All about Pre-filled Syringe Systems

From Initial Development to Final Fill Finish

Drug-Syringe interactions

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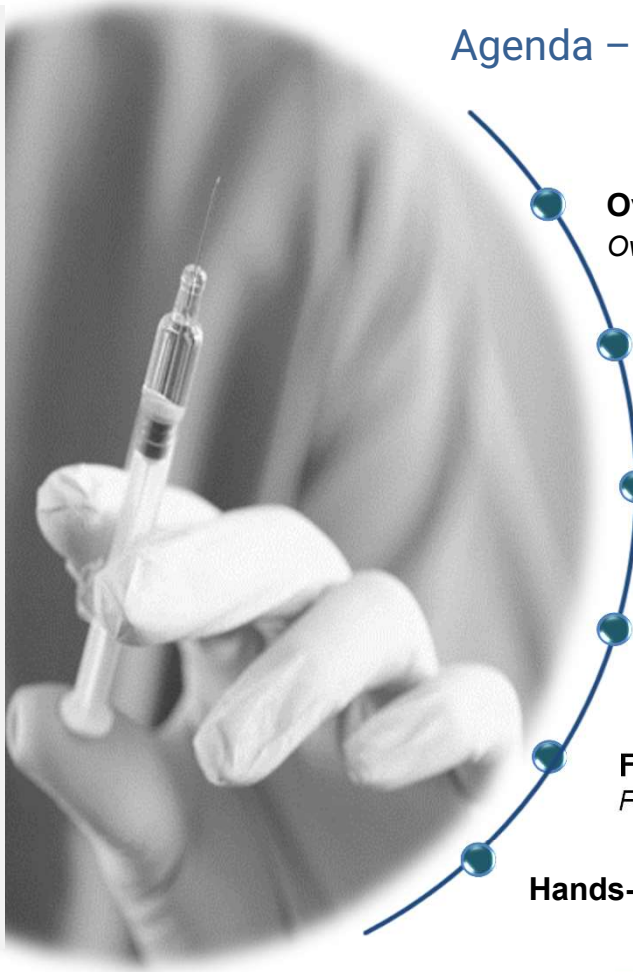
PDA Parenteral Drug Association

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

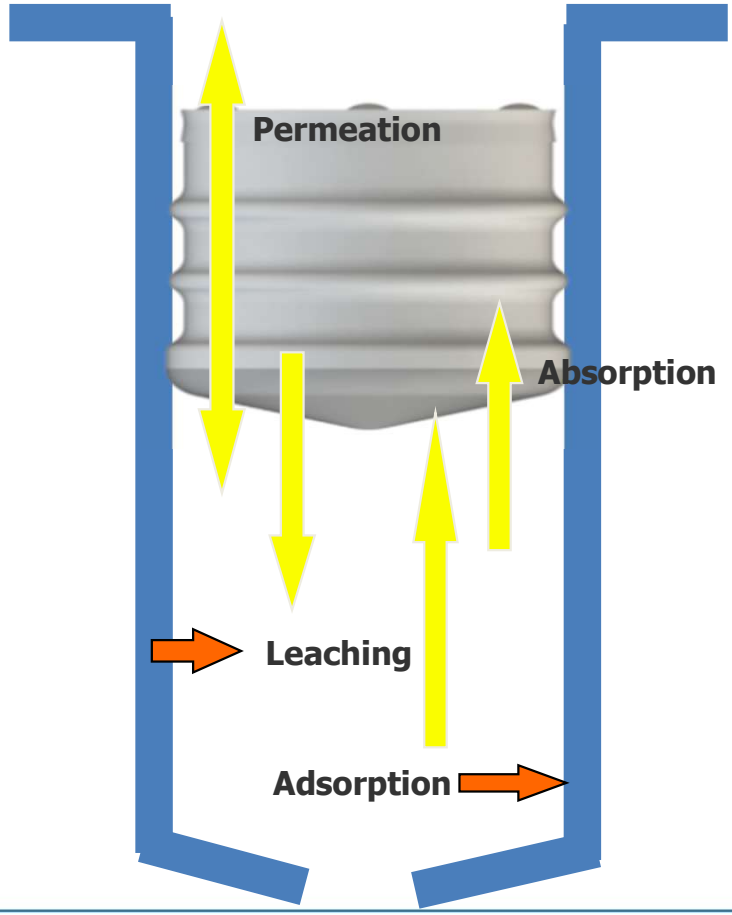
Drug features and possible interactions with syringe components

- Viscosity, pH, concentration, ionic strength, buffer…
- Volume - contact surface of formulation to container
- Sensitivity
  - Light
  - Oxygen
  - Temperature
  - Particles
  - Silicone oil
  - Storage
  - Vibration
  - Shear forces
  - Rubber components
  - Tungsten, glue, steel…
  - Terminal Sterilization
  - Handling in F&F, mixing, pumping

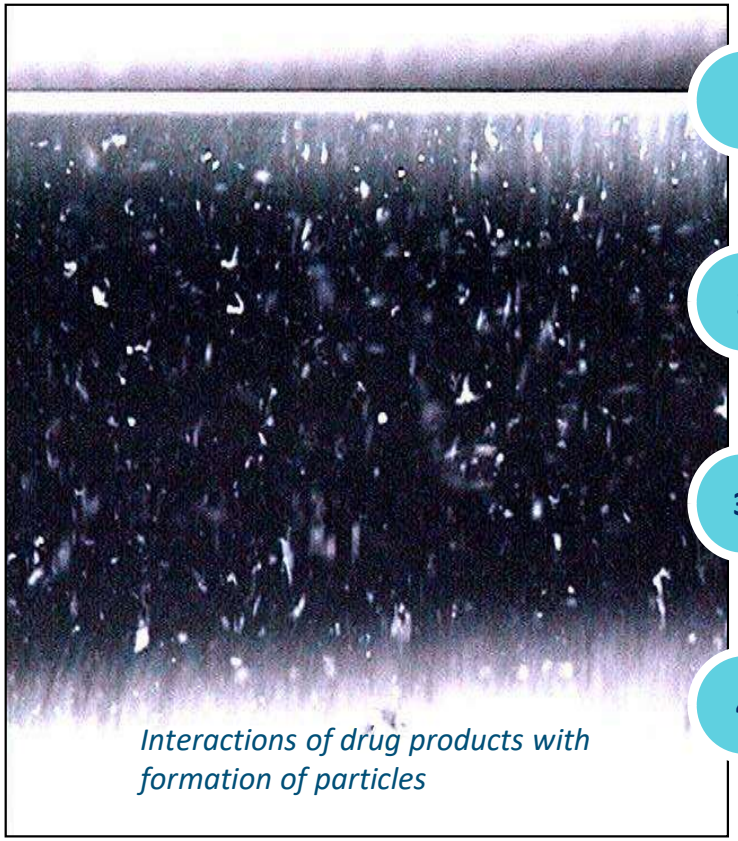
Composition of a formulation in a PFS

- API
- Water
- Buffer
- Tonicity Agent
- Surfactant
- Antioxidant
- …

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

Extractables

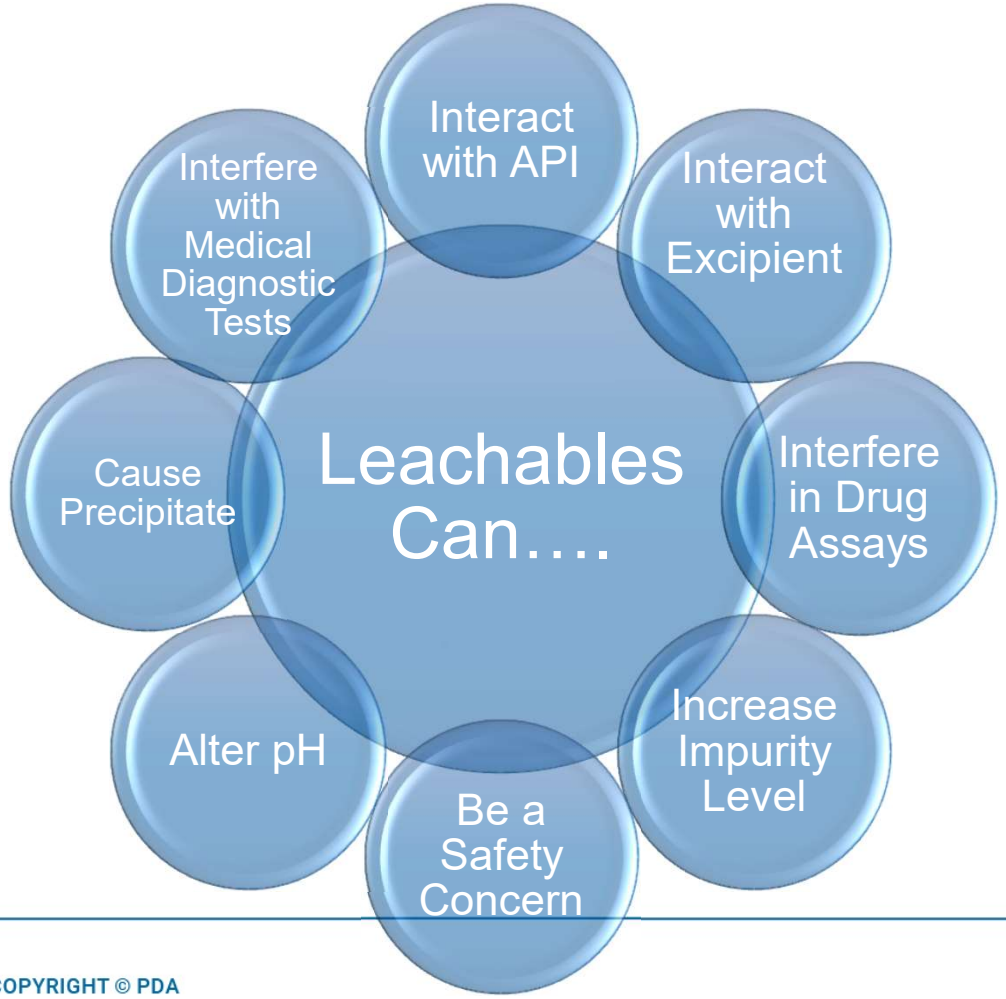
- Organic & inorganic substances in packaging components which can be extracted during forced or worst-case laboratory conditions
- **In theory**, these substances are mobile & have the **potential** to leach from the packaging, but this describes an ideal scenario

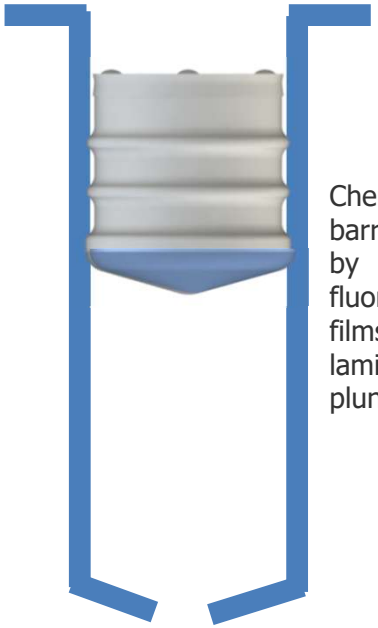
Leachables

- 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

Leachables





Chemical barrier formed by fluoropolymer films laminated to plungers

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.

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

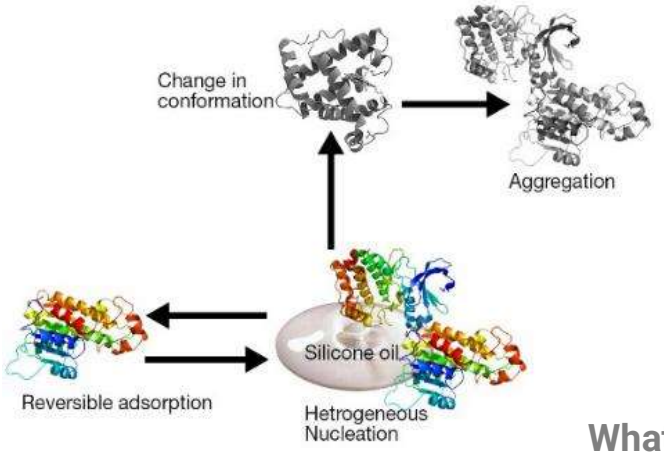
- Expansion and plunger movement risk in air transport (CCI harmed)
- Air means oxygen

Drug-syringe Interactions II

Various interactions possible
- Aggregation - e.g. with silicone oil
- Degeneration – temperature, transport
- Oxidation - plastic barrel, air bubble
- Adsorption - barrel surface

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



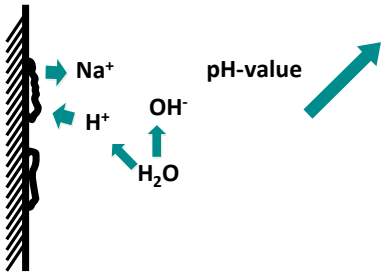
What can be done?
- Stability testing
- Low tungsten
- Low silicone oil
- Extractables profile of rubber components
- Coated plunger stoppers
- Reformulate or stay in vial

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

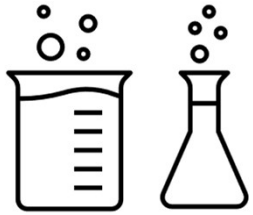
ISO 10040-8

ICHQ1A

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

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months



Test methods and Guidelines II

PDA Technical Report 73

ISO 10040-8

ICHQ1A

Drug-container interaction

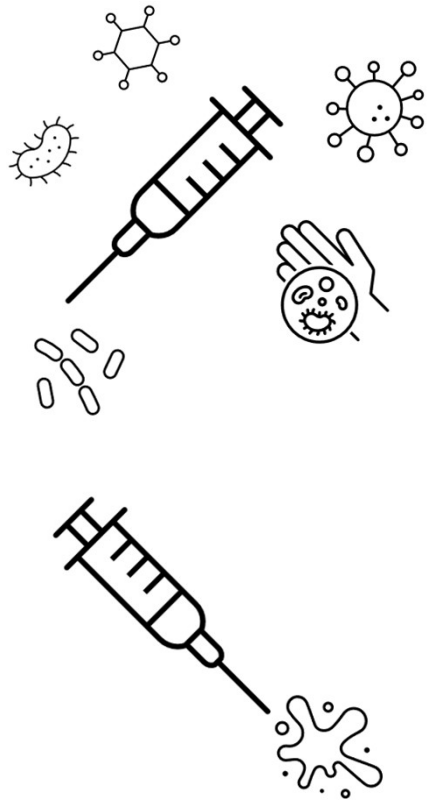
7. The container closure system shall maintain **sterility** throughout its shelf life including transportation

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



Summary - Drug-syringe interaction

- Drug and container can interact in many ways
- Effects on syringe performance possible
- Effects on drug quality possible
- All container materials to be evaluated
- Fill and Finish Process to be investigated
- Stability and Transport studies to be carried out

Sources

- Effect of Various Silicone Oil And Tungsten Levels on the Stability of a Monoclonal Antibody in Nine Commercially Available Prefilled Syringes. Markela Ibo Murphy, Jesse A. Leissa, Sandra B. Plata, Amy L. Chamberlain, Sajal M. Patel. March 16, 2023
- https://doi.org/10.1016/j.xphs.2023.03.009
- Characterization of Subvisible Particles in Biotherapeutic Prefilled Syringes: The Role of Polysorbate and Protein on the Formation of Silicone Oil and Protein Subvisible Particles After Drop Shock. Nancy Jiao, Gregory V. Barnett, Twinkle R. Christian, Nathan H. Joh, Marisa K. Joubert, Shawn Cao, November 02, 2019. https://doi.org/10.1016/j.xphs.2019.10.066
- The Impact of Syringe Age Prior to Filling on Migration of Subvisible Silicone-Oil Particles into Drug Product. Jing Song, Guangli Hu, Hassen Hamzaoui, Steven C. Persak, Hanmi Xi, Yongchao Su, September 19, 2022, DOI:https://doi.org/10.1016/j.xphs.2022.09.015
- Silicone oil induced aggregation of proteins: LaToya S. Jones, Allyn Kaufmann, C. Russell Middaugh, 25 February 2005 https://doi.org/10.1002/jps.20321
- Silicone Oil- and Agitation-Induced Aggregation of a Monoclonal Antibody in Aqueous Solution. Renuka Thirumangalathu, Sampathkumar Krishnan, Margaret Speed Ricci, David N. Brems, Theodore W. Randolph, John F. Carpenter, https://doi.org/10.1002/jps.21719
- Silicone-oil-based subvisible particles: their detection, interactions, and regulation in prefilled container closure systems for biopharmaceuticals. Flora Felsovalyi, Sébastien Janvier, Sébastien Jouffray, Hervé Soukiassian, Paolo Mangiagalli, PMID: 23023774 10.1002/jps.23328
- PDA Technical Report No. 73 (TR 73) Prefilled Syringe User Requirements for Biotechnology Applications (single user digital version)
- ISO 11040-8:2016 - Prefilled syringes — Part 8: Requirements and test methods for finished prefilled syringes
- ICHQ1A Stability testing of new drug substances and drug products - Scientific guideline
- ISO 10993-1:2018 - Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process