All about Pre-filled Syringe Systems

From Initial Development to Final Fill Finish

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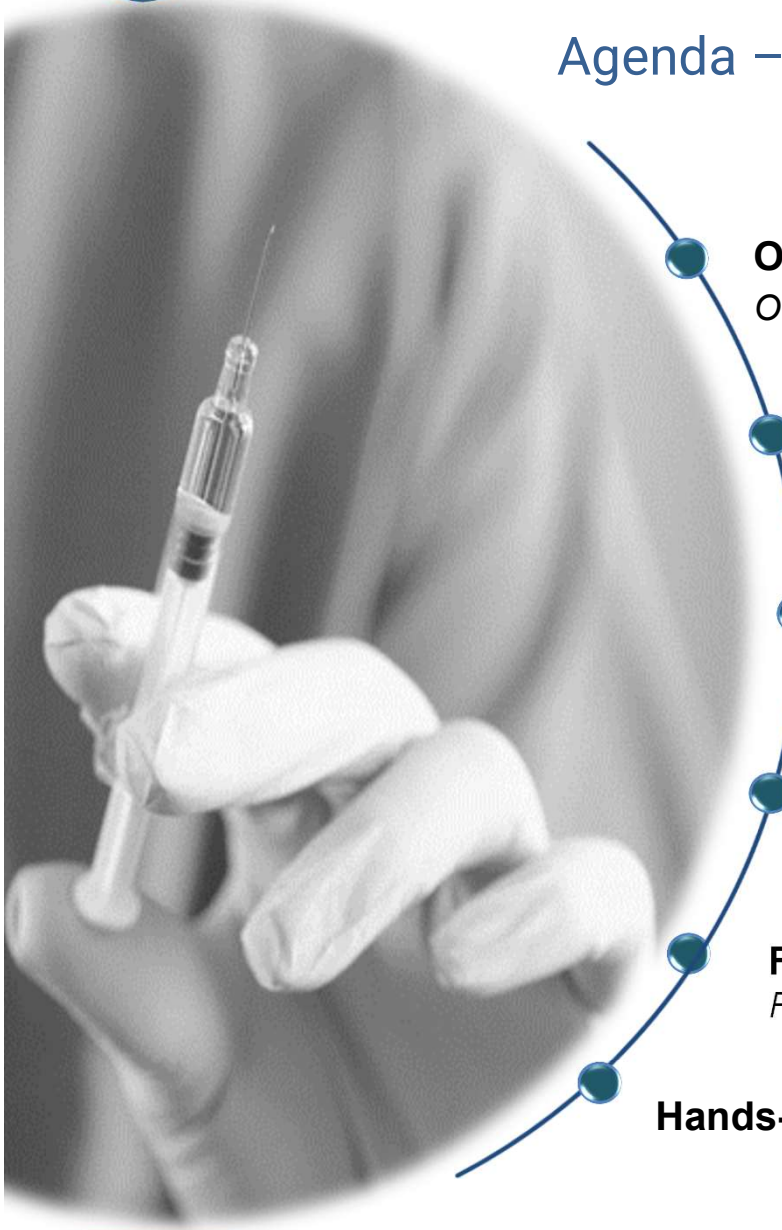
Agenda – DAY 1



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 …

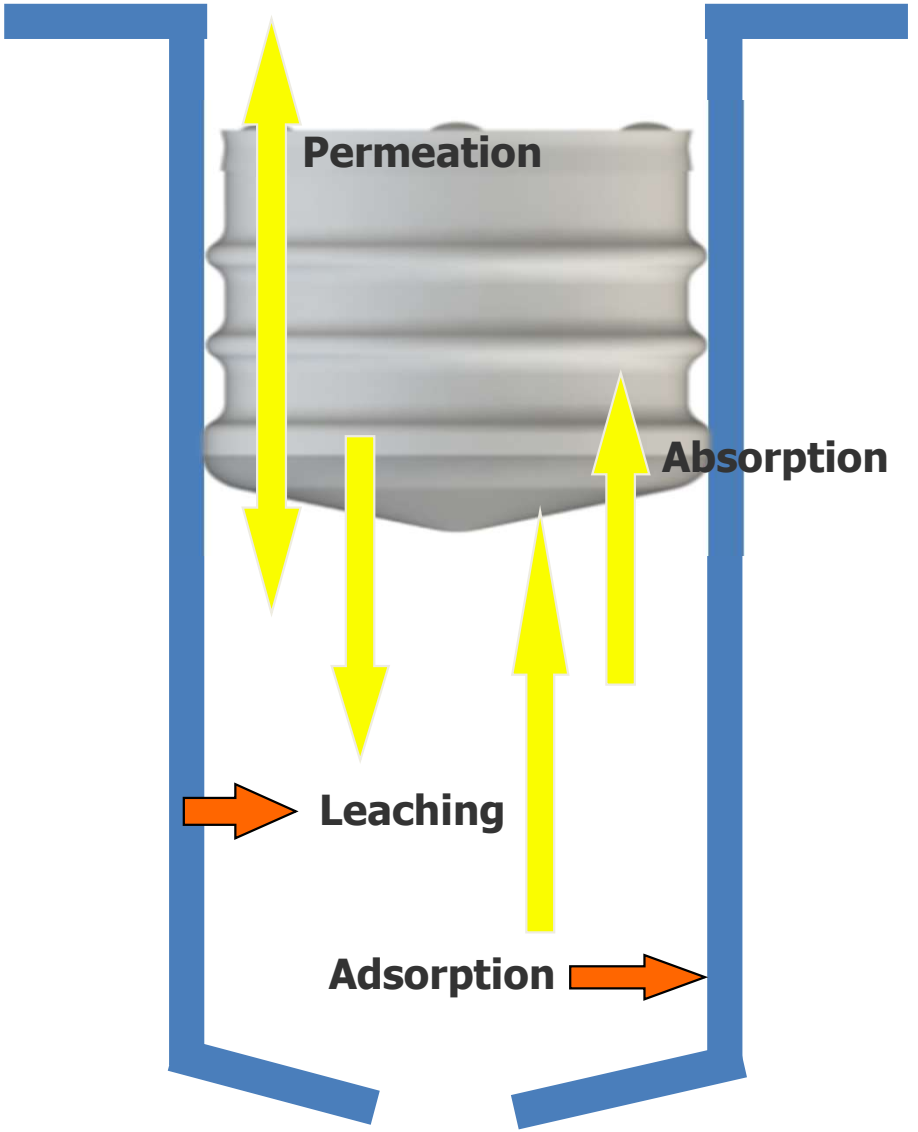
Fill and Finish
Filling • Stoppering • Assembly • Technical Standards

Hands-on Session 1

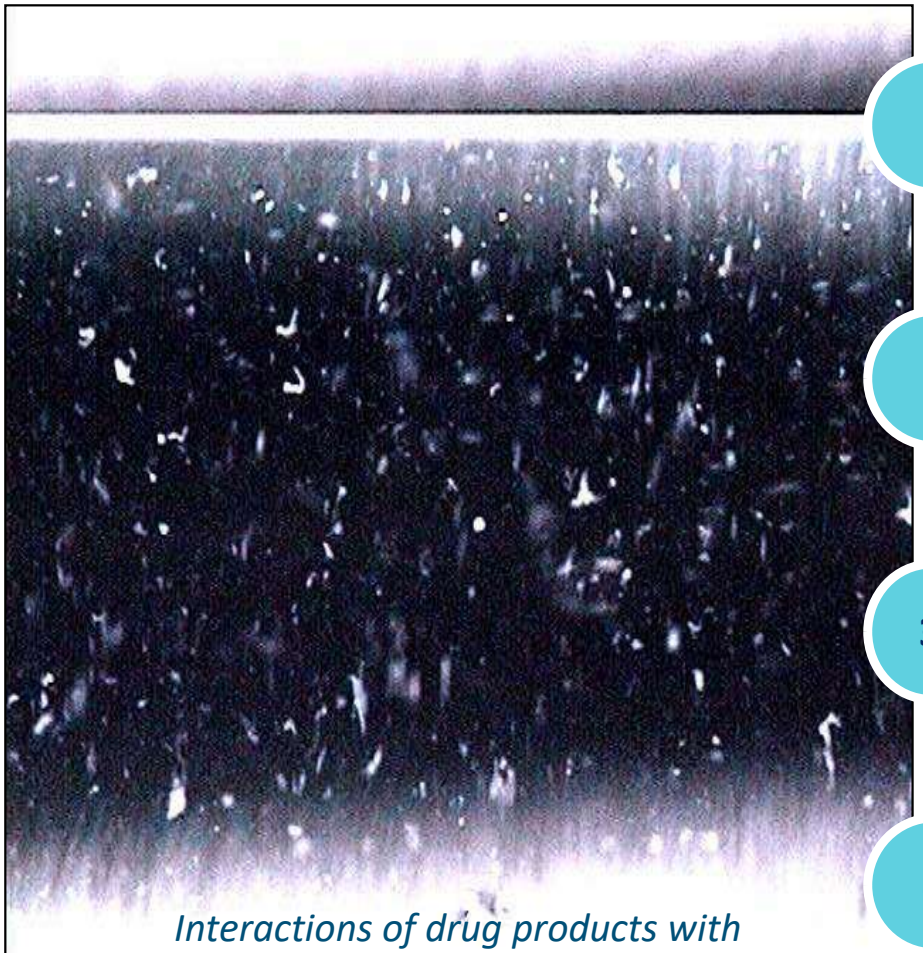
Drug features

- Viscosity, pH, concentration, ionic strength…
- Volume
- Sensitivity
  - Light
  - Oxygen
  - Temperature
  - Particles
  - Silicone oil
  - Storage
  - Vibration
  - Shear forces
  - Rubber components
  - Tungsten, glue, steel

Possible Interaction of Drug Product and Elastomeric Closures



Observed Interactions of Proteins with Pharmaceutical Elastomers



Interactions of drug products with formation of particles

1. Aggregation of proteins with silicone oil
2. Adsorption e.g. of Active Product Ingredient [API] at elastomers and container walls
3. Increased immunogenicity (interactions with leachables)
4. Out of Specifications [OOS] results for moisture content (e.g. for lyophilized products)

High Level Definitions

Extractabies

- Organic & inorganic substances in packaging components which can be extracted during forced or worst-case laboratory conditions
- **In theory**, these substances are mobile & have the **potential** to leach from the packaging, but this describes an ideal scenario

Leachables

- Organic & inorganic substances that migrate from primary packaging into the final **drug** product when manufactured & stored under normal conditions
- **In practice**, new substances **may be formed by the chemical interaction** of leachables & the drug product

Patient may be exposed to extractables; Patient will be exposed to leachables

Extractables & Leachables – Risks

Extractables & Leachables may pose risks to Product Quality and Patient Safety

- **Anaphylactic shock due to latex allergy**
- **Extractable elements**
  - Contribution to Elemental Impurities
  - Interaction with active ingredient and/or excipients
- **Leachables may react with the API**
  - Loss of efficacy
  - Safety concerns
- **Leachables may interfere with proteins**
  - Aggregation
  - Denaturing
- **Leachables may inhibit cell growth**

No container closure is free of extractables/leachables.
Risk must be evaluated on a case-by-case basis.

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Drug-syringe Interactions I

Bubbles

- Generated in filling process
- Less bubbles in vacuum stoppering
- Bigger bubble in vent tube stoppering

- Transport test recommended
- Moving bubble during transport
- Potential effect on drug formulation

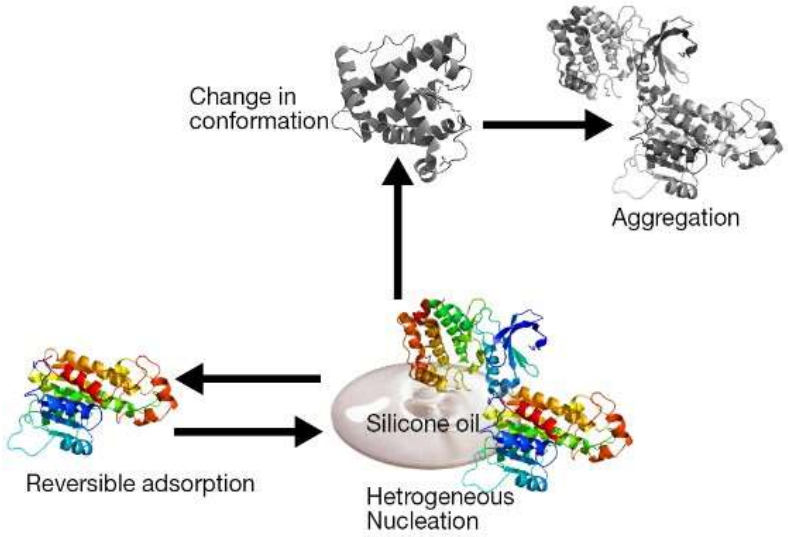
- Expansion and plunger movement risk in air transport (CCI harmed)
- Air means oxygen

Drug-syringe Interactions II

Various interactions possible
- Aggregation
- Degeneration
- Oxidation
- Adsorption

You see
- Precipitation
- Blurring
- Nothing

Triggered by
- Drug formulation itself
- Temperature changes, light, oxygen
- Bubbles and mechanical stress
- Barrel: silicone oil, tungsten, glue, steel
- Elastomer components: cap, stopper



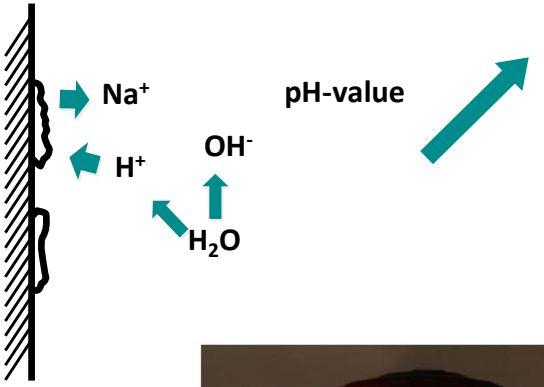
What can be done?
- Stability testing
- Low tungsten
- Low silicone oil
- Extractables profile of rubber components
- Coated plunger stoppers
- Reformulate or stay in vial

Drug-syringe Interactions III

Not seen in syringes – yet another benefit over vials
- pH shift
- Delamination

Why in vials, but not in syringes?
- Vial forming more stressing to glass
- Syringe inside covered by silicone oil
- More aggressive buffers and formulations filled in vials (?)
- Higher pH in vials than in PFS (?)
- PFS normally based on physiologic sodium chlorine solution

Options
- Surface treatment of vials (SiO_2, Ammonium sulphate)
- Special high resistance glass vials, delamination tested
- COP vials
- Reformulate



Test methods and Guidelines I

PDA Technical Report 73

ISO 10040-8

Drug-container interaction

1. Quality throughout shelf life when transported and stored - **stability studies**
2. The impact of components (e.g. needle, tubing)
3. **Extractables/leachables**, e.g residuals from forming, molding, assembly process, gluing, sterilization process, rubber ingredients, impurities and degradation products, free silicone, labels
4. Compatibility, e.g. loss of potency of the drug, adsorption, degradation of the drug, change of stability indicating parameters
5. Effect of shear forces
6. **Biological hazard assessment** for the finished prefilled syringe following, e.g. ISO 10993-1

Test methods and Guidelines II

PDA Technical Report 73

ISO 10040-8

Drug-container interaction

7. The container closure system shall maintain **sterility** throughout its shelf life including transportation

8. **Endotoxin** levels specified

9. The container closure system shall ensure **integrity** throughout filling, terminal sterilizations, further manufacturing steps, storage and transportation to ensure content sterility and to prevent leakage

10. **Deliverable volume** from the finished prefilled syringe shall comply with the required or labelled drug dose

11. **Particles** (visible and subvisible) see pharmacopoeias