Test Methods for Prefilled Syringes
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Regulatory References for Finished Pre-filled Syringes

ISO 11040-8

Prefilled Syringes

Part 8: Requirements and test methods for finished prefilled syringes

Pre-filled syringes TM

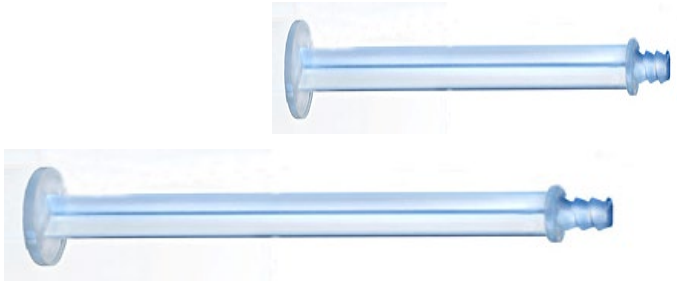
Regulatory Reference: 11040-8

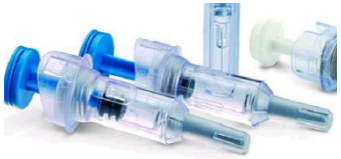
System characterization

Barrel (ISO 11040-4 or 11040-6 shall apply)

Plunger stoppers (ISO 11040-5 shall apply)

Additional components (plunger rod, finger flange extension, hypodermic needle, filter tubing etc)





Finished Pre-Filled Syringes TM

Regulatory Reference: 11040-8

Physical system characterization (* TM referenced to 11040-4 Annexes)

Break loose and extrusion forces* (E.1.)
Burst resistance* (G.2.)
Break resistance * (C.1. / C.2.)
Closure system forces and torques* (G.3. / G.6.)
Connectivity with fluid path connectors (80369-1)
Residual volume (ISO 7886-1)
Needle penetration force* (F.)
Needle pull-out force* (G.1)
Anti-needlestick requirements (ISO 23908)
Liquid leakage (beyond plunger ISO 7886-1)
Markings (ISO 7886-1)

Finished Pre-Filled Syringes TM

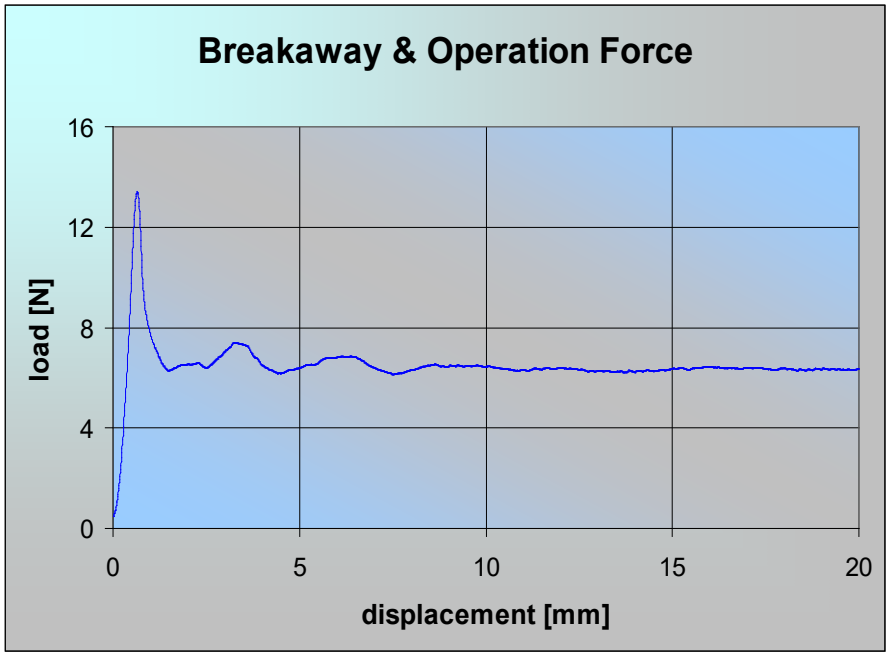
Regulatory Reference: 11040-8

Pharmaceutical requirements

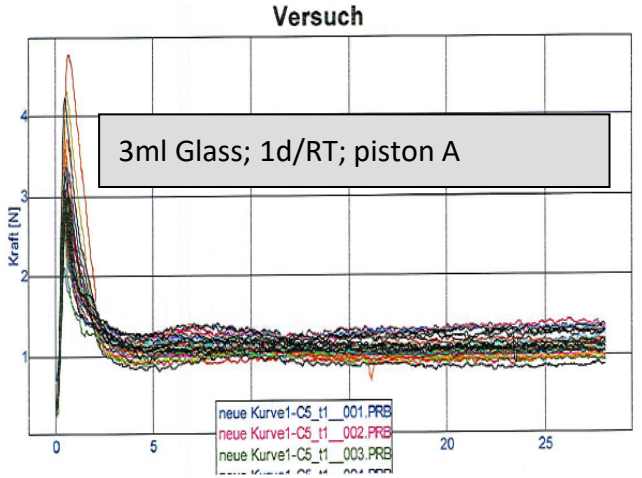
Drug – container interaction (extractables / leachables / compatibility / shear forces …)
Biological requirements (ISO 10993-1)
Container closure integrity (physical / microbiological)
Deliverable volume (as per IFU)
Particulates (visible and sub-visible) (applicable pharmacopeia)

Finished Pre-Filled Syringes TM

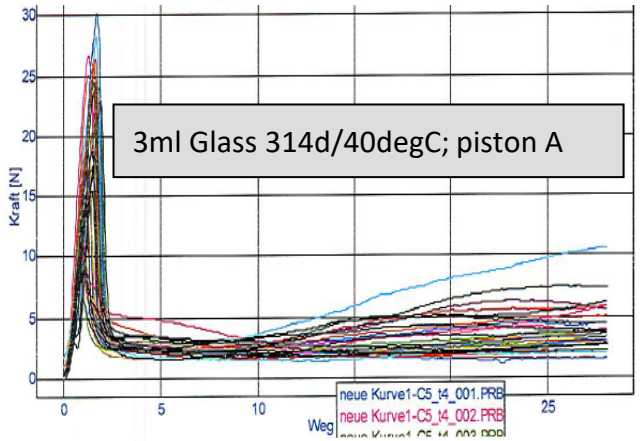
Breakloose and Extrusion Forces TM



4.5N



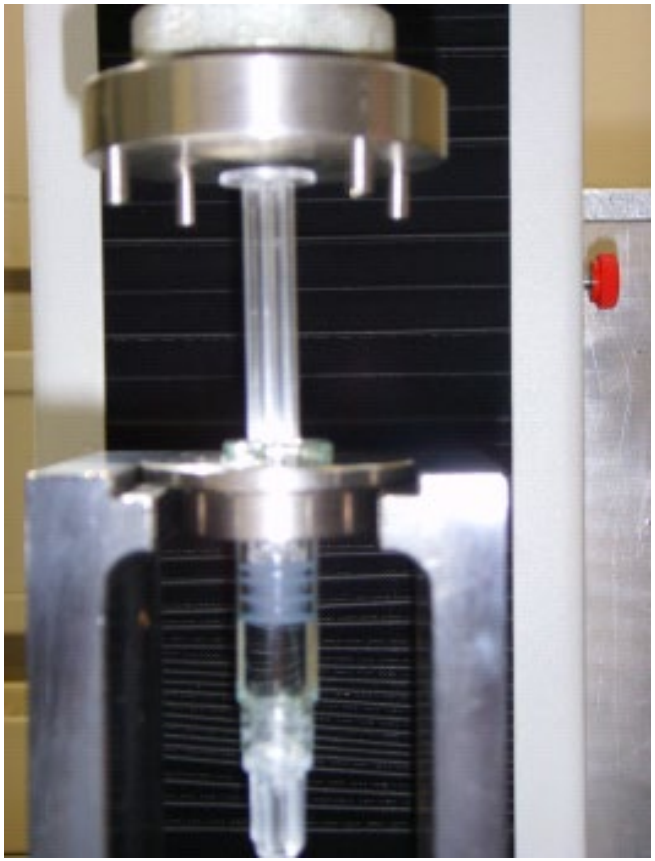
26N



- Breakloose force is (usually) time dependent

Finished Pre-Filled Syringes TM

Burst Resistance TM



Finished Pre-Filled Syringes TM

Connectivity with fluid path connectors TM

Principle

Fluid path connectors testing for connectivity and leakage with drug product filled syringe as designed for the intended use (environmental conditions etc.)

Procedure

Luer connector leakage method ISO 11040 – 4; (TM = Annex G)

Connectivity following ISO 80369-1

Interpretation of Results

Compare leakage results with pre-defined specification (as for the intended use)

Specify and list possible connectors which can be used with the syringe

Finished Pre-Filled Syringes TM

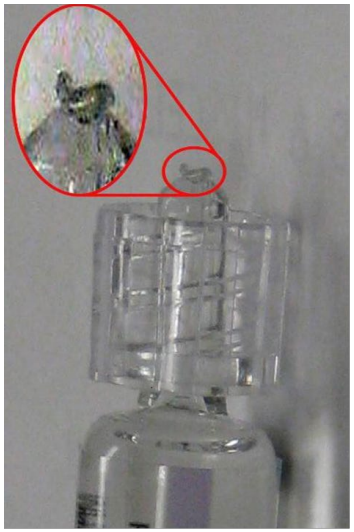
Connectivity with fluid path connectors TM

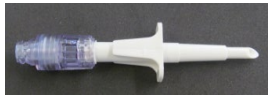
Luer connector leakage method ISO 11040 – 4; (TM = Annex G)

Connectivity following ISO 80369-1

Issues ?

ISO 11040-4 compliant PFS in combination with a needleless luer activated devices (NLAD's) → ISO 80369-7 Device (Thread)

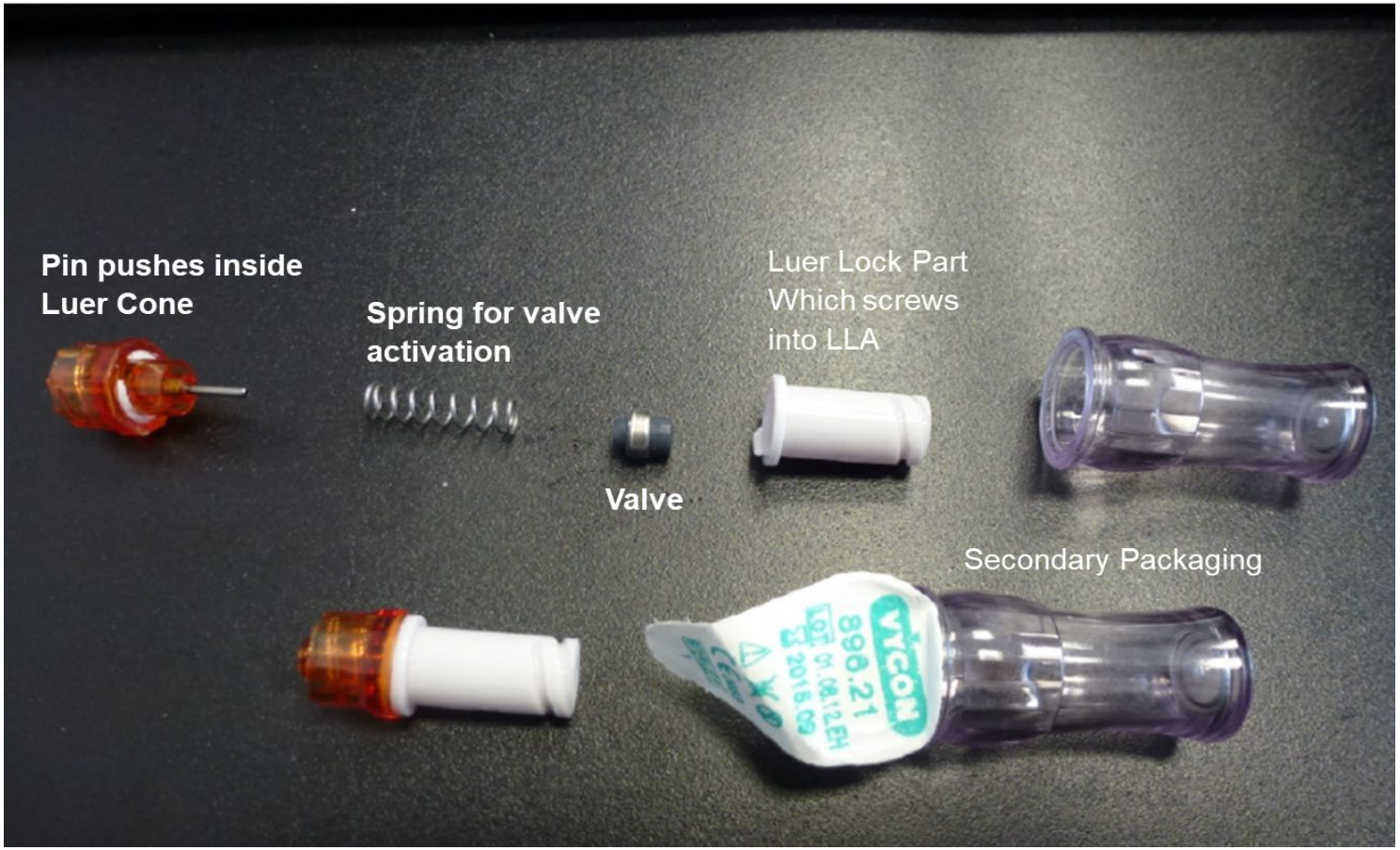




http://www.fda.gov/Drugs/DrugSafety/ucm254215.htm

Finished Pre-Filled Syringes TM

Connectivity with fluid path connectors TM



Finished Pre-Filled Syringes TM

Residual volume TM

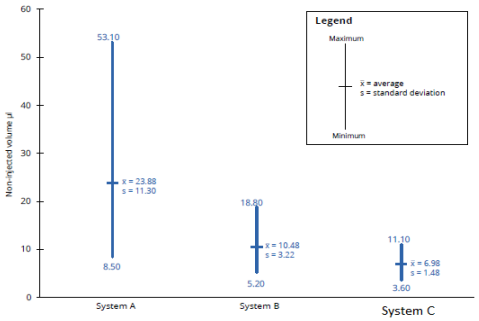
Principle

Determine the residual volume with drug product filled syringe as designed for the intended use (needle, environmental conditions etc.)

Procedure

Follow ISO 11040 – 4; 6.5.1.3 applies

(reference to ISO 7886-1; Annex C and ISO 11040-5)



Interpretation of Results

Compare residual volume with pre-defined specification (as for the intended use)

Finished Pre-Filled Syringes TM

Anti-needlestick requirements TM

Principle

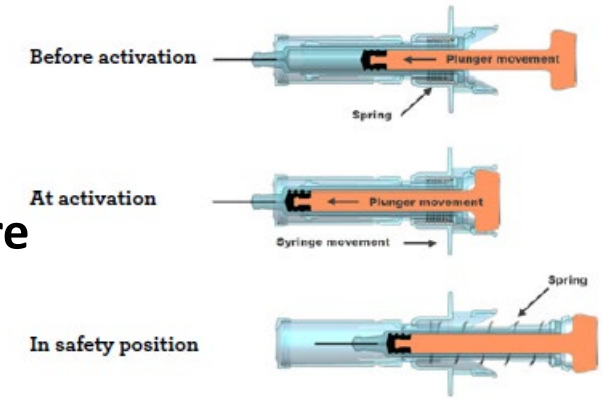
Determine the anti-needlestick prevention features with drug product filled syringe as designed for the intended use (environmental conditions etc.)

Procedure

Follow ISO 23908

Testing activation of sharp injury protection feature

Challenge the device in safe mode

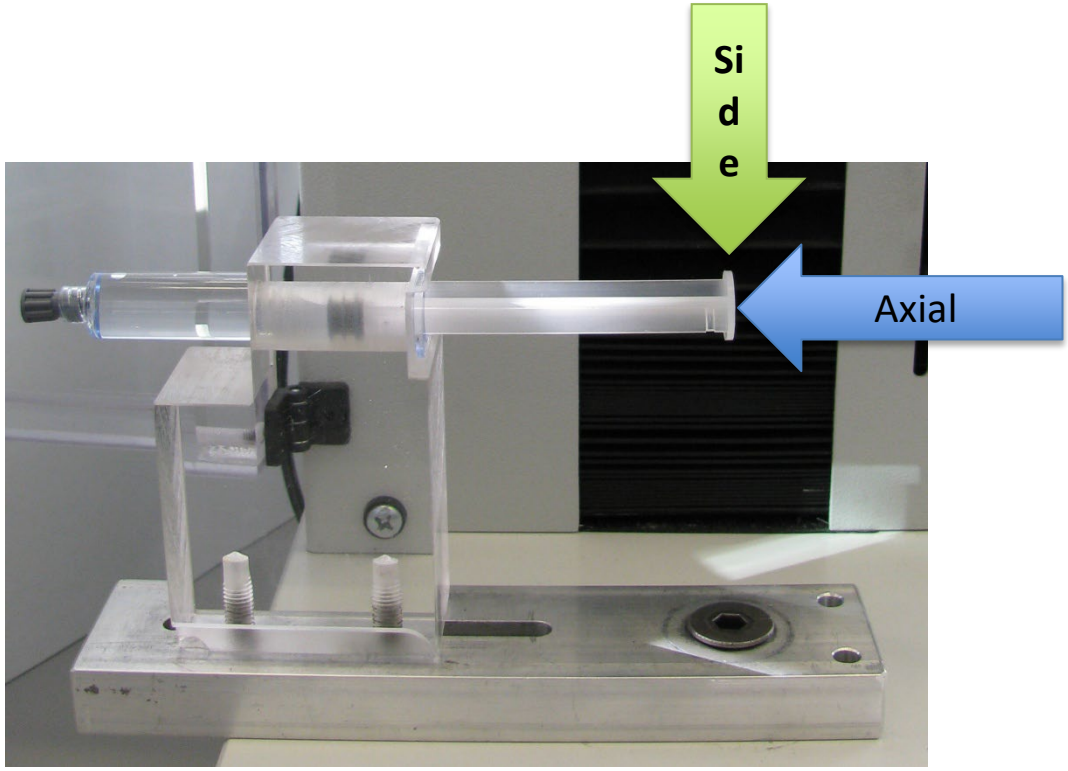


Interpretation of Results

Compare results with pre-defined specification (as for the intended use)

Finished Pre-Filled Syringes TM

Liquid Leakage beyond plunger TM



Nominal capacity of syringe V ml	Forces for leakage testing (see Annex D)	
	Side force (±5 %) N	Axial pressure (gauge) (±5 %) kPa
$V < 2$	0,25	300
$2 \leq V < 5$	1,0	300
$5 \leq V < 10$	2,0	300
$10 \leq V < 20$	2,0	300

Follow ISO 7886-1

Finished Pre-Filled Syringes TM

Markings TM

Principle

Determine the accuracy of the label / marking of drug product filled syringe as designed for the intended use (environmental conditions etc.)

Procedure

See 9.2.1 and 9.2.2

[ISO 7886-1]

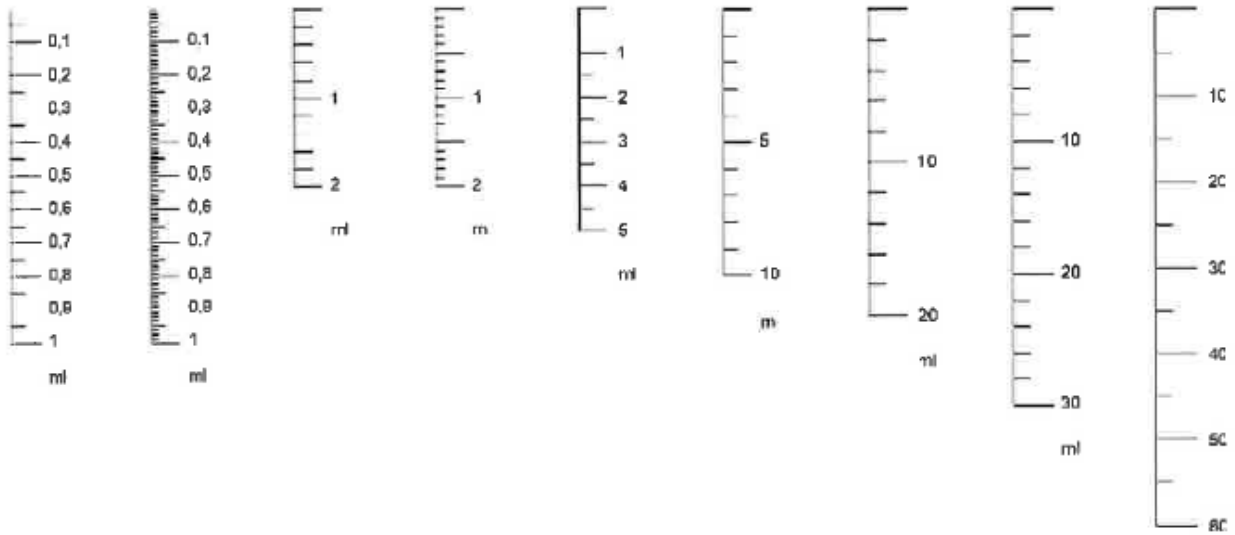
Interpretation of Results

Verify accuracy of printing on syringe and/ or label placement according to pre-defined specifications

Finished Pre-Filled Syringes TM

Markings TM

Examples of scales and the numbering of graduation lines are shown in Figure 2.



9.2 Numbering of scales

9.2.1 Graduation lines shall be numbered at least at the volume increments given in Table 1. In addition, the line denoting the nominal capacity or the lines denoting the nominal capacity and the total graduated capacity, if these differ, shall be numbered.

Examples of scale numbering are shown in Figure 2.

9.2.2 When the syringe is held vertically with the conical tip uppermost and with the scale to the front, the numbers shall appear vertical on the scale and be approximately centred on the graduation lines to which they relate. The numbers shall be close to, but shall not touch, the ends of the graduation lines to which they relate.

Finished Pre-Filled Syringes TM

Drug Container Interaction TM

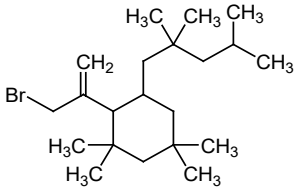
The content of the prefilled syringe shall meet the specified quality attributes throughout the shelf life when transported and stored according to the manufacturer's instructions. The impact of components (e.g. needle, tubing) on the content at the time of use shall be considered.

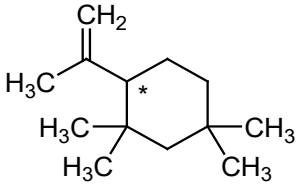
The following aspects shall be considered but might not be all inclusive:

— extractables/leachables, e.g residuals from forming, moulding, assembly process, gluing, sterilization process, rubber ingredients, impurities and degradation products, free silicone, as well as from labels;

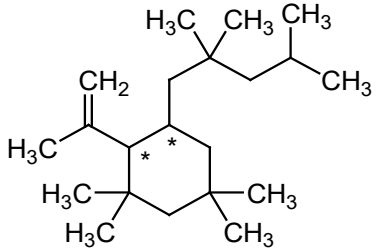
— compatibility, e.g. loss of potency of the drug, adsorption, degradation of the drug, change of stability indicating parameters;

— effect of shear forces during delivery on the drug quality.





C13 oligomer



C21 oligomer

Finished Pre-Filled Syringes TM

Biological requirements TM

Principle

Determine endotoxin level and perform biological hazard assessment ISO 10993-1 (sterility over shelf-life including transportation)

Procedure

Enotoxin limits and methods follow pharmacopoeial requirement

Sterility methods follow pharmacopoeial requirement

Biocompatibility evaluation according to ISO 10993-1 classification

Interpretation of Results

Consider results for sterility and safety of syringe system

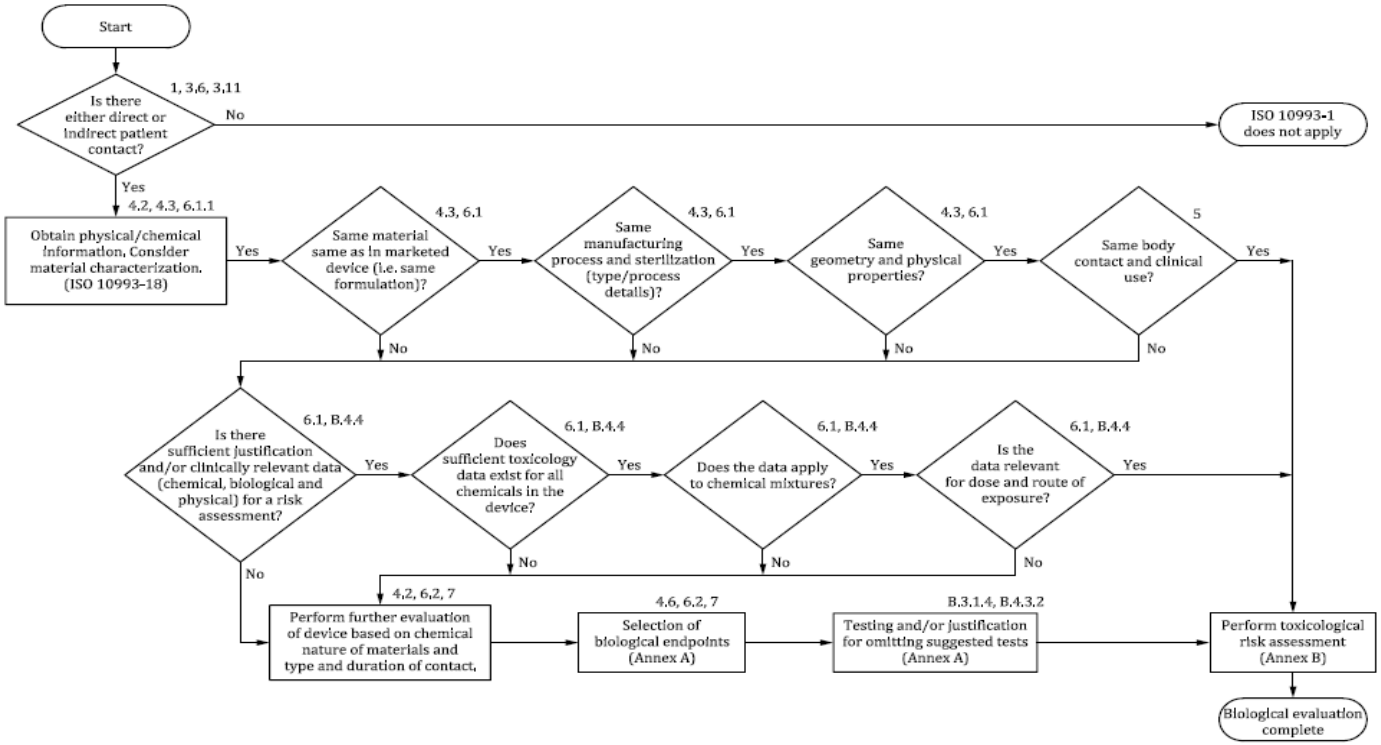
Finished Pre-Filled Syringes TM

Biological requirements TM

Biological hazard assessment shall be performed for the finished prefilled syringe following, e.g. ISO 10993-1.

The container closure system shall maintain sterility, achieved either by aseptic processing or by terminal sterilization, throughout its shelf life including transportation.

Endotoxin levels are specified in pharmacopoeial requirements.



Finished Pre-Filled Syringes TM

Biological requirements TM

Table A.1 — Endpoints to be addressed in a biological risk assessment

Medical device categorization by			Endpoints of biological evaluation														
Nature of body contact		Contact duration	Physical and/or chemical information	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Material mediated pyrogenicity[a]	Acute systemic toxicity[b]	Subacute toxicity[b]	Subchronic toxicity[b]	Chronic toxicity[b]	Implantation effects[b,c]	Hemocompatibility	Genotoxicity[d]	Carcinogenicity[d]	Reproductive/developmental toxicity[d,e]	Degradation[f]
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – Long term (>30 d)															
Surface medical device	Intact skin	A	X[g]	E[h]	E	E											
		B	X	E	E	E											
		C	X	E	E	E											
	Mucosal membrane	A	X	E	E	E											
		B	X	E	E	E		E	E			E					
		C	X	E	E	E		E	E	E	E	E		E			
	Breached or compromised surface	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E					
		C	X	E	E	E	E	E	E	E	E	E		E	E		

Finished Pre-Filled Syringes TM

Container closure integrity TM

Check the integrity of the final PFS system (sterility over shelf-life including transportation)

Follow principles described in <USP 1207>

Validate a suitable physical, chemical container closure integrity test method

Deterministic Methods:

- **Head space**
- **High voltage leakage**
- **Tracer gas detection**
- **Pressure decay**
- **Vacuum decay**
- **Etc**

- *Package Integrity and Test Method Selection* ⟨ 1207.1 ⟩
- *Package Integrity Leak Test Technologies* ⟨ 1207.2 ⟩
- *Package Seal Quality Test Methods* ⟨ 1207.3 ⟩

Probabilistic Method:

- **Microbial Challenge**
- **Bubble emission**
- **Etc**

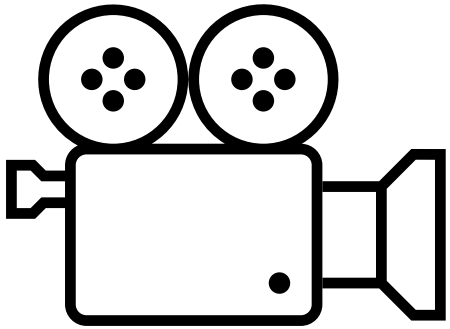
Finished Pre-Filled Syringes TM

Container closure integrity TM

Head Space

Finished Pre-Filled Syringes TM

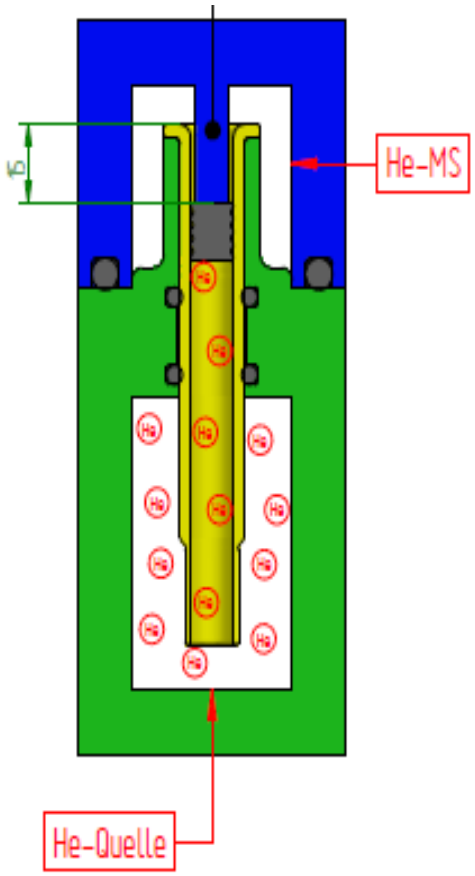
Container closure integrity TM



High Voltage Leakage

Finished Pre-Filled Syringes TM

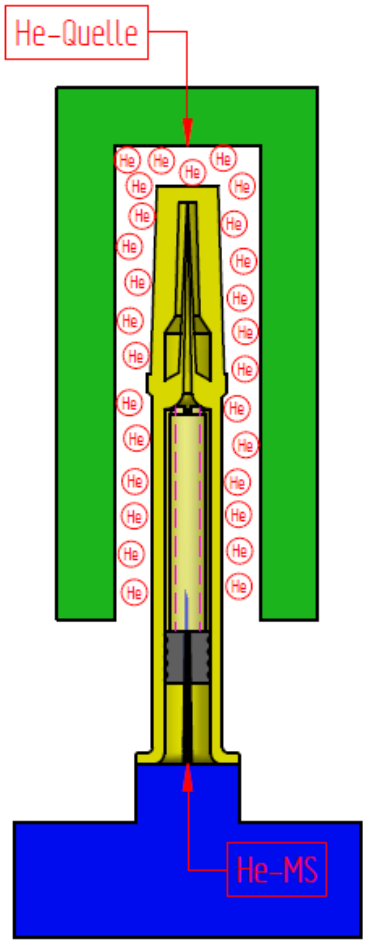
Container closure integrity TM



Plunger Tightness

Schematics of Test Concepts

Tracer Gas



Closure Tightness

Finished Pre-Filled Syringes TM

Deliverable volume / Extractable volume TM

Check the deliverable volume of the final drug product filled syringe as designed for the intended use.

Follow instructions of use and determine dose.

EP 2.9.17 Extractable Volume of parenteral preparations

Compliance with the requirements for extractable volume is assured by filling with a volume in slight excess of the nominal volume to be withdrawn. The excess volume is determined by the characteristics of the product.

CARTRIDGES AND PREFILLED SYRINGES

Select one container if the nominal volume is 10 ml or more, 3 containers if the nominal volume is more than 3 ml and less than 10 ml, or 5 containers if the nominal volume is 3 ml or less. If necessary, fit the containers with the accessories required for their use (needle, piston, syringe) and transfer the entire contents of each container without emptying the needle into a dry tared beaker by slowly and constantly depressing the piston. Determine the volume in millilitres calculated as the mass in grams divided by the density.

The volume measured for each of the containers is not less than the nominal volume.

Finished Pre-Filled Syringes TM

Deliverable volume / Extractable volume TM

Principle

Check the deliverable volume of the final drug product filled syringe *in an Autoinjector* as designed for the intended use.

Procedure

Follow instructions of use and determine dose.

Dose accuracy of PFS/Autoinjector in NIS follow ISO 11608-1

Interpretation of Results

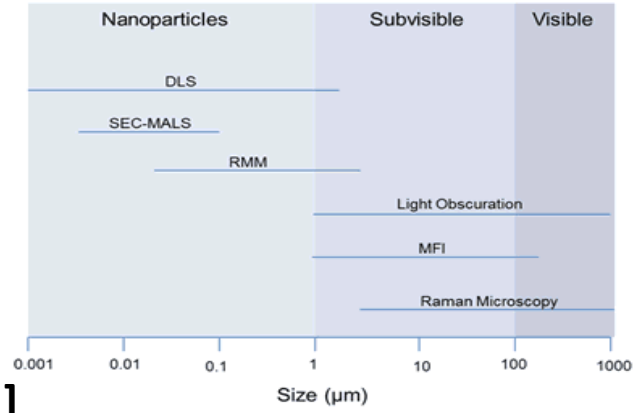
Compare actual deliverable volume with the labelled drug dose.

Finished Pre-Filled Syringes TM

Particulates (visible and sub-visible)

USP <790> Visible particle in injections

- **No**  **(magnification)**
- **Ilumination intensity 2000 – 3750 lux**
- **5s each against white and black background**



USP <788> subvisible particles parenterals [10µm / 25µm]

- **Light obscuration**
- **Membrane method**

USP <789> Subvisible particles ophthalmic products [10µm / 25µm / 50µm]

- **Light obscuration**
- **Membrane method**

Finished Pre-Filled Syringes TM

Coring needle test TM

Principle

Check if rubber particles are present after rubber penetration

*** current revision**

Procedure

Follow pharmacopoeia USP* <381> ; Ph Eur* 3.2.9 ; JP* 7.03

ISO 8871-series (Elastomeric parts for parenterals)

Interpretation of Results

Check for visible fragments; Shall be < 5 pcs (>50µm)