PDA Parenteral Drug Association

Training and Research Institute

All About Prefilled Syringes

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All about Pre-Filled Syringe Systems

From Initial Development to Final Fill Finish

Overview and Introduction into the Pre-filled Syringe Market

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Vienna, Austria

PDA Parenteral Drug Association Training and Research Institute

Agenda –
DAY 1

Welcome and Introduction

Overview and Introduction into the Pre-filled Syringe Market

- Overview & trends
- Stakeholders
- User's perspective
- Syringe system overview

Pre-fillable Syringe

- Glass and COP/COC syringes
- Barrel forming and needle mounting
- Washing with WfI
- Siliconization
- Nest and tub, bags
- Sterilization
- Syringe specification: Example
- Regulatory guidelines and technical standards: EU/US/ISO/...

Plunger Stoppers, Needle Shields, Tip Caps

- Materials
- Physical and chemical properties
- Supporting documents
- Design and functionality
- Processing
- Regulatory guidelines and standards

Fill and Finish

- Bag opening
- Tub opening
- Filling
- Stoppering

Hands-on session

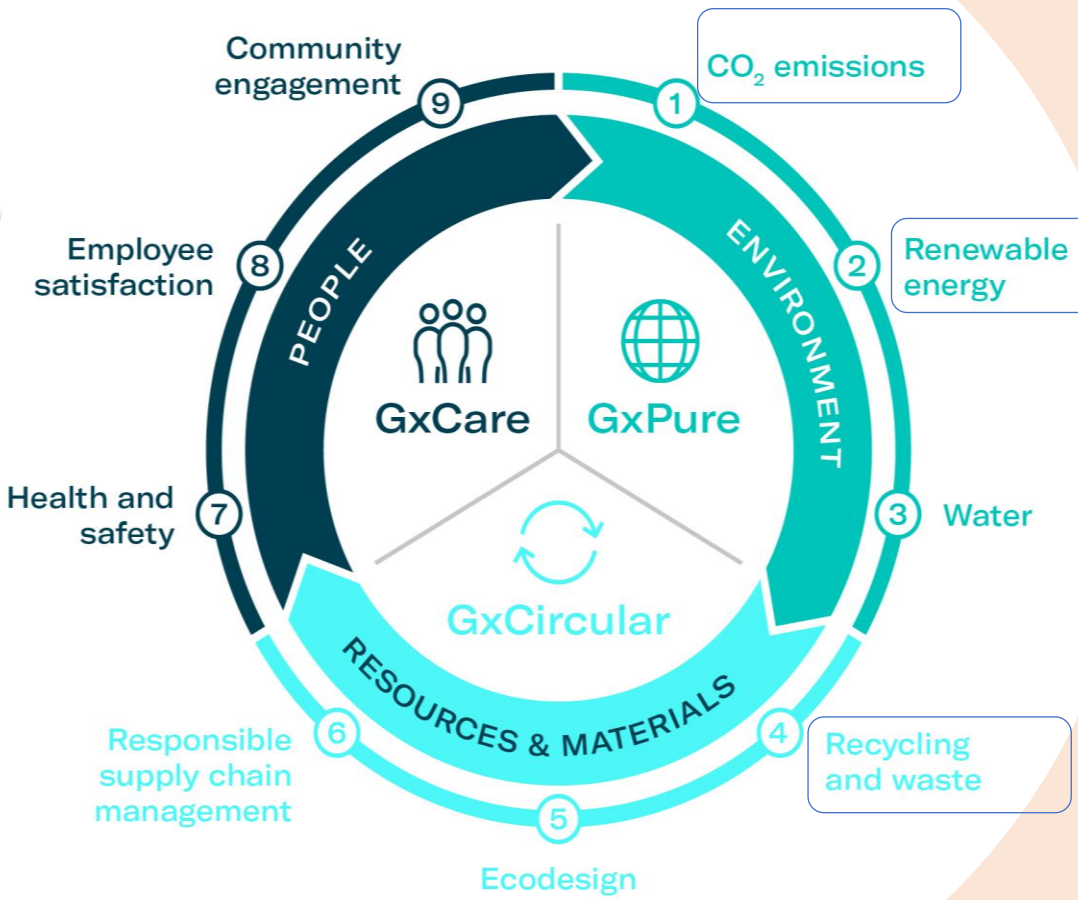
- 3 groups, 20 min pers station

Pre-Fillable Syringes Manufacturing

Sustainability – top prio at converters

Expectations of our stakeholders

- Customers
- Investors
- Employees
- Suppliers
- Society



Strong partner and solution provider

- Driver of innovation
- Driver of business growth
- Driver for employer attractiveness

Sterilized subassembled syringes ready for filling

ISO 11040-4
Prefilled syringes Glass barrels for injectables and
sterilized subassembled syringes
ready for filling

ISO 11040-6
Prefilled syringes Plastic barrels for injectables and sterilized subassembled syringes ready for filling

ISO 11040-7
Prefilled syringes Packaging systems for sterilized subassembled syringes ready for filling

Syringes are nested with the cone/needle downwards in a nest (polypropylene)

100-Nest (10x10): 0.5 ml,
1.0 ml long, 1 – 3 ml

160-Nest (10 x 16): 0.5 ml,
1.0 ml long

Nest is placed in tub (tub is made from polystyrene)

Tub is sealed by Tyvek®* foil

Complete tub is packed in a Tyvek®* pouch (single or double bag)

*Tyvek is a registered trademark of the DuPont company

RTF Syringe Product Specification

Finished Drug Product

Plunger rod and Backstop

Plunger stopper

n/a

Nest, Tub, Bags, Sterilization

Endotoxins

Particles

Sterilization

Shoulder and Cone

Needle Defects

Geometry

Needle Gauge

Glue

Tungsten

Needle Wall Thickness + ID

Needle

Needle Siliconization

Needle Bevel Design

Extractables

ISO 80369-7

LL adapter

Flange Geometry

Flange Strength

Flange Thickness

Flange

Glass Cane Source

Cosmetic defects

Extractables

Siliconization

Barrel Geometry

Lubrication

Material

Glass Barrel

Dimension and Geometry

RNS pull-off force

Cap Torque and pull-off

Needle Shield/Tip cap

Adapted from David A. Post, Sherwin Shang, Shweta A. Raina,and William Szechinski. Development of Biopharmaceutical Drug-Device Products. PFS characterization and Interaction with Biologic Formulations. AAPS Advances in the Pharmaceutical Sciences Series 35, 2019 - 831 ff

Glass barrel forming and needle mounting

Glass barrel production

- Type 1 glass based on standard suppliers
- Needle assembly, clean room class D (acc. GMP)
- 100 % in-process control (camera station for dimensions and cosmetic camera stations)
- Quality control

1

Glass cutting

2

Barrel forming

3

Printing

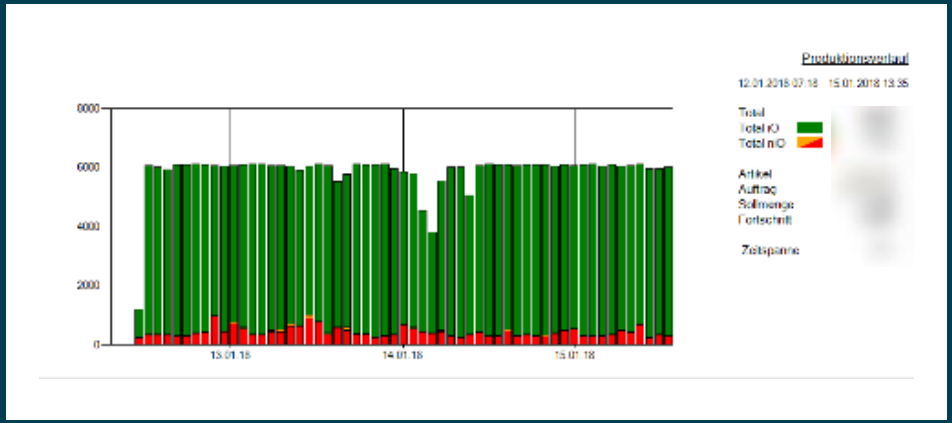
4

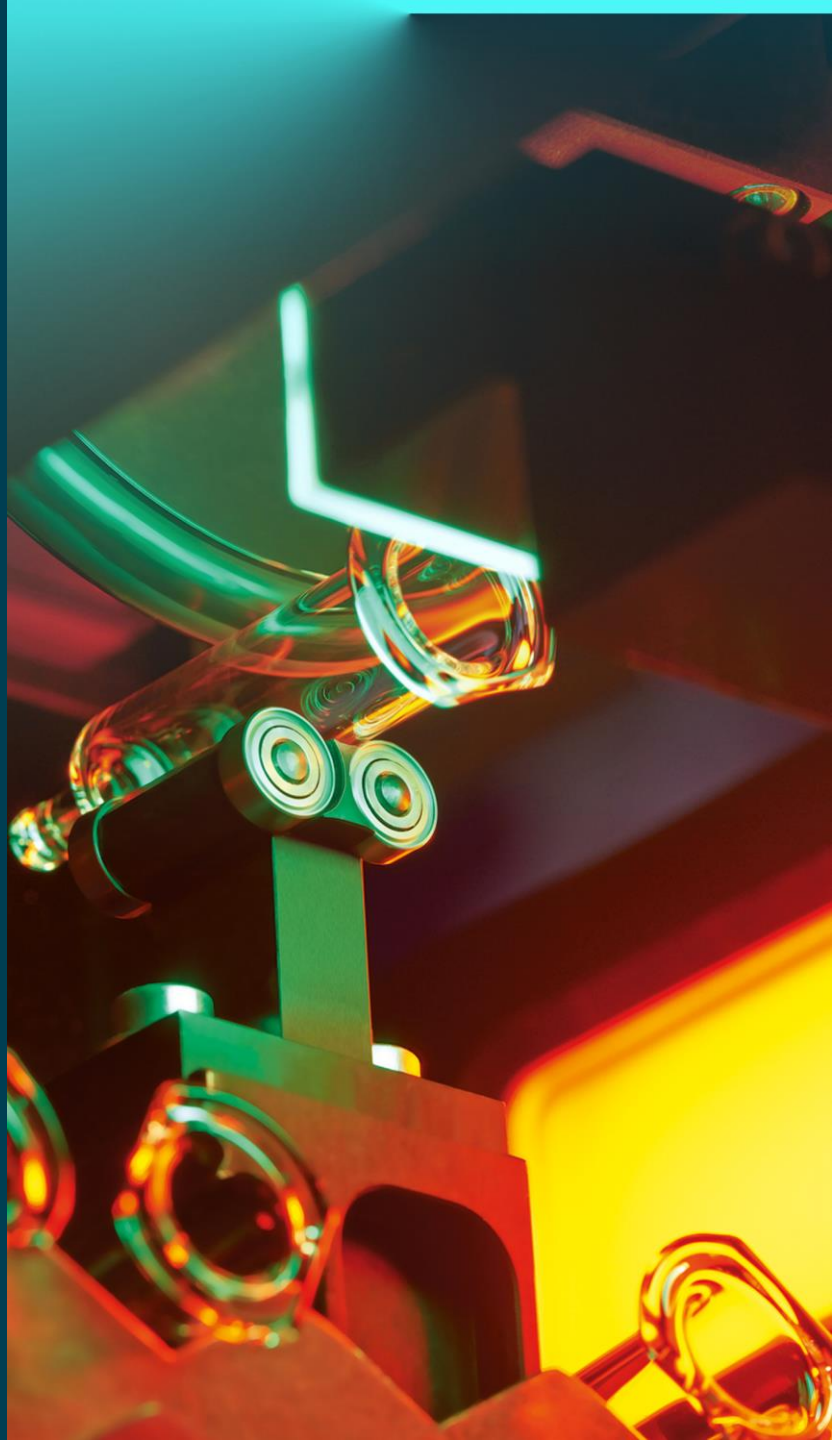
Cannula Assembly

Camera inspection system

Highest dimensional and cosmetic accuracy

- 100 % camera inspection of each syringe
- Cosmetic controls e.g. cracks, scratches, particles
- Dimensional inspection
- All data documented in a CAQ system
- Interfaces to external systems possible
- Implemented on all glass forming lines





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Video Barrel Forming – Glass Syringes

Click here

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Video Needle Mounting Glass Syringes

Click here

RTF-Process for Syringes

Washing and Packaging

RTF processing

- Clean room ISO class 7 acc. to class B under laminar flow
- 100 % in-process control
- Quality control
- Sterilization through external service
- Sterilization by EtO
  - Final quality control
  - Sterility testing
  - Certificate of Conformity (CoC)

1

Washing (WFI)

2

Siliconization

3

Closure setting

4

Nesting, Coding, Packaging

5

ETO Sterilization

RTF – „Ready-to-Fill“

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Video RTF – Glass Syringes

Click here

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Video COP Syringe Manufacturing

Click here

Pre-Fillable Syringes Regulatory Guidelines

Regulatory Guidelines for Prefillable Syringes

ISO 9001:
Quality management

ISO 15378:
Primary packaging materials for medicinal products

21 CFR 211 Subpart E
Control of Components and Drug Product Containers and Closures:
Glass, plastic or metal containers, bottles, vials, ampules, screw caps, lids, stoppers, seals, desiccants, fillers, etc.

Containers and Closures not defined in the cGMP regulations but

Interpreted as the primary packaging of a finished drug product and treated acc. 21 CFR 211 Subpart E

Control of Components and Drug Product Containers and Closures

- Products, methods procedures follow Ph. Eur. USP and JP
- Description of products, process and procedures in DMF type III
- Not fully covered with EU Medical Device Regulations, combination products regulations do not apply

New Annex 1 GMP

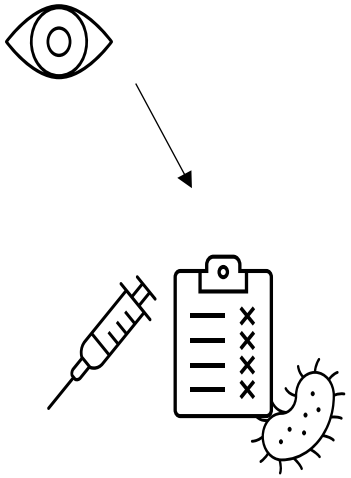
…also applicable to Prefillable Syringes

Annex 1
EU GMP

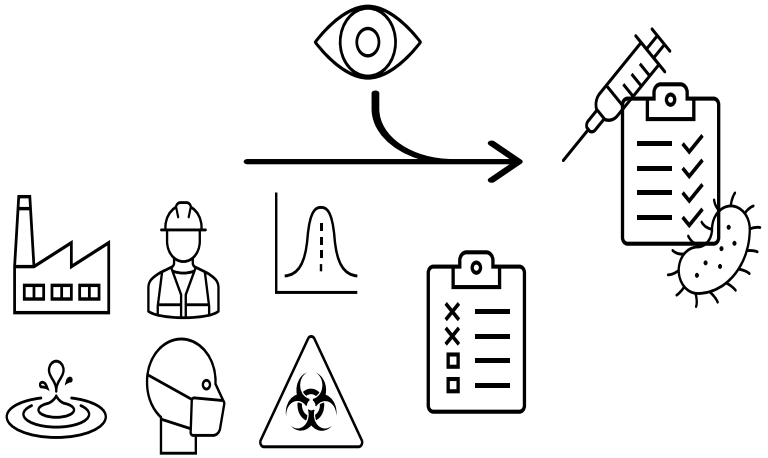
ICH Q9
Riskmanagement

ICH Q10
Pharma Quality System

Old:
Focus on end product



New:
Focus on process



1. Get away from „sterility“ testing in end process
2. Work towards deep process understanding, considering all potential sources of contamination
3. Implement Contamination Control Strategy
   - Identify and evaluate contamination risks
   - Plan for corrective actions
   - Prevention plan

Overall risk assessment

For a prefilled syringe as combination product

Risk Assessment Pharma

1. Formulation
2. Drug/Device Combination (prefilled syringe)
3. Device (prefilled syringe, AI)
4. Components (glass, elastomer…)

Component risk ass.

Raw materials, components, packaging materials

Description of the design & manuf.

General Safety and Performance Requirements

Biocompatibility

Device supplier risk ass.

Functionality

Raw materials, components, packaging materials

Description of the design

General Safety and Performance Requirements

Biocompatibility

Drug/Device Combination

Risk assessment

…

Drug formulation

Risk ass incl. Fill& Finish

…

Adapted from BSI, Webinar July 2020: BSI's perspective on Article 117 and Drug/ Device Combinations Dr Jennifer Durrant and Dr Jonathan Sutch

Summary – Manufacturing

Glass tubes are converted into syringe barrels

Syringe barrels are washed, siliconized, capped, put in nest and tub, into bags

Sterilization with EtO (glass syringe) ->“RTF“

As syringe becomes a sterile product after filling, high GMP requirements to be fulfilled even for empty containers

Risk management of supplier to be linked to Pharma filling risk management

Closer cooperation with component manufacturers necessary in future

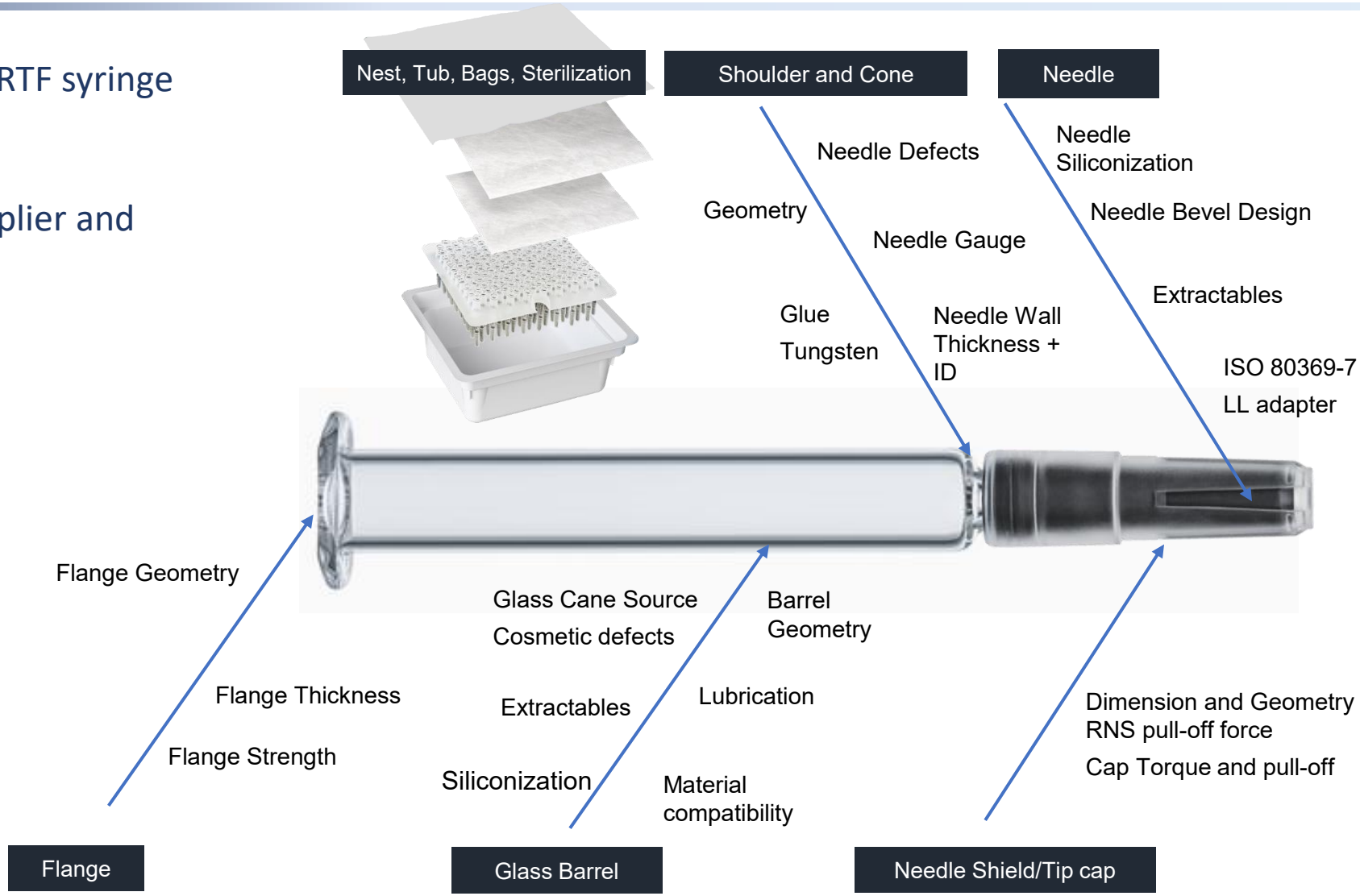
Pre-Fillable Syringes Specification Example

RTF Syringe Product Specification

Contains and describes all relevant RTF syringe information

Agreed on and signed between supplier and pharma company

- Product
- Product Packaging
- Shipment Packaging
- Labeling
- Storage
- Shelf Life
- Quality System
- Regulatory Compliance
- Sampling
- Documentation
- Attachments: Drawings and AQL
- Customer Responsibilities



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Specification acc. ISO 11040-4

Primary Packaging, RTU specification supports Finished Drug Product testing acc. ISO 11040-8

ISO 11040-4
Glass Syringe

ISO 11040-6
Plastic Syringe

ISO 11040-5

->
ISO 11040-8

1. User requirements	*Pharma or supplier data*
Definition of intended use	Pharma
Risk management	Pharma, input from supplier
Application of usability engineering	Pharma
System characterization	Pharma
Description of components and materials Barrel – Flange, barrel, cone, needle, cap	**Critical dimensions, Geometry, Strength, Extractables (tungsten, glue, siliconization), Glass/plastic source, Cosmetic defects, sterilization, pull-off force cap, tightness cap**
Description of components and materials Plunger stoppers	Critical dimensions, Elastomer material Compatibility, Extractables, Coating, Geometry, Siliconization, Sterilization
Additional components: rod, backstop, Autoinjector, safety system…	Pharma: Device interactions of syringe barrel, Luer lock adapter with attached needle, autoinjector, needle safety device
Description of the content of the finished prefilled syringe	Pharma

Available from suppliers – can be supplied/tested without drug
Pharma company input – no or limited data from supplier, drug needed

ISO 11040-8 under review

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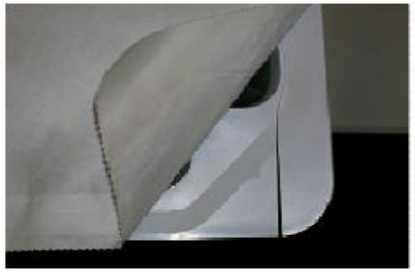
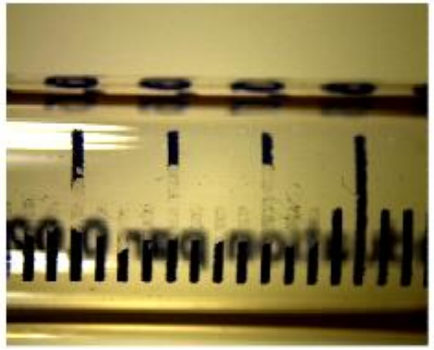
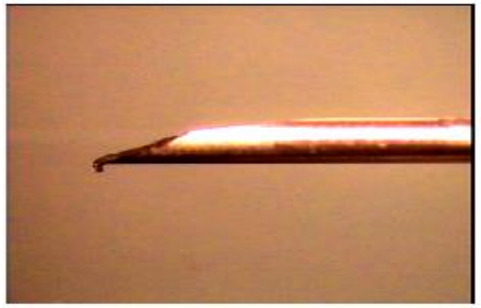
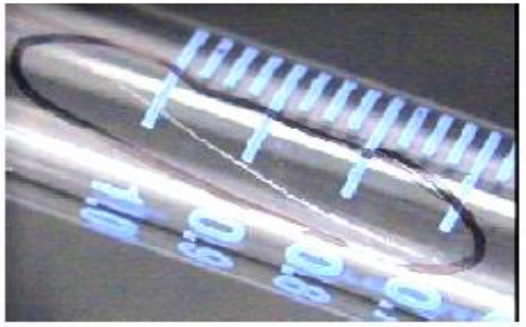
Possible Defects







- PDA Technical Report No. 43: Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical manufacturing Covering Ampoules, Bottles, Cartridges, Syringes and Vials
- Defect Evaluation List for containers made of Tubular Glass

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How suppliers can support ISO 11040-8 testing at Pharma

2. Performance requirements	*Pharma or supplier data*
Break loose and extrusion forces	Pharma, general performance data (water filled syr) from supplier
Break resistance: LL, FF	supplier
Closure system forces and torques	supplier
Connectivity with fluid path connectors	supplier
Residual volume	Pharma, general performance data (water filled syr) from supplier
Needle penetration force	Specification of supplier – not with tissue
Needle pull-out force	Specification of supplier
Sharps injury protection requirements	Pharma
Liquid leakage beyond plunger	Pharma, general performance data (water filled syr) from supplier
Markings	Specification of supplier, accuracy t.b.tested by Pharma

3. Pharmaceutical requirements	*Pharma or supplier data*
Drug-container interaction	Pharma, leachables, shear forces to be tested with drug
Biological requirements	Pharma, general performance data (water filled syr) from supplier
Container closure integrity (plunger)	Pharma, general performance data (water filled syr) from supplier
Deliverable volume	Pharma, general performance data (water filled syr) from supplier
Particles (visible and subvisible)	Pharma, general performance data (water filled syr) from supplier

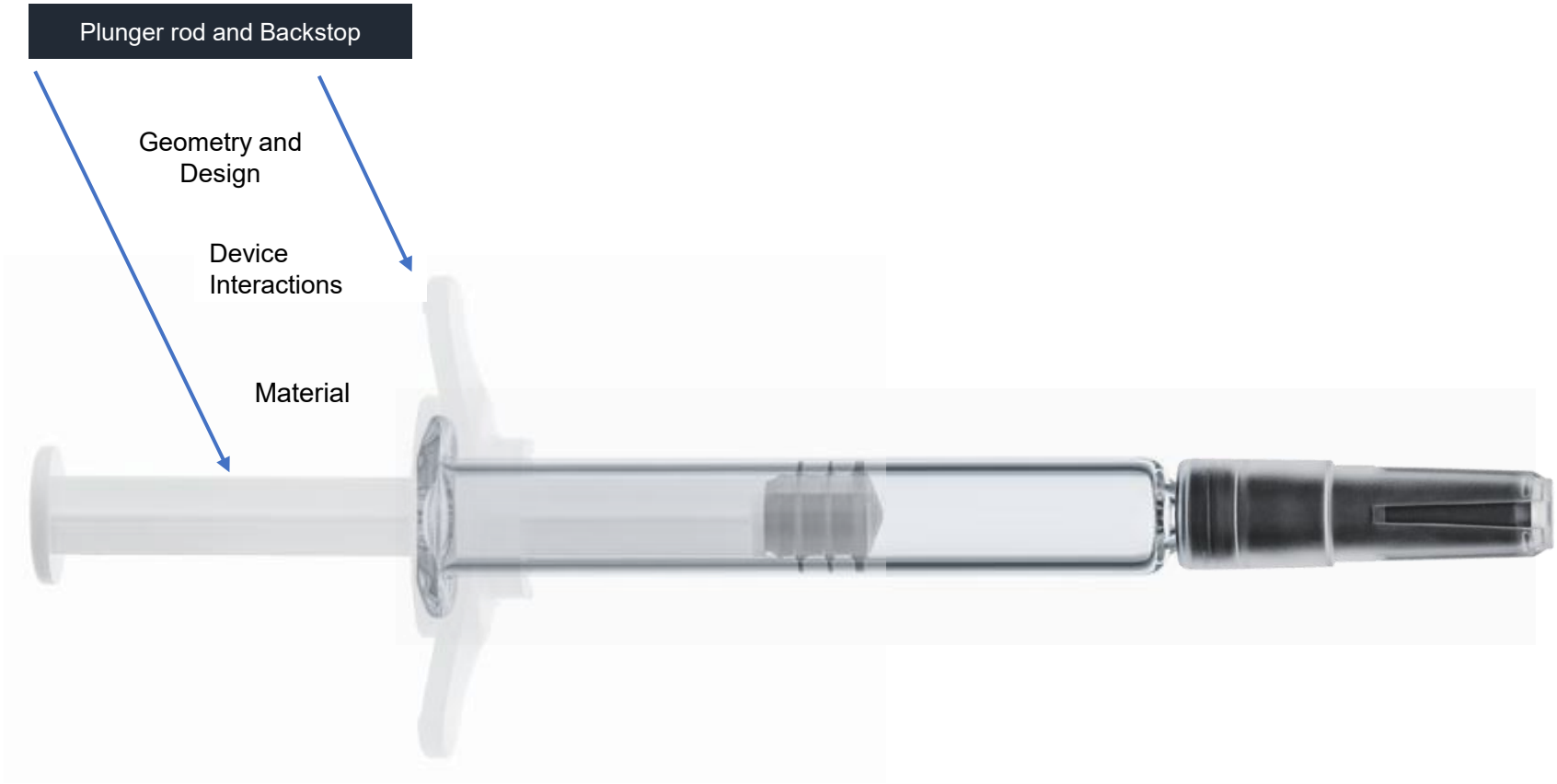
Available from suppliers – can be supplied/tested without drug
Pharma company input – no or limited data from supplier, drug needed

ISO 11040-8 under review

Back stops/Plunger Rods

Separate specifications

- Dimensions
- Material
- Pack size
- Can be sourced from syringe supplier –
- „one stop shop“



CoC and statements

Completing the syringe specification

- CoC Certificate of Confomance with every delivered batch
- Customized testing
- Customization of specifications possible (e.g. special AQL)
- Statements regarding Elemental Impurities, TSE, BSE, REACH, debarment etc. on demand

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Supplier Syringe Compendium

Modular Syringe Compendium - Intended Use		
Technical drawings	Biocompatibility data, Extractables List	White papers
Product Specifications	Material Characterization Package	Technical Bulletins
Functionality data (device part design verification)	Regulatory Compliance Statements	Scientific papers and posters
Certificates, CoC	DMF, LoA	Customer specific data
Not public: Development reports, validation reports, inhouse studies, partner studies, routine data		

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Summary – Syringe specification

Specification is the „contract“ between supplier and pharma company

Highly standardized: all syringe barrel features included

Prefillable (primary packaging) features covered

Not covering syringe system functionality (filled)

Certificate of Conformance for every batch delivered

Closer cooperation necessary in future to cover system functionality