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

Day 1:
10 September 2020; 2pm – 4pm CEST

Horst Koller, CEO,
HK Packaging Consulting GmbH

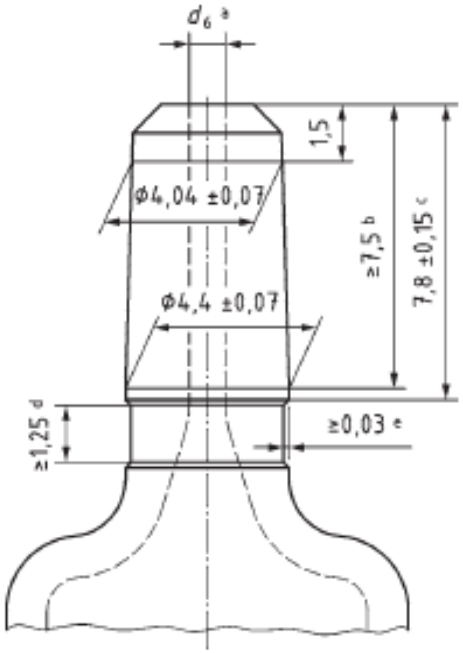
PDA
Parenteral Drug Association

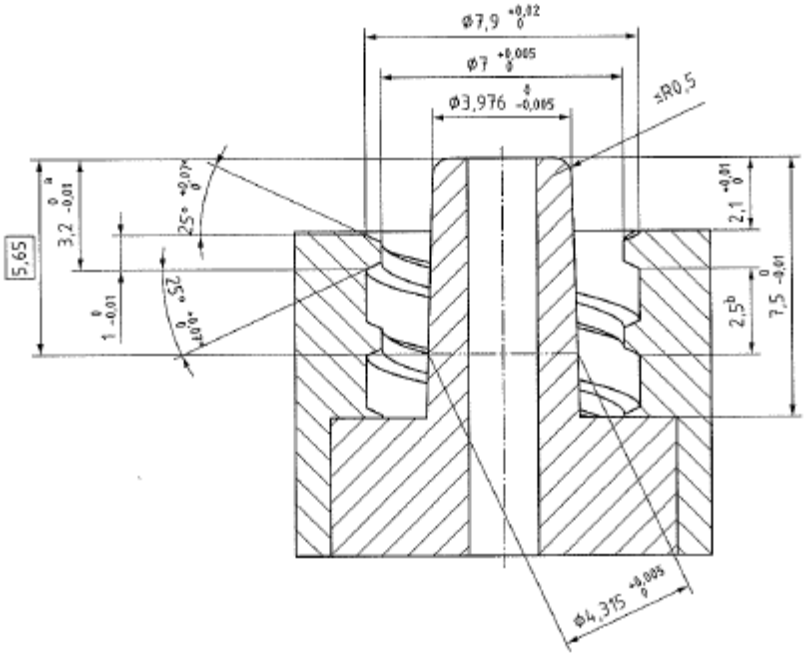
CONNECTING PEOPLE SCIENCE AND REGULATION®

Agenda

- Luer Cone (LC) and Luer Lock (LL) Compliance Testing
- TM for Sterile Subassembled Syringe ready for filling

- **Luer Cone & Luer Lock Compliance Testing**





Standards for Luer Cone & Luer Lock Compliance

ISO 80369-7 (TC 210)
Small-bore connectors for liquids and gases in healthcare applications
Part 7: Connector for intravascular or hypodermic applications

ISO 80369-20 (TC 210)
Small-bore connectors for liquids and gases in healthcare applications
Part 20: Common test methods

ISO 11040-4 (TC 76)
Prefilled Syringes
Part 4: Glass barrels for injectables and sterile subassembled syringes ready for filling

ISO 11040-6 (TC 76)
Prefilled Syringes
Part 6: Plastic barrels for injectables and sterile subassembled syringes ready for filling

Standards for Luer Cone & Luer Lock Compliance

ISO 80369-7

Small-bore connectors for liquids and gases in healthcare applications

Part 7: Connector for intravascular or hypodermic applications

(TC 210) Terms & Definitions

3.1
*** LUER CONNECTOR**
SMALL-BORE CONNECTOR that contains a conical mating surface with a 6 % (Luer) taper intended for use in intravascular or hypodermic APPLICATIONS of MEDICAL DEVICES and related ACCESSORIES.

NOTE 1 to entry: A LUER CONNECTOR can be either a LUER SLIP CONNECTOR or a LUER LOCK CONNECTOR.

NOTE 2 to entry: The term LUER used throughout this standard is a generically understood term that is not a trade name (brand name) or archaic or colloquial term.

3.2
*** LUER SLIP CONNECTOR**
LUER CONNECTOR without a lock

NOTE 1 to entry: The LUER SLIP CONNECTOR is also known by the abbreviated name of L1 CONNECTOR.

3.3
*** LUER LOCK CONNECTOR**
LUER CONNECTOR that contains a locking mechanism

NOTE 1 to entry: The LUER LOCK CONNECTOR is also known by the abbreviated name of L2 CONNECTOR.

Standards for Luer Cone & Luer Lock Compliance

ISO 80369-7

Small-bore connectors for liquids and gases in healthcare applications

Part 7: Connector for intravascular or hypodermic applications

(TC 210) Dimensional requirements - Luer Connectors (Annex B)

5 * Dimensional requirements for LUER CONNECTORS

LUER CONNECTORS shall comply with the relevant dimensions and tolerances as given in

— Figure B.1 and Table B.1 for a male LUER SLIP CONNECTOR (L1).

— Figure B.2 and Table B.2 for a female LUER SLIP CONNECTOR (L1).

— Figure B.3 and Table B.3 for a male LUER LOCK CONNECTOR (L2), with fixed collar.

Check compliance by verifying the relevant dimensions and tolerances specified in Annex B, as appropriate.

Standards for Luer Cone & Luer Lock Compliance

ISO 80369-7

Small-bore connectors for liquids and gases in healthcare applications

Part 7: Connector for intravascular or hypodermic applications

(TC 210) Dimensional requirements - Luer Connectors (Annex B)

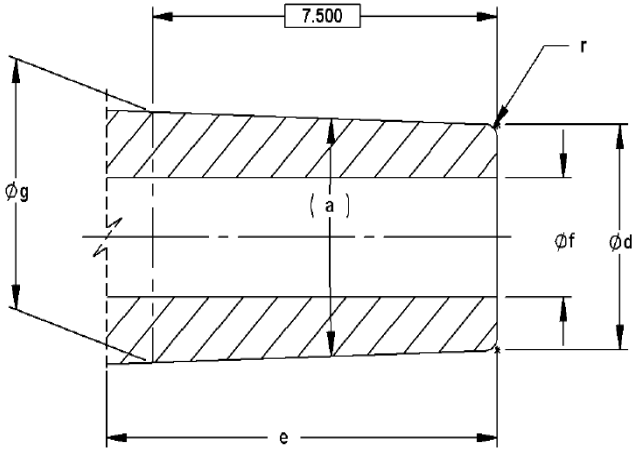


Table B.1 contains the dimensions for this figure.

Figure B.1 — Male LUER SLIP CONNECTOR (L1)

Table B.1 — Male LUER SLIP CONNECTOR dimensions (L1)

Dimensions in mm unless otherwise indicated

Male LUER SLIP CONNECTOR (L1)				
Reference	Designation	Dimension		
		Minimum	Nominal	Maximum
(a)	Angle of the taper (6 % taper nominal) (degrees, reference)	—	(3,43°)	—
Ød	Outside diameter at the tip of the male taper at the theoretical intersection, independent of *r*	3,925	3,976	4,027
e	Length of the male taper [a]	7,500	8,400	10,500
Øf	Inside diameter at the tip of the male taper	—	2,100	2,900
Øg	Outside diameter of the larger end of the male taper at 7,5 (basic dimension) from the tip (small end) of the male taper	4,376	4,426	4,476
r	Radius or chamfer at the outside tip of the male taper	0,000	0,250	0,500

[a] This dimension also defines the extant of the CONNECTOR. MEDICAL DEVICE features beyond the CONNECTOR may require evaluation to ISO 80369-1:2010, Annex B, to ensure NON-INTERCONNECTABLE characteristics.

Standards for Luer Cone & Luer Lock Compliance+

ISO 80369-7

Small-bore connectors for liquids and gases in healthcare applications

Part 7: Connector for intravascular or hypodermic applications

(TC 210) Performance requirements – Reference Connectors (Annex C)

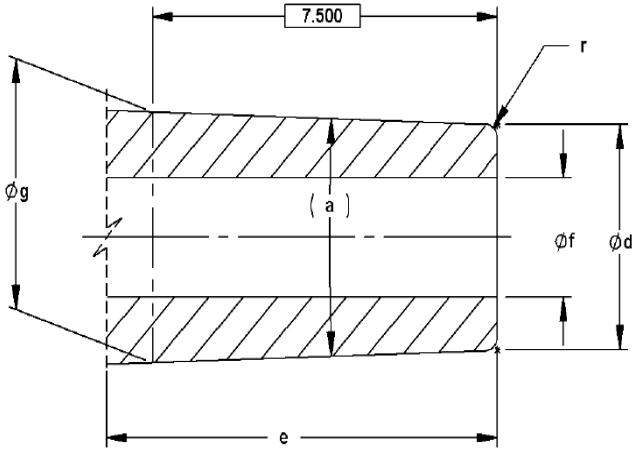


Table B.1 contains the dimensions for this figure.

Figure B.1 — Male LUER SLIP CONNECTOR (L1)

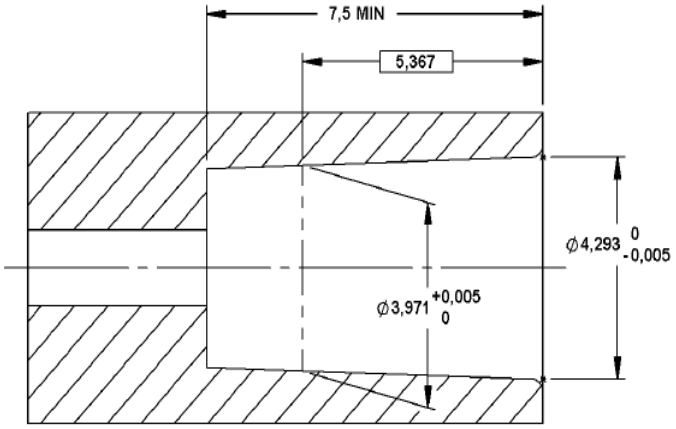


Figure C.5 — Female reference LUER SLIP CONNECTOR for testing male LUER CONNECTORS for leakage, separation from unscrewing, stress cracking and NON-INTERCONNECTABLE characteristics

Standards for Luer Cone & Luer Lock Compliance

ISO 80369-20

Small-bore connectors for liquids and gases in healthcare applications

Part 20: Common test methods

(TC 210) with reference connectors described ISO 80369-7 (Annex C)

Table 1 — TEST METHODS and corresponding Annex of this part of ISO 80369

Test method	Annex
Leakage by pressure decay	Annex B
Positive pressure liquid leakage	Annex C
Subatmospheric-pressure air leakage	Annex D
Stress cracking	Annex E
Resistance to separation from axial load	Annex F
Resistance to separation from unscrewing	Annex G
Resistance to overriding	Annex H
Disconnection by unscrewing	Annex I
Modification of the TEST METHODS to generate variable data for statistical analysis	Annex J
NOTE MANUFACTURERS can use the modified TEST METHODS of Annex J.	

Standards for Luer Cone & Luer Lock Compliance

ISO 80369-20

Small-bore connectors for liquids and gases in healthcare applications

Part 20: Common test methods

(TC 210) Performance testing

B.3 Apparatus

a) the male or female CONNECTOR under test;

b) the appropriate reference CONNECTOR, as specified in the relevant APPLICATION part of ISO 80369 for the leakage TEST METHOD, to be assembled to the CONNECTOR under test;

c) a means to simultaneously apply an axial force of 27,5 N and torque of 0,12 N·m, or more if required by the relevant APPLICATION part of ISO 80369;

d) a means to contain and pressurize the medium to the specified test pressure. Rigid fixtures and apparatus materials (such as metal) should be used to avoid inaccurate test results;

B.4 Procedure

b) For a non-locking (slip) CONNECTOR, assemble by applying an axial force of between 26,5 N and 27,5 N for 5 s to 6 s while rotating the CONNECTOR under test to a torque of between 0,08 N·m and 0,10 N·m and a rotation not exceeding 90°.

c) For a locking CONNECTOR with fixed threads, assemble by applying an axial force of between 26,5 N and 27,5 N for 5 s to 6 s while rotating the CONNECTOR under test to a torque of between 0,08 N·m and 0,12 N·m.

Standards for Luer Cone & Luer Lock Compliance

ISO 80369-20

Small-bore connectors for liquids and gases in healthcare applications

Part 20: Common test methods

(TC 210) with reference connectors described ISO 80369-7 (Annex C)

Table 1 — TEST METHODS and corresponding Annex of this part of ISO 80369

Test method	Annex	Criteria (Iso 80369-7)
Leakage by pressure decay	Annex B	NMT 0.005Pa x m3/s
Positive pressure liquid leakage	Annex C	No falling drop of water
Subatmospheric-pressure air leakage	Annex D	NMT 0.005Pa x m3/s
Stress cracking	Annex E	No sign of stress crack
Resistance to separation from axial load	Annex F	L1 = 23N-25N / L2 = 32N-35N for 10s-15s
Resistance to separation from unscrewing	Annex G	0.0198Nm – 0.02Nm for 10s-15s
Resistance to overriding	Annex H	0.15Nm-0.17Nm for 5s–10s
Disconnection by unscrewing	Annex I	N/A
Modification of the TEST METHODS to generate variable data for statistical analysis	Annex J	Modifications allowed
NOTE MANUFACTURERS can use the modified TEST METHODS of Annex J.		

Standards for Luer Cone & Luer Lock Compliance

ISO 80369-7 and ISO 11040-4 Relationship

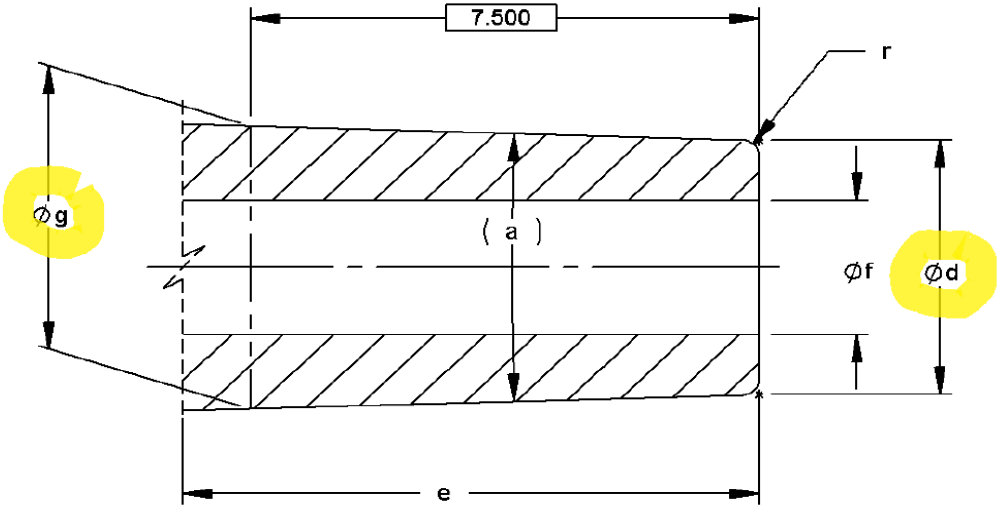
ISO 80369-7

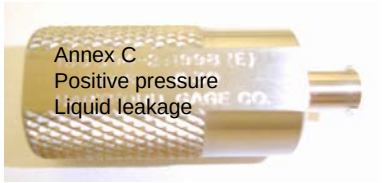
Commercially developed glass prefilled syringes routinely mate with LUER CONNECTOR equipped MEDICAL DEVICES in order to effectively administer the medication stored within the syringe. Examples: disposable needles, needless ports and other forms of luer access. Current state-of-technology syringe tip glass forming technology for manufacturing glass prefilled syringes cannot conform completely to either previous Luer fitting standard, ISO 594 or this International Standard. Both the previous standard and this standard have been developed using ground glass, metal and injection moulded technology and plastic resins as the baseline for compliance and capabilities.

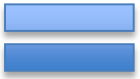
The committee acknowledges the differences in the manufacturing methodologies and the need for expanded tolerances in the glass forming manufacturing process. The baseline specifications of the tapered tip need to remain similar. However to accommodate the glass forming manufacturing process, there needs to be expanded dimensional tolerances. While these tolerances are outside of the range of this International Standard with respect to some of the dimensions, a glass formed tip does successfully mate with the injection moulded female LUER CONNECTORS. Refer to ISO 11040-4 [7] for a listing of those critical dimensions, their expanded corresponding tolerances and functional test methods that accommodate the formed tip manufacturing process.

Standards for Luer Cone & Luer Lock Compliance

ISO 80369-7 and ISO 11040-4 Relationship





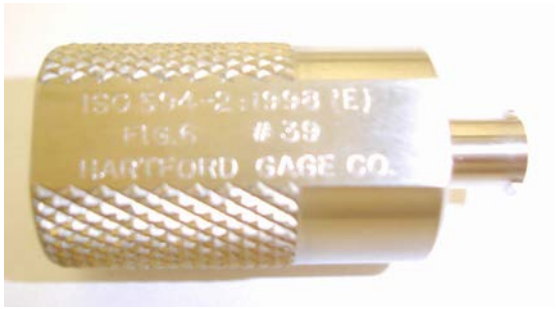


Dimension	ISO 80369-7	ISO 11040-4
d	± 0.05mm	± 0.07mm
g	± 0.05mm	± 0.07mm

i) Visually inspect for a falling drop of water from the CONNECTION during the specified hold period.

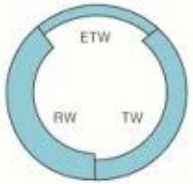
Standards for Luer Cone & Luer Lock Compliance

11040-6 Plastic PFS



11040-4 Glass PFS

SIZES	CLEAR COLOR CODE LENGTH OF THE CANNULA	color code
30G		light yellow
26G		brown
25G		orange
24G		purple
23G		blue
22G		black
21G		green
20G		yellow
19G		creamy yellow
18G		pink
16G		white
NOTE	Length scope:3/8"-1 1/2"(12mm-38mm)	



can choose RW,TW and ETW.

Requirements of the empty sterile subassembled syringes ready for filling

Standards for Glass & Polymer Syringes

ISO 11040-4

Prefilled Syringes

Part 4: Glass barrels for injectables and sterile subassembled syringes ready for filling

(TC 76)

ISO 11040-6

Prefilled Syringes

Part 6: Plastic barrels for injectables and sterile subassembled syringes ready for filling

(TC 76)

Syringe Barrel

Flange breakage resistance TM (Annex C1) *

Luer Cone breakage resistance TM (Annex C2) *

*** Normative Annex**

**** Informative Annex**

Standards for Glass & Polymer Syringes

ISO 11040-4

Prefilled Syringes

Part 4: Glass barrels for injectables and sterile subassembled syringes ready for filling (TC 76)

ISO 11040-6

Prefilled Syringes

Part 6: Plastic barrels for injectables and sterile subassembled syringes ready for filling (TC 76)

Sterilized subassembled syringe ready for filling

- **Endotoxine (limits and reference to TM) (Annex D1) ****
- **Particulate Matter (limits and reference to TM) (Annex D2) ****
- **Glide force to evaluate syringe lubrification TM (Annex E) ****
- **Needle Penetration TM (Annex F) ****
- **Needle Pull out force TM (Annex G1) ***

Standards for Glass & Polymer Syringes

ISO 11040-4

Prefilled Syringes

Part 4: Glass barrels for injectables and sterile subassembled syringes ready for filling (TC 76)

ISO 11040-6

Prefilled Syringes

Part 6: Plastic barrels for injectables and sterile subassembled syringes ready for filling (TC 76)

Sterilized subassembled syringe ready for filling

- **Closure system liquid leakage test TM (Annex G2) ***
- **LL – adapter collar pull-off force TM (Annex G3) ***
- **LL – adaptor collar torque resistance TM (Annex G4) ***
- **LL – rigid tip cap unscrewing torque TM (Annex G5) ***
- **Pull – off force of the tip cap or the needle shield TM (Annex G6) ***
- **Dye solution tightness test TM** (Annex H) ****

Flange Breakage Resistance TM

Principle

Syringe is tested for finger flange breakage by applying a axial force to the syringe

Procedure

Syringe is placed vertically (tip down) into a syringe holder where the flange holds the syringe. Axial force is supplied inside the syringe onto the shoulder area to simulate final use.

Interpretation of Results

Specification needs to be set between customer and manufacturer; depending on final usage of syringe

Flange Breakage Resistance TM

Cone Breakage Resistance TM

Principle

Syringe is tested for cone breakage by applying a side load force onto a defined area of the LC

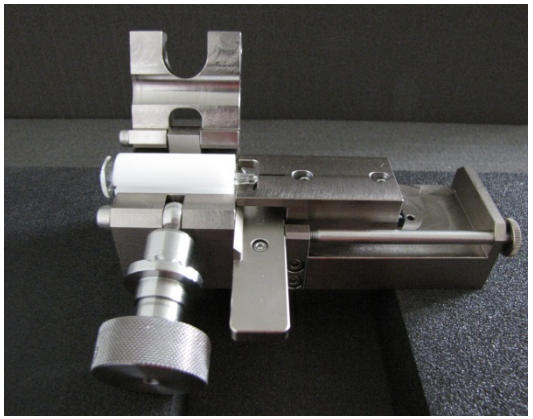
Procedure

Syringe is placed horizontal into a syringe holder which stabilizes the syringe. Side load is applied to the very front tip of the cone

Interpretation of Results

Specification needs to be set between customer and manufacturer; depending on final usage of syringe

Cone Breakage Resistance TM



Cone Breakage Resistance TM

Video

Endotoxine TM

Principle

* current revision

Pyrogenicity / endotoxin testing of sterilized subassembled syringe.
Check of cleanliness of syringe

Procedure

Extraction method according to USP* < 161> ;
Endotoxin Test according to USP* <85> ; Ph Eur* 2.6.14 ; JP* 4.01

Interpretation of Results

Result < 0.25EU/ml based on USP* monograph “sterile water for injection”
Sensitivity of reagent needs to be 0.02EU/ml to get to an alarm limit of 0.20EU/ml with a pool of 10 x 1ml long syringes

Particulate Matter TM

Principle

* current revision

Particulate matter contamination (subvisible). Check of cleanliness of syringe

Procedure

Sample preparation and method according to USP* < 788> ; Ph Eur* 2.9.19 / 2.9.20 ; JP* 6.06 / 6.07
Light obscuration method

Interpretation of Results

Contamination < 600 particles ≥ 10µm (10% of USP limit)
Contamination < 60 particles ≥ 25µm (10% of USP limit)

Glide Force to Evaluate Syringe Lubrication TM

Principle

Assess quality and consistency of syringe lubrication

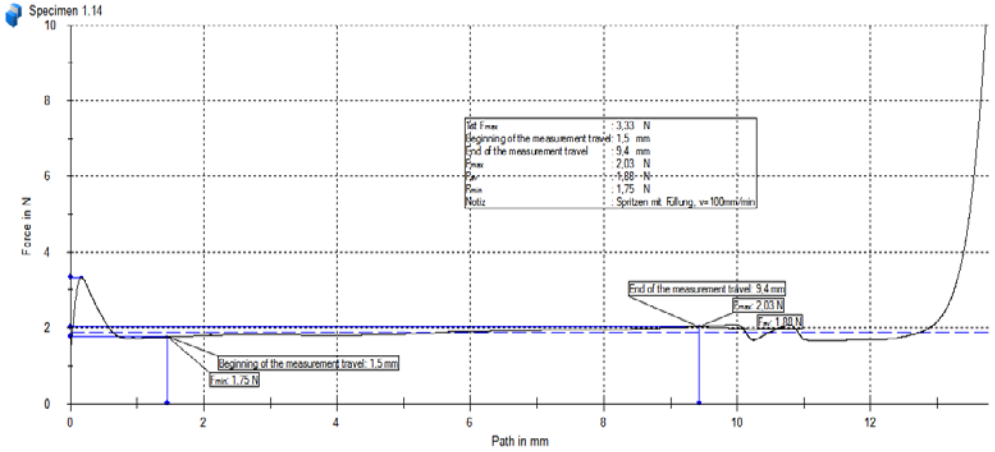
Procedure

Plunger stopper according to syringe size is placed into the empty syringe (nominal fill volume and / or 50% of nominal fill volume)
Use universal tensile and compression machine with recommended test speed of 100mm/min (or as appropriate e.g. 280mm/min – 500mm/min to simulate use of a PFS in an Autoinjector)
Test until end of stroke; record force versus displacement curve

Interpretation of Results

Glide force test region needs to be flat and consistent

Glide Force to Evaluate Syringe Lubrication TM



Glide Force to Evaluate Syringe Lubrication TM

Video

Needle Penetration Force TM

Principle

Measure needle penetration force by piercing a test foil

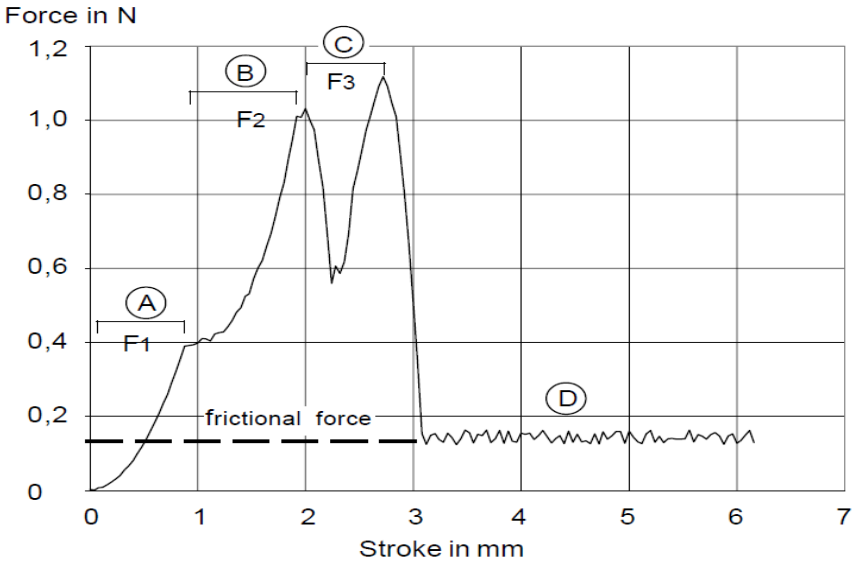
Procedure

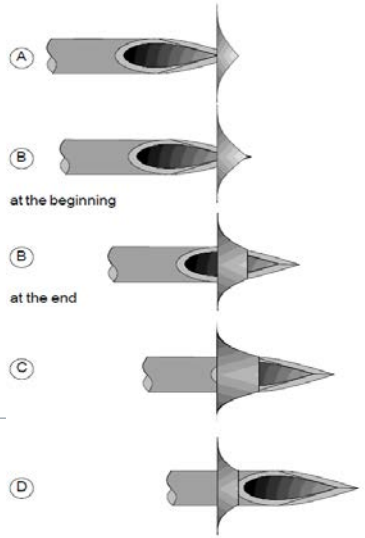
Foil is fixed in a holding device
SN – syringe is fixed perpendicular to the foil
Use universal tensile and compression machine with recommended test speed of 20mm/min – 200mm/min (or as appropriate)
Record force versus displacement curve

Interpretation of Results

Specification needs to be fixed between customer and manufacturer of SN – syringes.
Maximum penetration force as well as gliding force can be seen

Needle Penetration Force TM





Needle Pull-Out Force TM

Principle

Measure the bonding (fixation) of the needle in a syringe

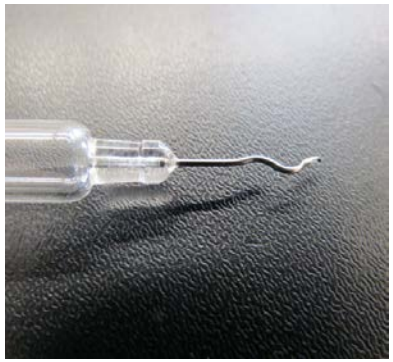
Procedure

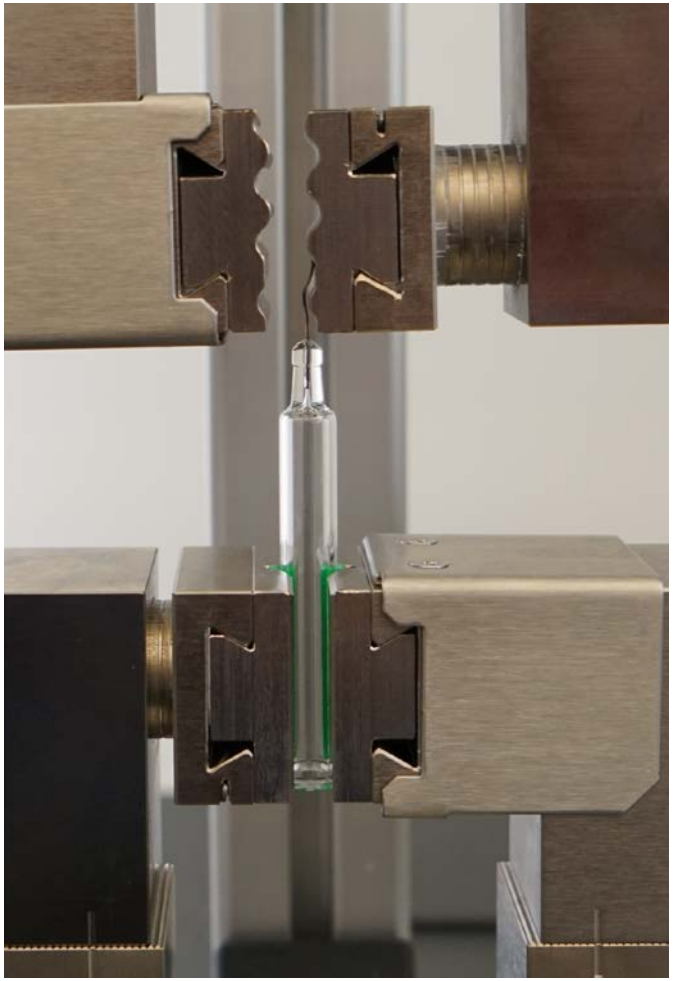
SN – syringe is fixed in a syringe holder
Use a needle gripper attached to an universal tensile and compression machine. Test speed is 50mm/min (or as appropriate)
Record force versus displacement curve

Interpretation of Results

Forces can be measured and evaluated at the time point where the bonding breaks and / or the needle come loose.
Minimum bonding strength depends on needle diameter; spec according to ISO 7864 (and will show differences between non-sterile and sterilized syringes)

Needle Pull-Out Force TM





Closure System Liquid Leakage TM

Principle

Assess liquid leakage resistance of tip cap, needle shield (during filling process or transportation)

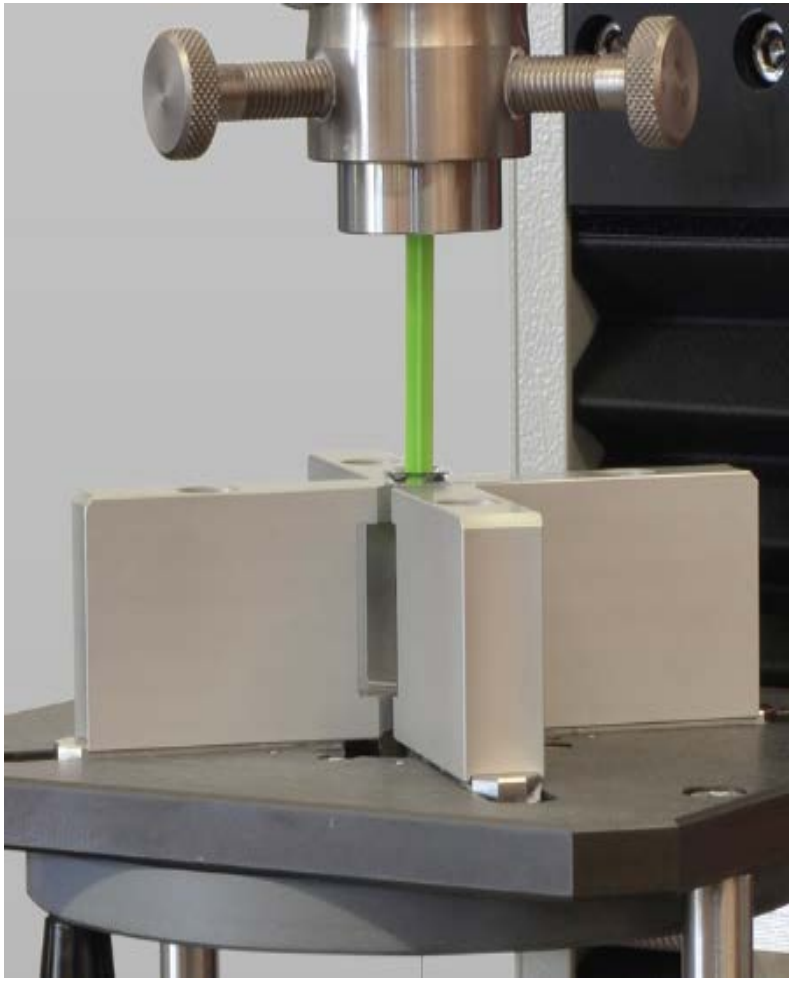
Procedure

Syringe is fixed in a syringe holder (vertically)
Fill the syringe half with water apply pressure either through compressed air directly onto water surface or by using a plunger stopper and a tensile testing machine
Applied pressure is 110 kPa for 5s (1ml long = 3.48N)

Interpretation of Results

Tip cap shall not fall off and no droplets shall be visible around the closure system

Closure System Liquid Leakage TM



LLA Collar Pull-Off Force TM

Principle

Assess pull-off force of a “snap-on” LLA collar system on a glass syringe.

Procedure

Syringe is fixed in a syringe holder by the flange (vertically)
Use a gripper device attached to an universal tensile and compression machine. Test speed is 20mm/min (or as appropriate)

Interpretation of Results

LLA shall not come off the syringe as <22N

LLA Collar Pull-Off Force TM

LLA Collar Torque Resistance TM

Principle

Assess torque resistance of a “snap-on” LLA collar system on a glass syringe.

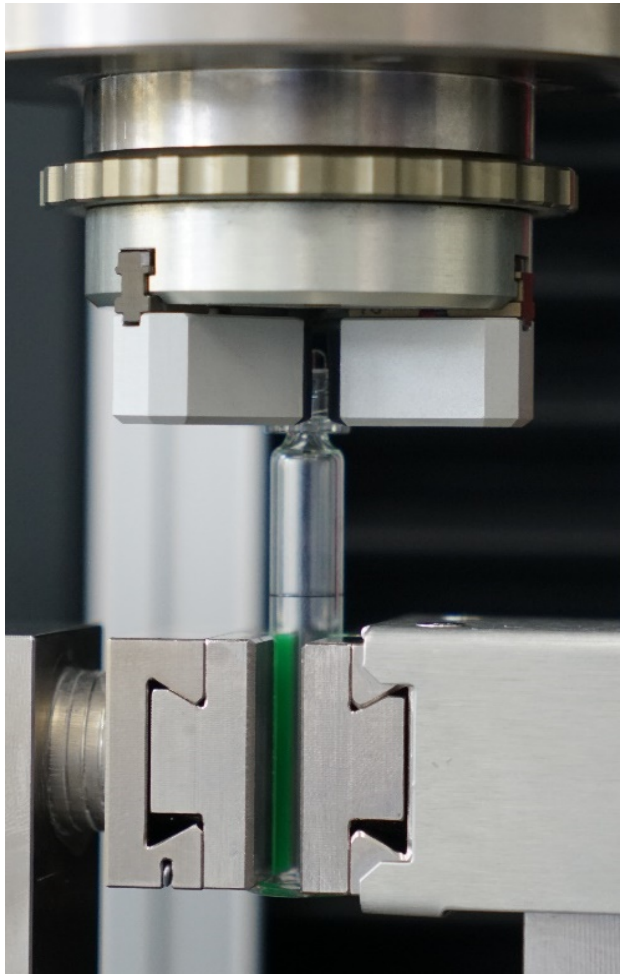
Procedure

Syringe is fixed in a syringe holder by the flange (vertically)
Use a gripper device attached to an universal tensile and compression machine.
Either the syringes fixation or the gripper device can be rotated.
Rotation speed is 20 rotations / min (or as appropriate) up to 90° rotation
Record the peak load of the applied torque

Interpretation of Results

Torque resistance needs to be fixed between customer and manufacturer

LLA Collar Torque Resistance TM



LL Rigid TC Unscrewing Torque TM

Principle

Assess torque resistance of a tip cap to verify that it can be removed from a syringe with reasonable torque

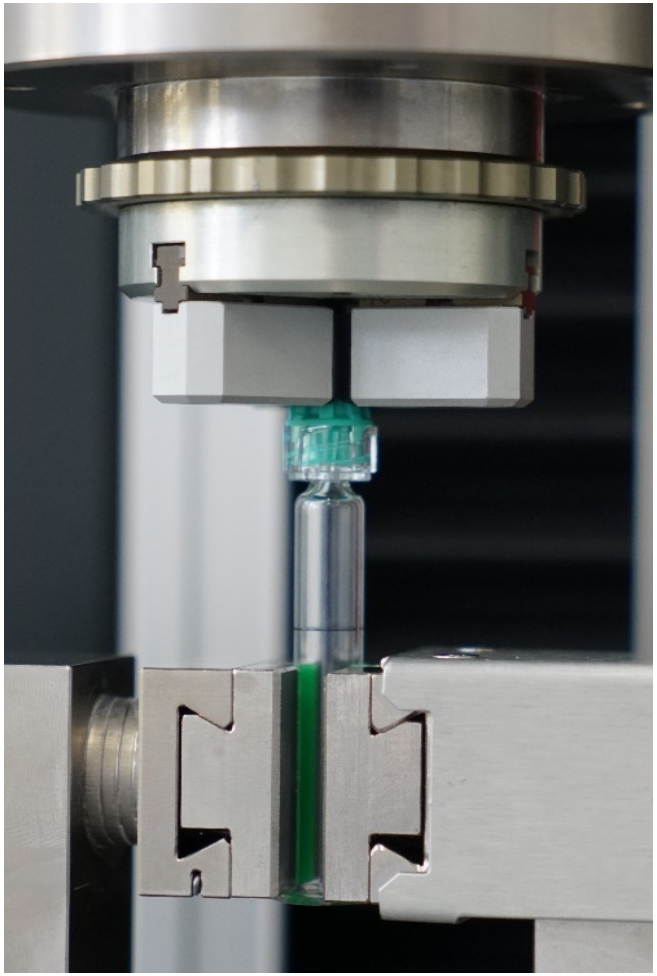
Procedure

Syringe is fixed in a syringe holder by the flange (vertically)
Use a gripper device attached to an universal tensile and compression machine.
Either the syringes fixation or the gripper device can be rotated
Rotation speed is 20 rotations / min (or as appropriate) up to 90° rotation
Record the maximum peak of the applied torque (tip cap comes off)

Interpretation of Results

Torque resistance needs to be fixed between customer and manufacturer

LL Rigid TC Unscrewing Torque TM



Pull-Off Force of TC or NS/RNS TM-1

Principle

Assess pull – off forces of a tip cap or needle shield to verify that it can be removed from a syringe with reasonable force

Procedure

Syringe is fixed in a syringe holder by the flange (vertically)
Use a gripper device attached to an universal tensile and compression machine.
Grip the tip cap or needle shield at the very upper (top) part of the closure
Test speed is 100mm/min (or as appropriate)
Record the maximum peak of the applied pull – off force

Interpretation of Results

Pull – off forces need to be fixed between customer and manufacturer

Pull-Off Force of TC or NS/RNS TM-1

Pull-Off Force of TC or NS/RNS TM-2

Principle

Assess pull – off forces of a tip cap or needle shield to verify that it can be removed from a syringe with reasonable force

Procedure

Syringe is fixed in a syringe holder by the flange (vertically)
Use a gripper device attached to an universal tensile and compression machine.
Grip the tip cap or needle shield from “underneath” the closure
Test speed is 100mm/min (or as appropriate)
Record the maximum peak of the applied pull – off force

Interpretation of Results

Pull – off forces need to be fixed between customer and manufacturer

Pull-Off Force of TC or NS/RNS TM-2

Dye Tightness TM

Principle

Filled and closed syringes are submerged into a dye solution. Different pressures are applied to verify tightness

Procedure

Syringe are filled with water and closed by a plunger stopper
Syringes are submerged into a dye solution e.g. methylene blue, rhodamine B or fluorescin. Dye solution should contain surfactant.
Positive sample is prepared by opening the fluid path to the syringe content
Reduce pressure by ΔP of 270 mbar and hold for 30min. Restore atmospheric pressure and hold for 30min. Take out syringes, clean and inspect by visual means

Interpretation of Results

No traces of the dye solution should be found inside the syringes

Dye Tightness TM

Video

Acknowledgements

Mr. Erik Berndt – Zwick / Roell, Germany

Thank You !

Q&A Session