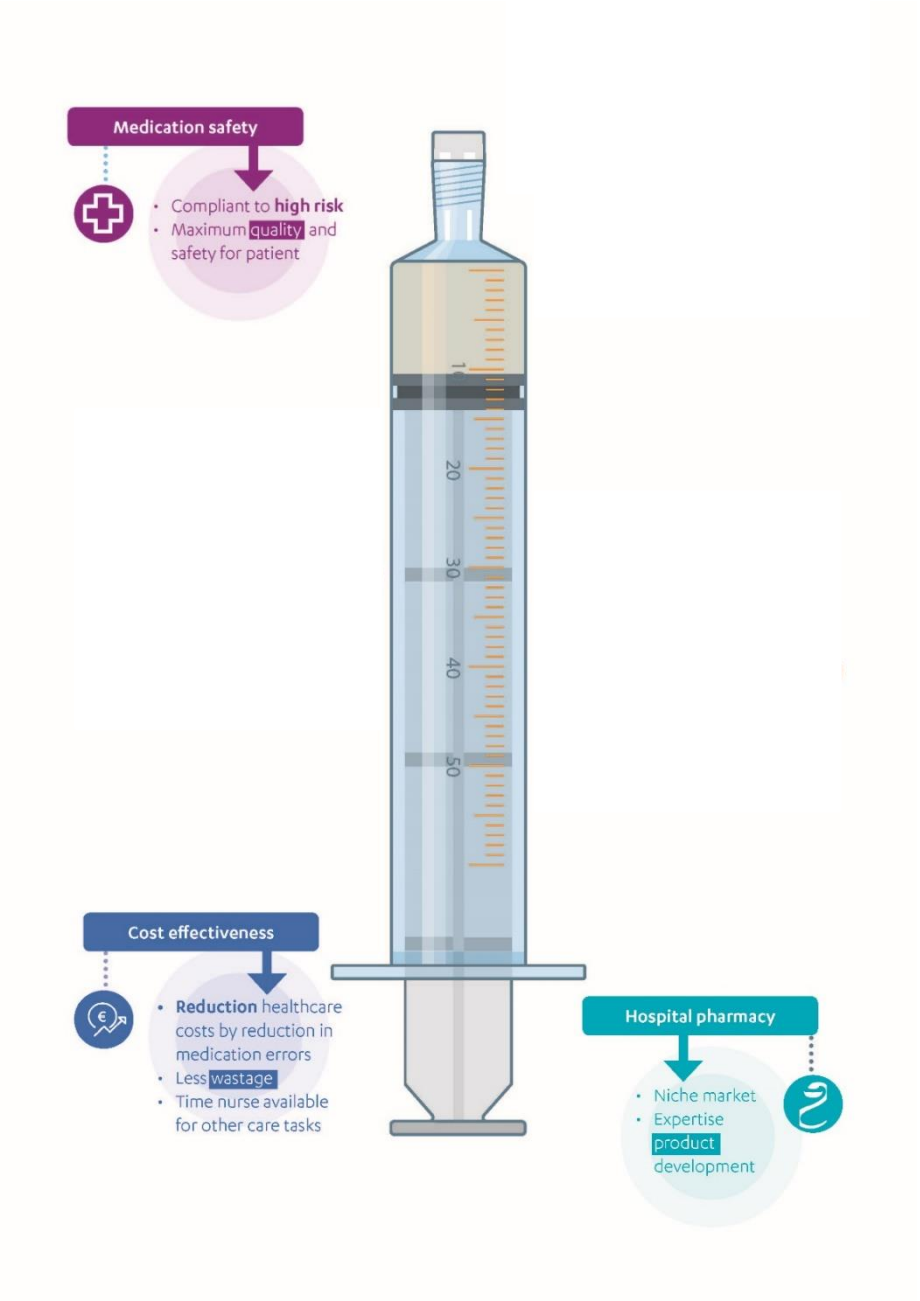
K.H.M. Larmené-Beld [1,2]; J. Touwen- Spronk [2]; J. Luttjeboer [1]; K. Taxis [1]; and M.J. Postma [1,3,4]

[1]Unit of Pharmacotherapy, Epidemiology, and Pharmacoeconomics, University of Groningen, Groningen Research Institute of Pharmacy, Groningen, the Netherlands; [2]Department of Clinical Pharmacy, Isala Hospital, Zwolle, the Netherlands; [3]Department of Health Sciences, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; and [4]Department of Economics, Econometrics, and Finance, University of Groningen, Faculty of Economics and Business, Groningen, the Netherlands

Conclusion

Significant cost savings in hospital budget when introducing PFSS compared to conventional preparation method (by nurse)

- Reduction in medication errors
- Reduction in microbial contamination of parenteral medications.



Isala Sterilized RTA syringes produced by the hospital pharmacy; a field report from The Netherlands

Product/ Process development

- Products ✓
- Syringe selected ✓

- Requirements:
  - Automatic process
  - Different sizes of syringes (5,10 and 50ml)
  - Machine speed

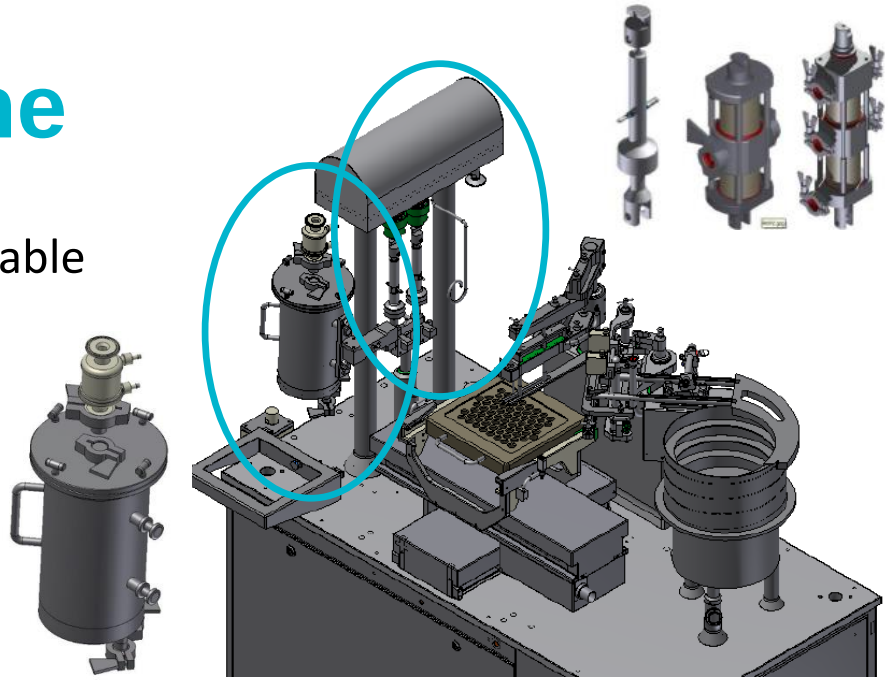
Process development

Automatic filling and closing machine:

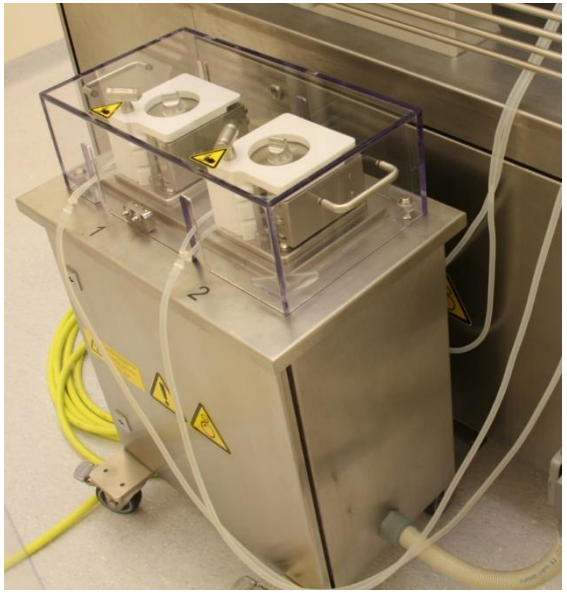
→ Groninger DFVN 1000EM

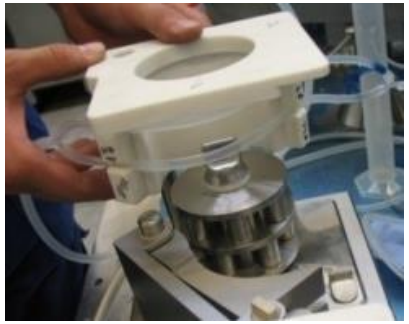
Customize the machine

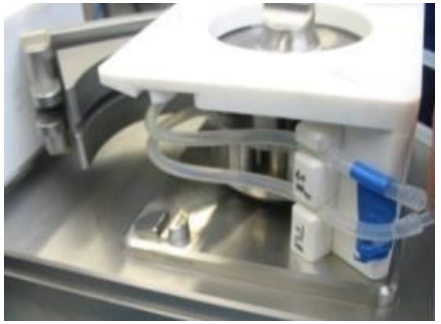
Product tank from stainless steel → disposable



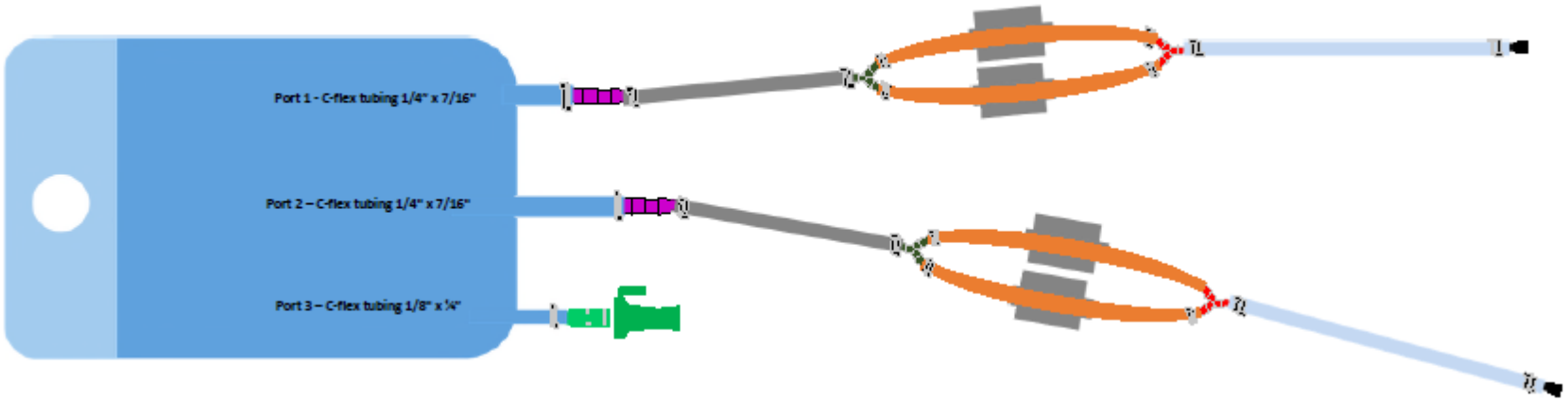
Piston pump → peristaltic pump







Disposable filling assembly

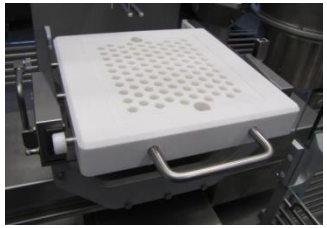


Platinum- cured silicone tubing

- Ultra-smooth inner bore reduces potential for particle entrapment
- Minimal extractables help maintain fluid integrity
- Excellent fluid flow characteristics
- Fully tested to ISO 10993 standards to facilitate validation process
- Complete inventory of standard sizes available, including metric sizes

Size parts

Syringe size	Volume	Filling speed (amount of syringes/ hour)	
		Without N_2	With N_2
5ml	1 ml	3700	3000
	2 ml	3700	3000
	5 ml	3700	3000
10ml	10 ml	2000	1600
50ml	50,0 ml	800	650

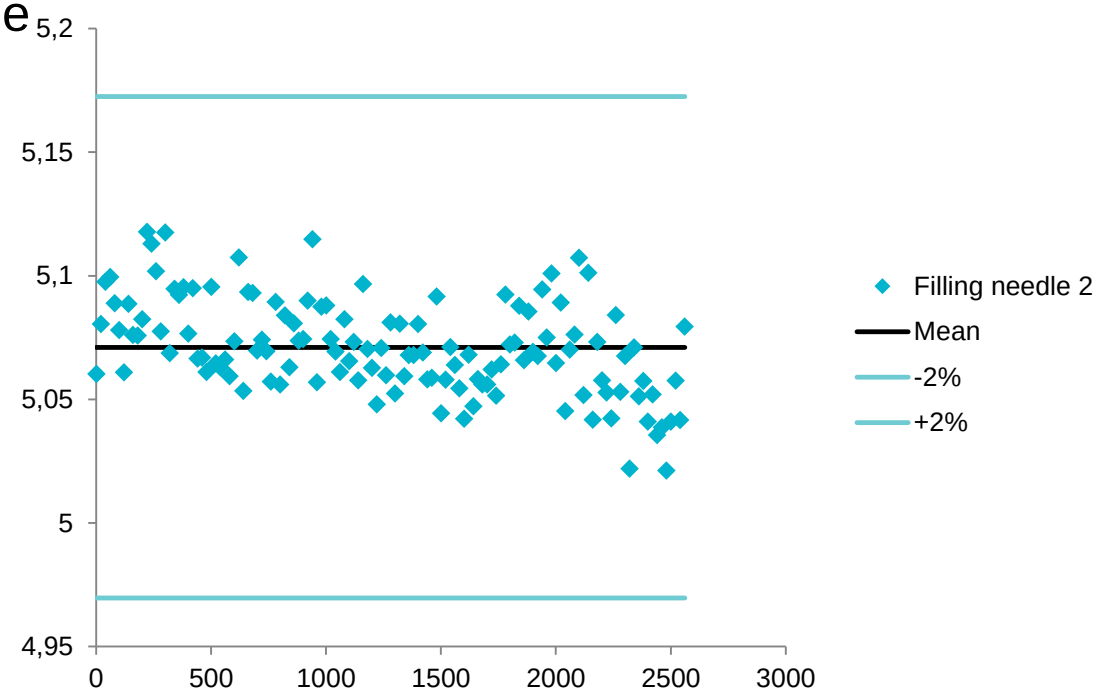


PQ of the filling machine

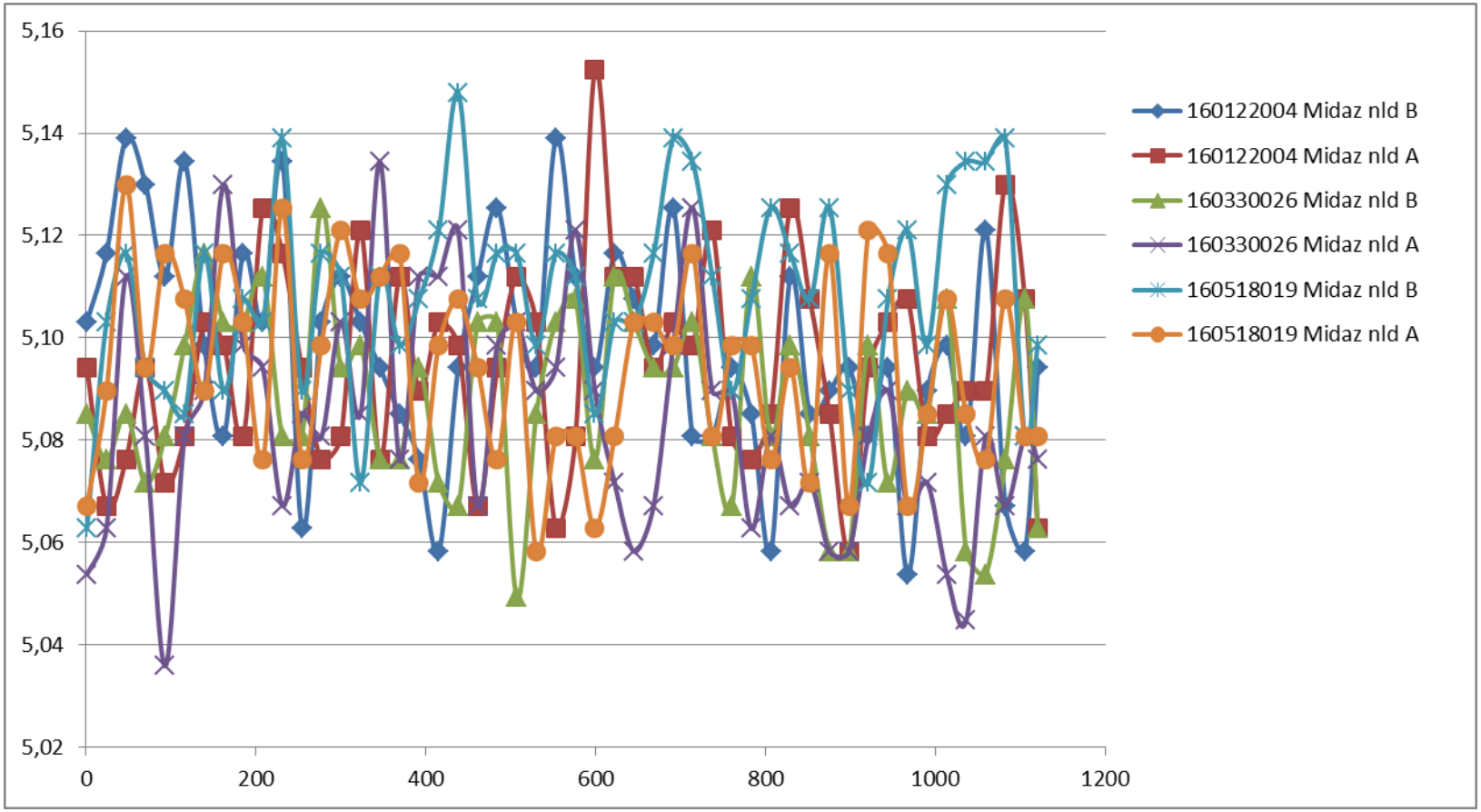
SAT: filling accuracy +/- 0,5-0,6% deviation relative to filling volume

Filling accuracy during one production batch

- AQL table -> sample size
- Extractable volume



Filling accuracy (II)



Product/ Process development

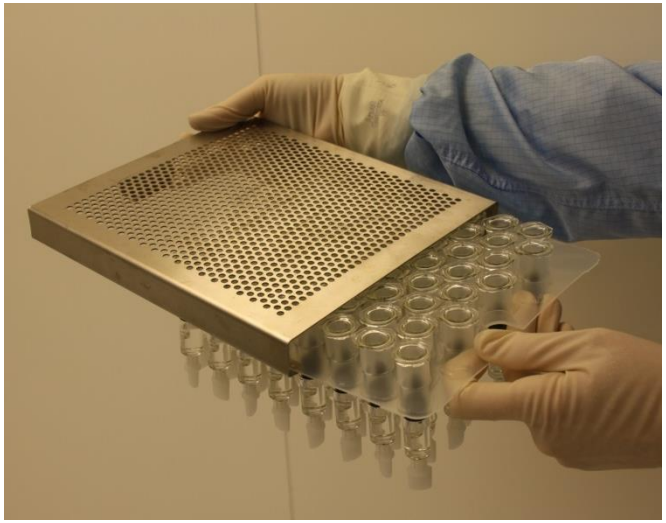
- Products ✓
- Syringe selected ✓
- Filled syringe ✓

Mixed air sterilisator

Validation process

- Stopper movement
- Reference

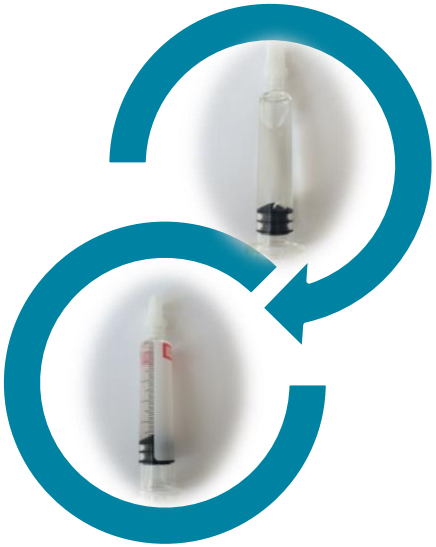
Sterilization



Isala Sterilized RTA syringes produced by the hospital pharmacy; a field report from The Netherlands

Product/ Process development

- Products ✓
- Syringe selected ✓
- Filled syringe ✓
- Sterilized syringe ✓



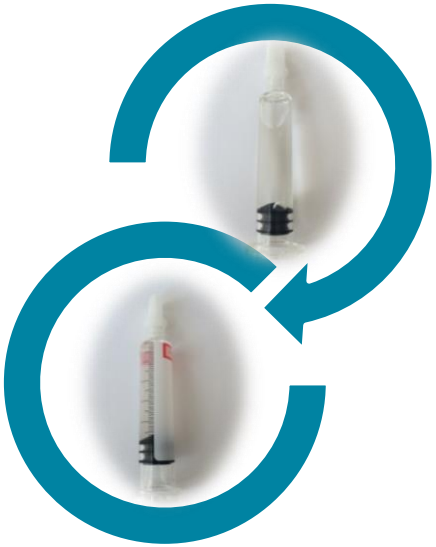
Requirements label:

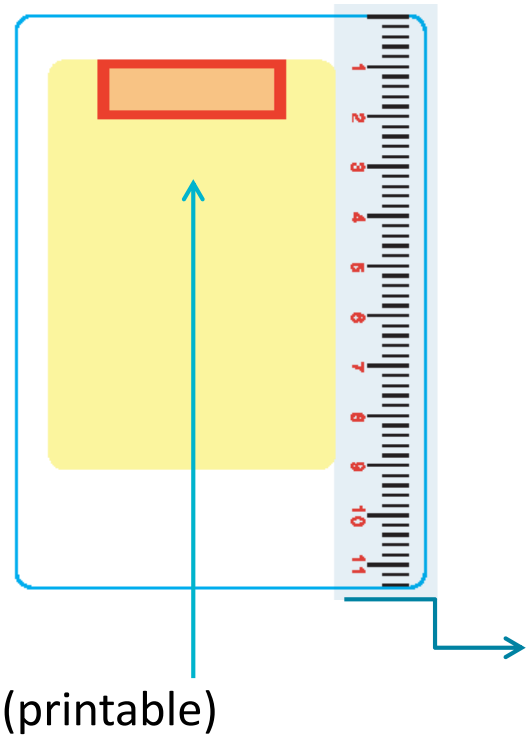
- Transparent
- Scale
- Detection
- Printable

Label

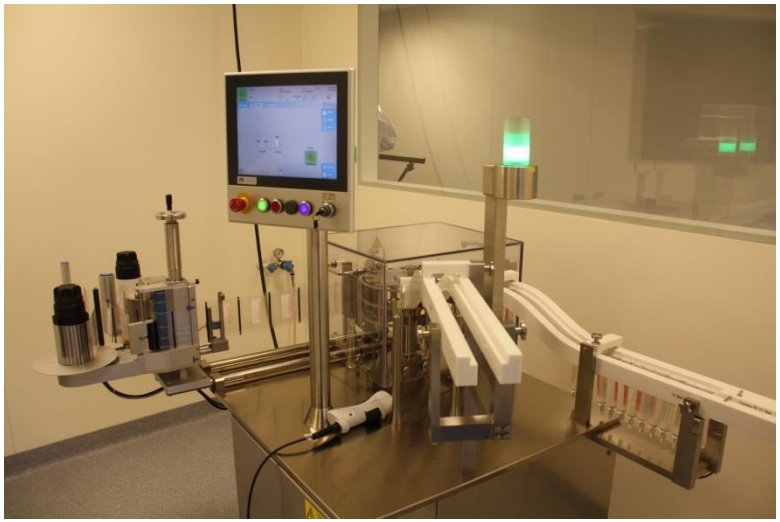
Standard lay-out for every format

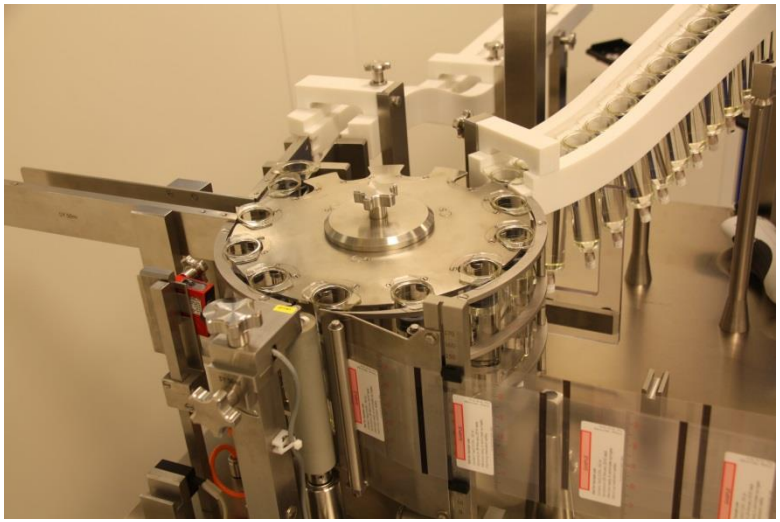
- 5 and 10ml mostly bolus injection/ short infusion
- 50ml syringe → infusion pump





Labelling machine ROTA RE 100

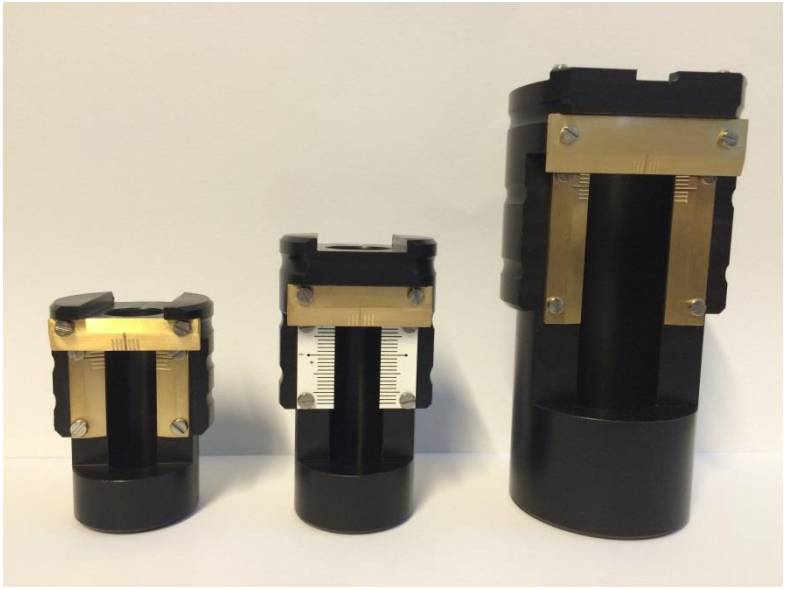




PQ of labelling machine

Acceptance criteria:

- Accuracy of placement relative to finger support (infusion pump)
- Accuracy of placement relative to bottom of syringe (graduation)



Product/ Process development

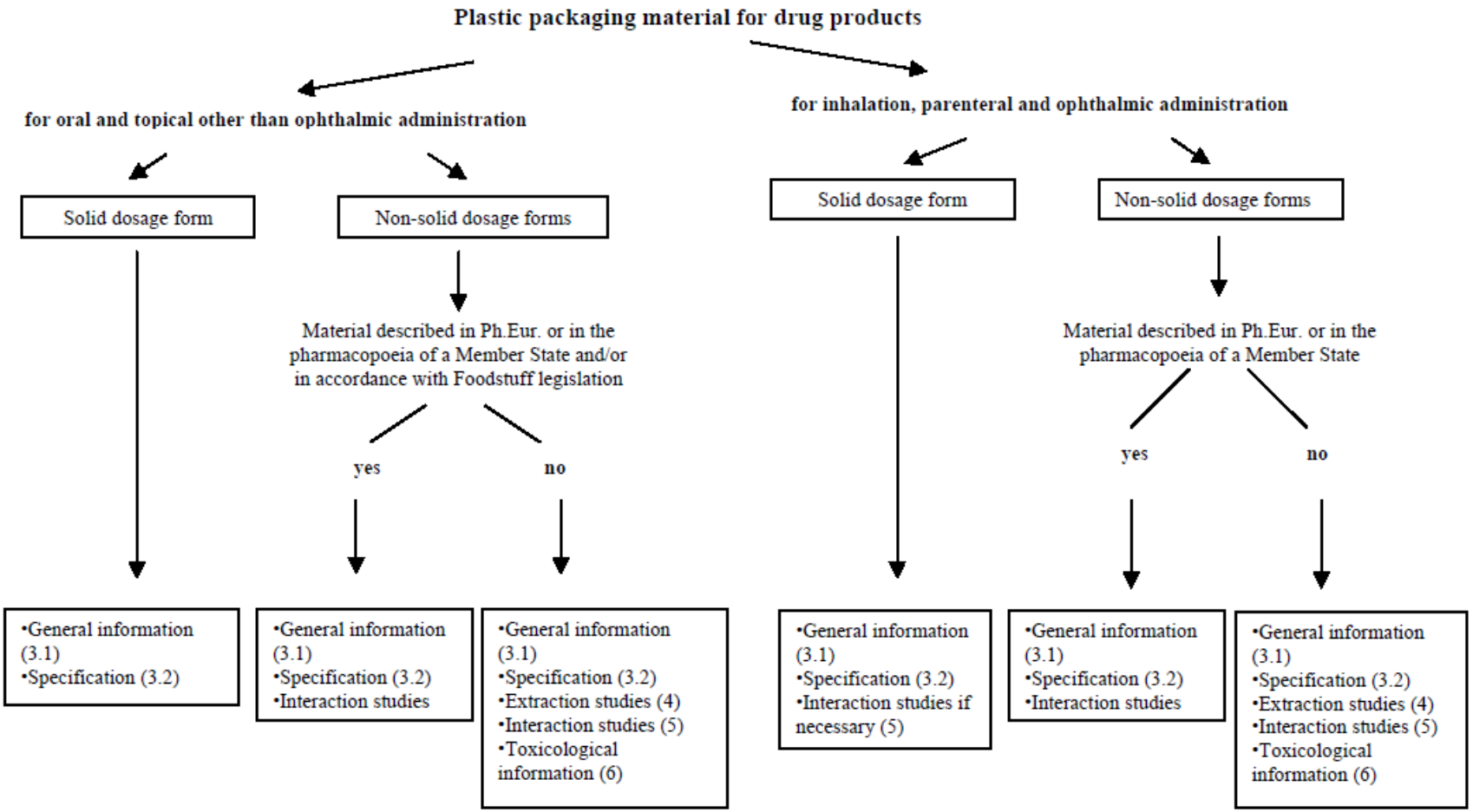
- Products ✓
- Syringe selected ✓
- Filled syringe ✓
- Sterilized syringe ✓
- Labelled syringe ✓

Qualification of the syringe; new primary packaging material

Ph. Eur. :

- 3.2.8: Sterile single use plastic syringes
- 3.2.2: Plastic containers and closures for pharmaceutical use
  - > The ingredients of the preparation in contact with the plastic material are not significantly adsorbed on its surface and do not significantly migrate into or through the plastic
  - > The plastic material does not release substances in quantities sufficient to affect the stability of the preparation or to present a risk of toxicity
- 3.2.2.1 Plastic containers for aqueous solutions for infusion

Qualification of the syringe



European Medicines Agency, committee for Medicinal Products for Human and Use (CHMP) and committee for Medicinal Products for Veterninary Use (CVMP). Guideline on Plastic Immediate Packaging Materials, 2005.

Qualification of the syringe BD plastipak NVZA

2012: GMPz NVZA

> NaCl 0,9%, glucose 5%

- Appearance
- pH
- Loss of weight (permeability of the plastic)
- Particulate contamination; subvisible particles
- Silicon oil
- Leachables (UV absorption)
- Closure integrity
- Sterility

NVZA = Dutch Association of hospital pharmacists

Extractables/ leachables

The **potential** versus the **actual** impact of the product on its user.

* **Extractable** = potential impact: *what "could" come out*
* **Leachable** = actual impact: *what "will" come out*

The object on which the testing is performed.

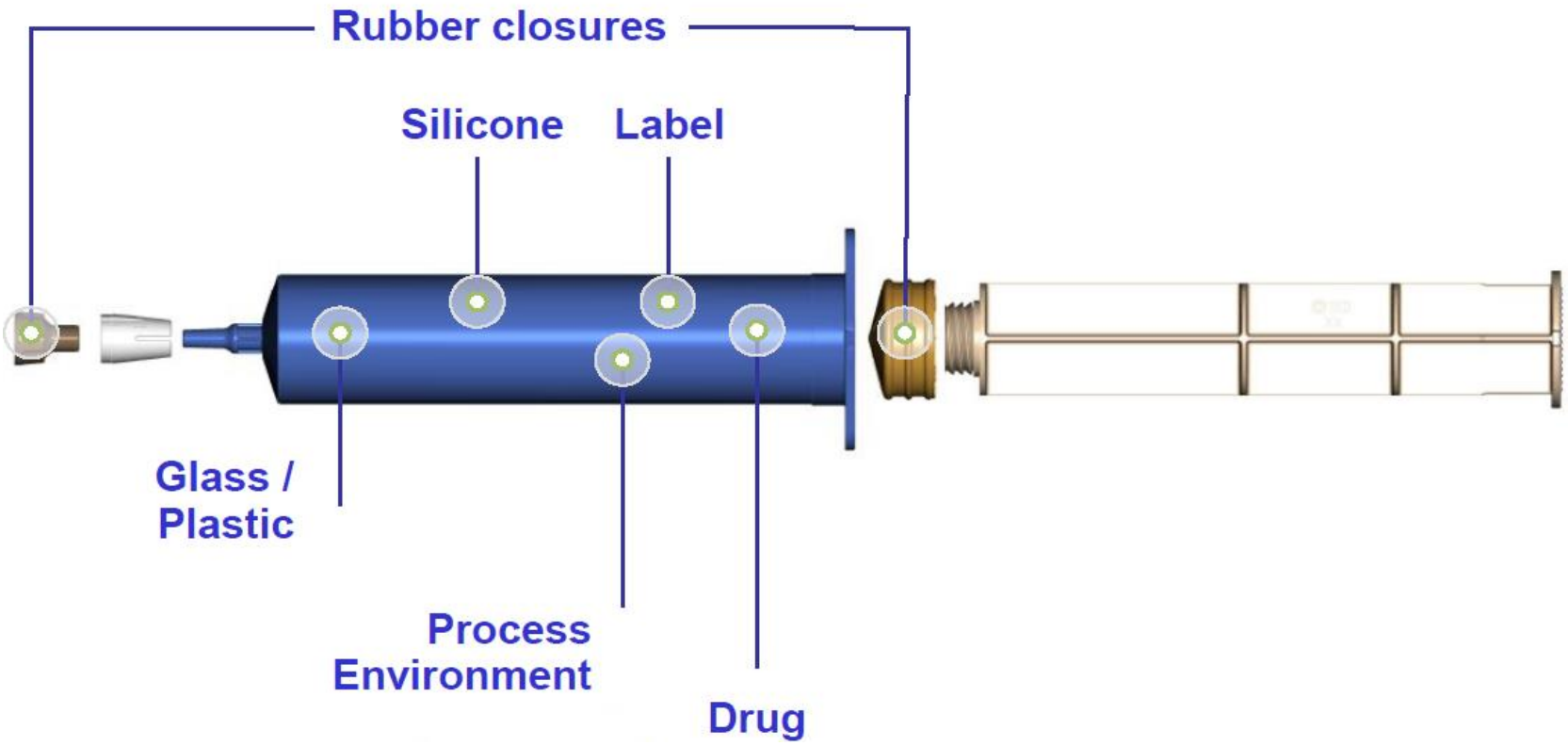
* **Extractable** = test the material
* **Leachable** = test the finished product

pH and polarity[6,7]

[6] 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.

[7] 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.

Components COP syringes



Strategy

Potential products for PFSS pH range 3,0-9,3

Validation guide manufacturer

- All individual components comply with the regulatory demands; e.g. for plastics; USP 661, JP 61, for rubber: USP381, Ph. Eur 3.2.9, JP 59, ISO 8871-1 and for biocompatibility/ toxicological USP 87, EMA , 88, ISP 10993, TSE Ph. Eur. 5.2.8
- Report with potential extractables form syringe and stopper

Risk based strategy for qualification

Influence of pH on extractables and leachables?

- Phosphate buffer batches pH 2.0 – 5.8 – 8.0 – 11.4

Influence of extractables and leachables on pH?

- NaCl 0,9%

Inlfuence of organic/ apolar solvent on extractables and leachables?

- Isopropyl alcohol (IPA) 5% in water

Silicon concentration in the syringe?

- WFI; pH 2 - 5 - 8 - 11

Tests extraction study

Test	Monograph	Description/ acceptance limit
Clarity and degree of opalescence of the solution	Ph. Eur. 2.2.1.	The clarity of the solution is the same as that of *water R*. The absence of any particles or inhomogeneities in a solution results in a clear solution
Degree of coloration of the solution	Ph. Eur. 2.2.2	examination of the degree of coloration of the solution in the range brown-yellow-red
pH of the solution	Ph. Eur. 2.2.3	
Absorbance (extractables and leachables)	Ph. Eur 3.2.2.1	The absorbance of the solution was measured from 230nm to 360nm. At these wavelengths the absorbance is not greater than 0.20
Reducing substances	Ph. Eur. 3.2.2.1	To 20.0ml of solution S add 1ml of dilute sulfuric acid R and 20.0ml of 0.002M potassium permanganate. Boil for 3 min. Cool immediately. Add 1 g of potassium iodide R and titrate immediately with 0.01 M sodium thiosulfate, using 0.25ml of starch solution R as indicator. Carry out a titration using 20.0ml of the blank. The difference between the titration volumes is not greater than 1.5ml.
Transparancy	Ph. Eur 3.2.2.1	Fill a container previously used for the preparation of solution S with a volume equal to the nominal capacity of the primary opalescent suspension (2.2.1) diluted 1 in 200 for a container made from polyethylene or propylene and 1 in 400 for other containers. The cloudiness of the suspension is perceptible when viewed through the container and compared with a similar container filled with water R.
Weight loss	Isala standard	≤ 2% weight loss according to the initial weight
Subvisible particles	Ph. Eur. 2.9.19	According to method 1. Light obscuration particle count test. The solutions complies with the test if the average number of particles present in the units tested does not exceed 6000 per container equal to or greater than 10µm and does not exceed 600 per container equal to or greater than 25µm.
Closure integrity test	Ph. Eur. 3.2.9./ manipulated	An Dye immersion test with 0,1% methylene blue. Immerse the syringes in a 1g/L solution of methylene blue and reduce the external pressure by 27 kPa for 10 min. Restore atmospheric pressure and leave the vials immersed for 30 min. Rinse the outside of the syringes . None of the vials contains any trace of coloured solution
Sterility	Ph. Eur. 2.6.1	
Silicon*	-	ICP- MS method

Production of validation batches

- Regular production process; filling syringes and terminally sterilised (121°C, 15 minutes)
- Storage conditions: 20°C± 5°C, product contact surface
- Analyses at t=0, 1, 2, 3, 4, 5, 6, 9, 12, 18, 24 and 36 months for the general chemistry tests
- Bracketing scheme for subvisible particles, sterility and closure integrity during 36 months

Component	5 mL syringe	50 mL syringe
Syringe barrel	BD Crystal Clear Polymer; (polycycloolefine) Lubrication: silicone coating	BD Crystal Clear Polymer (polycycloolefine) Lubrication: silicone coating
Plunger stopper – Silicone	SBR rubber – DC 360	FM457 butyl rubber – Rhodia 70 047
Tip cap	Luer lok: Thermoplastic elastomer blend	S-Lok; plastic part: Polypropylene Rubber part: Butyl rubber.

Results

5mL syringe

	Minimum- maximum level measured during 0–36 months						
Solvent	pH	Clarity	Colour	Weight loss	Transparency	Reducing substances	Absorbance (Au)
Phosphate buffer pH 2.0	2.2–2.3	Clear	<BY7	0%–0.6%	Cloudiness perceptible		<0.01–0.04
Phosphate buffer pH 5.8	5.7–5.9	Clear	<BY7	0%–0.8%	Cloudiness perceptible		<0.01–0.02
Phosphate buffer pH 8.0	7.8–7.9	Clear	<BY7	0%–0.6%	Cloudiness perceptible		<0.01–0.01
Phosphate buffer pH 11.4	11.4–11.5	Clear	<BY7	0%–0.6%	Cloudiness perceptible		0.02–0.08
NaCl 0.9%	4.0–10.0	Clear	<BY7	0%–0.7%	Cloudiness perceptible	0.1–1.2 mL	<0.01–0.02
IPA 5%	NA	Clear	<BY7	0%–0.8%	Cloudiness perceptible		<0.01–0.03

50mL syringe

	Minimum- maximum level measured during 0–36 months						
Solvent	pH	Clarity	Colour	Weight loss	Transparency	Reducing substances	Absorbance (Au)
Phosphate buffer pH 2.0	2.2–2.3	Clear	<BY7	0%–0.1%	Cloudiness perceptible		<0.01–0.03
Phosphate buffer pH 5.8	5.4–5.9	Clear	<BY7	0%–0.1%	Cloudiness perceptible		<0.01–0.03
Phosphate buffer pH 8.0	7.8–7.9	Clear	<BY7	0%–0.4%	Cloudiness perceptible		<0.01–0.02
Phosphate buffer pH 11.4	11.4–11.6	Clear	<BY7	0%–0.1%	Cloudiness perceptible		<0.01–0.06
NaCl 0.9%	4.7–8.9	Clear	<BY7	0%–0.1%	Cloudiness perceptible	0.2–1.3 mL	<0.01–0.02
IPA 5%	NA	Clear	<BY7	0%–0.1%	Cloudiness perceptible		0.01–0.03

Results (II)

- Subvisible particles:

  ≤ 6000 particles ≥10 µm and ≤ 600 particles ≥25 µm per syringe.

  Variation in time but no trend
- Sterility: all sterile
- Closure integrity; Dye immersion test (Ph. Eur.)

Test syringe

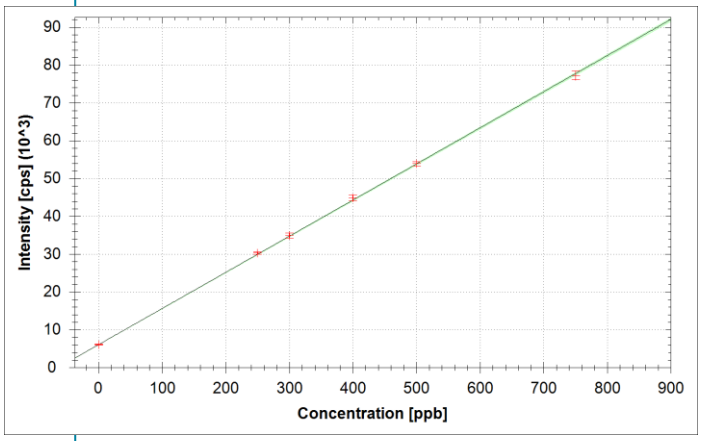
Negative control

Positive control

Method silicon – ICP- MS

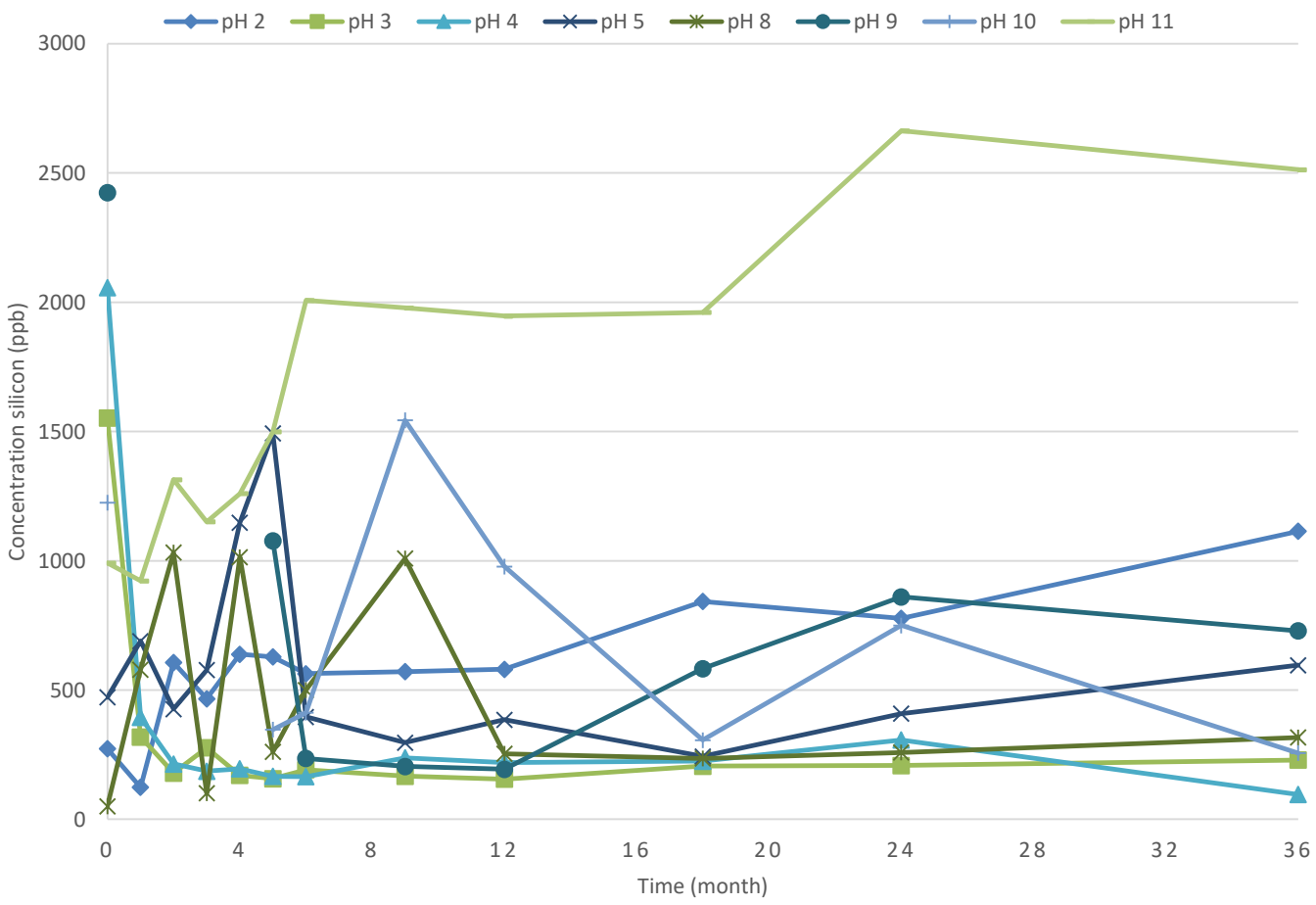
Settings ICP- MS

Parameter	Value
Pump tubing	PVC peristaltic pump tubing, id 0.51 mm, Orange/Yellow
Peristaltic pump speed	40 rpm
Nebulizer	PFA-ST
Interface cones	Nickel
RF Power	1550 W
Cool gas flow	14 L/min
Auxiliary gas flow	0.8 L/min
Nebulizer gas flow	1.19 L/min
Collision gas flow	4.7 L/min
Collision gas	Helium
Injector type	Quartz
Injector ID	2.5 mm
Measurement mode	KED (Kinetic Energy Discrimination)
KED barrier voltage	3 Volt
Autosampler	SC 2 DX Elemental Scientific Inc.

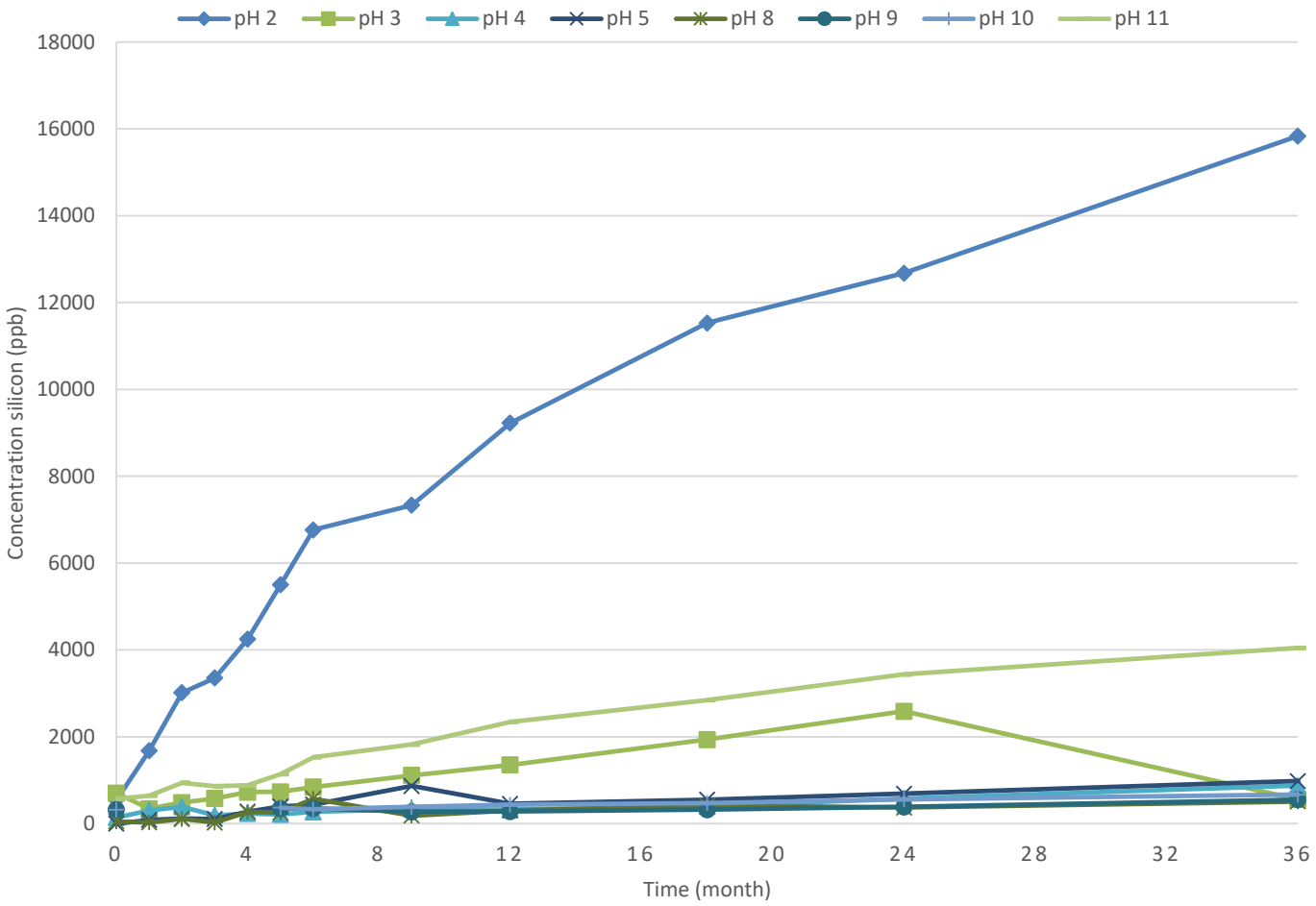


Calibration curve silicon method. f(x) = 95.5357*x + 6064.5831, R^2 = 0.9997, BEC = 63.480 ppb, LoD = 2.9079 ppb

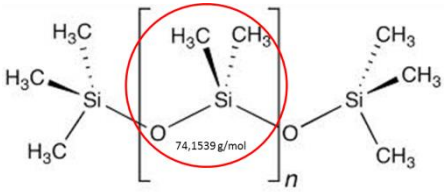
Concentration silicon 5mL syringe



Concentration silicon 50mL syringe



Discussion silicon



pH 2 and pH 11 higher silicon concentration

Silicon oil → aggregates/ particles → immunogenic responses

Our results <<< NOAEL levels/ LD50

Another approach Ph. Eur 3.2.8 maximum 0.25mg silicon/ cm^2

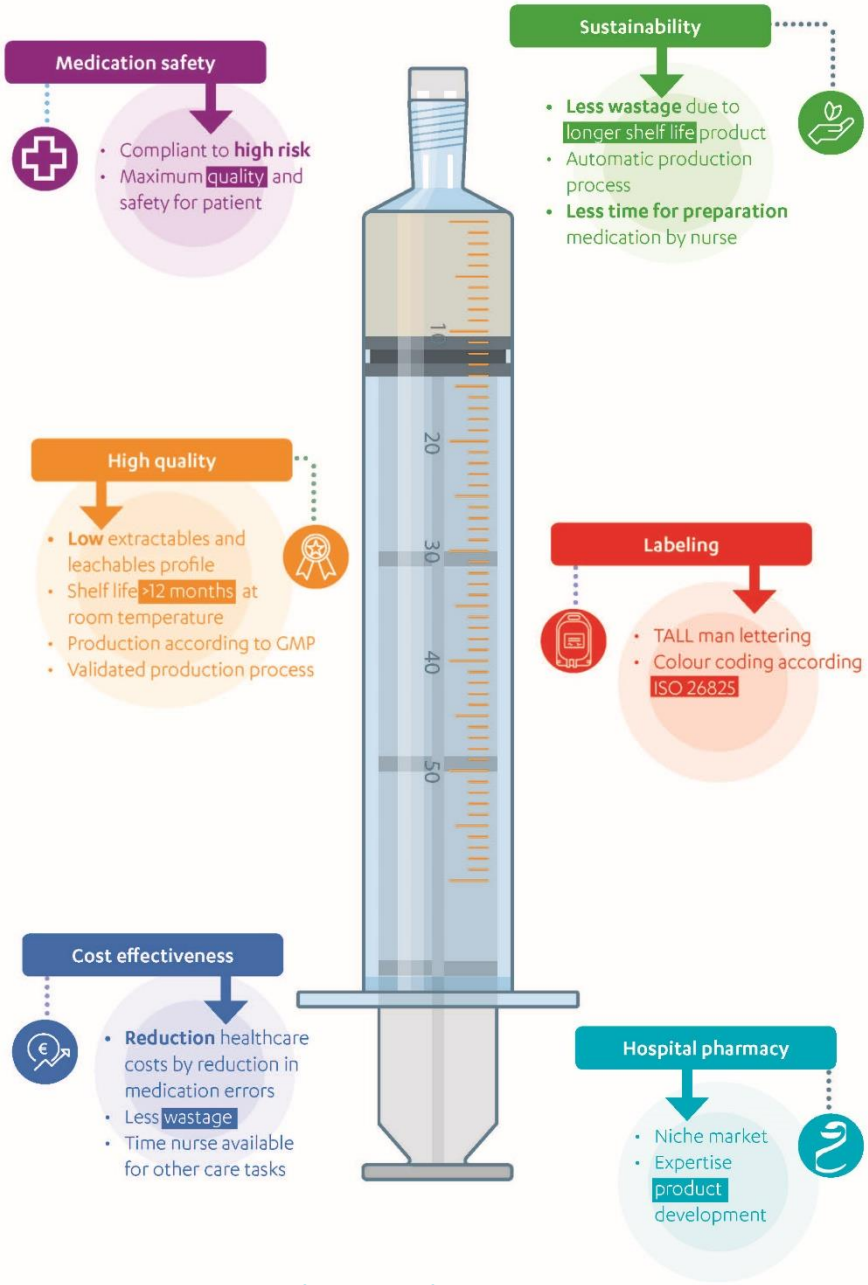
>>10 000 syringes could be administered without expecting adverse effects

Conclusion qualification

- Low extractables and leachables
  - Higher concentration extractables pH 2 and 11
  - Higher concentration silicon pH 2 and 11
  - All within acceptance limit/ safety
- Sterile
- Low subvisible particles
- Resistance wide pH range

Suitable as primary packaging material for the production of water soluble products with pH varying from 3 to 9

Larmené-Beld K, et al. Science- and risk-based strategy to qualify prefillable autoclavable syringes as primary packaging material. Eur J Hosp Pharm 2022;**29**:248–254.



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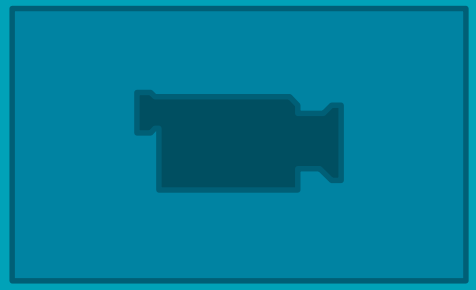
Preview production process



https://www.youtube.com/watch?v=UTIf5fqawoI&feature=youtu.be

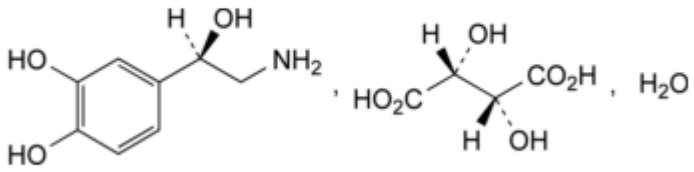
Product development

Ampoules, vials (glass/ polypropylene) → syringe (COP)

Norepinephrine 0.1mg/ mL solution

- Commercially available products contain sodium metabisulfite (anti oxidant)
- COP is not compatible with sodium metabisulfite

Noradrenalini tartras



Formulation tests 0.1mg/ mL norepinephrine

Ascorbic acid as antioxidant- 3 concentrations (0, 0.05 and 0.1%)

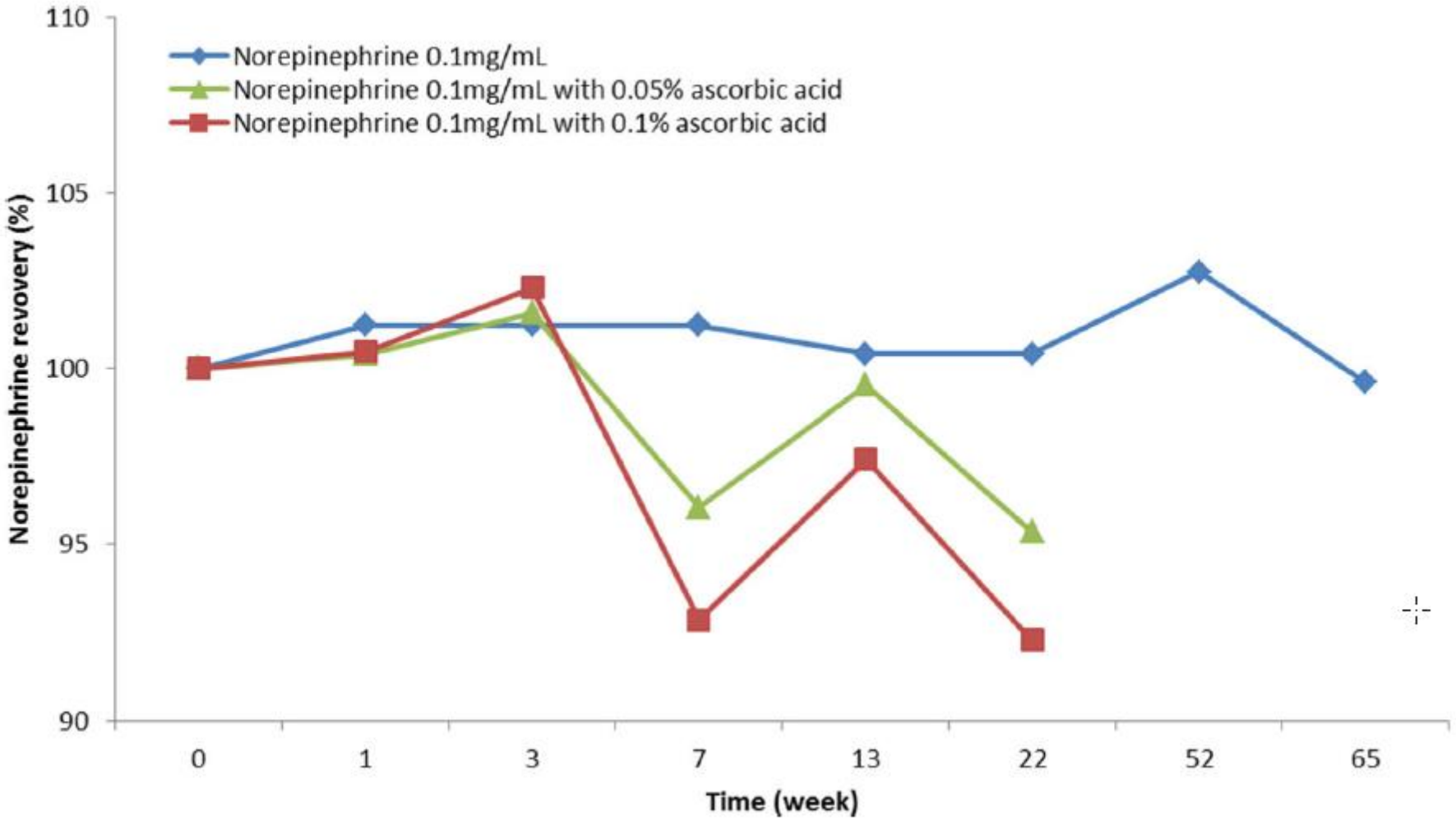
Other excipients: 0.1mg/ml edetate sodium, 8mg/ml sodium chloride and water for injections.

Production process:

- IPC pH was set to 3.8-3.9
- Filled under nitrogen gassing
- Sterilisation (15 min at 121°C)
- Stored at room temperature (20 ± 5ºC)
- Protected from day light

Analysis at t= 0, 1, 3, 7, 13 and 22 weeks

Results formulation tests



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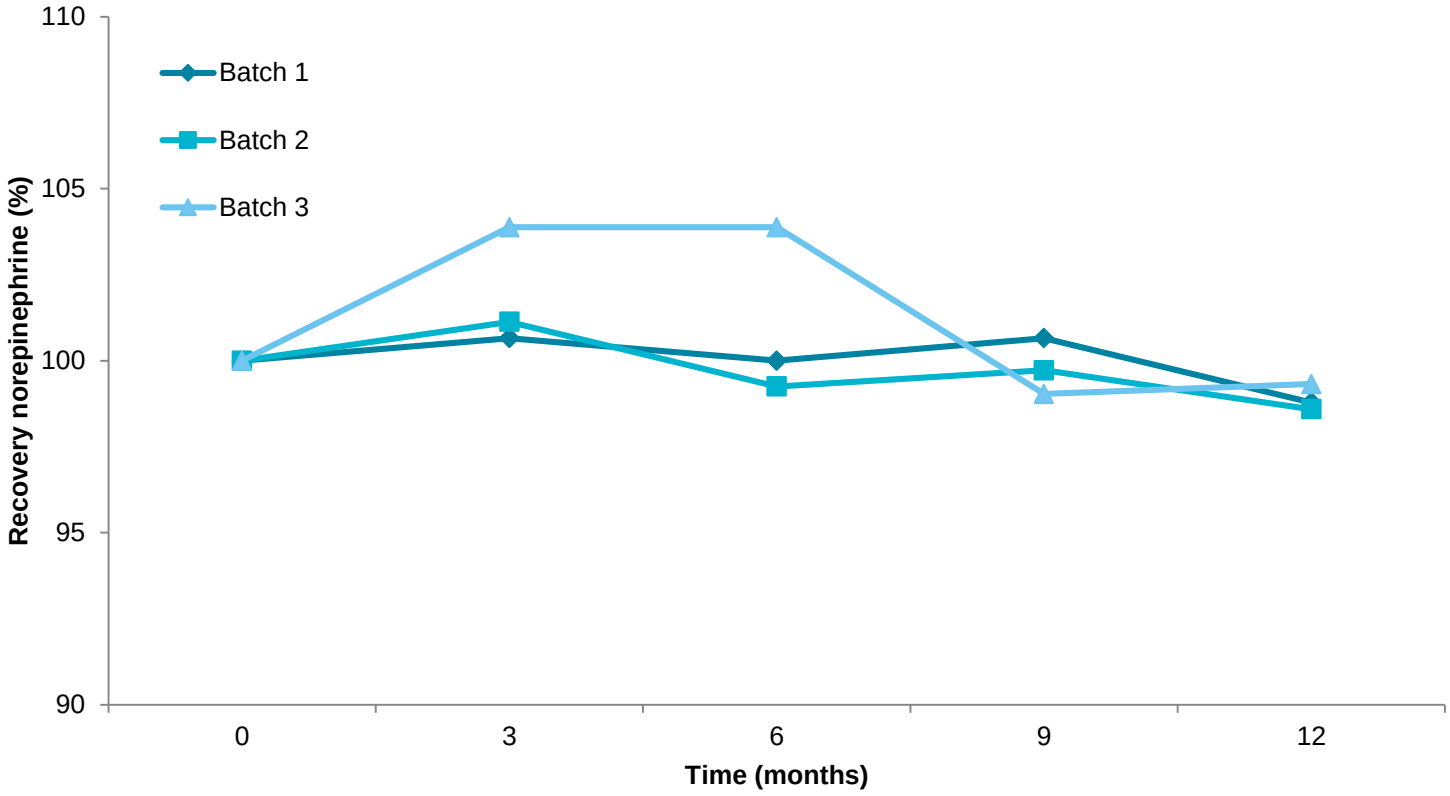
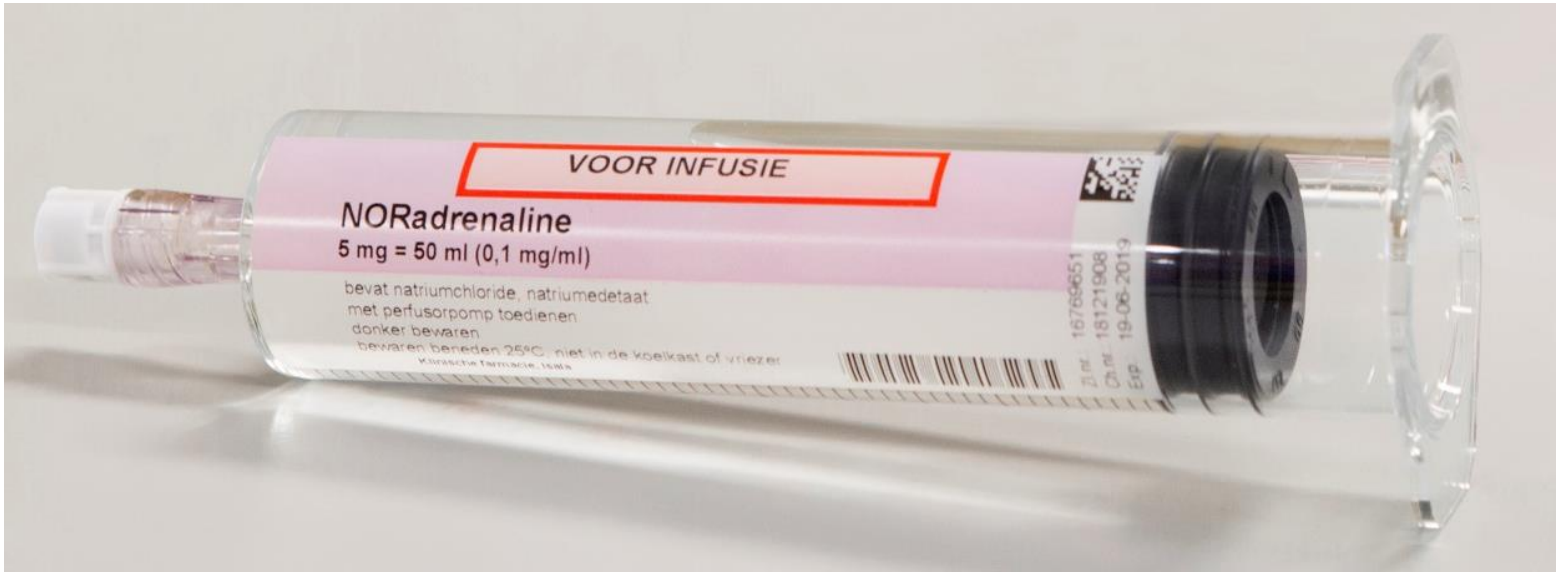
Stability study norepinephrine 0.1mg/ mL



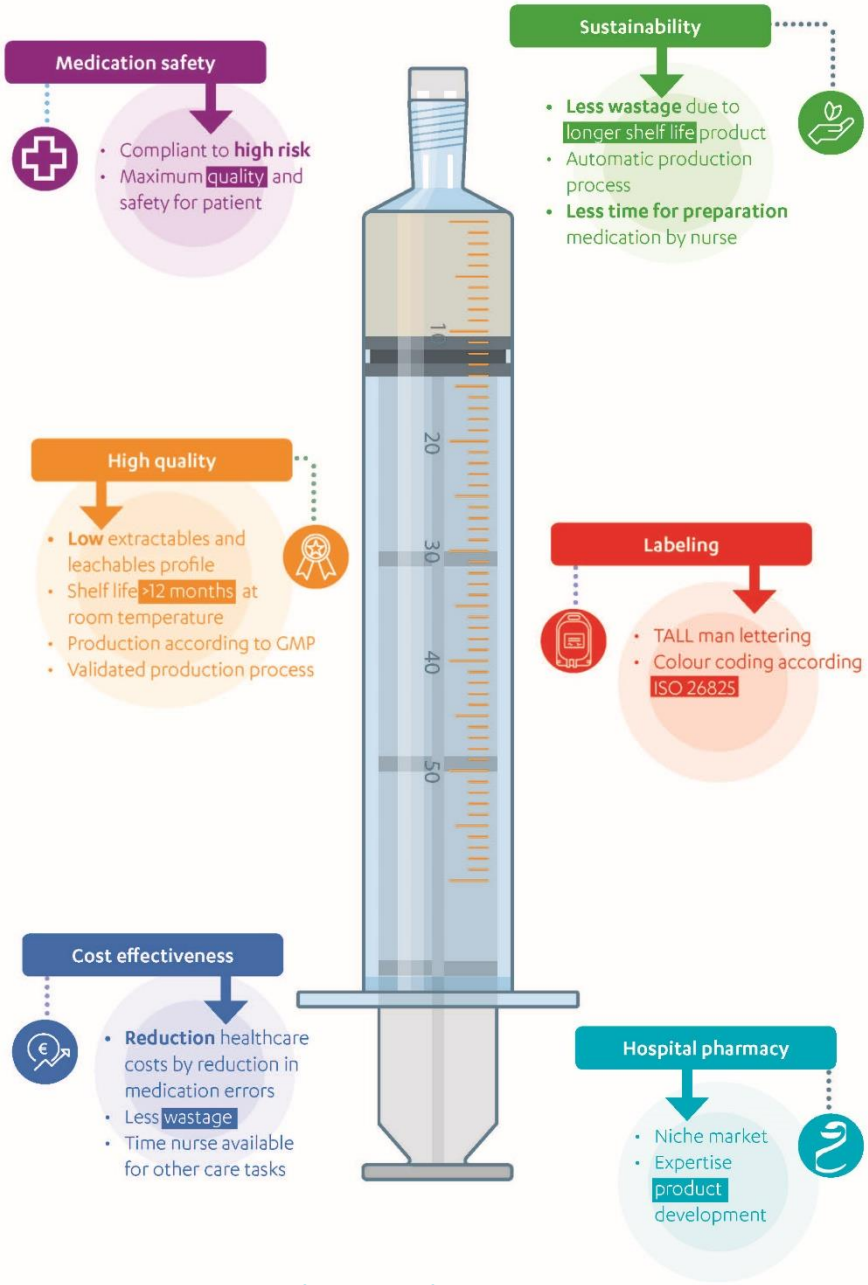
Results

Test	Acceptance criteria	Batch 1	Batch 2	Batch 3
Clarity and degree of opalescence of the solution	Clear solution	Clear	Clear	Clear
Degree of coloration of the solution	≤B9	B9	B9	B9
pH of the solution	3.6 - 6.0	3.8	3.8	3.8
Identity sodium	Positive	Positive	Positive	Positive
Concentration norepinephrine	95-105% at release; 90-110% end of shelf life.	98.8%	98.6%	99.3%
Concentration chloride	Concentration at release 95-105% Concentration end of shelf life 90-110%	100.6%	100.1%	101.5%
Subvisible particles	≤6000 particles/ syringe for particles ≥10µm ≤ 600 particles/ syringe for particles ≥ 25µm	1834 62	1160 44	3438 88
Closure integrity test	None of the vials contains any trace of blue coloured solution	No blue colour	No blue colour	No blue colour
Sterility	Sterile	Sterile	Sterile	Sterile
Extractable volume	The volume extracted is not less than the nominal volume.	Complies	Complies	Complies



Karin H.M. Larmené-Beld, S. van Berkel, R. Wijnsma, K. Taxis, H.W. Frijlink. Prefilled Cyclic Olefin Sterilized Syringes of Norepinephrine Injection Solution Do Not Need to Be Stabilized by Antioxidants. AAPS PharmSciTech, 2020 21:247

Product	Unit	Storage condition	Shelf life (month)
ADENOSINE 3MG/ML SYRINGE 50ML ISALA	50ml	Room temperature, dark	18
BUPIVACAINE/SUFENTANIL 1,25MG/1MCG/ML SYRINGE 50ML ISALA	50ml	Room temperature	24
EPHEDRINE HCL 5MG/ML SYRINGE 5ML ISALA	5ml	Room temperature, dark	36
PHENYLEPHRINE HCL 0,1MG/ML SYRINGE 10ML ISALA	10ml	Room temperature, dark	24
PHOSPHATE 1MMOL/ML SYRINGE 50ML ISALA	50ml	Room temperature	24
FUROSEMIDE 10MG/ML SYRINGE 2ML ISALA	2ml	Room temperature, dark	18
FUROSEMIDE 5MG/ML SYRINGE 50ML ISALA	50ml	Room temperature, dark	18
GRANISETRON 0.5MG/ ML SYRINGE 2ML ISALA	2 ml	Room temperature	18
POTASSIUM CHLORIDE 1MMOL/ML SYRINGE 50ML ISALA	50ml	Room temperature	36
LEVOBUPIVACAINE/SUFENTANIL 1,25MG/1MCG/ML SYRINGE 50ML ISALA	50ml	Room temperature	36
LIDOCAINE HCL 1 % SYRINGE 50ML ISALA	50ml	Room temperature	12
MEPIVACAÏNE HCL/ BUPIVACAÏNE HCL 10MG/2.5MG/ML SYRINGE 10ML ISALA	10ml	Room temperature	24
METOCLOPRAMIDE HCL 10MG/ML SYRINGE 2ML ISALA	2ml	Room temperature, dark	24
MIDAZOLAM 1MG/ML SYRINGE 5ML ISALA	5ml	Room temperature	24
MIDAZOLAM 1MG/ML SYRINGE 50ML ISALA	50ml	Room temperature	36
MIDAZOLAM 2MG/ML SYRINGE 50ML ISALA	50ml	Room temperature	24
MIDAZOLAM 5MG/ML SYRINGE 50ML ISALA	50ml	Room temperature	24
MORFINE HCL 5MG/ML SYRINGE 2ML ISALA	2ml	Room temperature, dark	12
MORFINE HCL 1MG/ML SYRINGE 50ML ISALA	50ml	Room temperature, dark	18
SODIUM CHLORIDE 0,9% SYRINGE 50ML ISALA	50ml	Room temperature	36
NOREPINEPHRINE 0,1MG/ML SYRINGE 50ML ISALA	50ml	Room temperature, dark	12
TRANEXAMINIC ACID 100MG/ML SYRINGE 10ML ISALA	10ml	Room temperature	24



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Thank you for your attention

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