All about Pre-filled Syringe Systems

From Initial Development to Final Fill Finish

The syringe – example specification

Bernd Zeiss

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PDA Parenteral Drug Association

PDA TRAINING

Agenda – DAY 2

The Syringe (Body)
Example Specification

Plunger stoppers, Needle Shields, Tip caps
Materials and Properties, Functionality, production; Extractables

Manufacturing Aspects in Fill & Finish and Assembly
Bulk versus Nested, Nest Sizes, Rod insertion, Handling of Syringes, Labeling, glass to glass contact

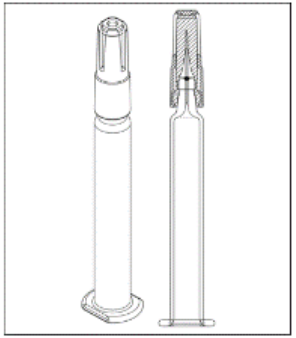
Hands-on Session 2, Mind map, Lottery

Syringe Example Specification 1

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
- Customer Responsibilities



Volume	1.0 mL long
Cannula/ Cone	staked needle, 27G, 1/2 inch, 3B NW
Closure	RNS grey Stelmi 4800GS
Finger Flange	Cut Finger Flange
Siliconization	Oily siliconized: 0.5 mg
Nest size	160 syringes
Packaging – Bag	Single Bag
Packaging – Pallet	Euro Pallet

What is missing?

- no plunger stopper, no rod, no drug

- RTF= „ready to fill“, i.e. *one component* of the final filled and stoppered syringe

-empty

Covered by syringe spec.

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 dimesions, Geometry, Strength, Extractables (tungsten, glue, siliconization), Glass source, Cosmetic defects, sterilization, pull-off force cap, CCI 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

2. Performance requirements	*Pharma or supplier data*
Break loose and extrusion forces	Pharma, general performance data (water filled syr) from supplier
Burst resistance	**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	
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

Syringe Example Specification 2

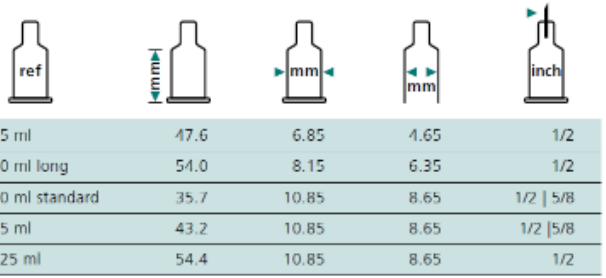
Materials glass or polymer (COC/COP)

The syringe is made from

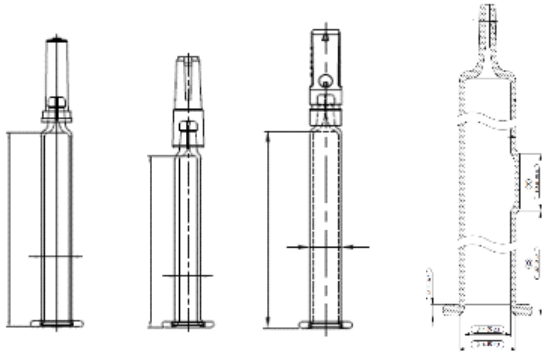
- borosilicate glass, hydrolytic resistance Type 1
- COP or COC

Shape, Diameter of syringe

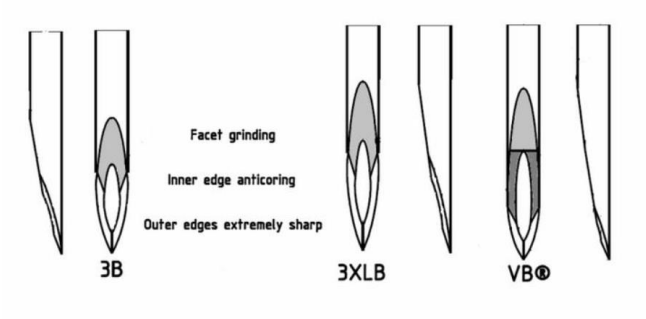
- Properties and dimensions are in accordance with DIN ISO 11040, if nothing different is specified
- Dimensions are according to the drawing no. xxx



0.5 ml	47.6	6.85	4.65	1/2
1.0 ml long	54.0	8.15	6.35	1/2
1.0 ml standard	35.7	10.85	8.65	1/2 | 5/8
1.5 ml	43.2	10.85	8.65	1/2 |5/8
2.25 ml	54.4	10.85	8.65	1/2



Syringe Example Specification 3



Cone

- Integrated needle syringe, luer lock adapter or luer cone - all with cap
- Description of cannula e.g. 27G ½“

Needle shield, tip cap

- Elastomer cap described in specification - rubber formulation, design

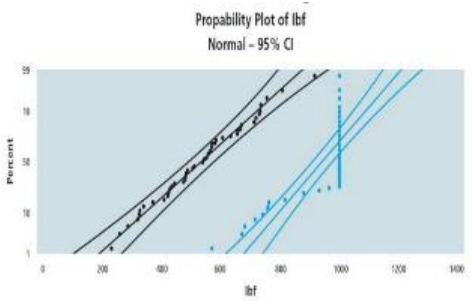
Free Needle Length	Outer diameter	Inner diameter	Grinding
1/2 “ [12.7 mm]	23 G [0.64 mm]	[0.41 mm] thin walled	3 Bevel
5/8 “ [15.9 mm]	25 G [0.5 mm]	[0.25 mm] standard	3 Bevel
1/2” [12.7 mm]	27 G [0.41 mm] 27 G [0.40 mm]	[0.21 mm] standard [0.20 mm] standard [0.22 mm] thin wall [0.24 mm] thin wall [0.27 mm] thin wall [0.28 mm] thin wall	3 Bevel 3 Bevel XL V®-bevel
1/2” [12.7 mm]	29 G [0.33 mm]	[0.19 mm] thin wall	V®-bevel

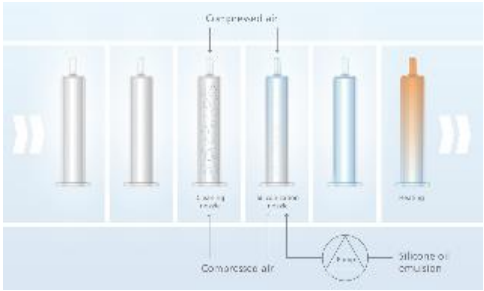
Syringe Example Specification 4

Mechanical properties
- Special mechanical tests can be defined:
  cone breakage, shoulder breakage, finger flange breakage
- Needle shield or cap pull-off force range given

Siliconization
- Often Dow Corning DC 360
- Special siliconization types defined
  e.g. baked-on siliconization (to meet USP 789)
- Needle siliconization, glue description

Chemical Properties
- Borosilicate glass Type 1, supplier name often stated
- Tungsten levels can be specified
- EtO - treatment according to DIN EN ISO 11135 and ISO 10993-7-Ethylene Oxide Sterilization Residuals





Syringe Example Specification 4

Mechanical properties
- Special mechanical tests can be defined:
  cone breakage, shoulder breakage, finger flange breakage
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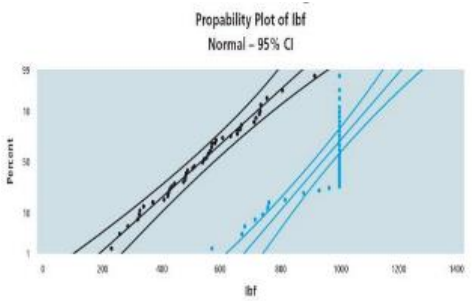
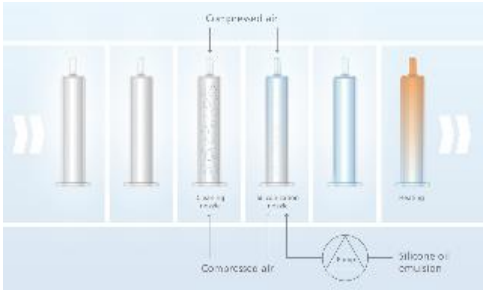




Syringe Example Specification 5

Quality and Regulatory guidelines and technical standards: EU / US / ISO

- ISO 9001 “Quality Management Systems - Requirements”
- ISO 15378 “Primary packaging materials for medicinal products - Particular requirements for the application of ISO 9001:2008, with reference to Good Manufacturing Practice (GMP)”
- 21 CFR 211, Subpart E “Current Good Manufacturing Practice for Finished Pharmaceuticals”
- 21 CFR 820 „Quality System Regulation - Medical Devices“
- ISO 13485 „Medical Devices - Quality Management Systems”

Syringe Example Specification 6

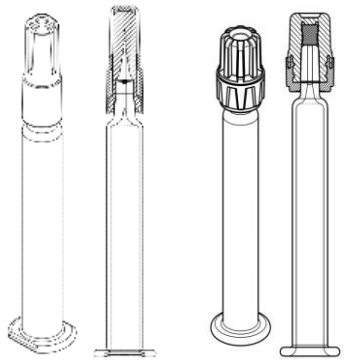
Sterility
- Ph. Eur. 2.6.1 USP <71>
- Sterility Tests according to ICH Q4B Annex 8

Bacterial Endotoxins
- Ph. Eur. 2.6.14 and USP <85>

Glass container
- Ph. Eur. 3.2.1, USP <660>, JP 7.01
- ISO 4802-2 Hydrolytic Resistance, Container Class HC1
- ISO 11040-4 “Prefilled syringes - Part 4: Glass barrels for injectables”
- Ph. Eur. 2.4.20, USP <211> Arsenic

Cannula
- ISO 9626 ” Stainless steel needle tubing for the manufacture of medical devices”

Syringe Example Specification 7



RNS and tip caps: Rubber formulation
- Ph. Eur. 3.2.9, USP <381>
- ISO 8871 "Elastomeric parts for aqueous parenteral preparations"
- USP <87>, USP <88>: "Biological Reactivity Tests"

Lubricant
- Conformity to applicable Monographs of EP and USP

Adhesive
- USP <88>´"Biological Reactivity Tests, in Vivo"

General
- BSE/TSE
- CONEG Toxic Packaging legislation
- Mercury and hexavalent Chromium

Syringe Example Specification 8

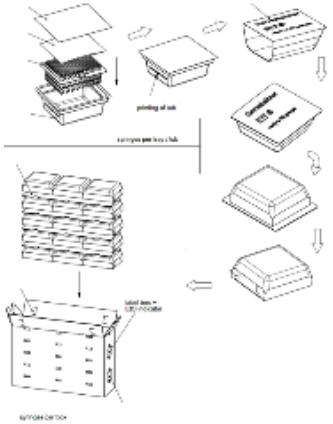
Drawings and description of packaging
- Syringe
- Nest, tub
- outer packaging and labeling
- pallet

Sampling
- According to DIN ISO 2859-1

Documentation
- Certificate of Conformance (CoC) with each delivery
- The CoC states the batch information
- conformance of all components
- EtO residues
- Sterility
- Endotoxin level of the syringe

Approval page
- Signatures of supplier
- Signatures of customer

Storage and shelf life information



Syringe Example Specification 9

Defect evaluation lists
- describe possible defects

Acceptance Quality Limit – AQL
- Define Pharma quality criteria
- “Quality level that is the worst tolerable” ISO 2859-1 - Give a probability of defects

Possible defects:
- Packaging e. g. labeling or damaged tub
- Syringe barrel e.g. cracks or deformations
- Dimensional defects e.g. of total length with cap
- Cannula e.g. hooks or contamination
- Closure e.g. pull-off force oot or pierced
- Chemical tests esp. hydrolytic resistance
- Sterility issues after EtO
- Siliconization e.g. glide force oot

How many samples should be picked and inspected among a batch of product or parts?

Where is the limit between acceptability and refusal when it comes to defective products?

Example:
“I want no more than 1.5% defective items in the whole order quantity, on average over several production runs with that supplier” means the AQL is 1.5%.

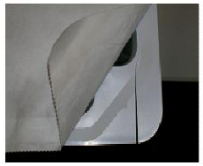
For most consumer goods, the limits are:

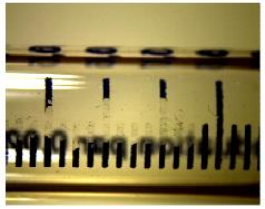
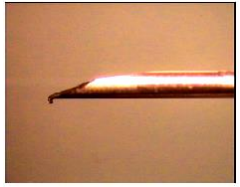
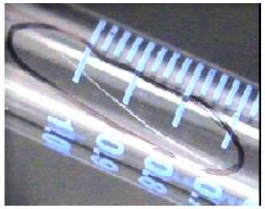
- 0% for critical defects (totally unacceptable: a user might get harmed, or regulations are not respected).
- 2.5% for major defects (these products would usually not be considered acceptable by the end user).
- 4.0% for minor defects (there is some departure from specifications, but most users would not mind it).

This tool is used during final inspections (before the products are ready to be shipped out)

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

Syringe Example Specification

Back stops/Rods/Plunger stoppers
Can be sourced from syringe supplier -„one stop shop“

- Separate specifications
- Dimensions
- Material
- Pack size

Test procedures

11040-4 ISO
11040-7 ISO
11040-8 ISO
80369-7 ISO

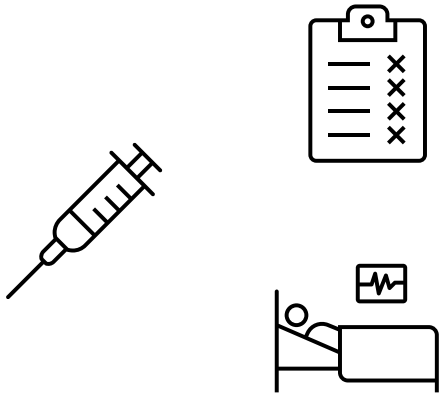
CoC and statements

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…on demand

Risk assessment 2

1. Drug Critical Quality Attributes
2. Product risk - Hazard risk
3. Use risk: dose accuracy, overdose, underdose, chemical, biological, mechanical hazards?
4. Risk benefit analysis
5. Production and post-production analysis



Sources:

Supplier data:
Design history file, test data, reports, dossiers, specifications

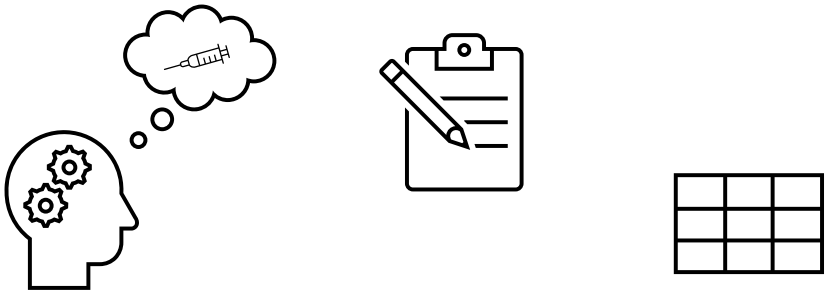
Manufacturer data:
Chemical evaluation
Complaint/market data if available

Risk assessment 3

ISO 14971
Medical devices
Application of
risk management
to medical devices

ICH Q9
Quality risk management
Scientific guideline

1. Define possible failure modes
2. Assign numerical values to it - “criticality”
3. What can go wrong?
4. What can be done to lower the risk – “CAPA”
5. What supportive data is available/is needed?



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

Sources

- Gerresheimer Product Specifications
- DIN EN ISO 11135 and ISO 10993-7- Ethylene Oxide Sterilization Residuals
- ISO 9001 “Quality Management Systems - Requirements”
- ISO 15378 “Primary packaging materials for medicinal products - Particular requirements for the application of ISO 9001:2008, with reference to Good Manufacturing Practice (GMP)”
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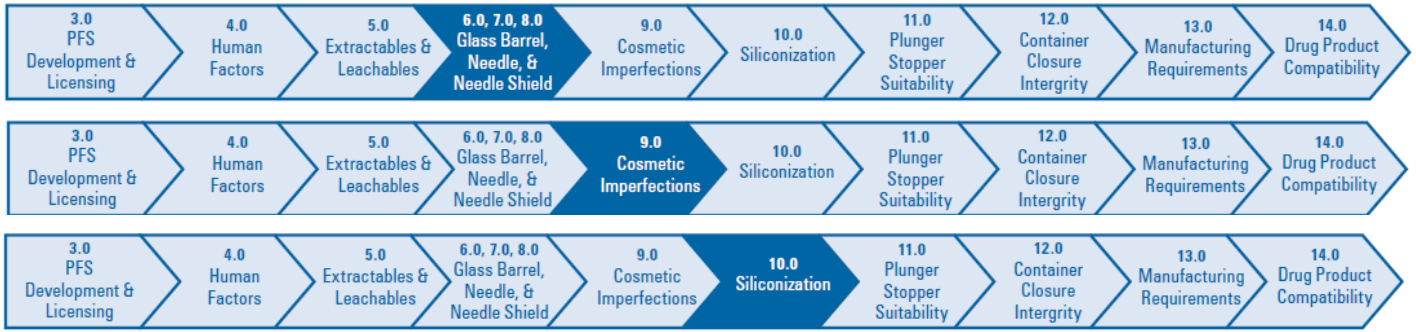
- Ph. Eur. 2.6.1 USP <71>
- ICH Q4B Annex 8
- Ph. Eur. 2.6.14, USP <85>
- Ph. Eur. 3.2.1, USP <660>, JP 7.01
- ISO 4802-2 Hydrolytic Resistance, Container Class HC1
- ISO 11040-4 “Prefilled syringes - Part 4: Glass barrels for injectables”
- Ph. Eur. 2.4.20, USP <211> Arsenic
- ISO 9626 ” Stainless steel needle tubing for the manufacture of medical devices”
- ISO 2859-1Sampling procedures for inspection by attributes — Part 1: Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection
- 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
- ISO 11040-4 series

backup

Limits of a Syringe Specification 1

Drug interface is not part of the syringe specification

- Impact of different drug properties not covered
- Stability testing with drug needs to be performed at Pharma site
- Risk of drug interactions with syringe components to be tested
- Risk of impaired functionality not tested
- Leacheables test impossible
- Syringe is not a combination product or finished Medicinal product



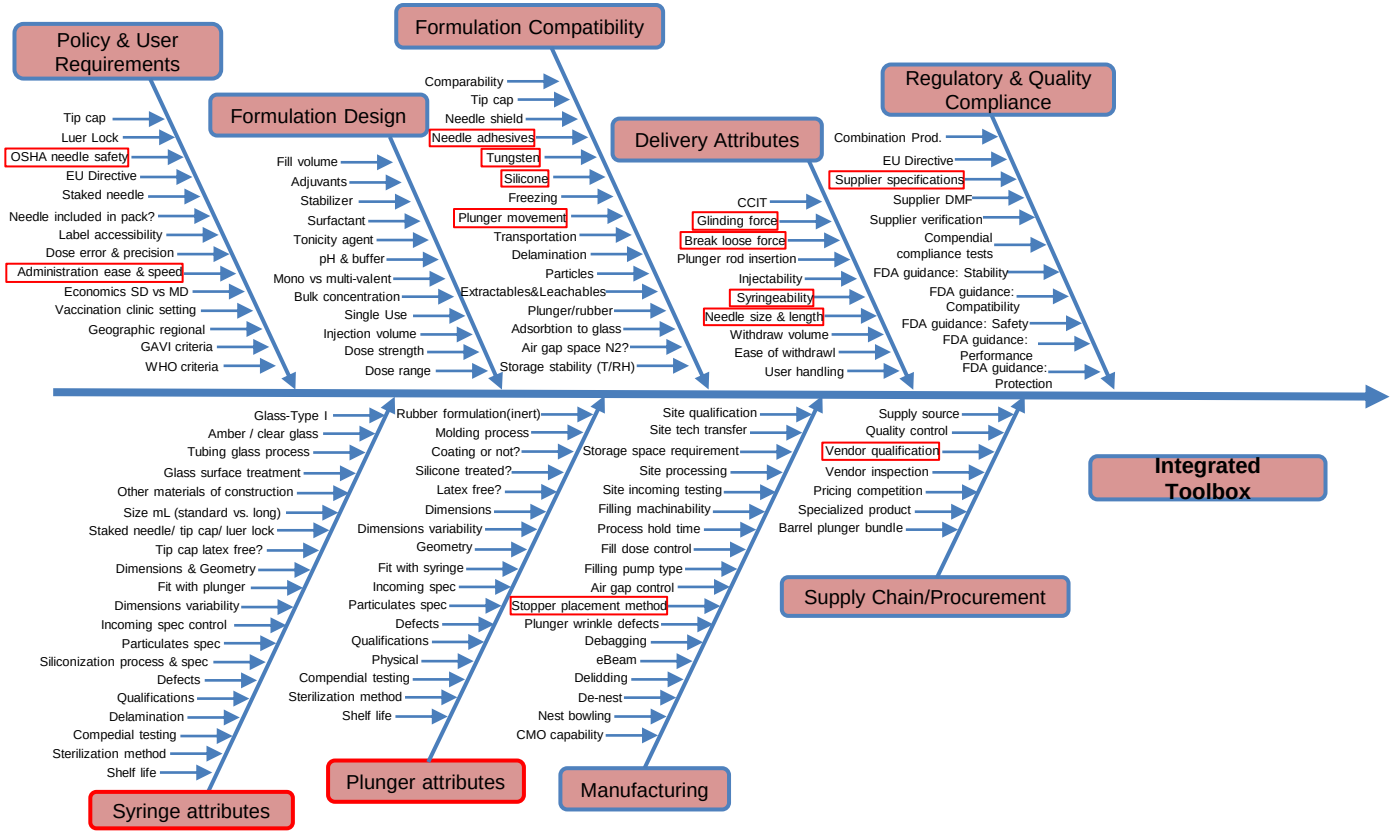
- PDA Technical Report No. 73: Prefilled Syringe User Requirements for Biotechnology Applications
- Amendment to Report 73: autumn 2023

Limits of a Syringe Specification 2

Prefillable syringe becomes a combination product after filling
MDR not fully applicable
Usability studies not fully covered with empty syringes

Comprehensive tests need to be carried out at the Pharma company

- Stability testing with drug
- Mechanical tests e.g. with Autoinjector and drug
- Performance with formulation (e.g. glide force, break tests), particles to be tested with drug formulation



An Integrated Prefilled Syringe Platform Approach for Vaccine Development
By: Kingman Ng, Ronald Malone, Changyun Xiong, Xuefeng Yi
Novartis Vaccines and Diagnostics, Inc.;BioPharm International, Jun 1, 2013; Volume 23, Issue 6, pp. 22-29 Pharmaceutical Sciences