Test Methods for Prefilled Syringes
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Test Methods for Prefilled Syringes

- **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

ISO 11040-6

Prefilled Syringes

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

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

ISO 11040-6

Prefilled Syringes

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

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

ISO 11040-6

Prefilled Syringes

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

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

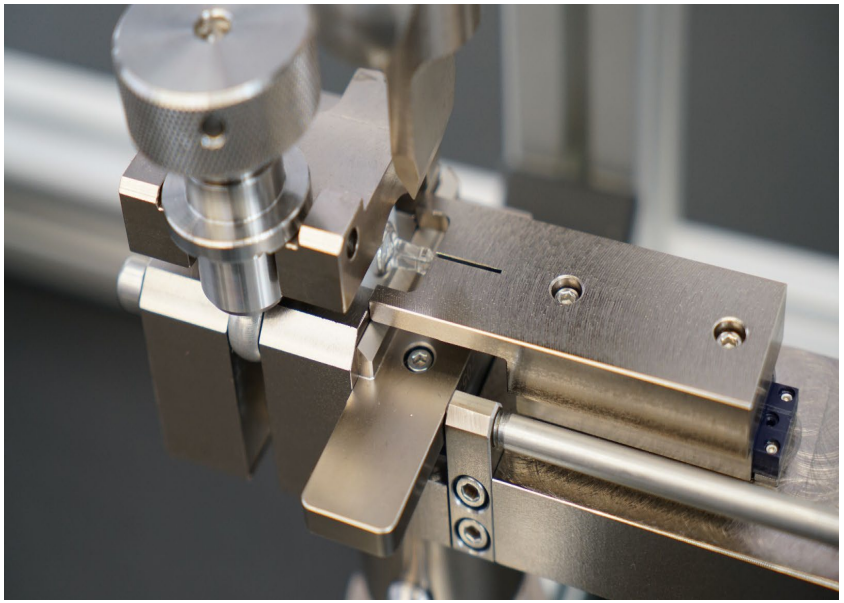
Procedure

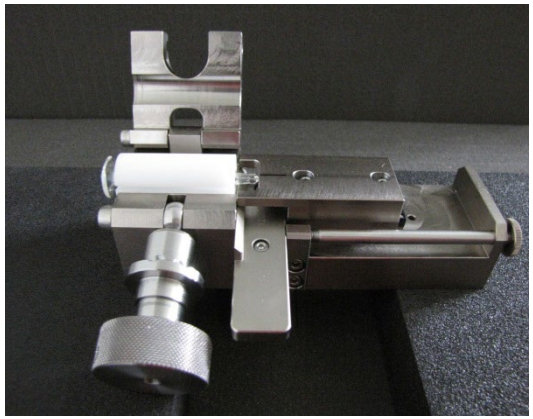
Syringe is placed horizontal into a syringe holder which stabilizes the syringe. Side load is applied to the very front tip of the cone

Interpretation of Results

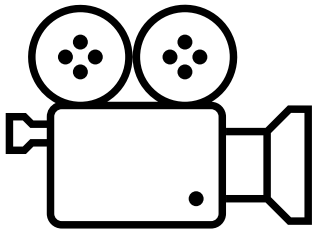
Specification needs to be set between customer and manufacturer; depending on final usage of syringe

Cone Breakage Resistance TM





Cone Breakage Resistance TM



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 Lubrification TM

Principle

Assess quality and consistency of syringe lubrication

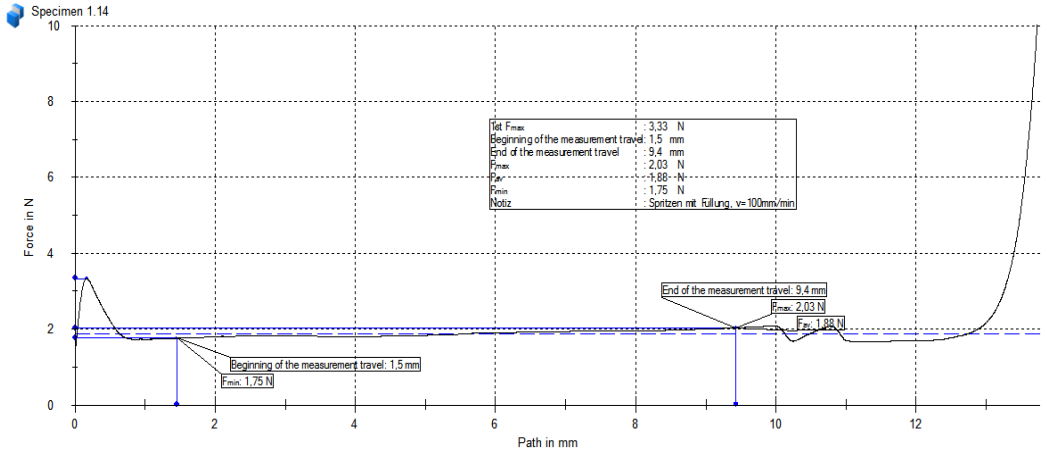
Procedure

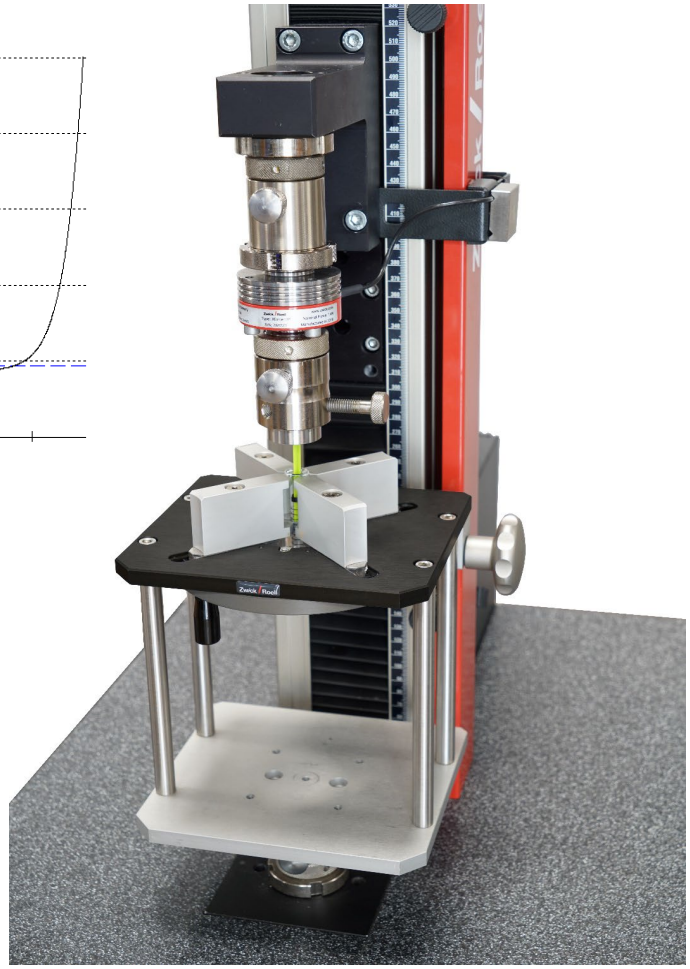
Plunger stopper according to syringe size is placed into the empty syringe (nominal fill volume and / or 50% of nominal fill volume)
Use universal tensile and compression machine with recommended test speed of 100mm/min (or as appropriate e.g. 280mm/min – 500mm/min to simulate use of a PFS in an Autoinjector)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

Interpretation of Results

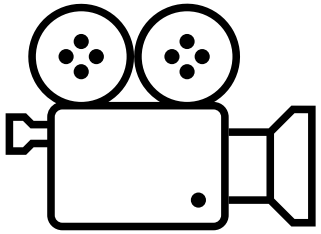
Glide force test region needs to be flat and consistent

Glide Force to evaluate Syringe Lubrification TM





Glide Force to evaluate Syringe Lubrification TM



Needle Penetration TM

Principle

Measure needle penetration force by piercing a test foil

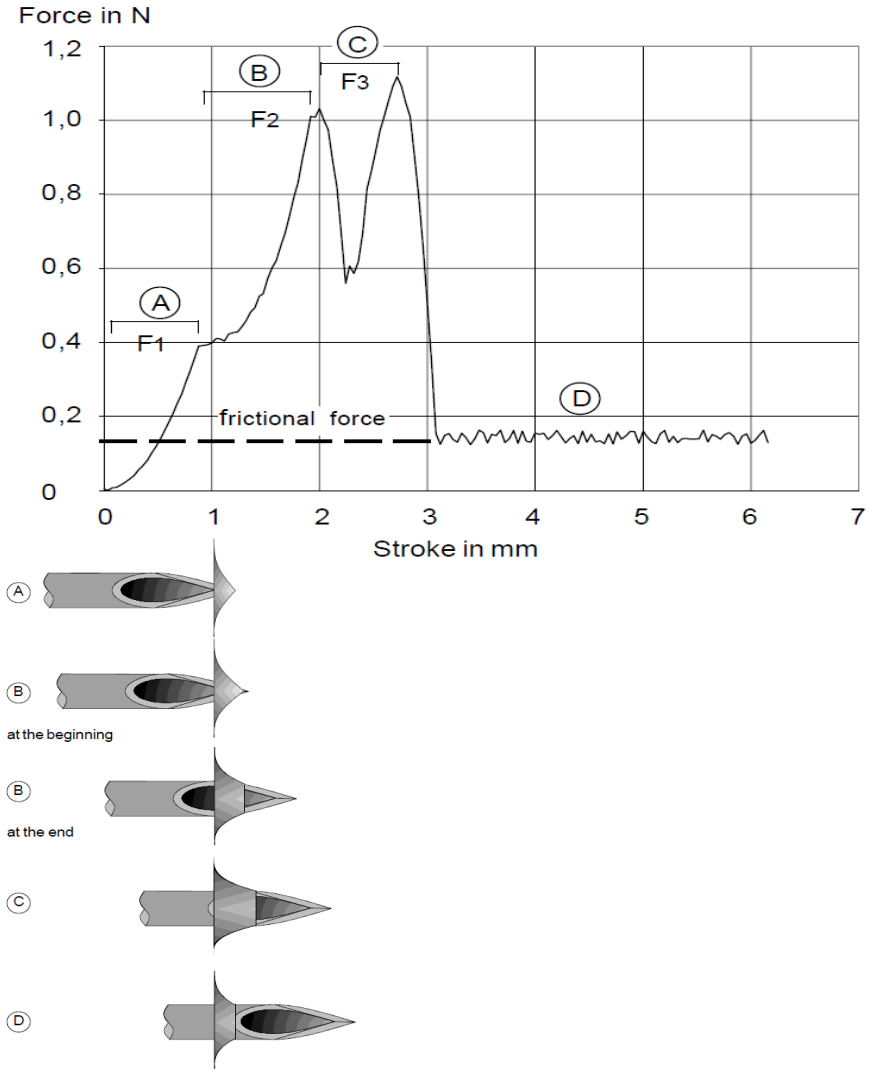
Procedure

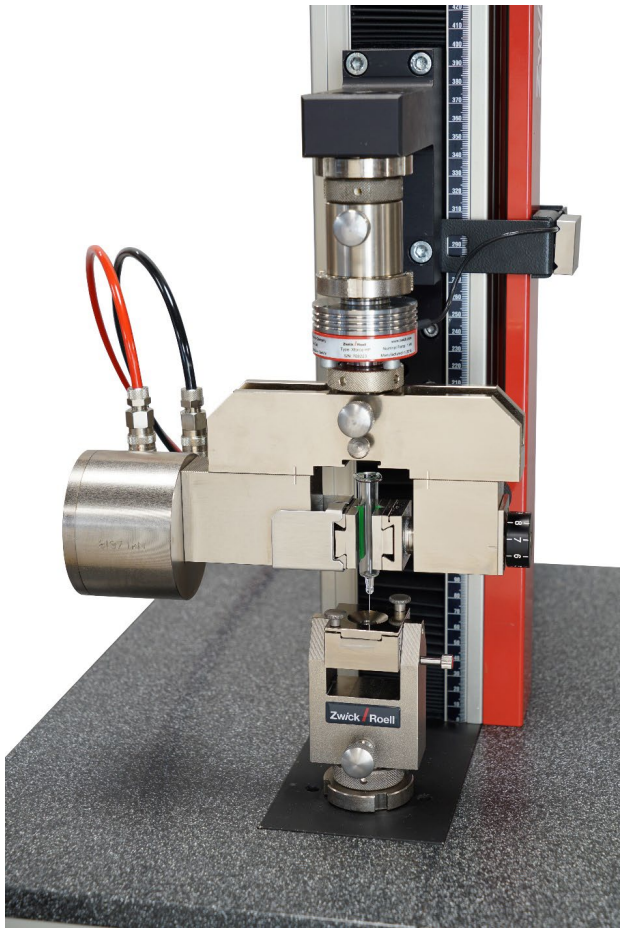
Foil is fixed in a holding device
SN – syringe is fixed perpendicular to the foil
Use universal tensile and compression machine with recommended test speed of 20mm/min – 200mm/min (or as appropriate)
Record force versus displacement curve

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 TM





Needle Pull Out Force TM

Principle

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

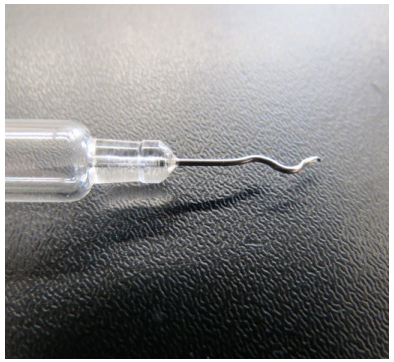
Procedure

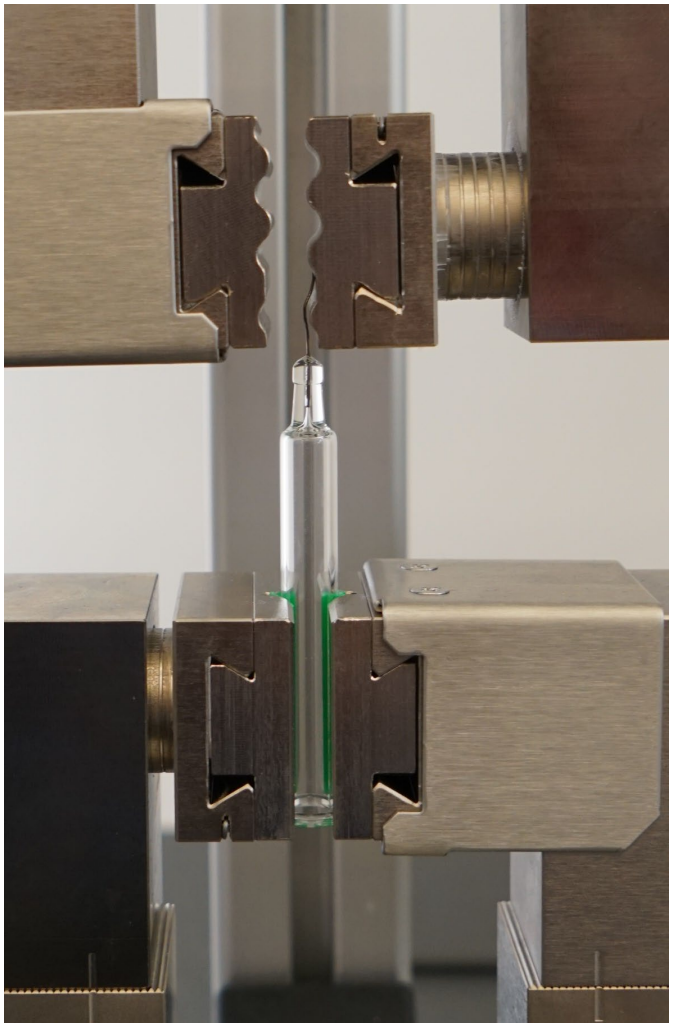
SN – syringe is fixed in a syringe holder
Use a needle gripper attached to an universal tensile and compression machine. Test speed is 50mm/min (or as appropriate)
Record force versus displacement curve

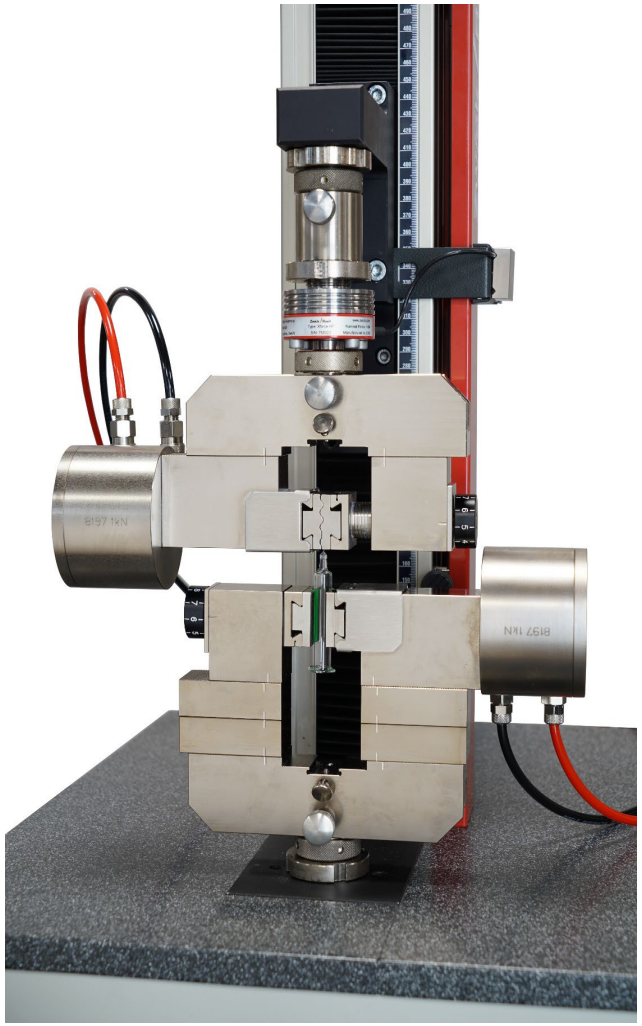
Interpretation of Results

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 Leackage TM

Principle

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

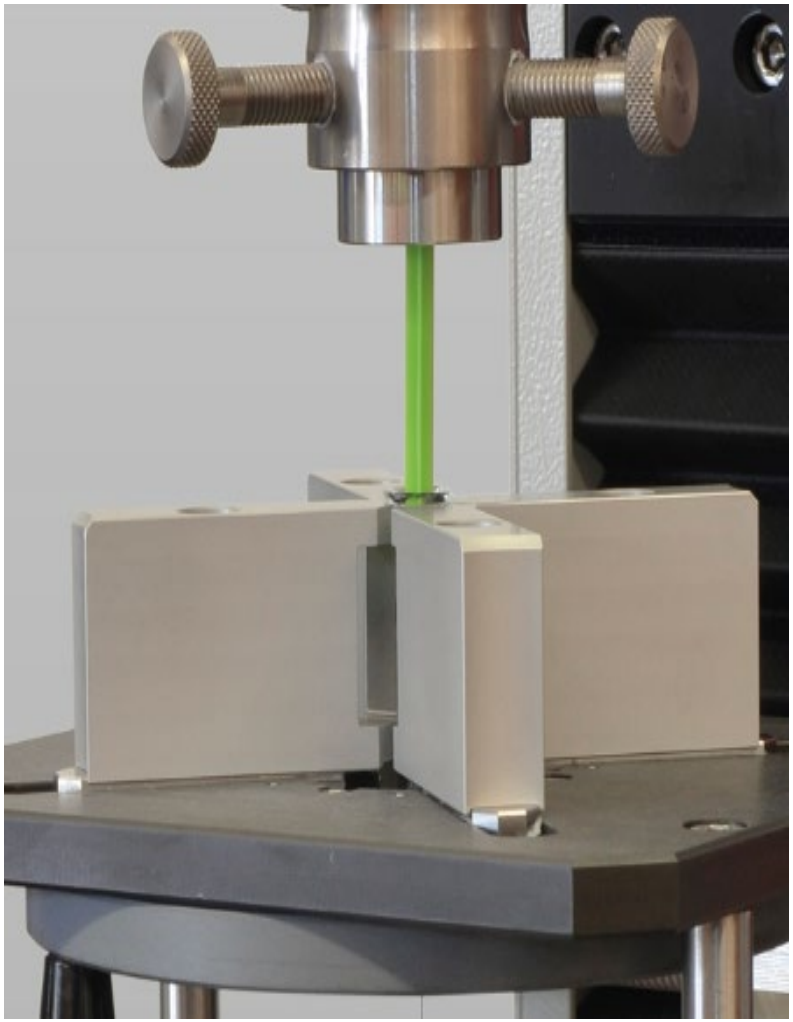
Procedure

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 Leackage TM



LLA Collar Pull-Off Force TM

Principle

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

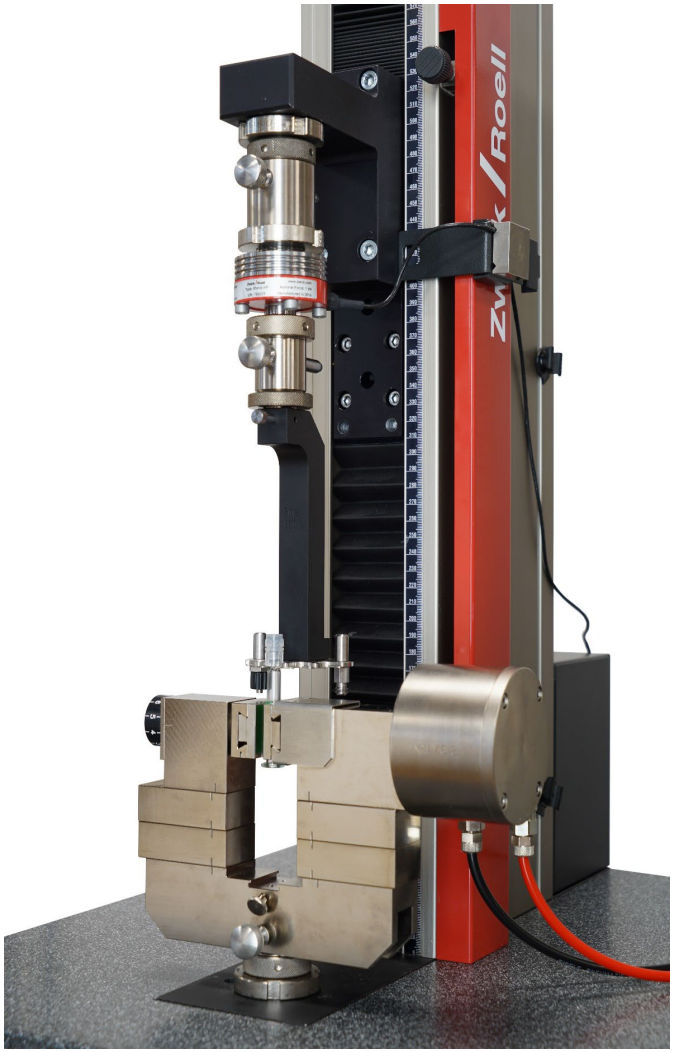
Procedure

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.

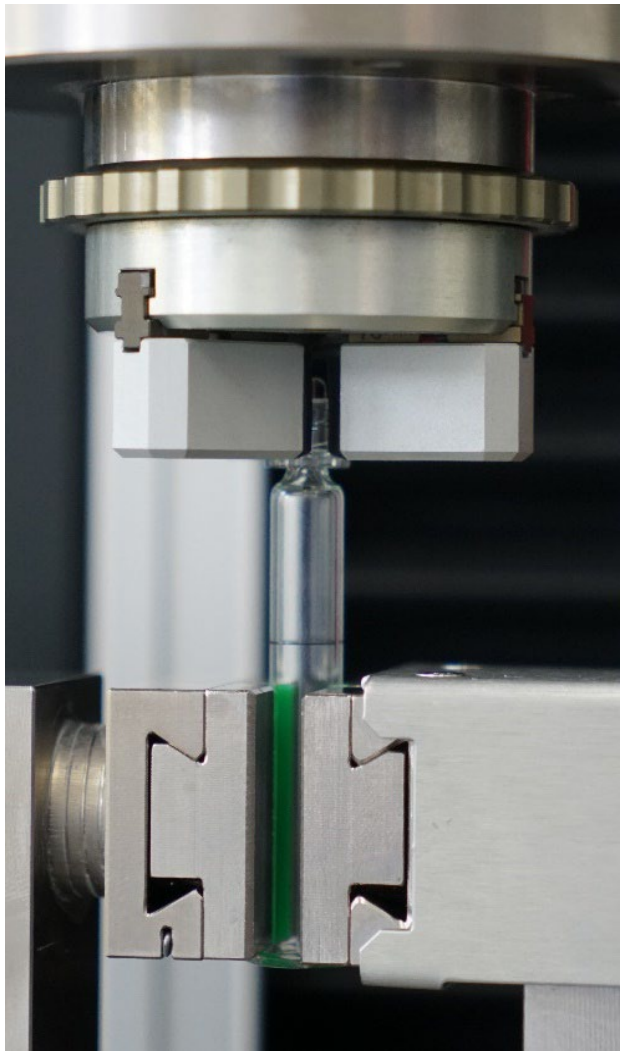
Procedure

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

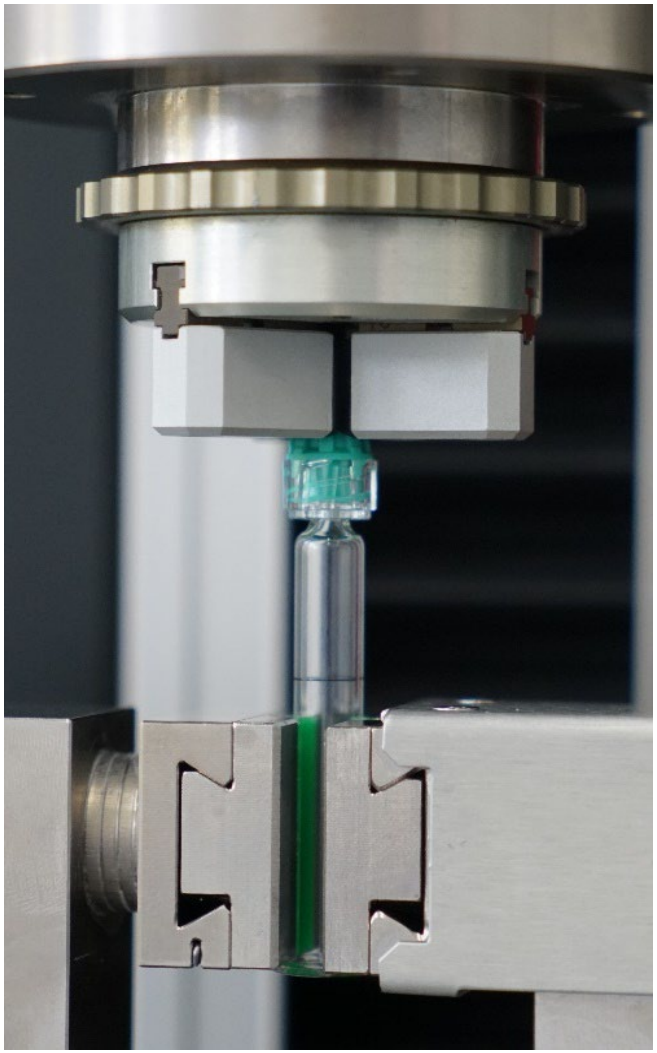
Procedure

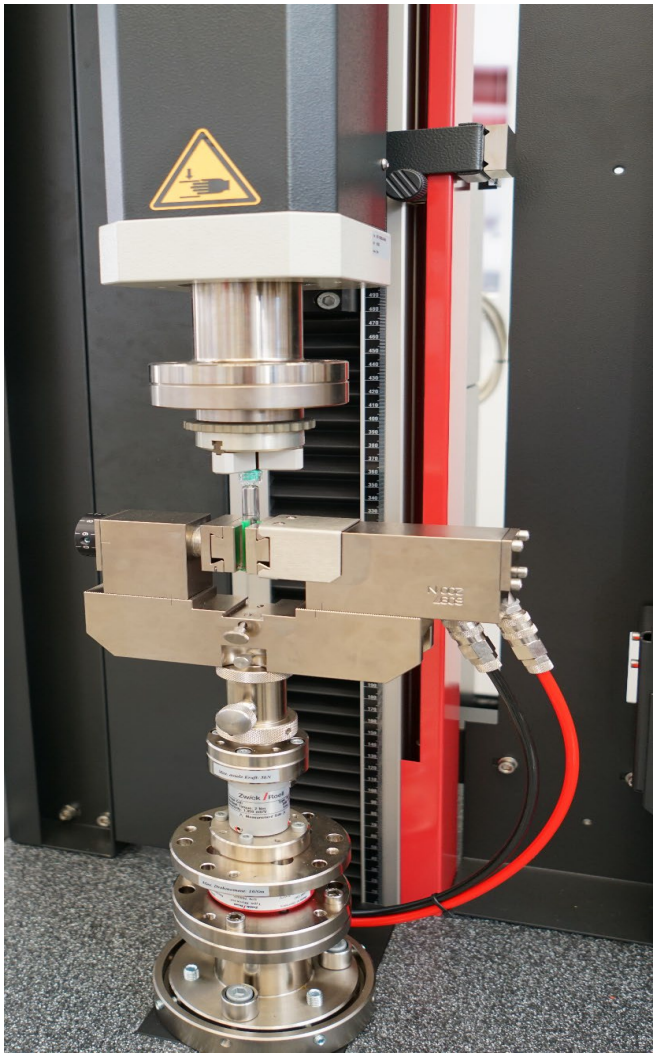
Syringe is fixed in a syringe holder by the flange (vertically)
Use a gripper device attached to an universal tensile and compression machine.
Either the syringes fixation or the gripper device can be rotated
Rotation speed is 20 rotations / min (or as appropriate) up to 90° rotation
Record the maximum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

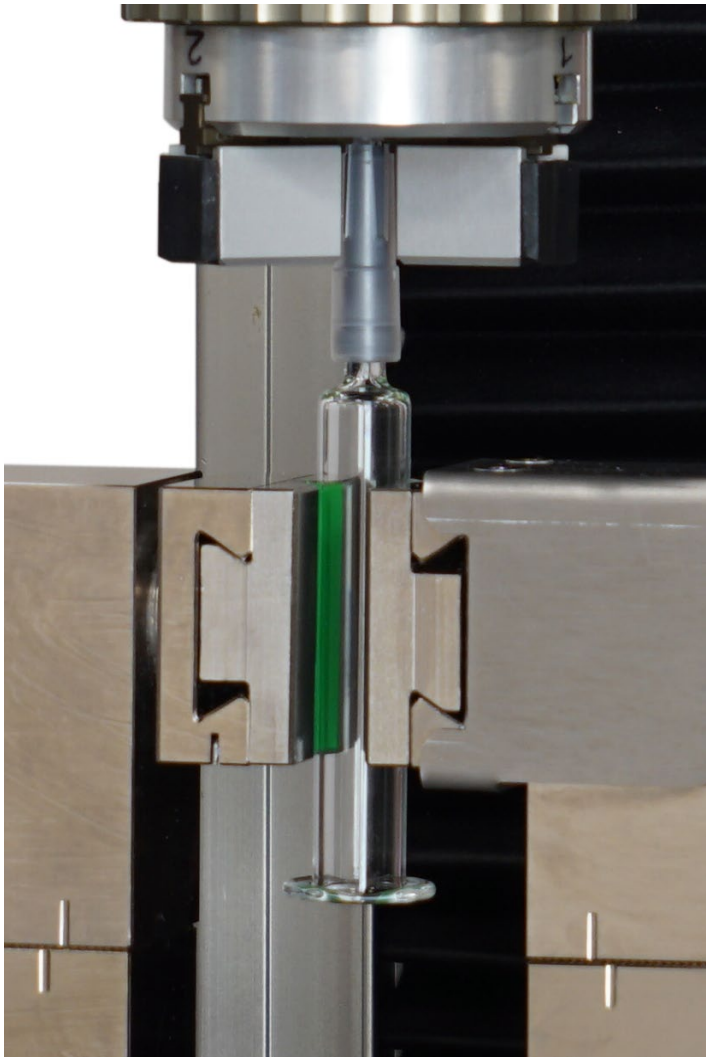
Procedure

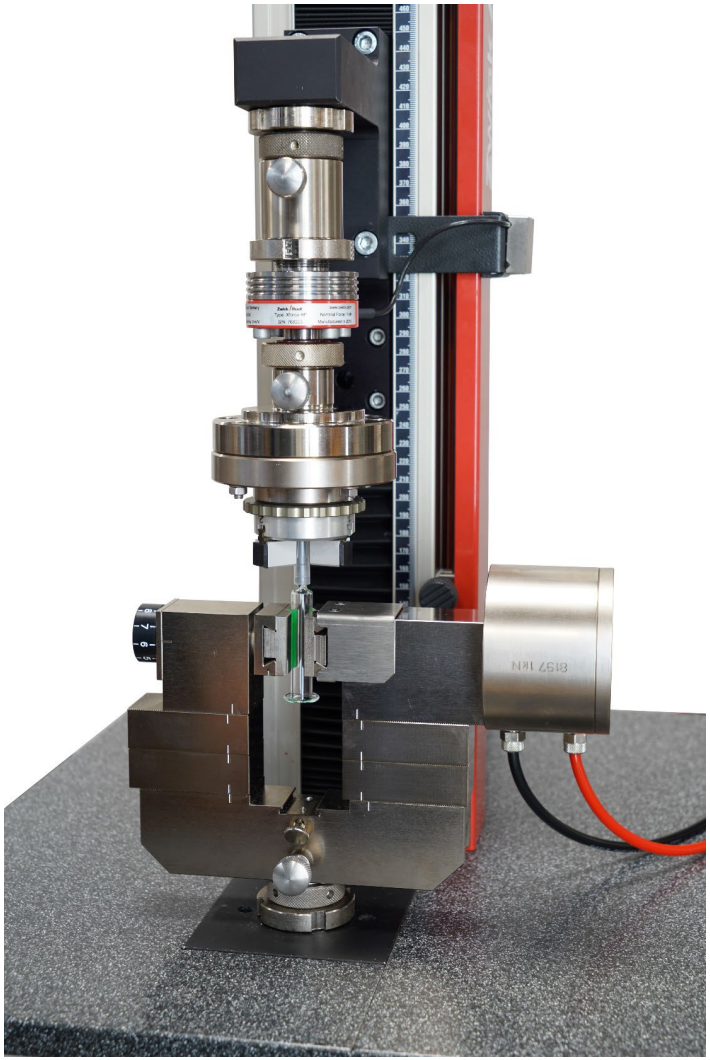
Syringe is fixed in a syringe holder by the flange (vertically)
Use a gripper device attached to an universal tensile and compression machine.
Grip the tip cap or needle shield at the very upper (top) part of the closure
Test speed is 100mm/min (or as appropriate)
Record the maximum peak of the applied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

Interpretation of Results

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

Pull-Off Force of TC or NS TM-1





Pull-Off Force of TC or NS 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

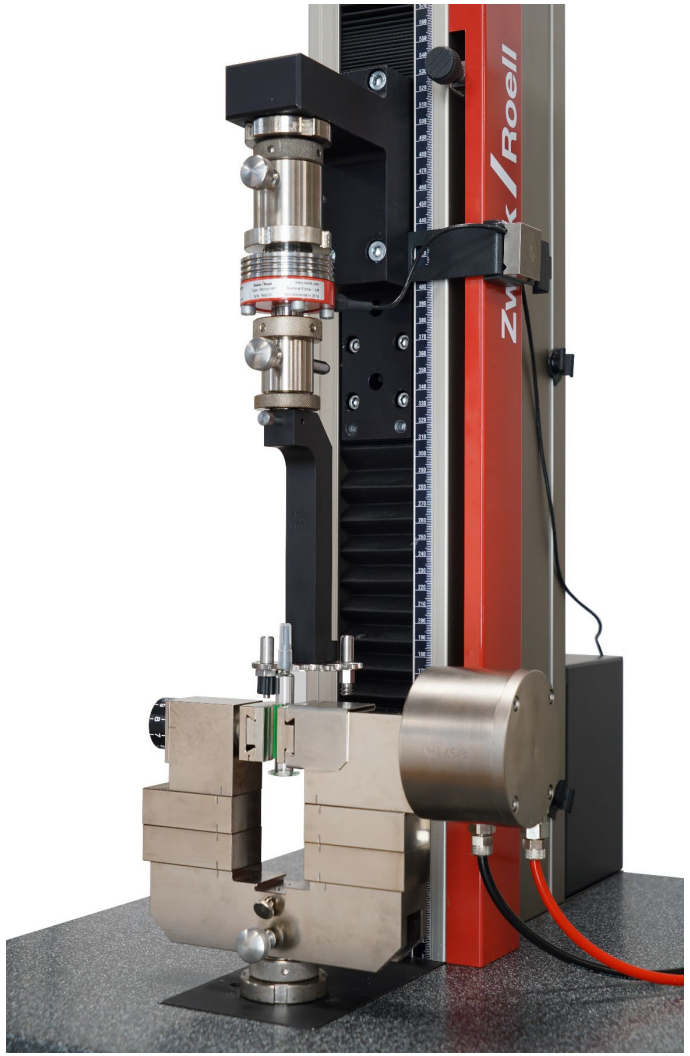
Procedure

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 TM-2



Dye TM

Principle

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

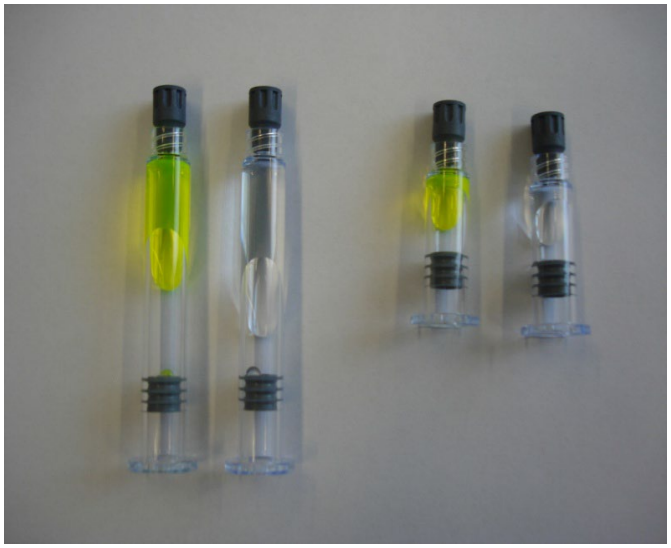
Procedure

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 surfactants e.g. Tween 80
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 TM



Summary Test Methods