All about Pre-filled Syringe Systems

From Initial Development to Final Fill Finish

Manufacturing Process of PFS

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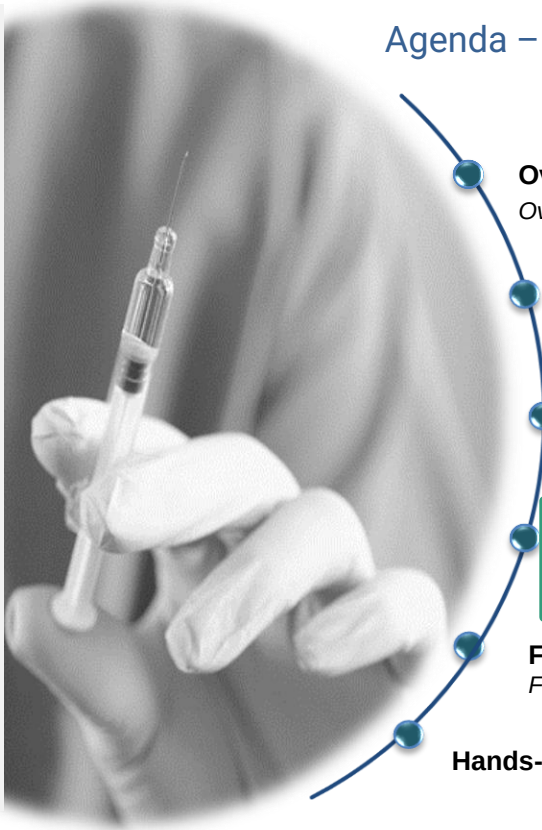
Gothenburg, October 19th and 20th 2023

PDA Parenteral Drug Association

PDA TRAINING



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

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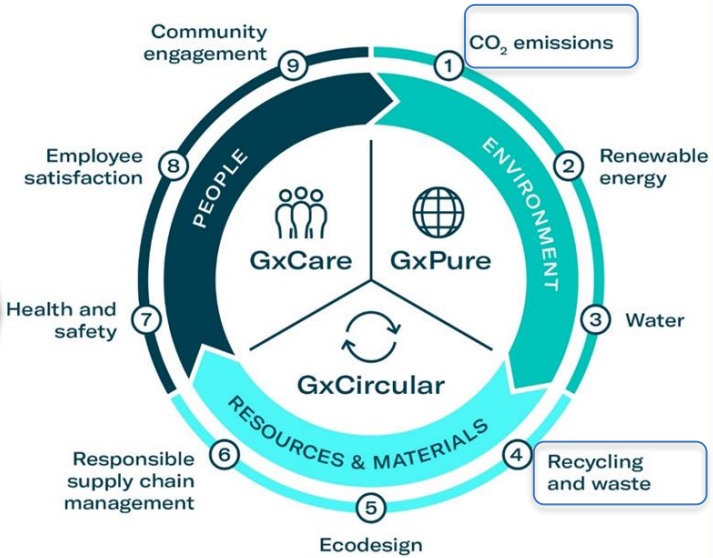
Sustainability – top prio at converters

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

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Barrel forming of prefillable syringes

1

Glass cutting

2

Barrel forming

3

Printing

4

Cannula Assembly

Glass barrel production

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

- 100 % in-process control (several camera stations for dimensions and cosmetic defects)
- Quality control

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Washing and Siliconization of prefillable syringes

1 Washing (WFI)

2 Siliconization

3 Closure setting

4 Nesting, Coding, Packaging

5 ETO Sterilization

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

- 100 % in-process control
- Quality control

Sterilization by EtO treatment

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

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Video

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Regulatory Guidelines for Prefil**lable** Syringes

ISO 9001: Quality management

ISO 15378: Primary packaging materials for medicinal products

21 CFR 211 Subpart E

Containers and Closures had not been 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

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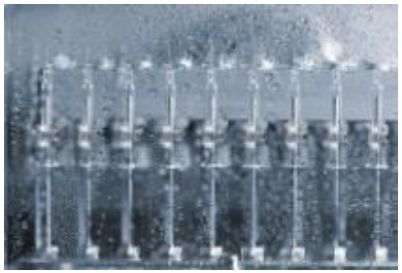
Regulatory Guidelines for Prefil**lable** Syringes

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



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New Annex 1 – also applicable to Prefil**lable** Syringes

Annex 1
EU GMP

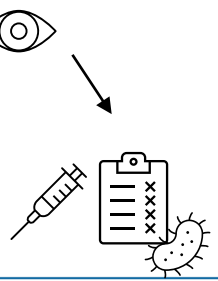
ICH Q9
Riskmanagement

ICH Q10
Pharma Quality System

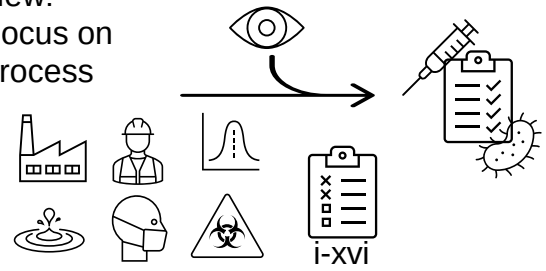
1. Get away from „sterility“ testing in end process
2. Work towards deep process understanding, considering all potential sources of contamination, facility design
3. Implement Contamination Control Strategy
   - Identify and evaluate contamination risks
   - Plan for corrective actions
   - Prevention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

Already existing at Pharma suppliers: BUT means more documentation, change of mind set

Old:
Focus on end product



New:
Focus on process



Contamination Control Strategy (**CCS**) also at supplier:
i. plant and processes documentation
ii. Premises and equipment
iii. Personnel
iv. Utilities
v. Raw material controls
vi. Product containers and closures
vii. Vendor approval – such as key component suppliers, sterilisation of components
viii. Management of outsourced activities
ix. Process risk management (e.g air, WFI)
x. Process validation
xi. Validation of sterilisation processes
xii. Preventative maintenance
xiii. Cleaning and disinfection
xiv. Monitoring systems
xv. Prevention mechanisms (CAPA)
xvi. Continuous improvement

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Overall risk assessment

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

…

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

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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>

Component	Patient contact	Clinician/User contact	Drug contact
Syringe barrel	Indirect	Direct	Direct
Plunger stopper	Indirect	No contact	Direct
Front Closure System (rubber part)	Indirect	Direct	Direct
Plunger rod	No contact	Direct	No contact
Backstop	No contact	Direct	No contact

Dedicated workshop recommended

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

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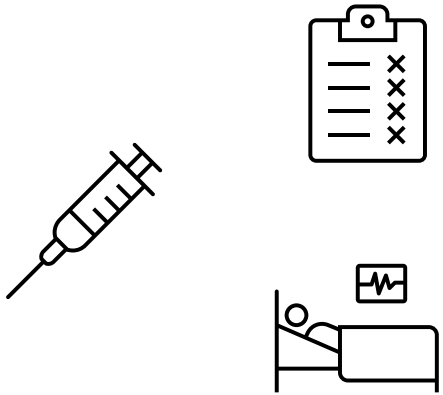
Risk assessment 2

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

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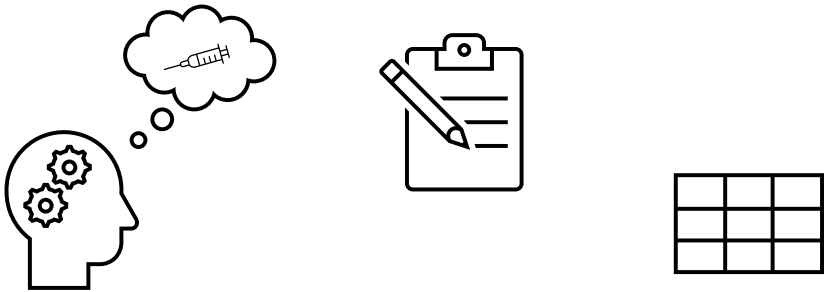
Risk assessment 3

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?



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Risk assessment

FMEA example

Failure mode	Severity	Probab-ility	Detection likelyhood	Cause	"CAPA"	Input from syringe supplier
Needle detatchment	8	2	10	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	4	8	faulty seal or closure system	Test, define method validate human factor study manual	ISO 11040-4 test certificate
Inaccurate dosing	9	8	6	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	6	5	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, input from supplier limited
Breakage or cracking of the syringe barrel	8	1	10	poor material selection or inadequate design	Define intended use - autoinjector? When does brekage occur? Breakage during production - adapt line?	Test with device, input from syringe supplier limited
Mislabeling or incorrect labeling	6	2	4	human error during the labeling process or use of incorrect label	SOP, training of operators Poka Yoke?	Quality assurance, input limited
…	…			…		

Risk assessment

FMEA exercise

Failure mode	Severity	Cause	"CAPA"	Input from syringe supplier

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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

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Sources

- https://www.gerresheimer.com/en/sustainability/sustainability-strategy
- Gerresheimer internal manufacturing information
- ISO 9001: Quality management
- ISO 15378: GMP Primary packaging
- 21 CFR 211 Subpart E
- ISO 14971: Medical devices. Application of risk management to medical devices
- ICH Q9: Quality risk management, Scientific guideline
- ICH Q10 Pharmaceutical quality system - Scientific guideline
- Annex 1: 2008_11_25_gmp-an1.doc (europa.eu)
- 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)
- ISO 11607-1:2019: Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly processes (ISO 11607-2:2019)
- BSI's perspective on Article 117 and Drug/ Device Combination: https://bsi.learncentral.com/shop/Course.aspx?id=25841&name=BSI%27s+perspective+on+Article+117+and+drug-device+combinations+webinar
- https://www.packagingdigest.com/medical-packaging/medical-device-packaging-exec-guides-you-through-eu-mdr-compliance

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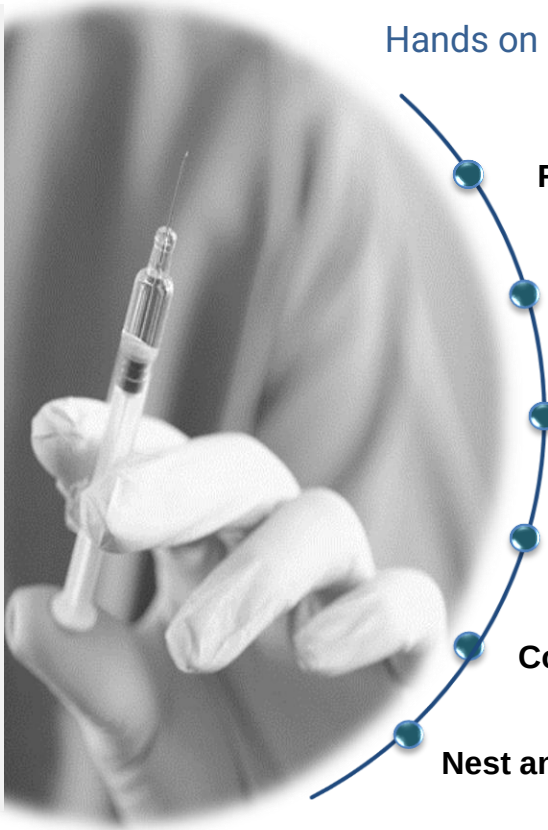

Hands on Session I

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

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Hands-on Session 1

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

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