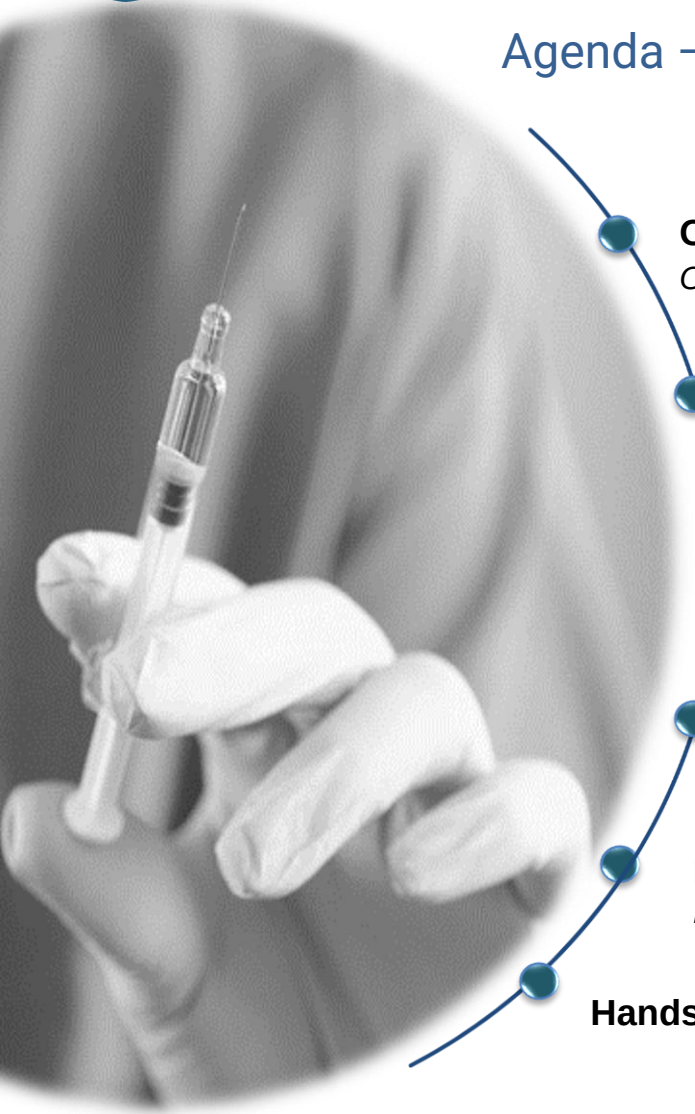
Agenda – DAY 1



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

Barrel forming

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

Needle Assembly

Video

Washing and Siliconization

Washing (WFI)

Siliconization

Closure setting

Nesting/coding
Packaging

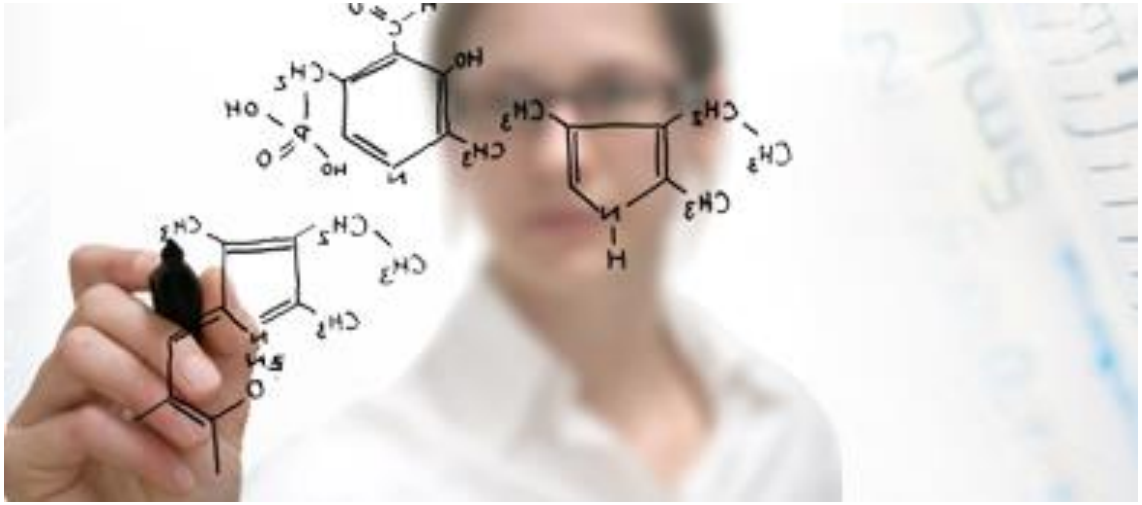
RTF processing
Clean room ISO class 7 acc. class B under laminar flow

- 100 % in-process control
- Quality control

Washing and Siliconization

Video

Sterilization



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*

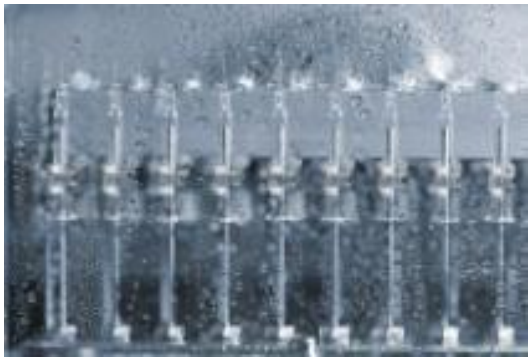
  > ***Interpreted*** as the primary packaging of a finished drug product and treated acc. **21 CFR 211 Subpart E –** Control of Components and Drug Product Containers and Closures:
  > glass, plastic or metal containers, bottles, vials, ampules, screw caps, lids, stoppers, seals, desiccants, fillers,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

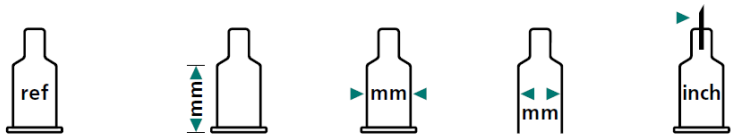
- Ensure compatibility/suitability of containers and closures
- Maintain inventory control
  - identification, storage, handling, sampling, testing
- Written and approved procedures
- Prevent contamination
  - Aseptic Processing cGMPs (high purity for rinse water)
  - Water system validation, USP <1231>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



Regulatory Guidelines

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



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

- 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 -> very complex!

- Medical device Regulation and Combination Products

Regulatory Guidelines
for Pre**fillable** Syringes

Combination Products/ EU Medical Device Regulation regulation not applicable:
Prefill**able** syringe only *becomes* a combination product when filled

- ISO 10040-8 test procedures for filled PFS at pharma site/CMO
- **21 CFR Part 4**
  - Combination product comprises two or more medical products
  - Co- development necessary, e.g. Biologic in a PFS in an AutoInjector
  - Mandatory steps: Design Control, Design History File, Risk Management, Design Verification, Validation, Usability studies

Regulatory Guidelines

for Prefillable Syringes – *not final product yet*

Combination product (USA) development steps:

- Drug characterization
- **Primary container selection**
- Manufacturing, labeling, logistics…

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

Further Reading:

Guidance for Industry and FDA Staff:
Current Good Manufacturing Practice Requirements for Combination Products

FINAL GUIDANCE

Define and select primary packaging container early in development: *the syringe brings the drug into the patient*

Regulatory Guidelines

Medical Device Regulation 2022 – *final drug product*

Pharma Packaging departments require sound data on

1. Improved product handling and storage
2. Reduced risk of contamination
3. Better evidence of integrity
4. Aseptic presentation of devices
5. Usability evaluation

ISO 11607 Part 1 and Part 2 compliance

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)

Aristotle:
The whole is greater than the sum of the parts:

Drug+ Packaging < combination product

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*

Pharma Packaging has to

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

Nothing really new, but…

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

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*

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. Gap assessment 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

Dedicated workshop recommended

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

Risk assessment

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

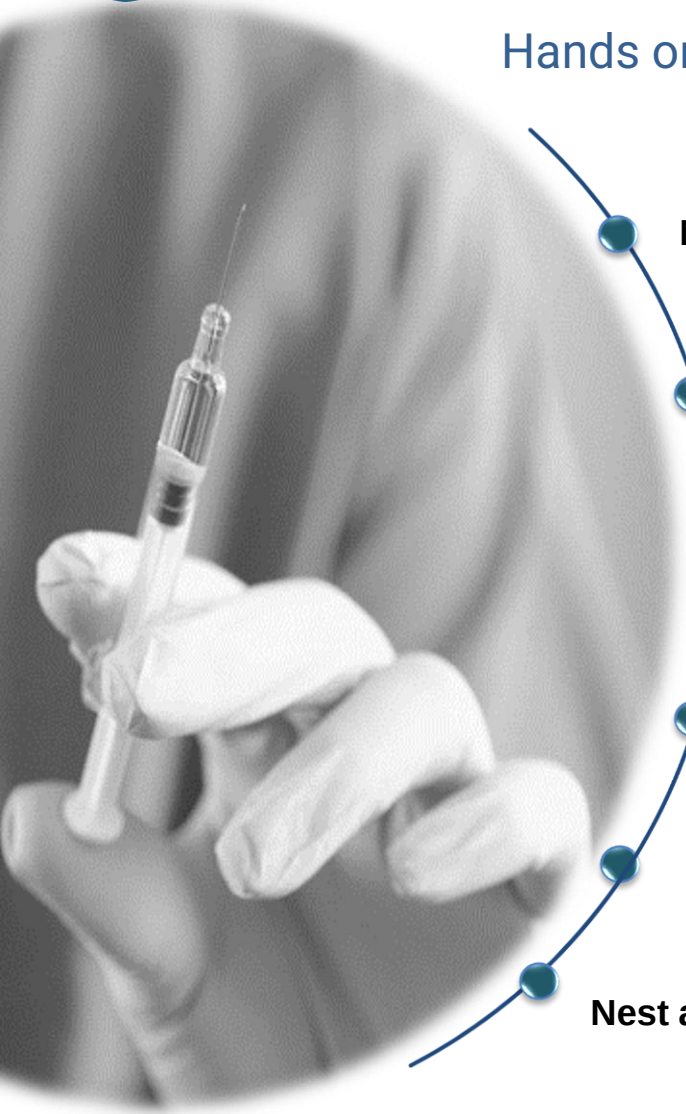
2. Risk factors
   - Material compatibility
   - Duration and distance to drug product contact
   - Surface area/volume
   - Temperature, contact time (storage)
   - …
3. Risk score
   - ICH Q9 Quality Risk Management
   - USP <1665>

Dedicated workshop recommended

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Hands on Session I



- Mount syringe, use syringe – feel and push
- Glass vs. Plasic syringe
- Big Syringe vs. small 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