# PDA Europe
# Virtual Training Course
## Test Methods for Pre-Filled Syringe Systems

## Day 2:
## 11 September 2020; 2pm – 4pm CEST


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HK Packaging Consulting GmbH

PDA
Parenteral Drug Association

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# Agenda

- TM for final drug product filled syringes
- PFS combined with devices

# Standard for Glass & Polymer Syringes

**ISO 11040-8**

**Prefilled Syringes**

**Part 8: Requirements and tests methods for finished prefilled syringes**

**(TC 76)**

# Standard for Glass & Polymer Syringes

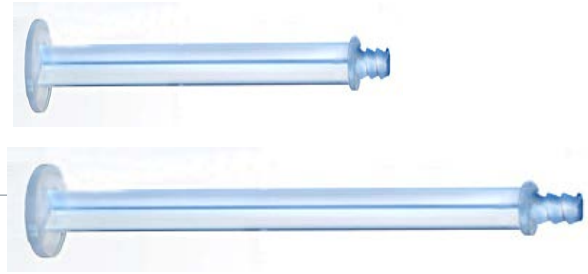
**ISO 11040-8**
**Prefilled Syringes**

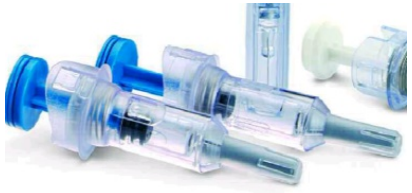
## System characterization

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

**Plunger stoppers** (ISO 11040-5 shall apply; talks about laminated plungers in view of plunger setting)

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





# Standard for Glass & Polymer Syringes

**ISO 11040-8**
**Prefilled Syringes**

**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)

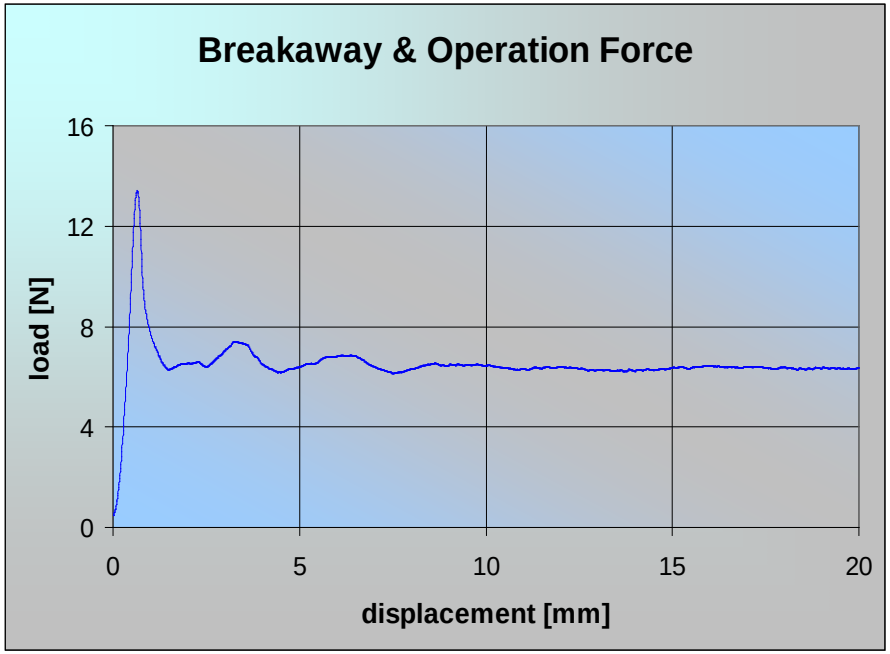
# Standard for Glass & Polymer Syringes

**ISO 11040-8**
**Prefilled Syringes**

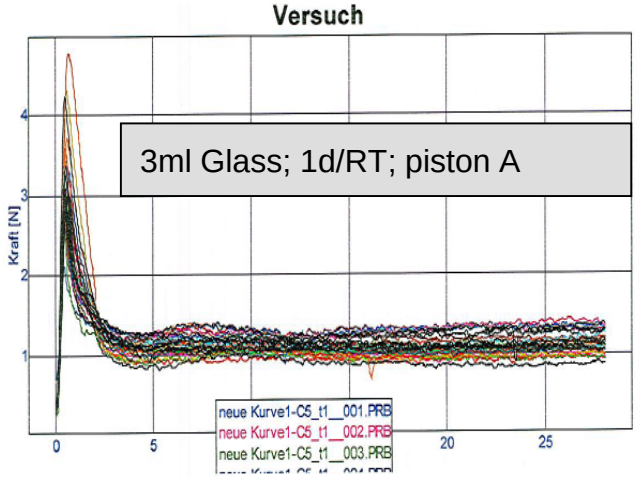
## Pharmaceutical requirements

**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)

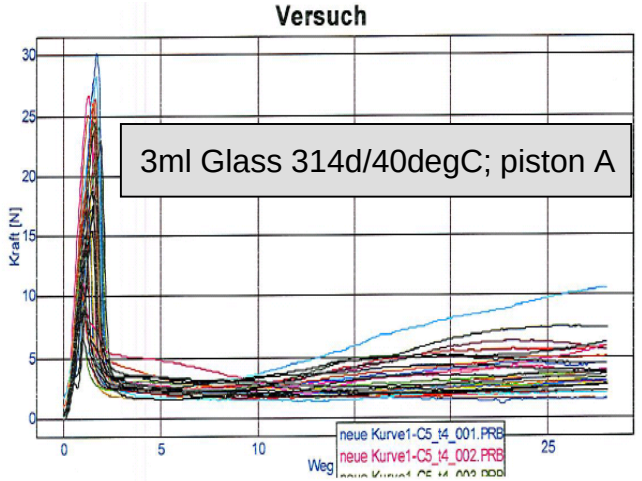
# Breakloose and Extrusion Forces TM




4.5N




26N




- Breakloose force is (usually) time dependent

# Burst Resistance TM

# Connectivity with  Fluid path connectors

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

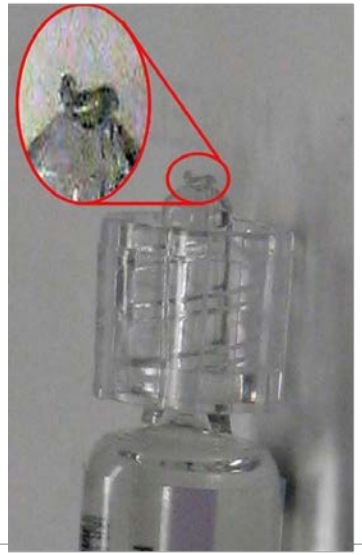
**Connectivity following ISO 80369-1**





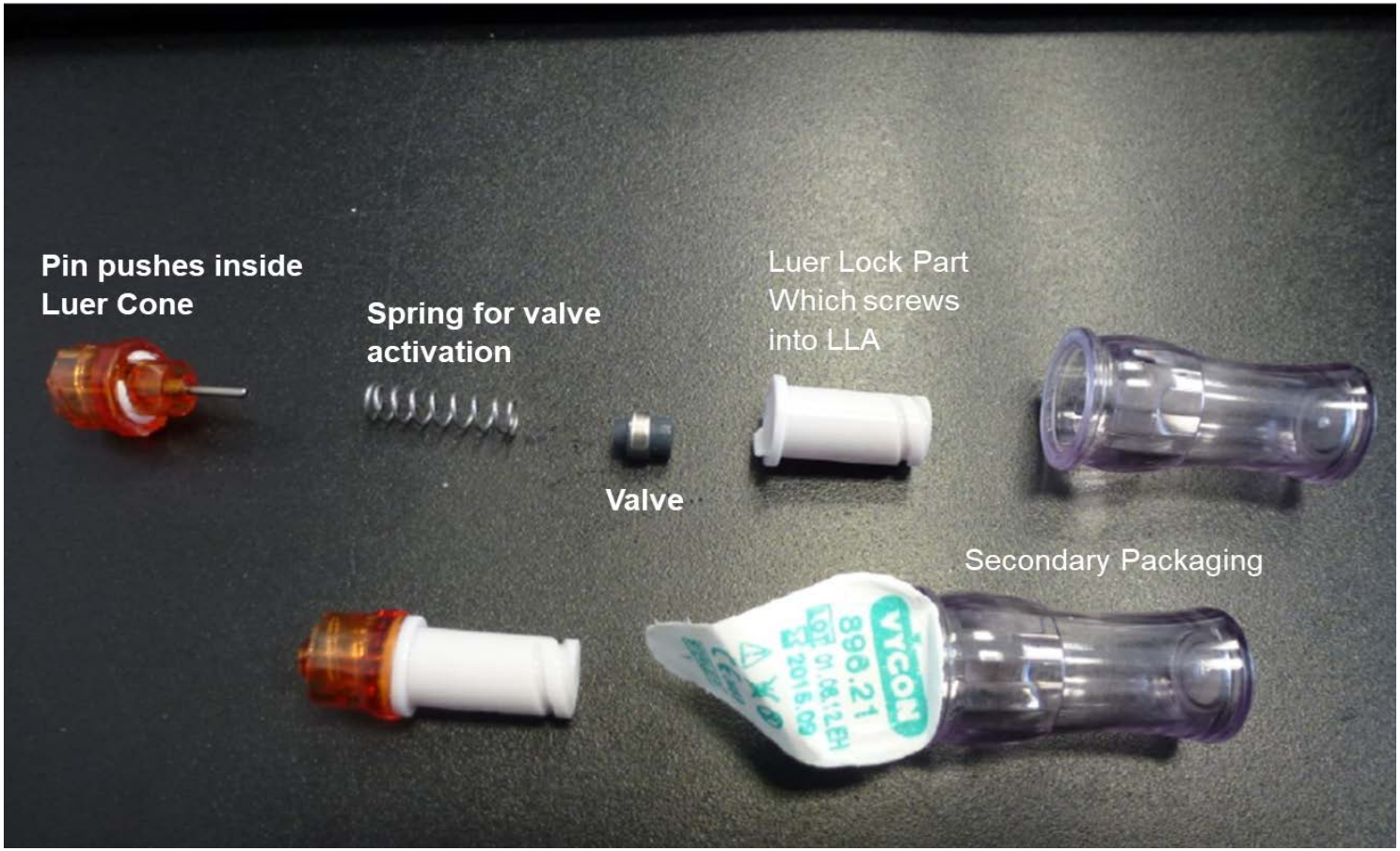

## Issues ?

**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

# Connectivity with  Fluid path connectors

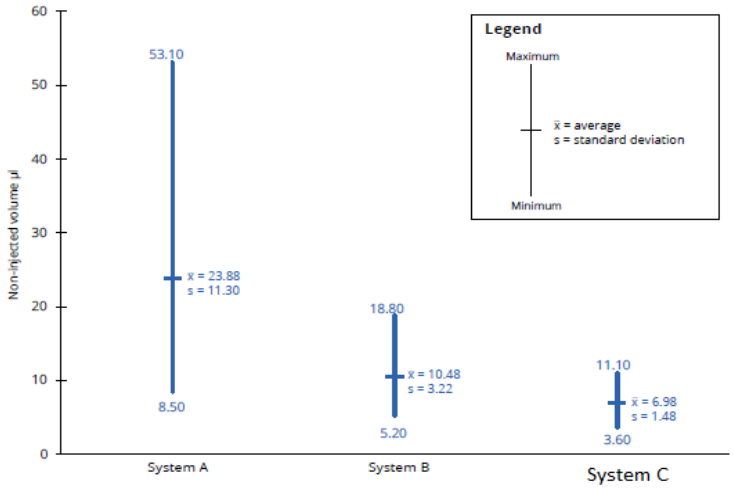


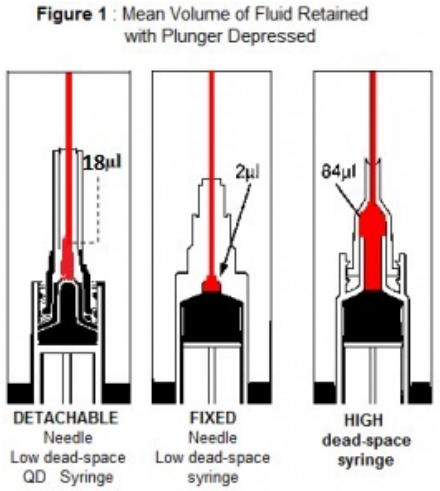
# Residual Volume TM

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

**Follow ISO 11040 – 4; 6.5.1.3 applies**

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



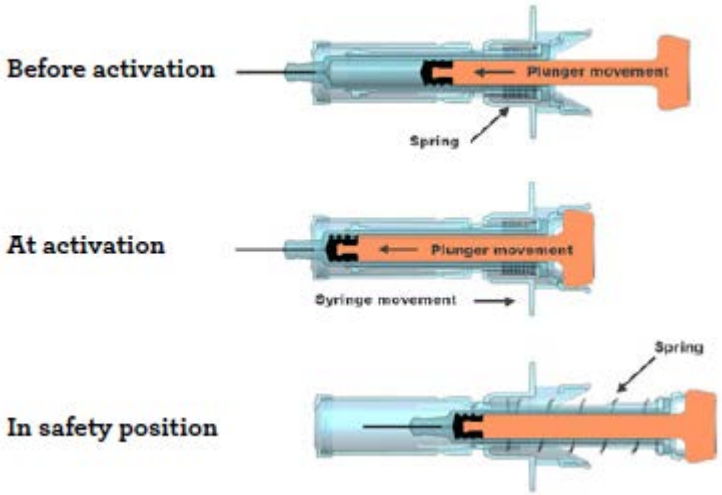
# Anti-needlestick requirements

**Determine the anti-needle stick prevention features**

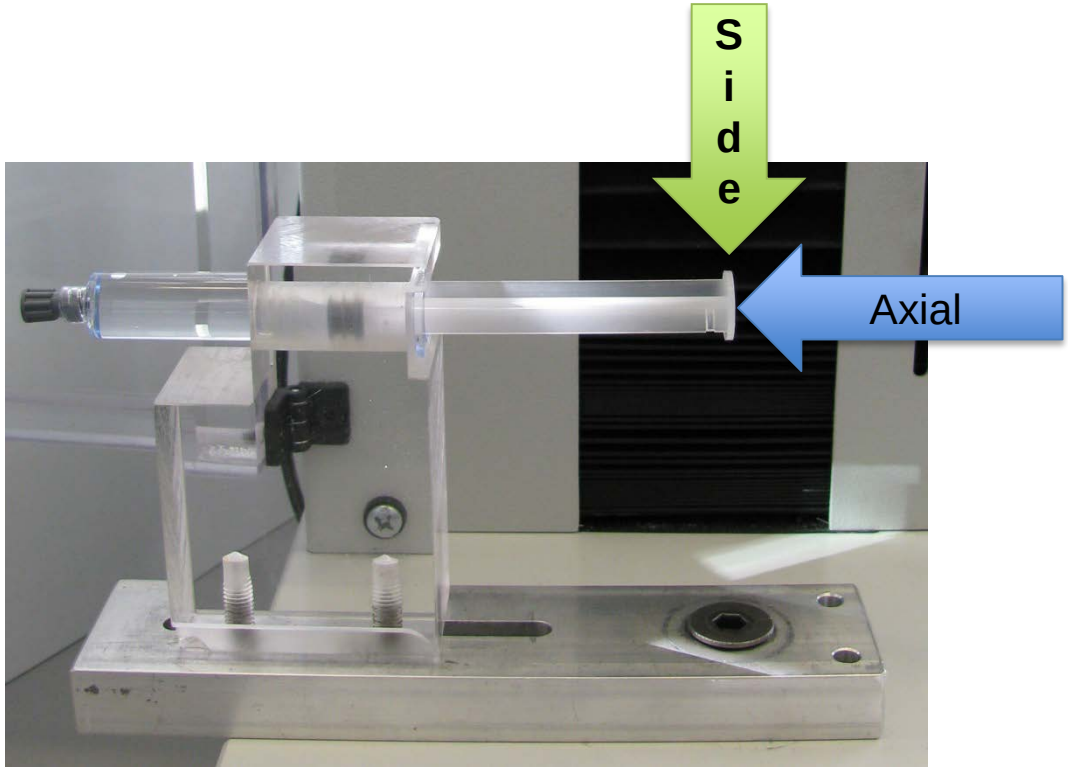
**Follow ISO 23908**

**Testing activation of sharp injury protection feature**

**Challenge the device in safe mode**



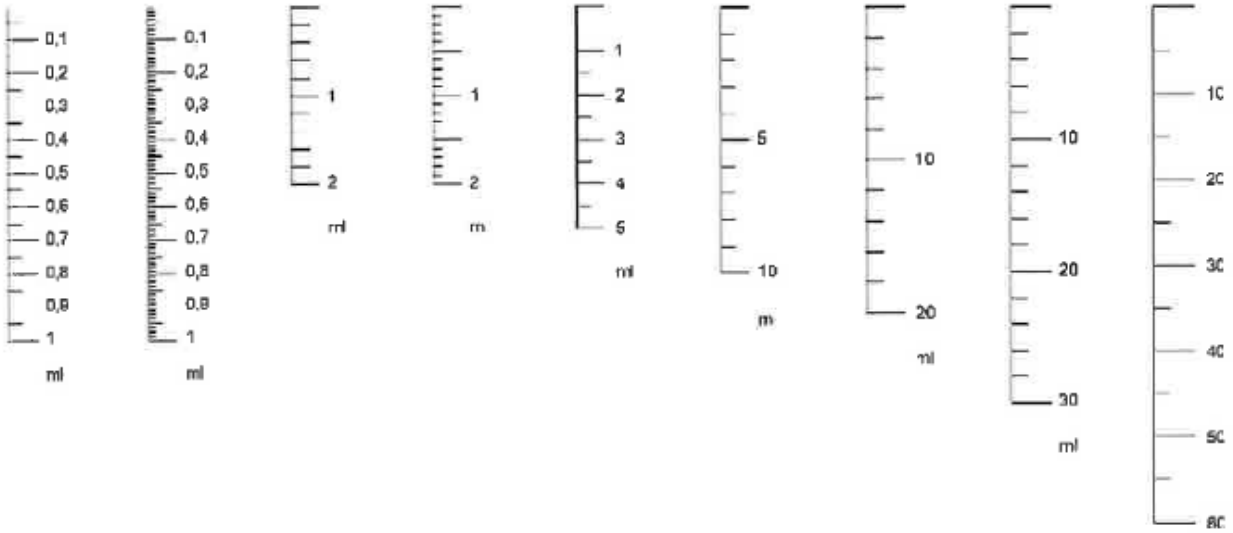
# Liquid leakage beyond plunger




| 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 |

# Markings

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.

# Drug- Container interaction

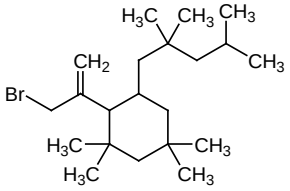
The content of the prefilled syringe shall meet the specified quality attributes throughout the shelf life when transported and stored according to the manufacturer's instructions. The impact of components (e.g. needle, tubing) on the content at the time of use shall be considered.

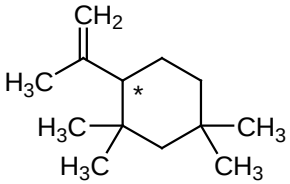
The following aspects shall be considered but might not be all inclusive:

— 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;

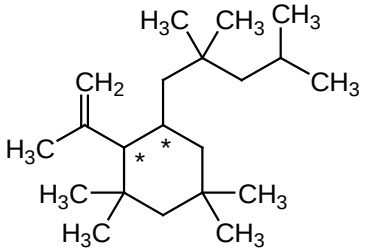
— compatibility, e.g. loss of potency of the drug, adsorption, degradation of the drug, change of stability indicating parameters;

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




C13 oligomer



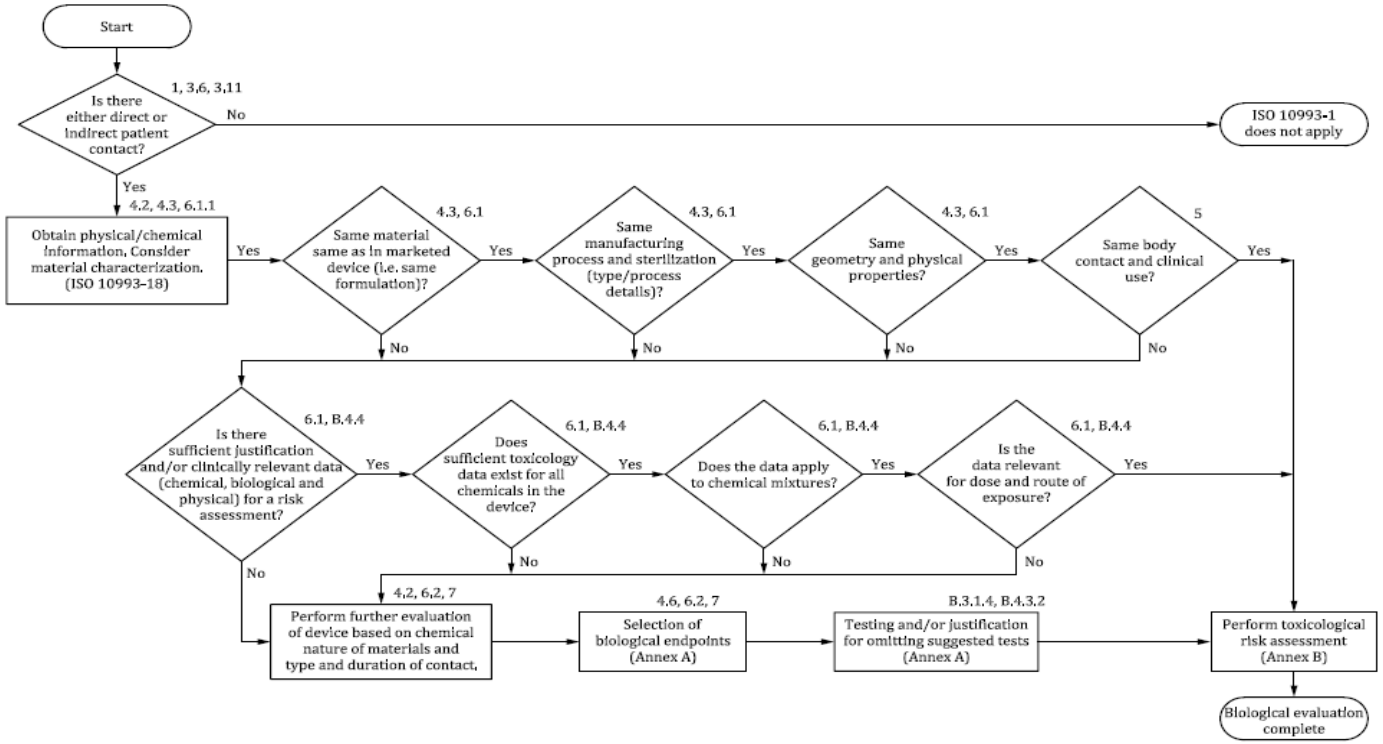

C21 oligomer

# Biological requirements

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.



# Biological requirements

**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 | | | |

# Container closure integrity

**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:**

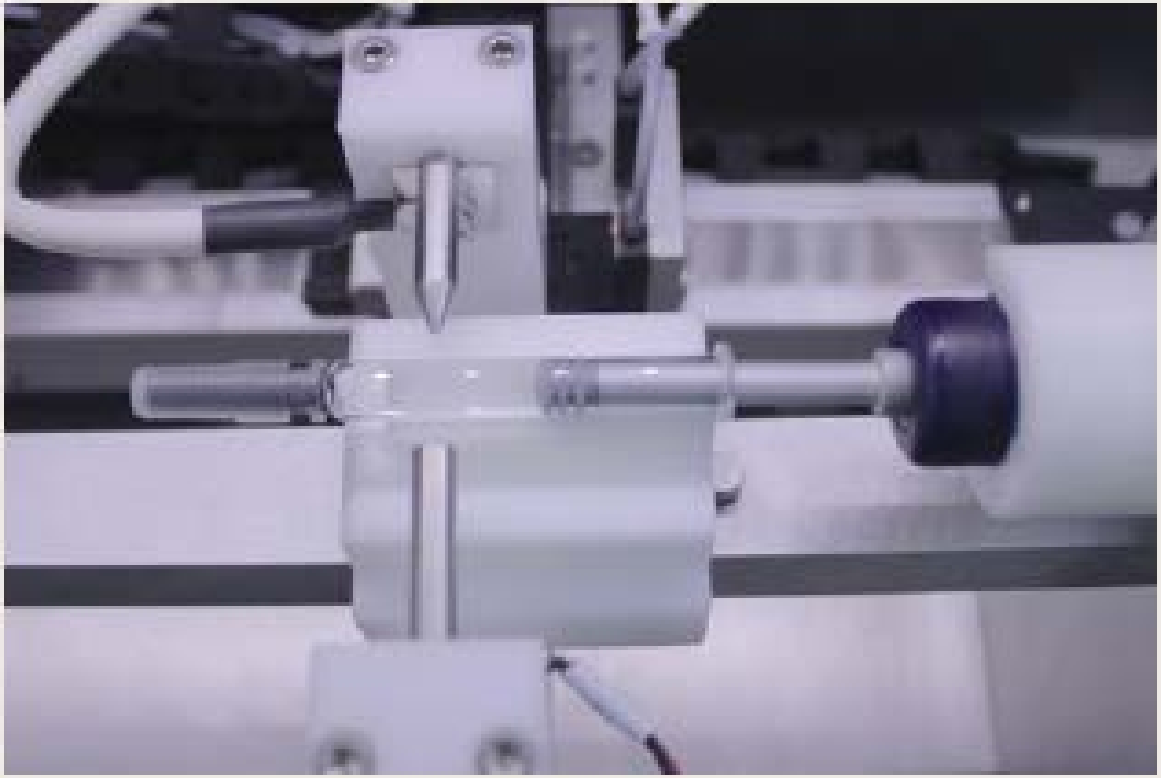
- **Microbial Challenge**
- **Bubble emission**
- **Etc**

# Container closure integrity

**Head Space**

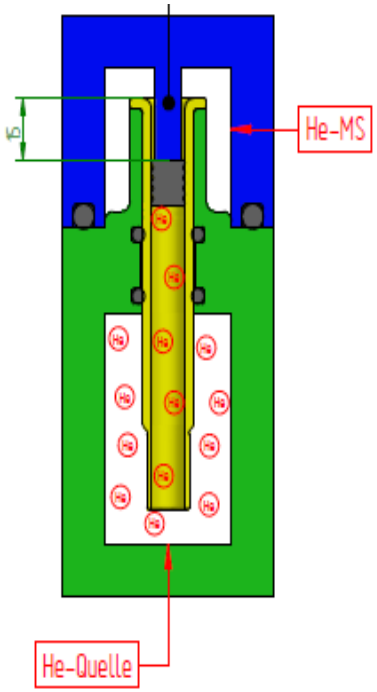
# Container closure integrity

**High Voltage Leakage**



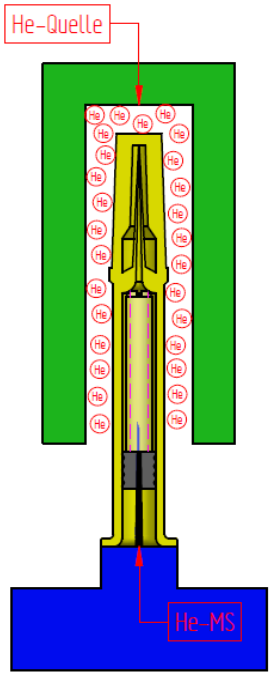
# Container closure integrity

**Tracer Gas**




**Plunger Tightness**

**Schematics of Test Concepts**




**Closure Tightness**

# Deliverable volume / Extractable volume

**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**

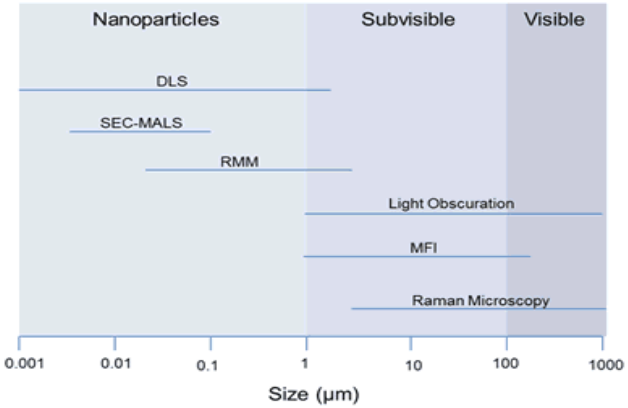
Compliance with the requirements for extractable volume is assured by filling with a volume in slight excess of the nominal volume to be withdrawn. The excess volume is determined by the characteristics of the product.

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.

# Particulates (visible and sub-visible)




**USP <790> Visible particle in injections**

- **no**
- **Ilumination intensity 2000 – 3750 lux**
- **5s each against white and black background**

**USP <789> subvisible particles parenterals [10µm / 25µm]**

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

**USP <788> Subvisible particles ophthalmic products [10µm / 25µm / 50µm]**

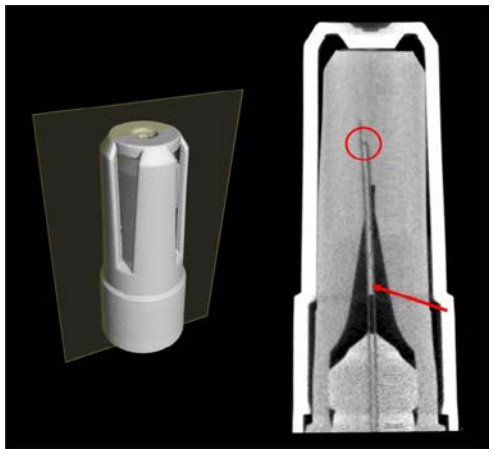
- **Light obscuration**
- **Membrane method**

# Coring Test Needle

**Check if rubber particles are present after rubber penetration**

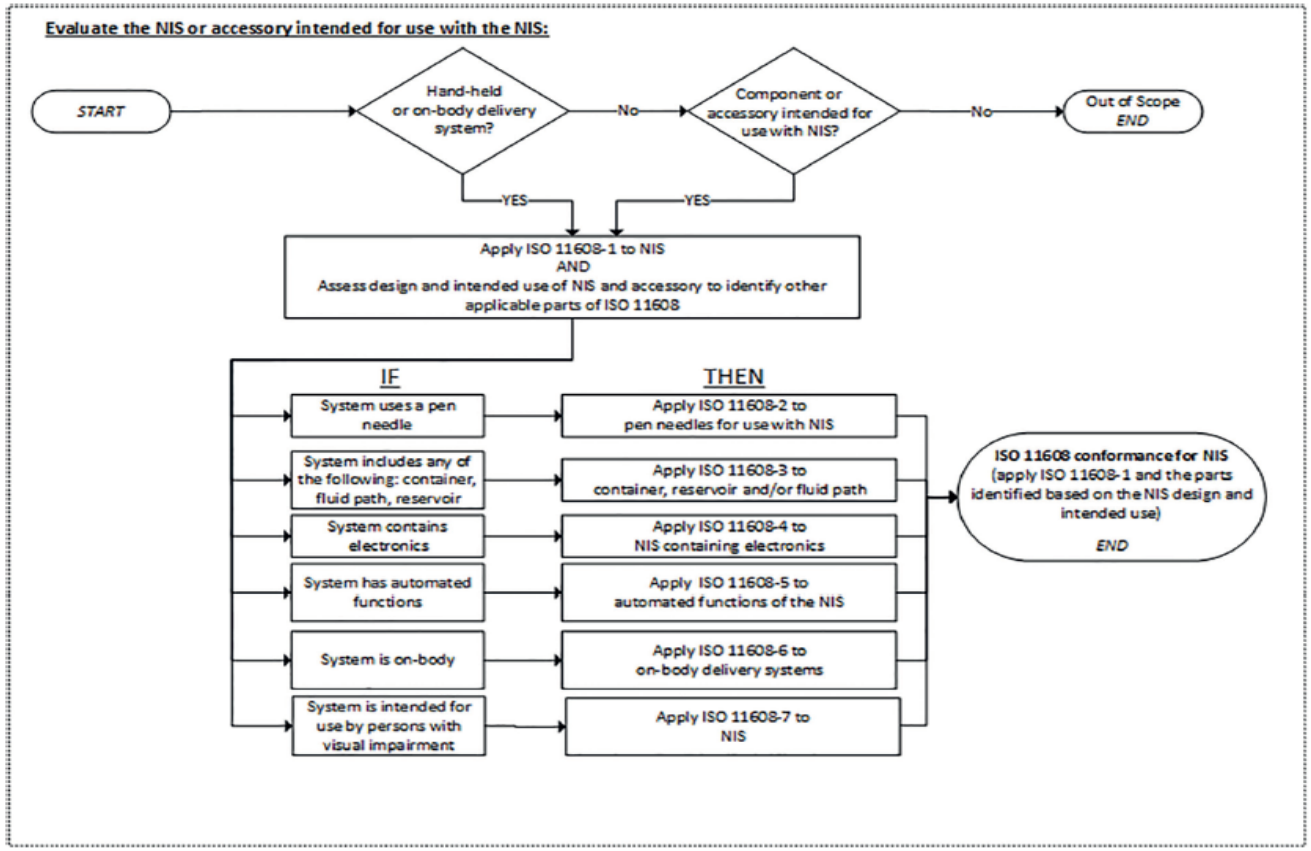
**Follow pharmacopoeia USP* <381> ; Ph Eur* 3.2.9 ; JP* 7.03**
**ISO 8871-series (Elastomeric parts for parenterals)**

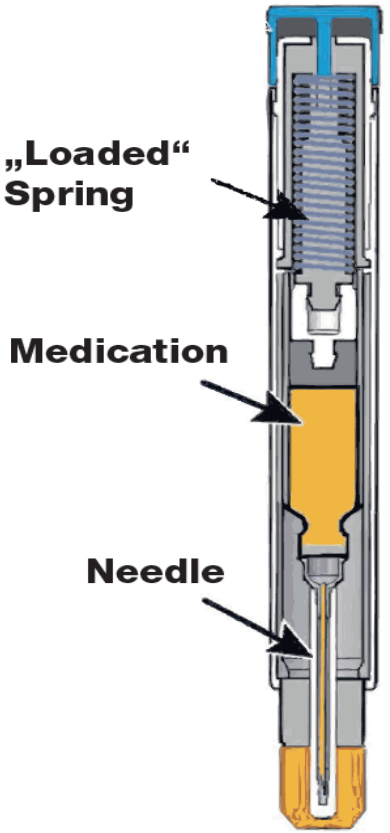
**Check for visible fragments; Shall be < 5 pcs (>50µm)**



# PFS combined with Devices

**ISO 11608-1**
**Needle-based injection systems for medical use - Requirements and Testmethods**
**Part 1: NIS (TC 84)**

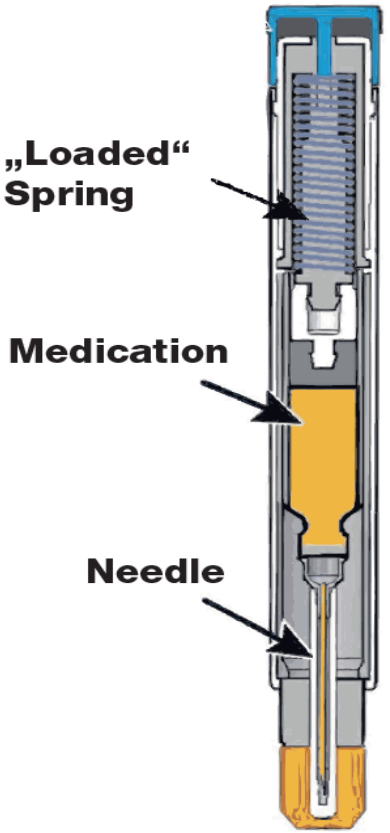


# PFS combined with Devices

**ISO 11608-1**
**Needle-based injection systems for medical use - Requirements and Testmethods**
**Part 1: NIS (TC 84)**



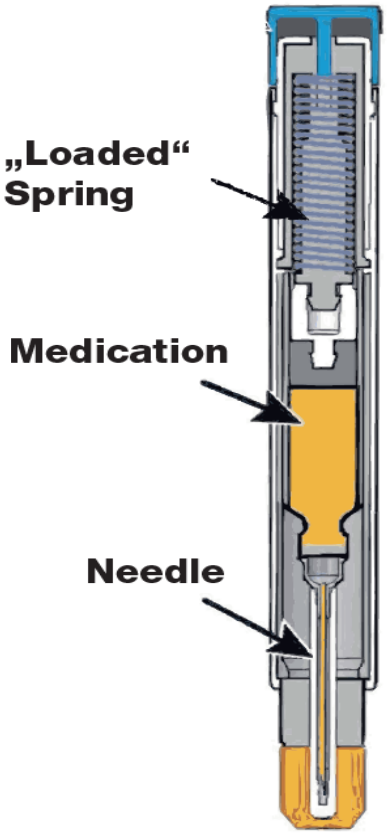


# PFS combined with Devices

**ISO 11608-1**
**Needle-based injection systems for medical use - Requirements and Testmethods**
**Part 1: NIS (TC 84)**

Table 1 — System designations

| | Multi-dose container | Single-dose container |
|---|---|---|
| NIS with replaceable container | A<br>Each container holds multiple doses, the size of which may be fixed or variable (set by the user) | B1<br>Each container holds a single dose, and the entire deliverable volume is expelled |
| | | B2<br>Each container holds a single dose, and a portion of the deliverable volume is expelled |
| NIS with non-replaceable container which is integrated, or user assembled | C<br>Each container holds multiple doses, the size of which may be fixed or variable (set by the user) | D1<br>Each container holds a single dose, and the entire deliverable volume is expelled |
| | | D2<br>Each container holds a single dose, and a portion of the deliverable volume is expelled |



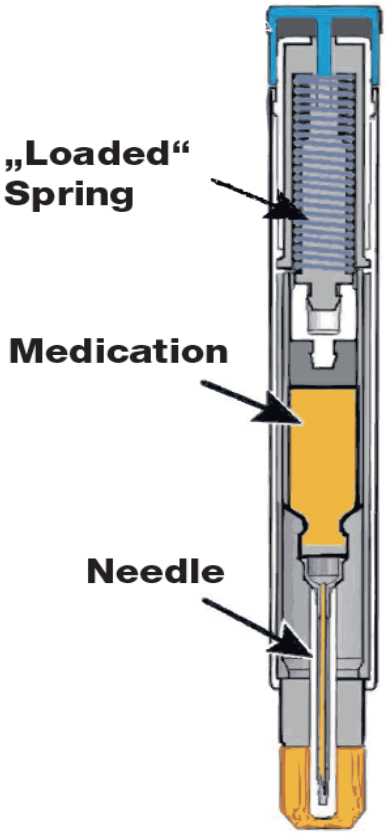
# PFS combined with Devices

**ISO 11608-1**
**Needle-based injection systems for medical use - Requirements and Testmethods**
**Part 1: NIS (TC 84)**

Table 2 — Dose accuracy assessment matrix

| Dose accuracy matrix | System designation | | | | | |
|---|---|---|---|---|---|---|
| | A | B1 | B2 | C | D1 | D2 |
| Determine doses needed | 7.2.3.1 | 7.2.4 | 7.2.4 | 7.2.3.1 | 7.2.4 | 7.2.4 |
| Determine accuracy limits | 7.4.2.1 | 7.4.2.2 | 7.4.2.1 | 7.4.2.1 | 7.4.2.2 | 7.4.2.1 |
| Determine last-dose accuracy limits (variable dose only) | 7.4.3 | N/A | N/A | 7.4.3 | N/A | N/A |
| Calculate last-dose error (variable dose only) | 7.4.3 | N/A | N/A | 7.4.3 | N/A | N/A |
| Calculate dose delivery efficiency (user-filled only) | N/A | 7.4.4 | N/A | N/A | 7.4.4 | N/A |
| Calculate tolerance intervals | 7.4.5 | 7.4.5 | 7.4.5 | 7.4.5 | 7.4.5 | 7.4.5 |

Refer to Annex F for a detailed discussion of sampling plans for both variable and attribute data.



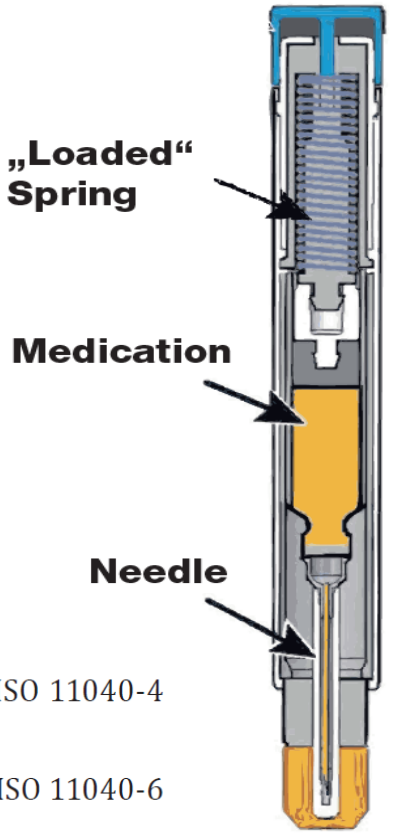
# Video

# PFS combined with Devices

**ISO 11608-3**
**Needle-based injection systems for medical use - Requirements and Testmethods**
**Part 3: NIS containers and integrated fluid path**

**(TC 84)**

**Prefilled Syringes are described in the ISO 11040-4 series but PFS out of 11040-8 are included when used with a NIS.**




Specific requirements for NIS primary container closure system components are:

a) glass syringes (including integrated needles) shall comply with applicable clauses of ISO 11040-4 and ISO 11040-8;

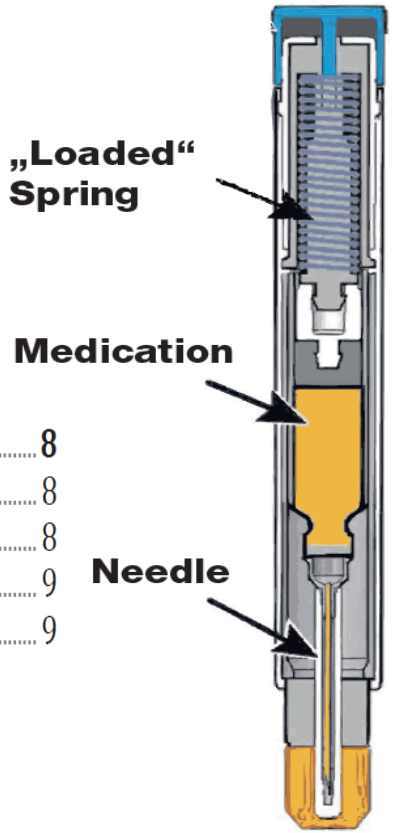
b) plastic syringes (including integrated needles) shall comply with applicable clauses of ISO 11040-6 and ISO 11040-8;

c) syringe plunger stoppers shall comply with applicable clauses of ISO 11040-5;

# PFS combined with Devices

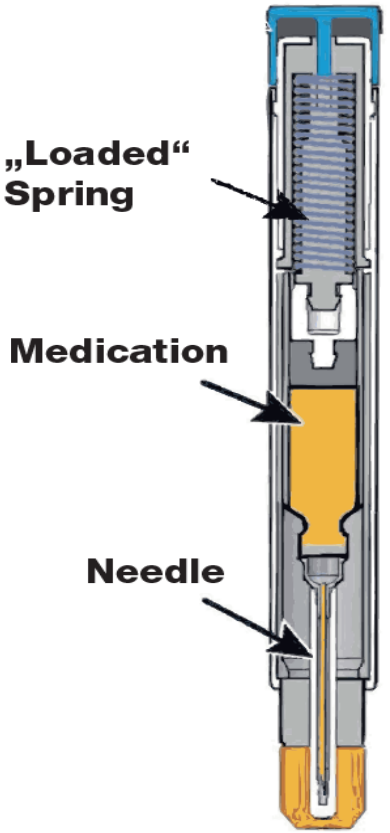
**ISO 11608-3**
**Needle-based injection systems for medical use - Requirements and Testmethods**
**Part 3: NIS containers and integrated fluid path**

**(TC 84)**



# PFS combined with Devices

## ISO 11608-3
## Needle-based injection systems for medical use - Requirements and Testmethods
## Part 3: NIS containers and integrated fluid path
## (TC 84)




### 5.3 Sub-visible particulates

Prepare a test sample by filling or flushing the reservoir and/or integrated fluid path of 10 NISs with particle-free water as defined by pharmacopeia (using the filling device and/or mechanism specified in the instructions for use) into a container rinsed with particle-free water. Prepare a control sample (using the same filling device and/or mechanism specified in the instructions for use) to expel particle-free water into an appropriately cleaned container. Enumerate the sub-visible particulate matter content of the reservoir and/or integrated fluid path in accordance with applicable pharmacopeia. The number of particulates is the difference between the test samples and control.

### 5.4 Visible particulates

Prepare a test sample by filling or flushing the reservoir and/or integrated fluid path of 10 NISs with particle-free water as defined by pharmacopeia (using the filling device and/or mechanism specified in the instructions for use) into a container rinsed with particle-free water. Prepare a control sample (using the same filling device and/or mechanism specified in the instructions for use) to expel particle-free water into an appropriately cleaned container. The test sample shall be visually inspected for the presence of visible particulates (> 150 µm in diameter) in the test sample as compared to the control.

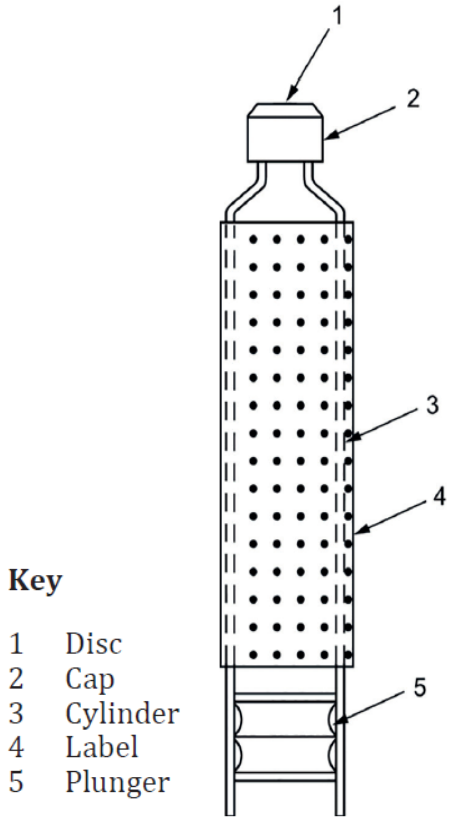
# PFS combined with Devices

**ISO 11608-3**
**Needle-based injection systems for medical use - Requirements and Testmethods**
**Part 3: NIS containers and integrated fluid path**

**(TC 84)**

**Annex B**
(informative)

**Historical references to ISO 11608-3:2012, *Pen-injector cartridges dimensions and test methods* (Clauses 4 and 5)**



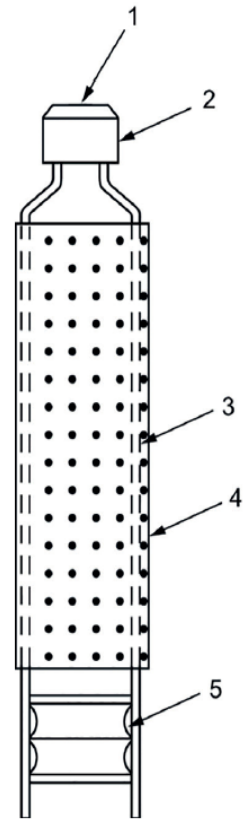

**Key**

1 Disc
2 Cap
3 Cylinder
4 Label
5 Plunger

# PFS combined with Devices

**ISO 11608-3**
**Needle-based injection systems for medical use - Requirements and Testmethods**
**Part 3: NIS containers and integrated fluid path**

**(TC 84)**




**Key**

1 Disc
2 Cap
3 Cylinder
4 Label
5 Plunger

**4 Requirements (historical 11608-3:2012)**

**4.3 Plunger force (cartridge only)**

The initiating force for cartridges shall not exceed 15 N, when tested in accordance with the test method given in 5.4.

The sustaining force for cartridges shall not exceed 10 N, when tested in accordance with the test method given in 5.4.

**5 Test methods (historical 11608-3:2012)**

**5.4 Plunger forces**

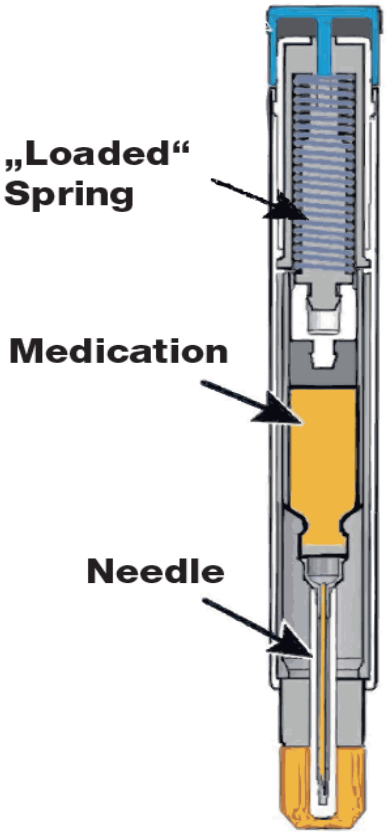
Measurements shall be made at a test speed of 50 mm/min with test cartridges that are open to the atmosphere (i.e. no septum present, fluid to be removed immediately prior to testing), so that only the plunger friction is measured. The initiating force is the peak force seen at the start of the plunger movement. The maximum sustaining force is measured over the measurement zone, which comprises not less than 75 % of cartridge deliverable volume.

# PFS combined with Devices

**ISO 11608-5**
**Needle-based injection systems for medical use - Requirements and Testmethods**
**Part 5: Automated Functions**

**(TC 84)**



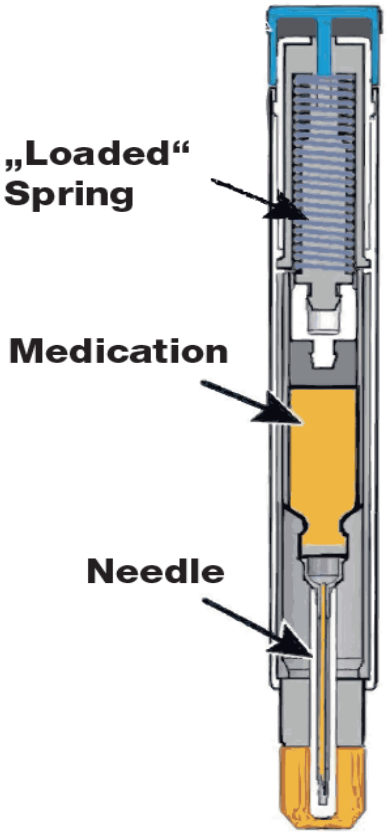


# PFS combined with Devices

**ISO 11608-5**
**Needle-based injection systems for medical use - Requirements and Testmethods**
**Part 5: Automated Functions**

**(TC 84)**





# Video

# Acknowledgements

Mr. Erik Berndt – Zwick / Roell, Germany

# Thank You !

# Q&A Session