All about Pre-filled Syringe Systems

Overview & Introduction to manufacturing Process of PFS

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Venice, April 20st and 21st 2023

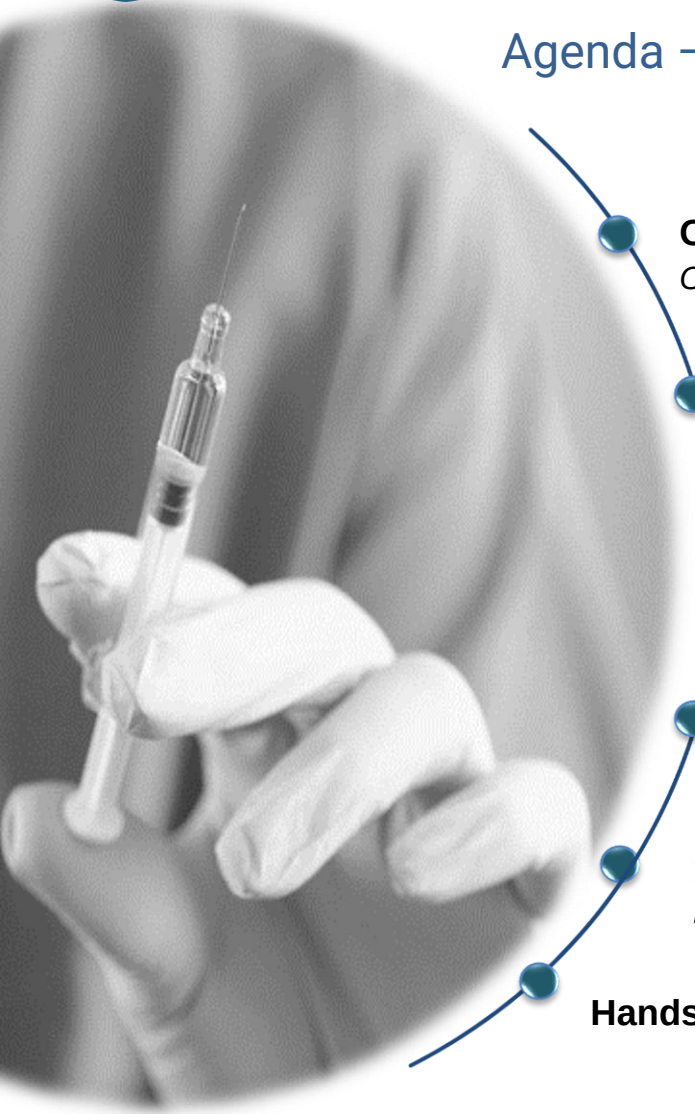
PDA Parenteral Drug Association

West

GERRESHEIMER

CONNECTING PEOPLE SCIENCE AND REGULATION®

Agenda – DAY 1



Overview and Introduction into Pre-filled Syringe Market
Overview & Trends • Stakeholders • User's perspective

Technical Aspects
Syringe • Plunger • Needle • Needle shield or Tip cap • Autoinjector • Regulatory guidelines and technical standards

Overview & Introduction into Drug-Syringe Interactions
Aggregation • Degeneration • Oxidation • Viscosity • Bubbles

Overview & Introduction to manufacturing Process of PFS
Syringes Barrel Forming • Washing • Siliconization • Sterilization • Regulatory guidelines and technical standards …

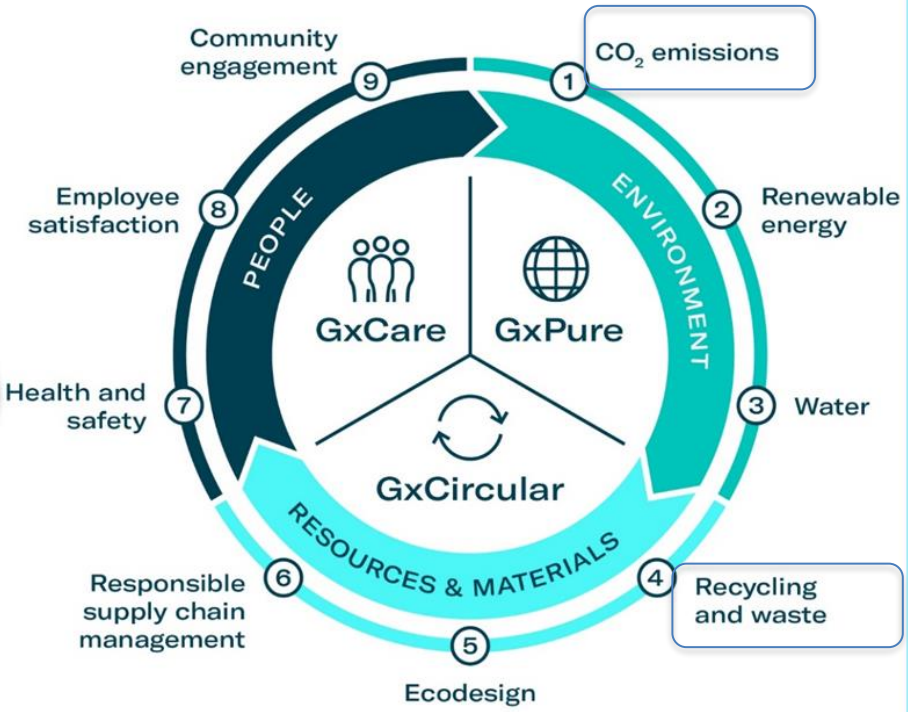
Fill and Finish
Filling • Stoppering • Assembly • Technical Standards

Hands-on Session 1

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

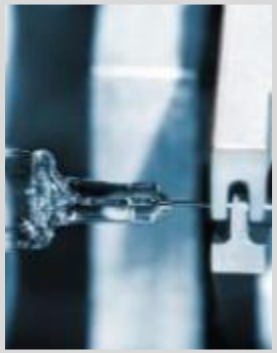
Driver for employer attractiveness

Barrel forming of prefillable syringes

Glass cutting

Barrel forming

Printing



Cannula Assembly

Glass barrel production Needle assembly, clean room class D (acc. GMP)

- 100 % in-process control (camera station for dimensions and cosmetic camera system)
- Quality control

Barrel forming

Video

Washing and Siliconization of prefillable syringes

Washing (WFI)

Siliconization

Closure setting

Nesting/coding
Packaging

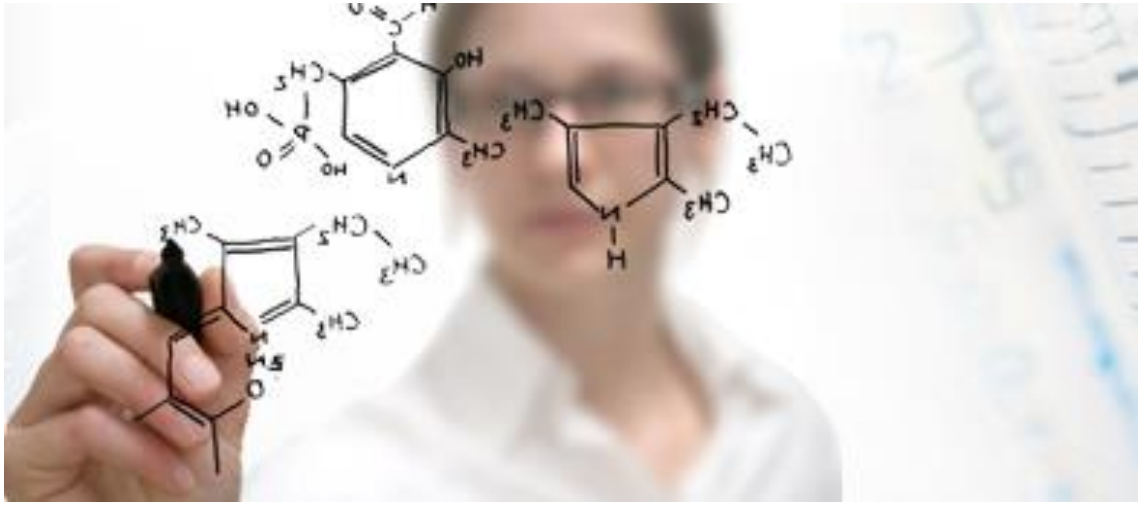
RTF processing
Clean room ISO class 7 acc. class B under laminar flow

- 100 % in-process control
- Quality control

Washing and Siliconization

Video

Sterilization of prefillable syringes



Sterilization by EtO treatment

- Pre-conditioning
- Desorption
- Final quality control
- Sterility testing
- Certificate of Conformity (CoC)

Regulatory Guidelines for Prefillable Syringes

ISO 9001: Quality management ->ISO 15378: GMP Primary packaging:

Primary packaging materials for medicinal products — Particular requirements for the application of ISO 9001:2015, with reference to good manufacturing practice (GMP)

Containers and Closures are not defined in the cGMP regulations *but*

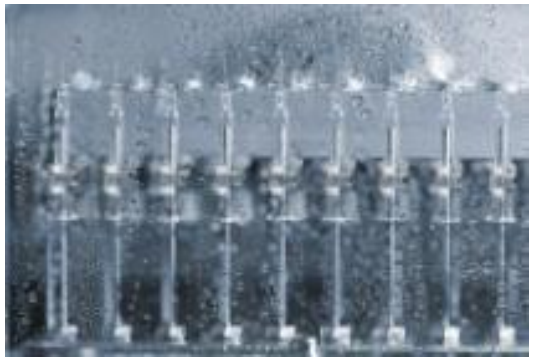
Interpreted as the primary packaging of a finished drug product and treated acc. **21 CFR 211 Subpart E –** Control of Components and Drug Product Containers and Closures:
glass, plastic or metal containers, bottles, vials, ampules, screw caps, lids, stoppers, seals, desiccants, fillers, etc.

- 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

Regulatory Guidelines for Prefillable Syringes

21 CFR 211 Subpart E – Control of Components and Drug Product Containers and Closures

1. Ensure compatibility/suitability of containers and closures
2. Maintain inventory control
   - identification, storage, handling, sampling, testing
3. Written and approved procedures
4. Prevent contamination
   - Aseptic Processing cGMPs (high purity for rinse water)
   - Water system validation, USP <1231> Water for Pharmaceutical Purposes
5. Know suppliers and supply chain
6. Appropriate sampling and testing



Regulatory Guidelines for Prefillable Syringes

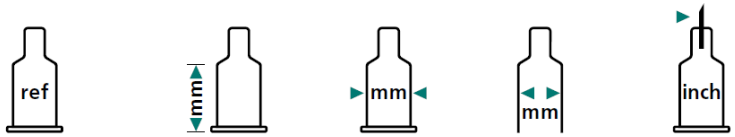
Relevant standards and regulations

- **ISO 11040-4: Glass syringes ready for filling**
- **ISO 80369-7: Luer connectors**
- **ISO 11040-5: Plunger stoppers**
- ISO 11040-6: Plastic syringes ready for filling
- ISO 11040-7: Nest & tub
- **ISO 11040-8: Test methods for finished prefilled syringes**

- ISO 13926-1: Pen cartridges
- ISO 9187-1: Ampoules
- ISO 8362-1: Vials from tubular glass
- ISO

- ISO 9001: Quality management
- ISO 15378: GMP Primary packaging
- 21 CFR 211 Subpart E – Control of Components and Drug Product Containers and Closures
- DMF type III
- Ph. Eur. USP and JP

- Medical Device and Combination Products Regulations



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

Regulatory Guidelines for Prefillable Syringes

Combination Products/ EU Medical Device Regulation regulation not fully applicable:

Prefill**able** syringe only *becomes* a combination product or medicinal product *when filled*

This workshop!
Vendors can help, but don´t have all the data… and no data on final drug product

ISO 11040-8 Pharma contribution -comprehensive
User requirements
Definition of intended use
Risk management
Application of usability engineering
System characterization
Critical dimensions
Description of components and materials
General
Barrel
Plunger stoppers
Additional components: rod, backstop, Autoinjector, safety system…
Description of the content of the finished prefilled syringe
Performance requirements
General
Break loose and extrusion forces
Burst resistance
Break resistance: LL, FF
Closure system forces and torques
Connectivity with fluid path connectors
Residual volume
Needle penetration force
Needle pull-out force
Sharps injury protection requirements
Liquid leakage beyond plunger
Markings
Pharmaceutical requirements
General
Drug-container interaction
Biological requirements
Container closure integrity
Deliverable volume
Particles (visible and subvisible)

Regulatory Guidelines
Medical Device Regulation 2022 – final drug product

ISO 11607-1:2019
Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging systems (ISO 11607-1:2019)

Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly processes (ISO 11607-2:2019)

Pharma Packaging departments require sound data on

1. Improved product handling and storage
2. Reduced risk of contamination
3. Better evidence of integrity - ISO 11607 Part 1 and Part 2 compliance
4. Aseptic presentation of devices
5. Usability evaluation – human factor studies

From https://www.packagingdigest.com/medical-packaging/medical-device-packaging-exec-guides-you-through-eu-mdr-compliance

Regulatory Guidelines

Medical Device Regulation 2022 (Europe)– final drug product

Nothing really new, but…

1. (Much) more documentation
2. Closing gaps
3. Risk assessment

Pharma Packaging has to

1. Protect medical device characteristics
2. Test performance during transport and storage
3. Minimize the risk posed to patients by contaminants and residues
4. Maintain sterility of devices throughout transport and storage
5. Package integrity to the final user
6. Validated methods: Processing, manufacturing, packaging, and sterilizing devices using

From https://www.packagingdigest.com/medical-packaging/medical-device-packaging-exec-guides-you-through-eu-mdr-compliance

Regulatory Guidelines
Medical Device Regulation 2022 (Europe) – final drug product

Dedicated workshop recommended

Planning for EU MDR compliance

1. **Knowledge base** with full understanding of the EU MDR requirements and ISO 11607, Parts 1 and 2
2. Create an essential-requirements checklist for **gap assessment**, based on the regulation's requirements
3. Checklist to review packaging designs, processes, and testing, ultimately identifying gaps in compliance
4. Close gaps, **determining the risk** of retesting a package for compliance with EU MDR vs. making changes to the package to bring it into compliance

From https://www.packagingdigest.com/medical-packaging/medical-device-packaging-exec-guides-you-through-eu-mdr-compliance

Risk assessment 1

1. Product contact materials
   - Container and process
   - Potential leachables

2. Risk factors
   - Material compatibility
   - Duration and distance to drug product contact
   - Surface area/volume
   - Temperature, contact time (storage)
   - …
3. Risk score
   - ICH Q9 Quality Risk Management
   - USP <1665>

Dedicated workshop recommended

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

From ICH Q9 Quality risk management | European Medicines Agency (europa.eu)

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

ISO 11040-8 Pharma requirements
Limited knowledge at suppliers
User requirements
Definition of intended use
Risk management
Application of usability engineering
System characterization
Critical dimensions
Description of components and materials
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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?

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

Manufacturer data
Chemical evaluation
Complaint/market data if available

Risk assessment

FMEA example

Failure mode	Severity	Cause	"CAPA"	Input from syringe supplier
Needle detatchment	8	poor assembly of the needle to the syringe barrel	Test, define method validate human factor study manual	ISO 11040-4 test certificate ISO 80369-7 connector
Leaking of drug product	7	faulty seal or closure system	Test, define method validate human factor study manual	ISO 11040-4 test certificate
Inaccurate dosing	9	variability in the manufacturing process or incorrect filling volume	…	n/a Exact positioning of markings (Test with Placebo acc. ISO 11040-8)
Presence of particulate matter in the drug product	9	contamination during the manufacturing process or use of poor quality raw materials	raw materials process	Test acc. USP 788/789 or Pharm. Eur. 2.9.19/20 Stability testing
Breakage or cracking of the syringe barrel	8	poor material selection or inadequate design	Define intended use - autoinjector? When does brekage occur? Breakage during production - adapt line?	Test with device
Mislabeling or incorrect labeling	6	human error during the labeling process or use of incorrect label	SOP, training of operators Poka Yoke?	Quality assurance
…	…	…		

Risk assessment

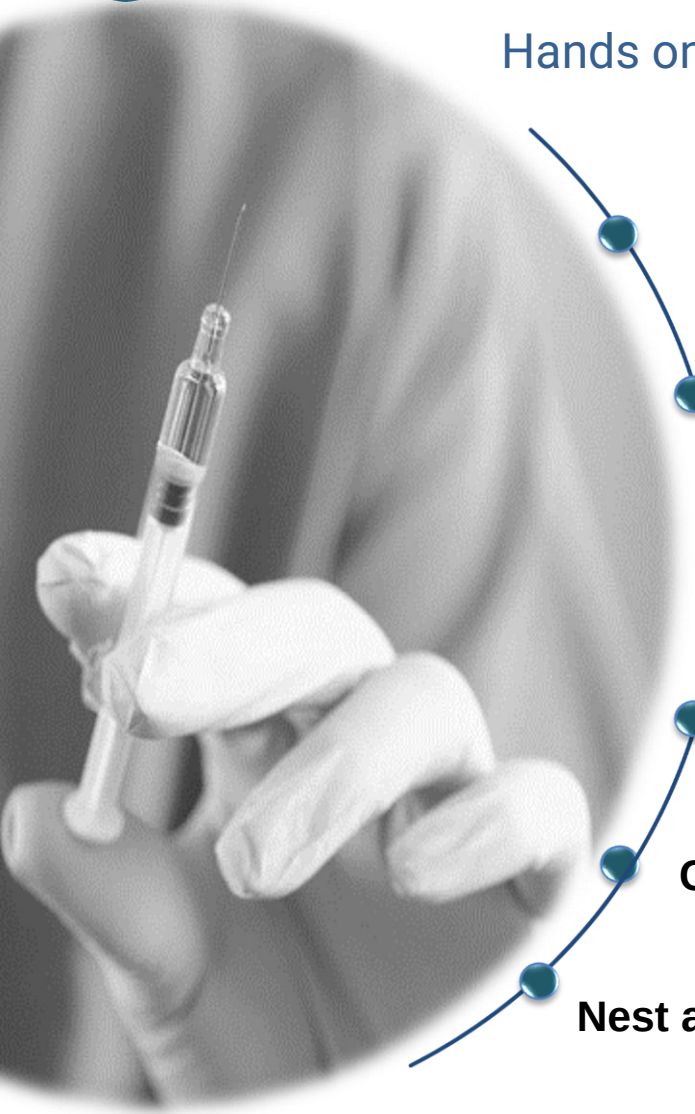
FMEA exercise

Failure mode	Severity	Cause	"CAPA"	Input from syringe supplier

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

Hands on Session I



- **Risk Assessment exercise**
- **Mount syringe, use syringe – feel and push**
- **Glass vs. Plasic syringe**
- **Assembly of Syringe into Safety device**
- **Compare Safety Devices**
- **Nest and tub**

Hands-on Session 1

- Prefilled syringes
- Test break loose and gliding force, “just inject”
- Safety devices