Test Methods for Pre-Filled Syringes

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Regulatory References for Finished Pre-filled Syringes

ISO 11040-8 (under development)

Prefilled Syringes

Part 8: Requirements and test methods for finished pre-filled syringes

ISO 11040-8 / under development (TC 76)

Pre-filled syringes TM

Regulatory Reference: 11040-8

System characterization

Barrel

Plunger stoppers

Additional components

Pre-filled syringes TM

Regulatory Reference: 11040-8

Physical system characterization

Break loose and extrusion forces

Burst resistance

Break resistance

Closure system forces and torques

Connectivity with fluid path connectors

Residual volume

Needle penetration force

Needle pull-out force

Anti-needlestick requirements

Liquid leakage

Markings

Pre-filled syringes TM

Regulatory Reference: 11040-8

Pharmaceutical requirements

- **Drug – container interaction**
- **Biological requirements**
- **Container closure integrity**
- **Deliverable volume**

Particulates (visible and subvisible)

Break loose and extrusion forces TM

Principle

Force testing with drug product filled syringe as designed for the intended use (including needle, environmental conditions etc.)

Procedure

ISO 11040 – 4; Annex E, Figure E.1.

Interpretation of Results

As described in Annex E of ISO 11040-4

Burst resistance TM

Principle

Burst resistance testing with drug product filled syringe as designed for the intended use (including needle, environmental conditions etc.)

Procedure

ISO 11040 – 4; Annex G, Figure G.2.

With sealed front to allow actual burst pressure testing

Interpretation of Results

Compare data of burst resistance testing with pre-defined burst pressure specification (as for the intended use)

Burst resistance TM

Principle

Burst resistance testing with drug product filled syringe as designed for the intended use (including needle, environmental conditions etc.)

Procedure

ISO 11040 – 4; Annex G, Figure G.2.

With sealed front to allow actual burst pressure testing

Interpretation of Results

Compare data of burst resistance testing with pre-defined burst pressure specification (as for the intended use)

Break resistance TM

Principle

Flange break resistance and Luer cone breakage resistance testing with drug product filled syringe as designed for the intended use (including needle, environmental conditions etc.)

Procedure

Flange break resistance ISO 11040 – 4; 5.4.4 applies (TM = Annex C)

Luer cone break resistance ISO 11040 – 4; 5.4.5 applies (TM = Annex C)

Interpretation of Results

Compare data of flange break and luer cone resistance testing with pre-defined breakage resistance specification (as for the intended use)

Closure system forces and torques TM

Principle

Closure system testing with drug product filled syringe as designed for the intended use (environmental conditions etc.)

Procedure

Closure system methods ISO 11040 – 4; G.3 – G.6 applies (TM = Annex G)

Interpretation of Results

Compare closure system forces and torque data with pre-defined closure specification (as for the intended use)

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)

Needle penetration force TM

Principle

Determine the needle penetration force with drug product filled syringe as designed for the intended use (environmental conditions etc.)

Procedure

Follow ISO 11040 – 4; (Annex F)

Interpretation of Results

Compare needle penetration forces with pre-defined specification (as for the intended use)

Needle pull-out force TM

Principle

Determine the needle pull-out force with drug product filled syringe as designed for the intended use (environmental conditions etc.)

Procedure

Follow ISO 11040 – 4; 6.5.2.5 applies (TM = Annex G)

Interpretation of Results

Compare needle pull-out forces 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)

Liquid leakage TM

Principle

Determine the leakage resistance of the plunger during use, with drug product filled syringe as designed for the intended use (environmental conditions etc.)

Procedure

Follow ISO 7886-1 – 4; (Annex B)

300 kPa / 30s [>10ml syringe = 200 kPa / 30s]

Interpretation of Results

Shall be no leakage of drug product beyond the plunger stopper

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

Validate a suitable physical, chemical or microbiological container closure integrity test method.

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

Interpretation of Results

Consider results for sterility and safety of syringe system

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.

Particulates (visible and subvisible) TM

Principle

Check visible and subvisible particulates of the final drug product filled syringe as designed for the intended use.

Procedure

Follow instructions pharmacopoeial requirements

[ISO 11040-4; Annex D for subvisible particulates]

Interpretation of Results

Compare actual particle contamination with pre-defined specification.

FDA Requirement TM

Problem

ISO 11040-4 compliant PFS in combination with a needleless luer activated devices (NLAD's) → ISO 594 Device (Thread)

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
- 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