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

(TC 76)

Pre-filled syringes TM

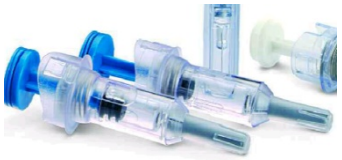
Regulatory Reference: 11040-8

System characterization

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

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

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



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)

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 subvisible) (applicable pharmacopeia)

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

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)

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)

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)

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

N/A no reference made

[ISO 7886-1]

Interpretation of Results

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

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

Container closure integrity TM

Principle

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

Procedure <USP 1207>

Validate a suitable physical, chemical container closure integrity test method

[Deterministic Methods: vacum decay, high voltage leakage, tracer gas detection..]

Microbial Challenge [Probabilistic Method]

Interpretation of Results

Consider results for sterility and safety of syringe system

Container closure integrity TM

Product quality risks
Posed by leaks of concern

Leaks of Concern	Product Quality Risks Posed by Leaks
Capable of allowing entry of microorganisms	Failure of **product sterility**
Capable of allowing escape of the product dosage form or allowing entry of external liquid or solid matter	Failure of **relevant** product physicochemical **quality attributes**
Capable of allowing change in gas headspace content	Failure of **relevant** product physicochemical **quality attributes** and/or **hindrance of product** access by the end-user

The container closure integrity must ensure absence of all package leaks that risk product quality.

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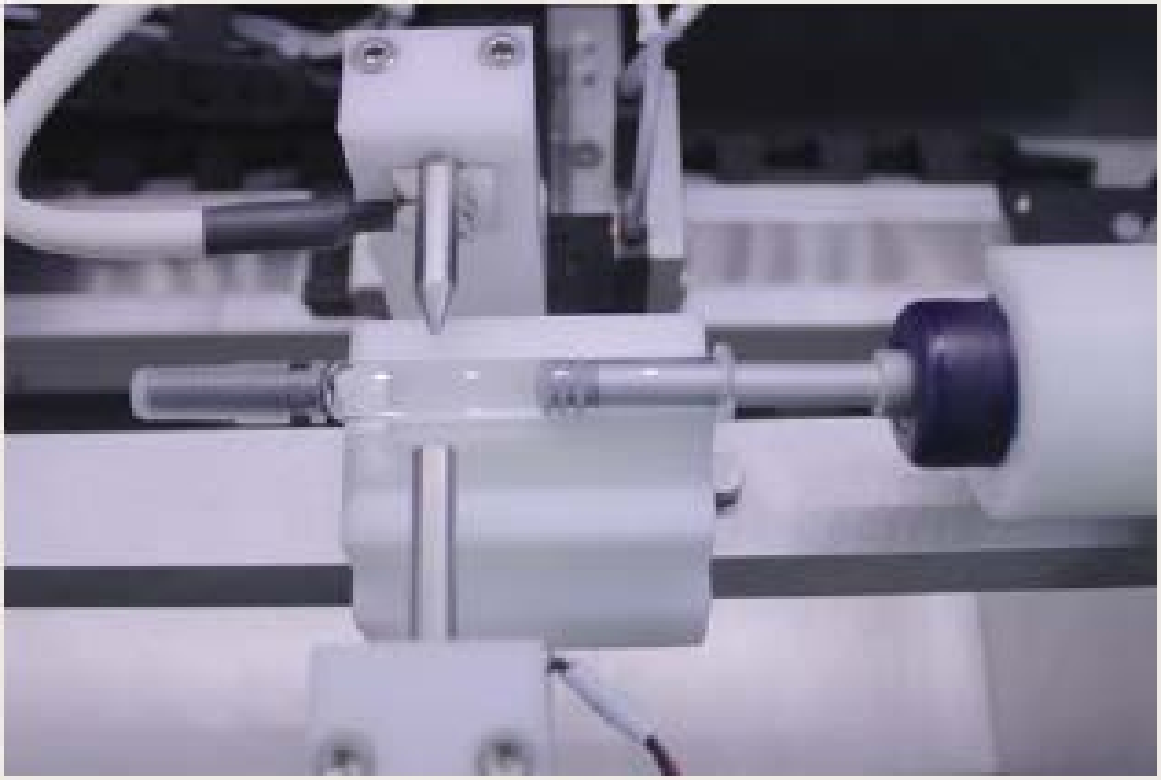
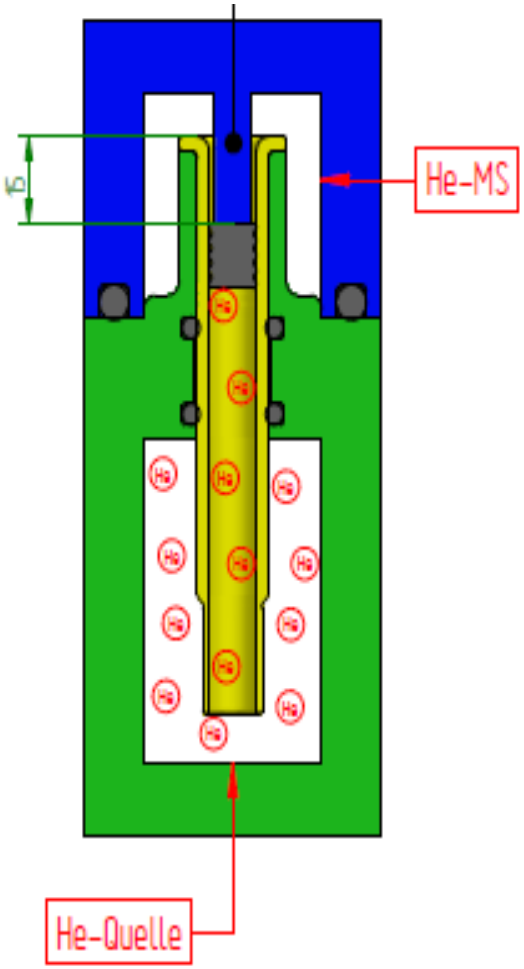
Container closure integrity TM

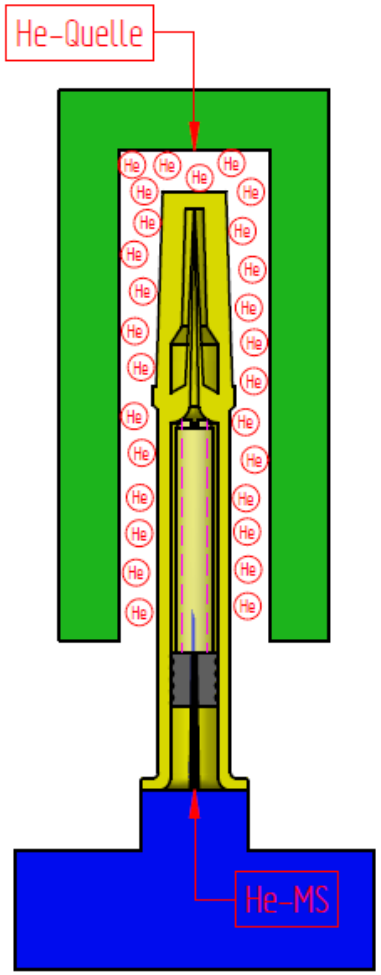


Container closure integrity TM

Schematics of Test Concepts



Plunger Tightness



Closure Tightness

Container closure integrity TM

Characterizing headspace gas composition

Laser-based Headspace Analysis

Described in USP <1207>

Non-destructive (product not lost, sample can be re-measured)

Rapid (~1 sec)

Flexibility and ease-of-use of this analytical technique makes it ideal for fundamental packaging integrity studies:

- Closure integrity
- Permeation

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Deliverable volume TM

Principle

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

Procedure

Follow instructions of use and determine dose.

Dose accuracy of PFS in NIS follow ISO 11608-1

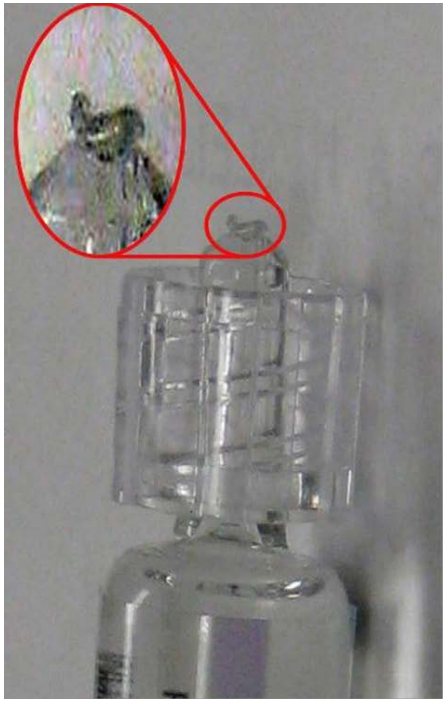
Interpretation of Results

Compare actual deliverable volume with the labelled drug dose.

FDA Requirement TM

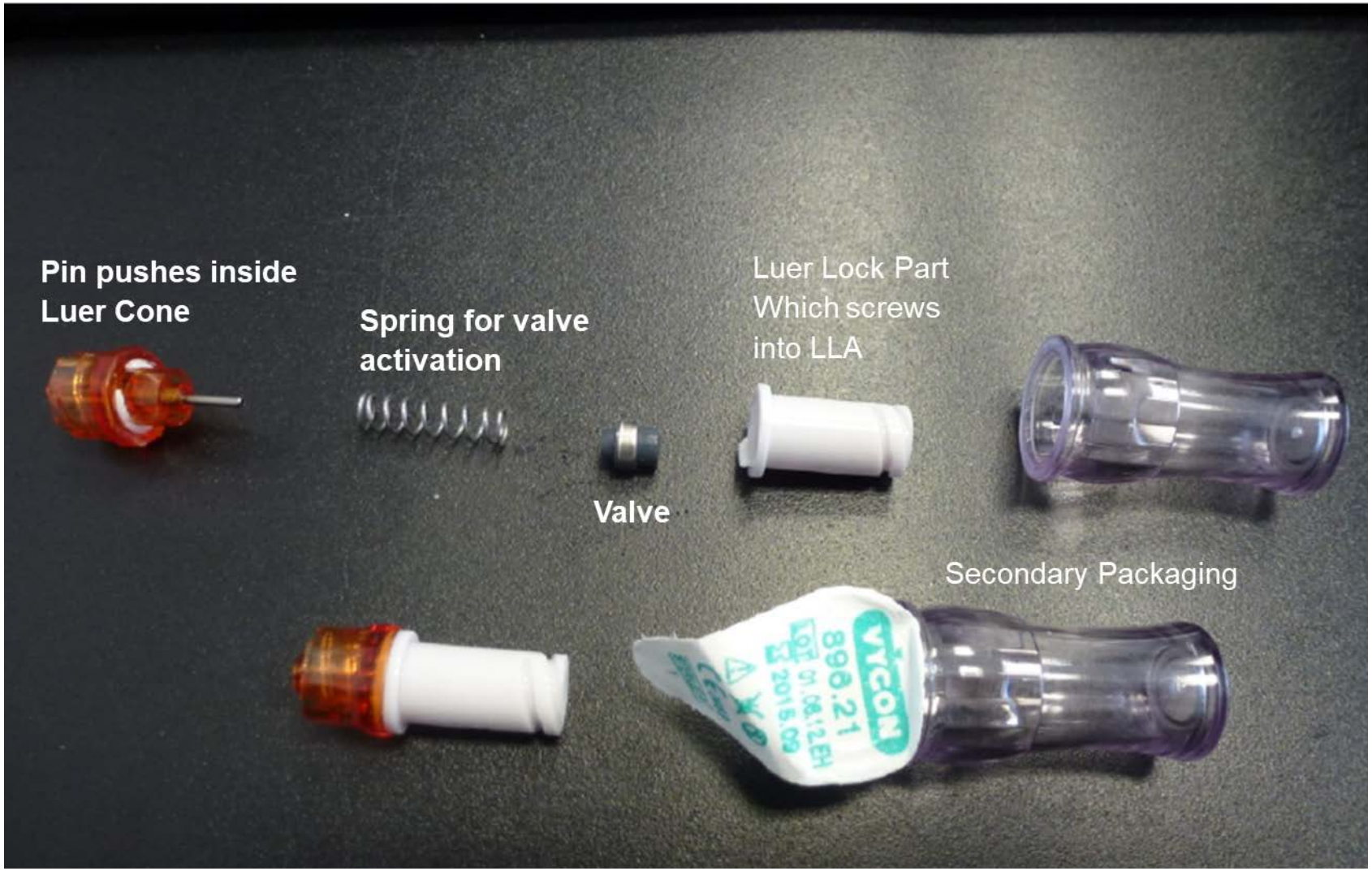
Problem

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

FDA Requirement TM



FDA Guidance (non binding recommendations)

Functional Performance

*“additional test request”

- **Seal Integrity (liquid leakage, air ingress, dye ingress)**
- **Glide force**
- **Break force**
- **Separation force**
- **Unscrewing torque**
- **Ease of assembly**
- **Resistance to overriding**
- **Stress cracking**
- **Validation of graduation markings**

FDA Guidance (non binding recommendations)

Functional Performance

*“additional test request”

- **Dead space**
- **Coring needle test***
- **Anti-needlestick mechanism**
- **Connectivity (needles, adapter, tubing, sharp prevention features)**
- **Injection force (during use)**
- **Tip cap removal**
- **Piston seal blowback**

FDA Guidance (non binding recommendations)

Functional Performance

- **Biocompatibility (ISO 10993)**
- **Sterilization (ISO 11135 - EO or 11137- Radiation)**
- **Human Factors (Design Control requirements 21 CFR part 820)**
- **PFS and Co-packages (empty glass syringe)**
- **Other testing (lyophilized etc)**
- **PFS / device compatibility**

Coring needle test TM

Principle

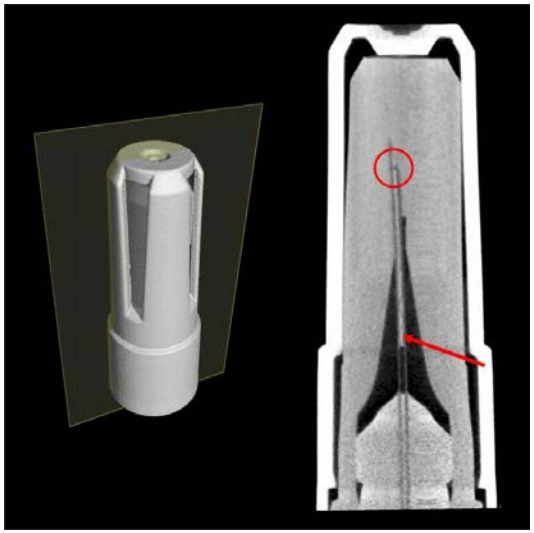
* current revision

Check if rubber particles are present after rubber penetration

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)

Acknowledgements