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

Recap from yesterday

Requirements Primary Packaging Containers

Consider container materials from the beginning

- Critical contact material
- Device (functions) and container at the same time

Fill and Finish compatibility

- Standardization needed
- Transparency (visual inspection)
- Sterilization

Recap from yesterday

Requirements Primary Packaging Containers

Physical characteristics

- Material/ breakability
- Design, size, wall thickness
- standardized by ISO

- Long term storage
- Opening forces
- Delivery forces
- Closure integrity (CCI)

Pharmaco-chemical characteristics

- USP, EP, JP tests
- L&E, Trace metals, impurities

- Stability/interactions with drug substance
- Endotoxin level
- Biocompatability
- Subvisible particles

Recap from yesterday

Requirements Primary Packaging Containers

Patient /end user

- Functionality
  - Cap removal, gliding force, needle pentration pain
- Adminstration volume

- Autoinjectors
- Safety syringes and needle stick prevention
- Frequency of administration

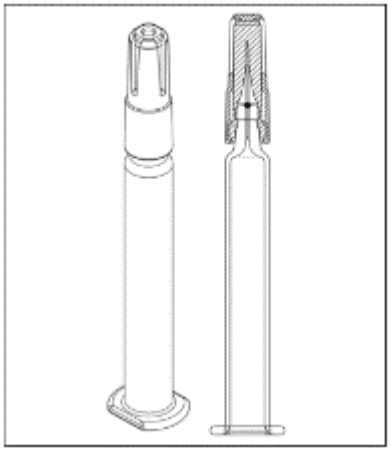
- Intended use
- Market
- Pricing

Syringe Example 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
- 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

Syringe Example Specification

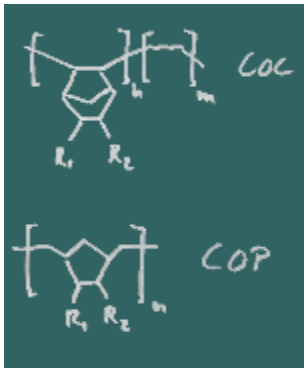
Materials (glass, polymer)

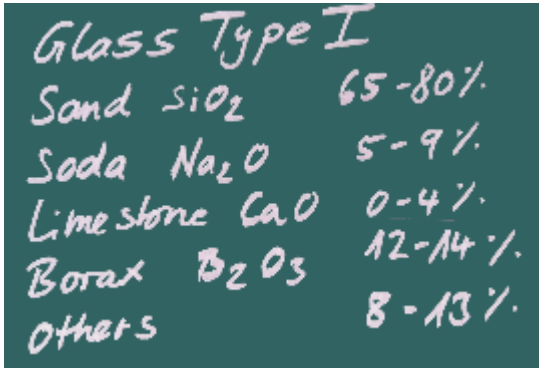
- The syringe is made from borosilicate glass, hydrolytic resistance type 1…
- COP or COC

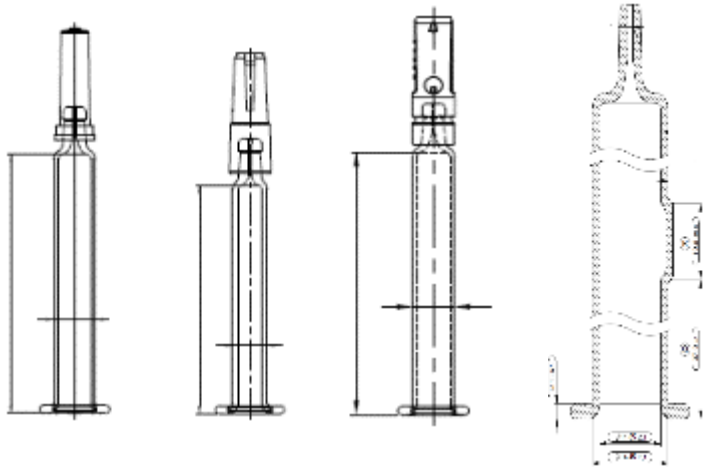
Shape, Diameter of syringe

- 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



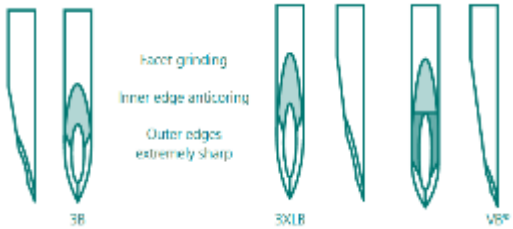




Syringe Example Specification

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
5/8" [15.9 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 [0.32 mm] thin walled	3 Bevel
5/8" [15.9 mm]	26 G [0.45mm]	[0.24mm]	3 Bevel
1/2" [12.7 mm]	27 G [0.41 mm] 27 G [0.425 mm] 27 G [0.40 mm]	[0.21 mm] standard [0.20 mm] standard [0.24 mm] standard [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 [0.20 mm] standard	3 Bevel 3 Bevel XL V®-bevel

Syringe Example Specification

Mechanical properties

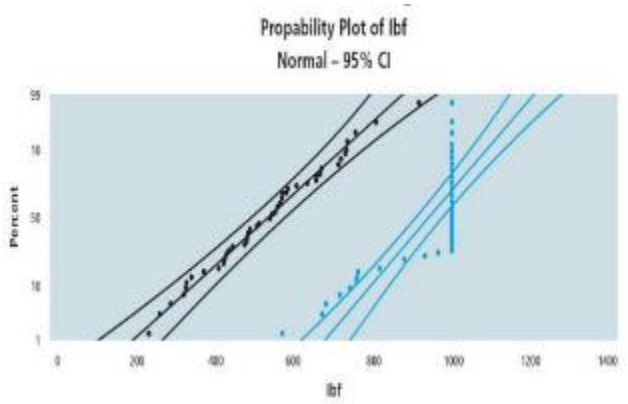
- Special mechanical tests can be defined:
  - cone breakage, shoulder breakage, finger flange breakage
- Needle shield or cap pull-off force range given

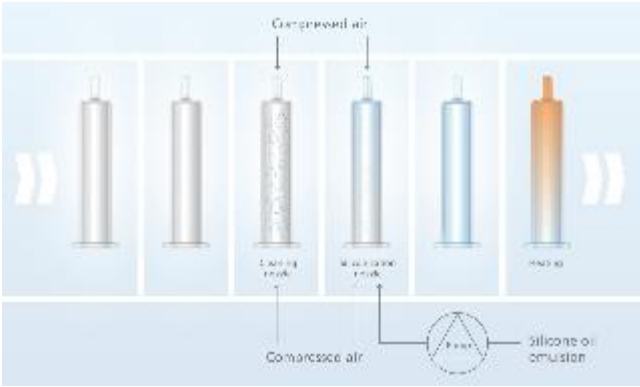
Siliconization

- Mostly 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

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

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>

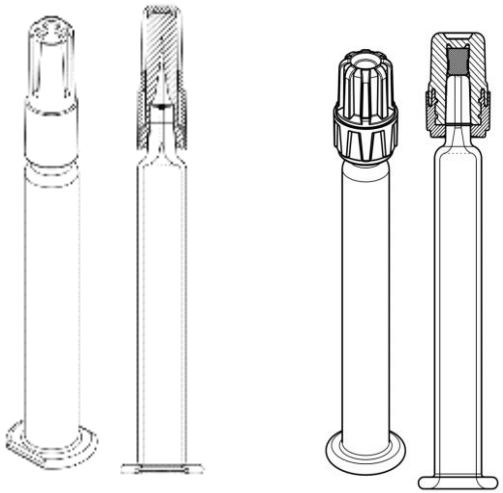
Glass container

- 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



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, current editions

Adhesive

- USP <88>´“Biological Reactivity Tests, in Vivo”

General

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

Syringe Example Specification

Drawings and description of packaging

- Syringe
- Nest, tub
- outer packaging and labeling
- pallet

Sampling

- According to DIN ISO 2859-1

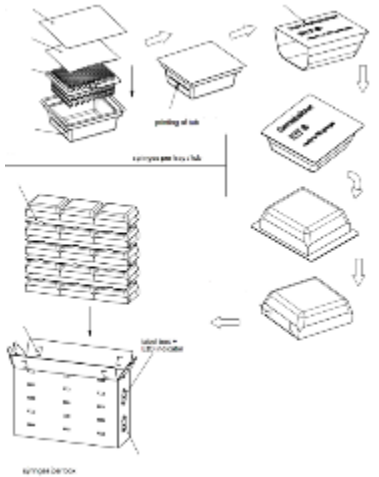
Documentation

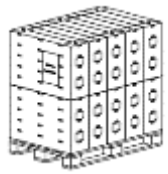
- Certificate of Conformance (CoC) with each delivery
- The CoC states the batch information
  - conformance of all components
  - EtO residues
  - Sterility
  - Endotoxin level of the syringe

Approval page

- Signatures of supplier
- Signatures of customer

Storage and shelf life information





Syringe Example Specification

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?

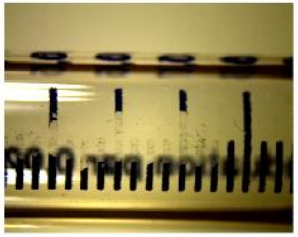
Example:
“I want no more than 1.5% defective items in the whole order quantity, on average over several production runs with that supplier” means the AQL is 1.5%.

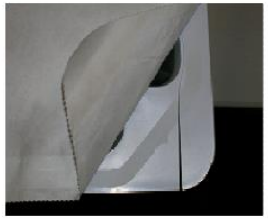
For most consumer goods, the limits are:

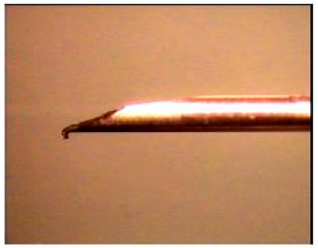
- 0% for critical defects (totally unacceptable: a user might get harmed, or regulations are not respected).
- 2.5% for major defects (these products would usually not be considered acceptable by the end user).
- 4.0% for minor defects (there is some departure from specifications, but most users would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

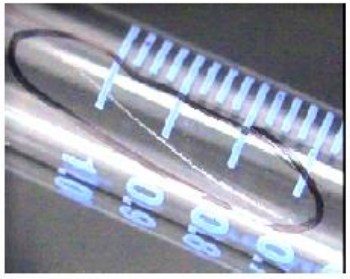
This tool is used during final inspections (before the products are ready to be shipped out)

Possible Defects





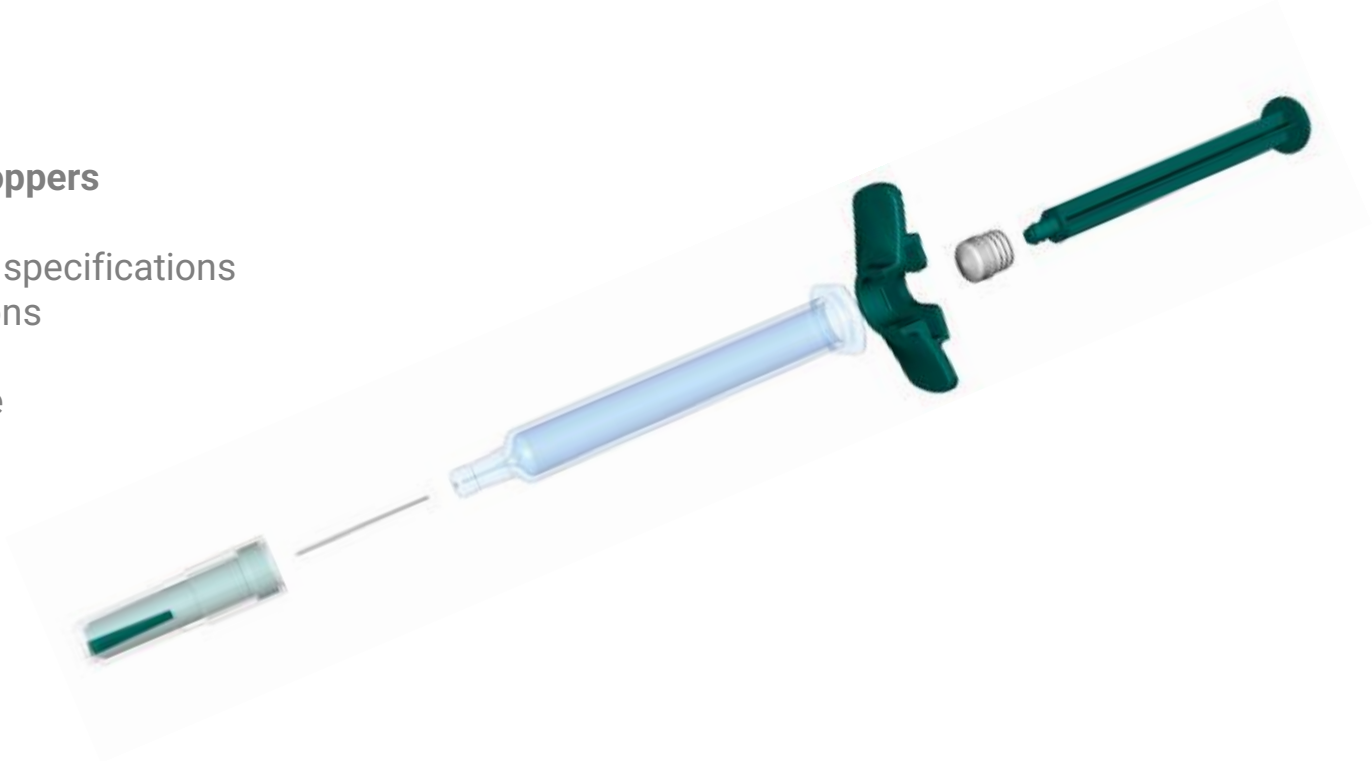




Syringe Example Specification

Back stops
Rods
Plunger stoppers

- Separate specifications
- Dimensions
- Material
- Pack size



Test procedures

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

CoC and statements

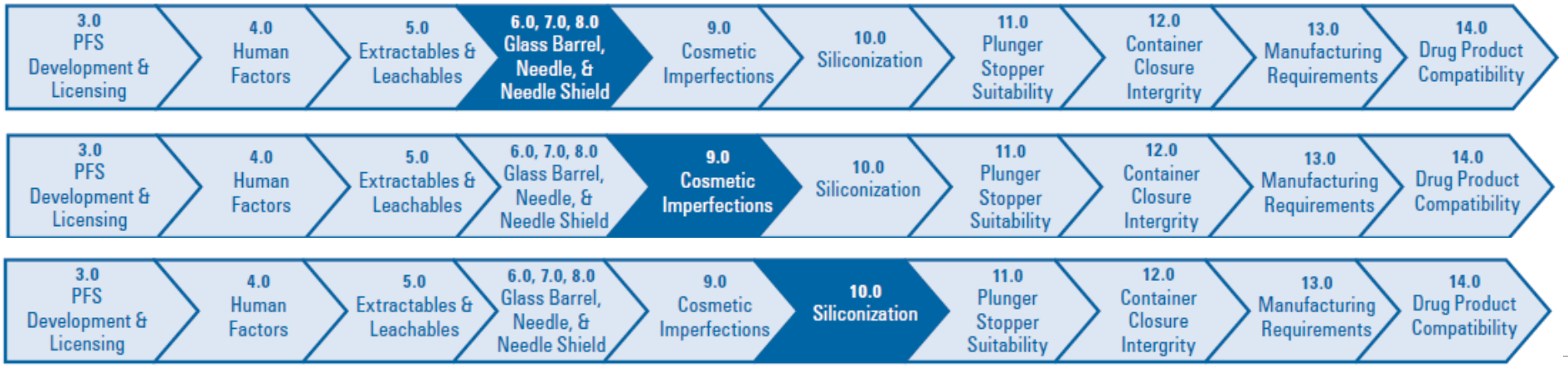
Completing the syringe specification

- CoC Certificate of Confomance with every delivered batch
- Statements regarding Elemental Impurities, TSE, BSE, REACH, debarment…on demand

Limits of a Syringe Specification - Drug properties

Not part of the syringe specification

- Impact of different drug properties
- Stability testing with drug
- Risk of drug interactions with syringe components
- Risk of impaired functionality
- Leacheables test
- Syringe is not a combination product - yet

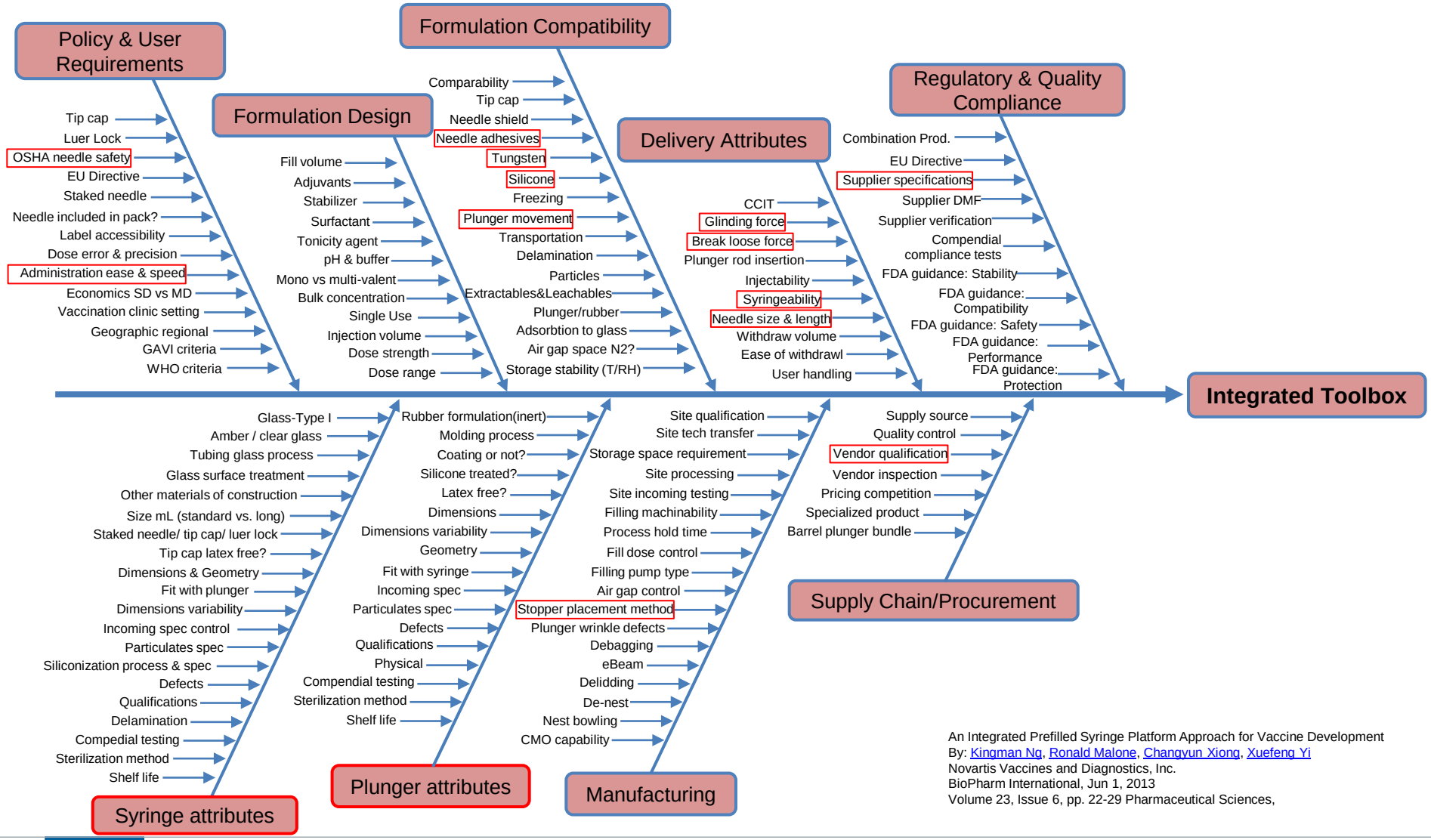


Limits of a Syringe Specification
Drug properties

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 – see e.g. PDA report 73
- 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,