All about Pre-filled Syringe Systems

From Initial Development to Final Fill Finish

Technical Aspects

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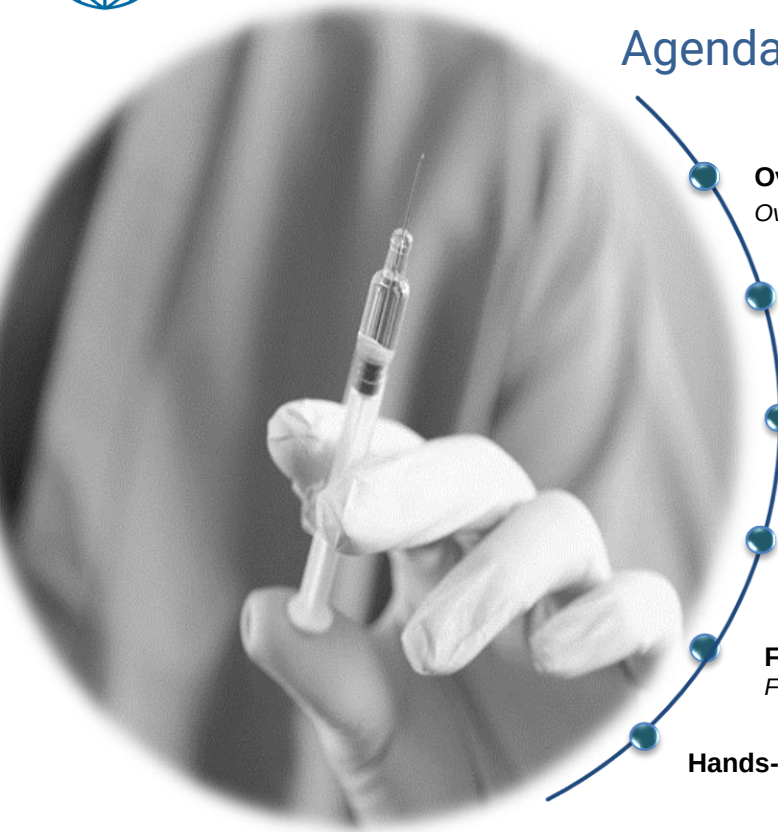
Copenhagen, 25th and 26th April 2024

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

Requirements towards Injections and Ophthalmics*

- Packaging Description is part of the Registration Dossier
- Material in direct contact to the dosage form
- Storage/stability - transport - functionality (prefilled syringe is a device)
- Standards help all stakeholders

Protection

- ✓ Temperature
- ✓ Light
- ✓ Water loss
- ✓ Loss of solvent
- ✓ Oxygen
- ✓ Microbial ingress

Compatibility

- ✓ Adsorption
- ✓ pH change
- ✓ Precipitation
- ✓ Colour change
- ✓ Packaging brittleness

Safety

- ✓ Leachables
- ✓ Extractables
- ✓ Toxicity
- ✓ Glue or ink migration
- ✓ Breakage, drop test

Performance

- ✓ CCI
- ✓ Drug delivery
- ✓ NS pull off
- ✓ Break loose and gliding
- ✓ Usability: elderly people, children
- ✓ Connections

*FDA Guidance Container Closure Systems for Packaging Human Drugs and Biologics

Prefilled Syringes to fulfill many needs

PFS makes the final drug product together with the formulation

- Chemical and pharmaceutical interface

Needs to work seamlessly in F&F

- Technical interface

Syringe is packaging and device at the same time

- Physical interface to user

Formulation - compatibility

- ✓ Stability
- ✓ Volume
- ✓ Concentration
- ✓ Interaction

Fill and Finish- manufaturing

- ✓ Accuracy
- ✓ Viscosity
- ✓ Machinability
- ✓ Stoppering method
- ✓ Plunger rod
- ✓ Label and blister

Patient/HCP - usability

- ✓ Functionality
- ✓ Sterility
- ✓ Leakage
- ✓ Accuracy of Dosing
- ✓ Safety of use
- ✓ Integration into AI

Regulatory Guidelines

Mainly Dimensions and Test methods

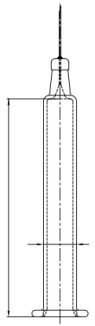
Relevant standards and regulations

- 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

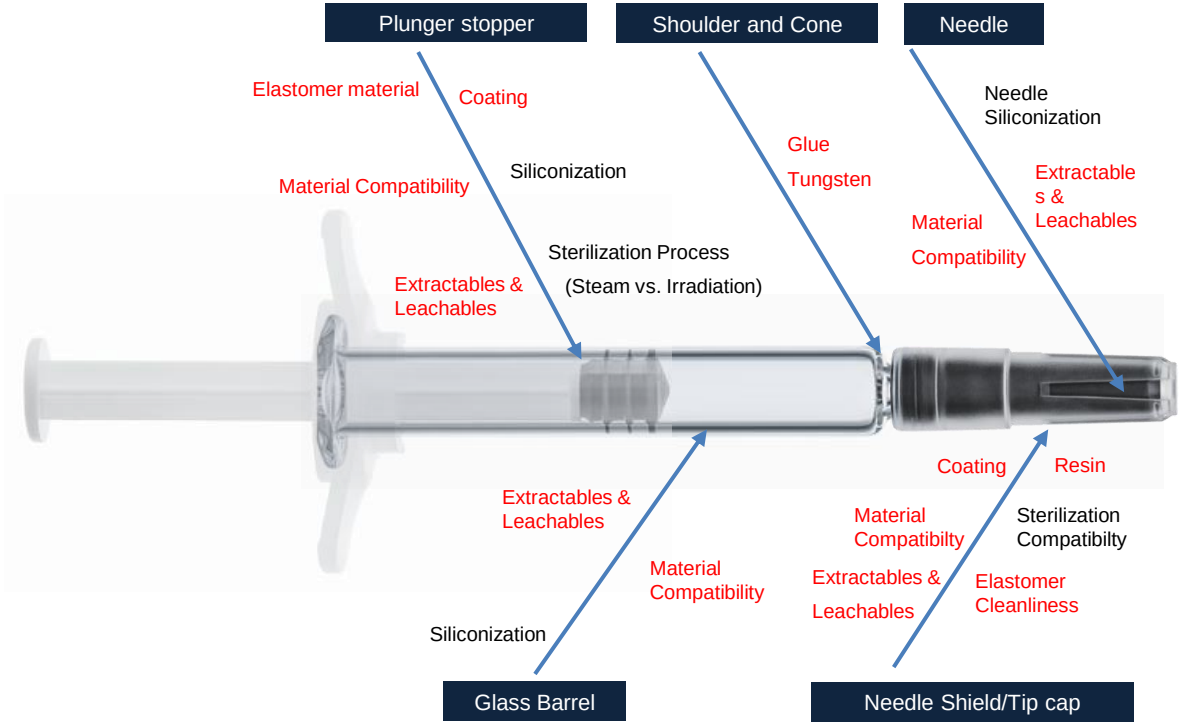
- ISO 9001: Quality management
- ISO 15378: GMP Primary packaging
- 21 CFR 211 Subpart E – Control of Components and Drug Product Containers and Closures
- DMF Type III
- Ph. Eur. USP and JP

- ASTM D4169-22 Shipping
- ASTM D6653-13 Plunger movement
- …

0.5 ml	47.6	6.85	4.65
1.0 ml long	54.0	8.15	6.35
1.0 ml standard	35.7	10.85	8.65
1.5 ml	43.2	10.85	8.65
2.25 ml	54.4	10.85	8.65
3.0 ml	72.2	10.85	8.65
5.0 ml	66.8	14.45	11.85

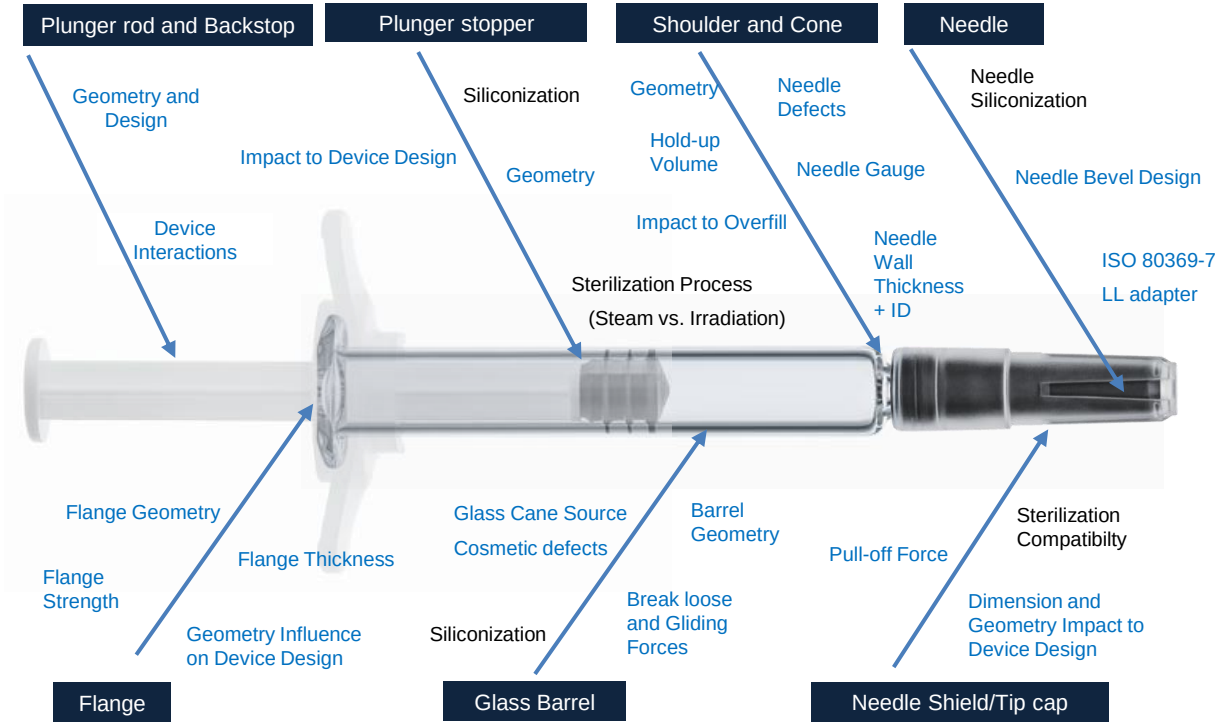


PFS components - Pharmaco-chemical interfaces to the drug



Adapted from David A. Post, Sherwin Shang, Shweta A. Raina,and William Szechinski. Development of Biopharmaceutical Drug-Device Products. PFS characterization and Interaction with Biologic Formulations. AAPS Advances in the Pharmaceutical Sciences Series 35, 2019 - 831 ff

PFS components: Physical interfaces to the drug



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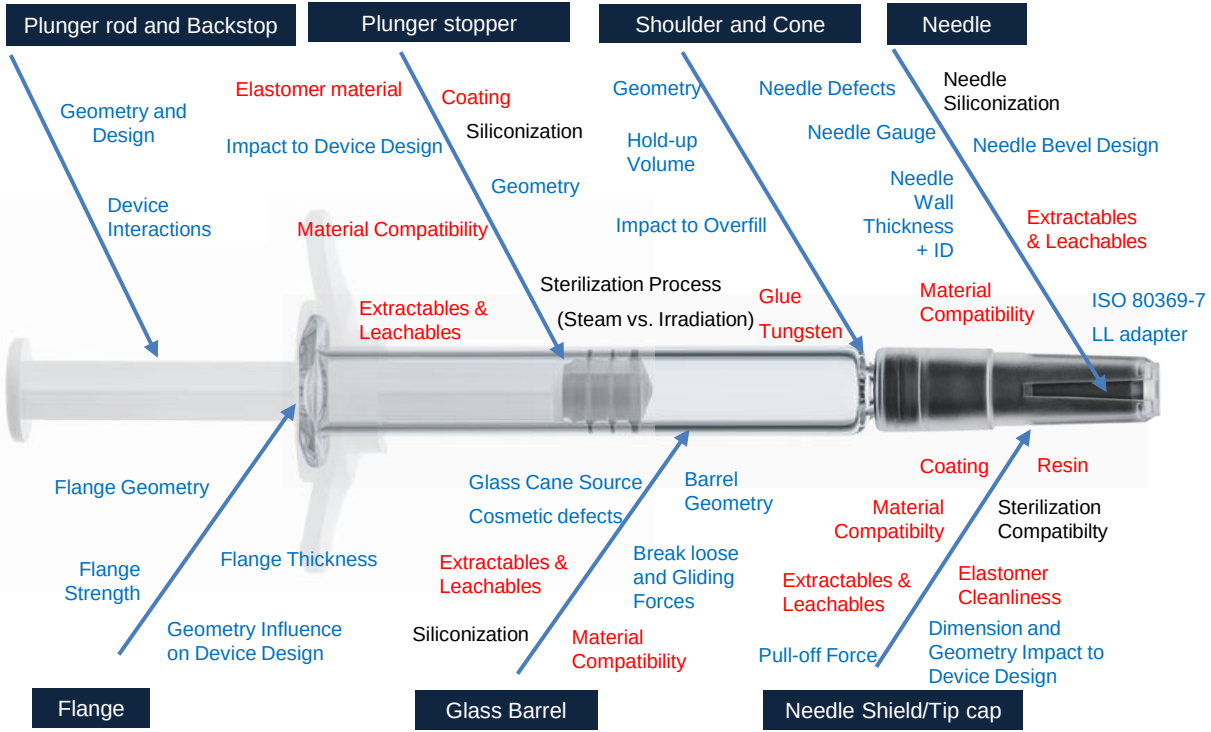
Does the syringe perform well with the formulation?

Finished Drug Product

ISO 11040-8
BioComp
Sterilisation
Sterility
Stability
Fill& Finish
Shipping/ Vibration
Studies

ISO 11040-8 is a good starting point



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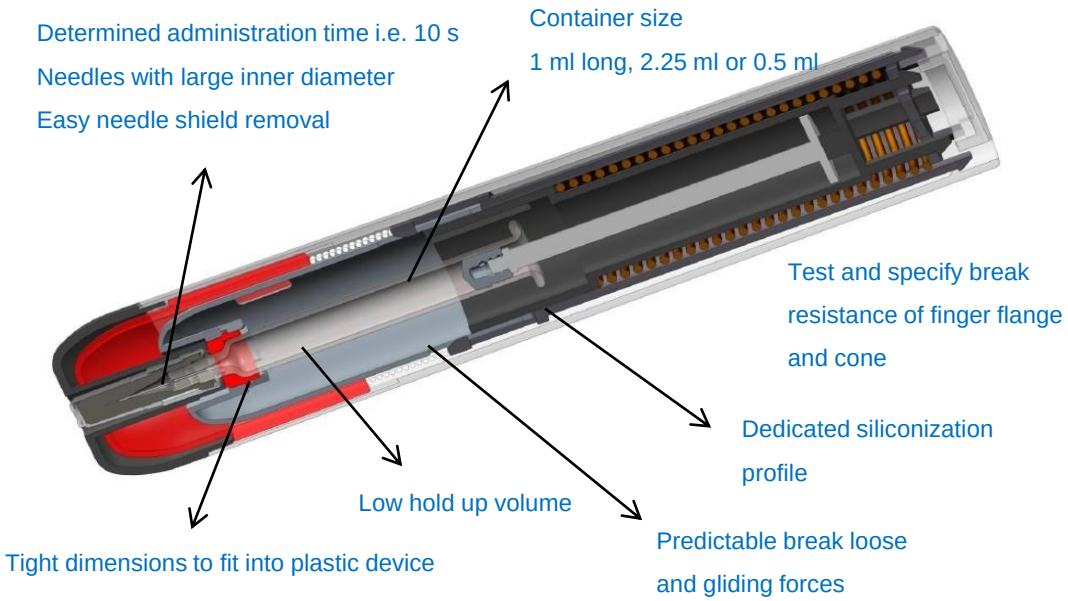
How suppliers can support ISO 11040-8

1. User requirements	*Pharma or supplier data*
Definition of intended use	Pharma
Risk management	Pharma, input from supplier
Application of usability engineering	Pharma
System characterization	Pharma
Description of components and materials Barrel – Flange, barrel, cone, needle, cap	Critical dimesions, Geometry, Strength, Extractables (tungsten, glue, siliconization), Glass source, Cosmetic defects, sterilization, pull-off force cap, CCI cap
Description of components and materials Plunger stoppers	Critical dimensions, Elastomer material Compatibility, Extractables, Coating, Geometry, Siliconization, Sterilization
Additional components: rod, backstop, Autoinjector, safety system…	Pharma: Device interactions of syringe barrel, Luer lock adapter with attached needle, autoinjector, needle safety device
Description of the content of the finished prefilled syringe	Pharma

2. Performance requirements	*Pharma or supplier data*
Break loose and extrusion forces	Pharma, general performance data (water filled syr) from supplier
Burst resistance	supplier
Break resistance: LL, FF	supplier
Closure system forces and torques	supplier
Connectivity with fluid path connectors	supplier
Residual volume	Pharma, general performance data (water filled syr) from supplier
Needle penetration force	Specification of supplier – not with tissue
Needle pull-out force	Specification of supplier
Sharps injury protection requirements	Pharma
Liquid leakage beyond plunger	Pharma, general performance data (water filled syr) from supplier
Markings	Specification of supplier, accuracy t.b.tested by Pharma
3. Pharmaceutical requirements	
Drug-container interaction	Pharma, leachables, shear forces to be tested with drug
Biological requirements	Pharma, general performance data (water filled syr) from supplier
Container closure integrity (plunger)	Pharma, general performance data (water filled syr) from supplier
Deliverable volume	Pharma, general performance data (water filled syr) from supplier
Particles (visible and subvisible)	Pharma, general performance data (water filled syr) from supplier

Available from suppliers – can be supplied/tested without drug
Pharma company input – no or limited data from supplier, drug needed

Syringe system with Autoinjector



Limit of syringes in Autoinjectors

- Dose volume < 3 ml
- Viscosity < 10 cP
- Subcutaneous application
- Mechanical (spring), ~10 s

→Wearables

- Dose volume > 3ml
- Viscosity > 10 cP
- Subcutaneous
- Electric drive, minutes

→Infusion

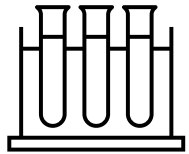
- Intraveneous (vial + disposable syringe)
- home use limited

Advait V Badkar, Rajesh B Gandhi, Shawn P Davis & Michael J LaBarre (2021) Subcutaneous Delivery of High-Dose/Volume Biologics: Current Status and Prospect for Future Advancements, Drug Design, Development and Therapy, 15:, 159-170, DOI: 10.2147/DDDT.S287323

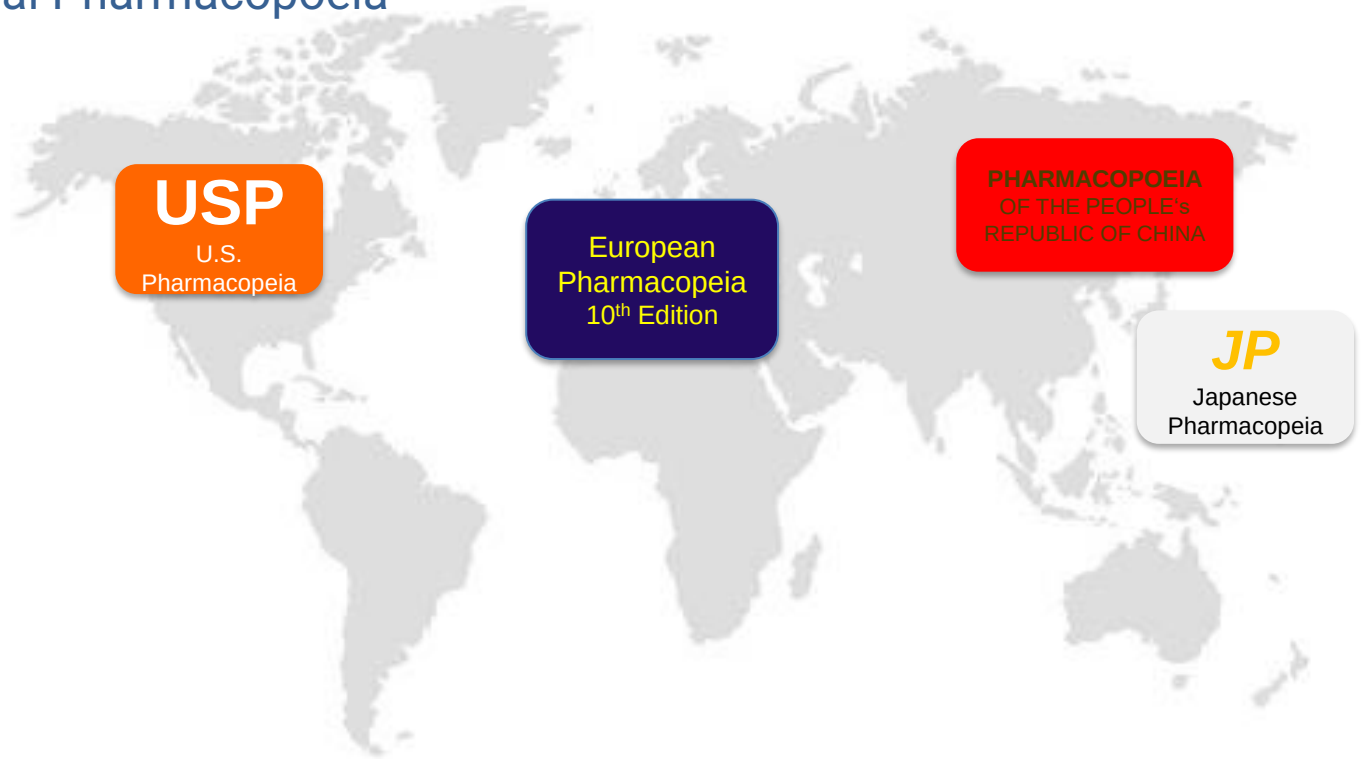
Regulatory Guidelines

ISO 10993-1 to-18
Biocompatibility:
Biological evaluation
of medical devices

1: Evaluation and testing
2: Animal welfare requirements
3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
4: Selection of tests for interactions with blood
5: Tests for in vitro cytotoxicity
6: Tests for local effects after implantation
7: Ethylene oxide sterilization residuals
8: Selection and qualification of reference materials for biological tests
9: Framework for identification and quantification of potential degradation products
10: Tests for irritation and delayed-type hypersensitivity
11: Tests for systemic toxicity
12: Sample preparation and reference materials
13: Identification and quantification of degradation products from polymeric medical devices
14: Identification and quantification of degradation products from ceramics
15: Identification and quantification of degradation products from metals and alloys
16: Toxicokinetic study design for degradation products and leachables
17: Establishment of allowable limits for leachable substances
18: Chemical characterization of materials

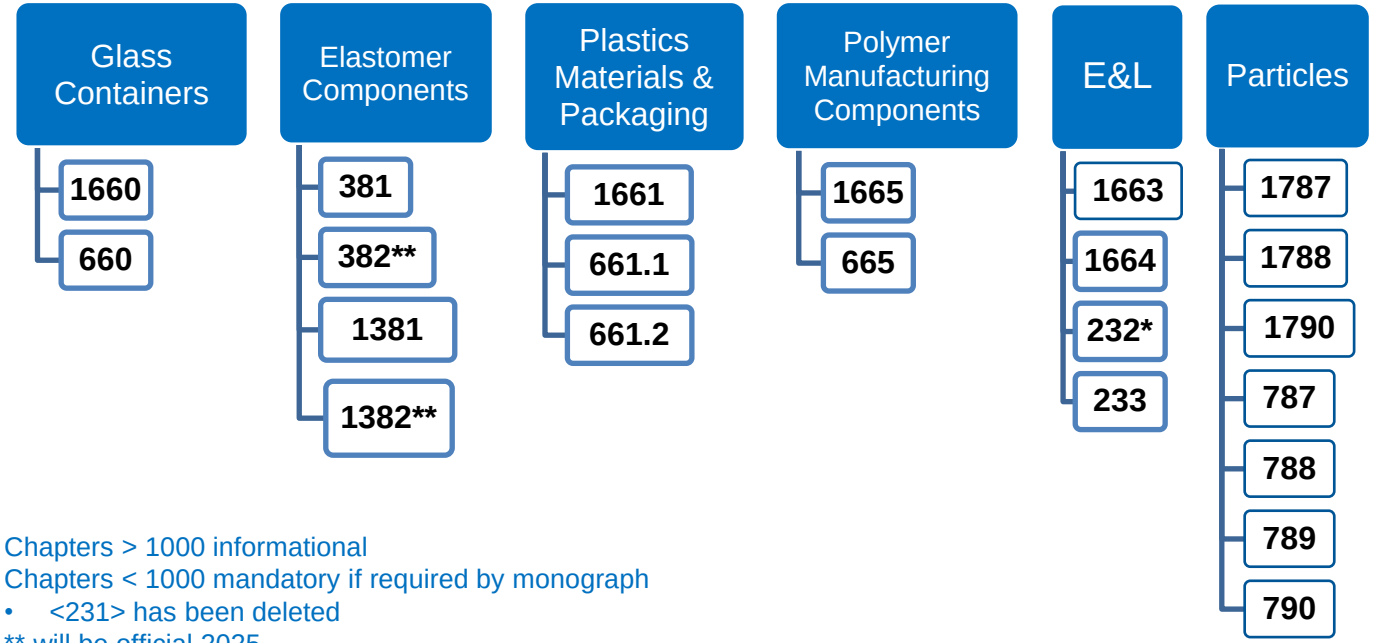


Global Pharmacopoeia



Overview of Relevant USP Chapters

USP
U.S. Pharmacopeia



Chapters > 1000 informational
Chapters < 1000 mandatory if required by monograph
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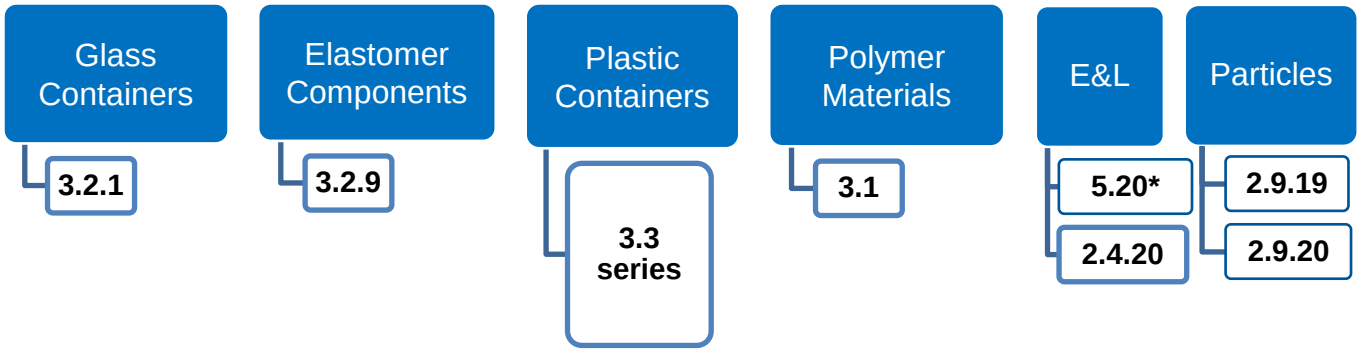
** will be official 2025

Overview of Relevant Pharmacopeia European Chapters

European Pharmacopeia 10th Edition



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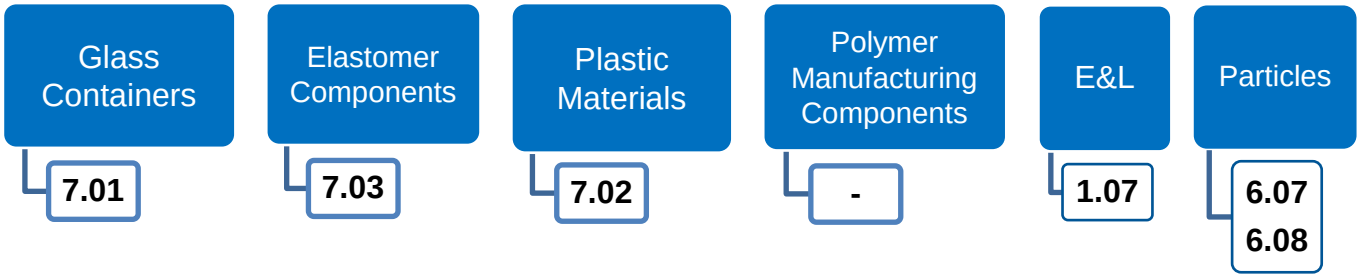
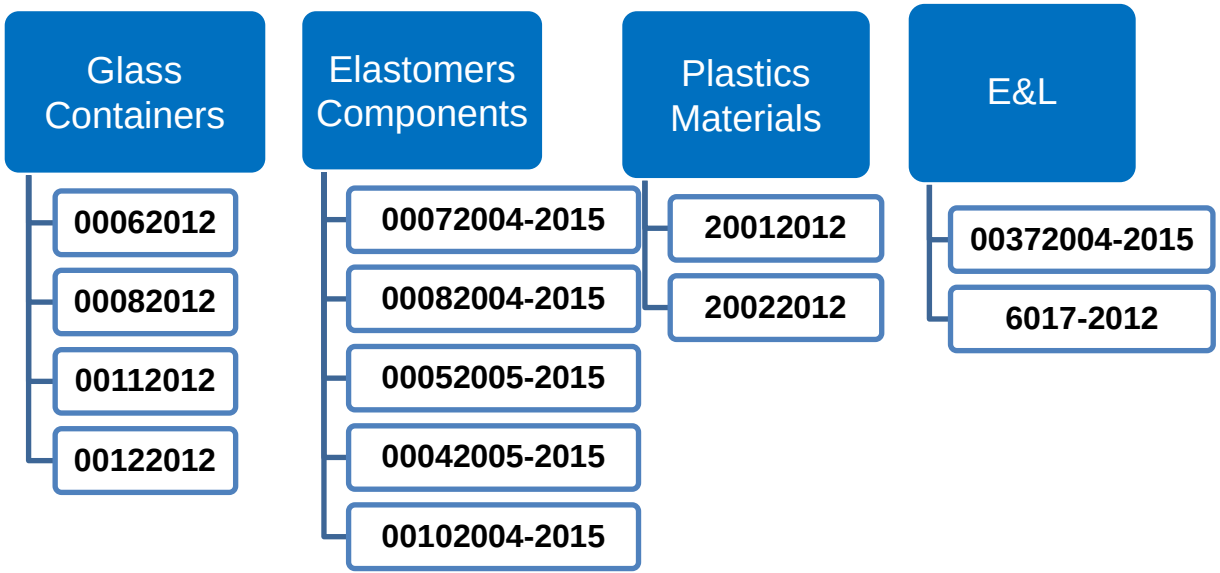
Overview of relevant JP Chapters

JP
Japanese Pharmacopeia



Examples of relevant YBB Standards

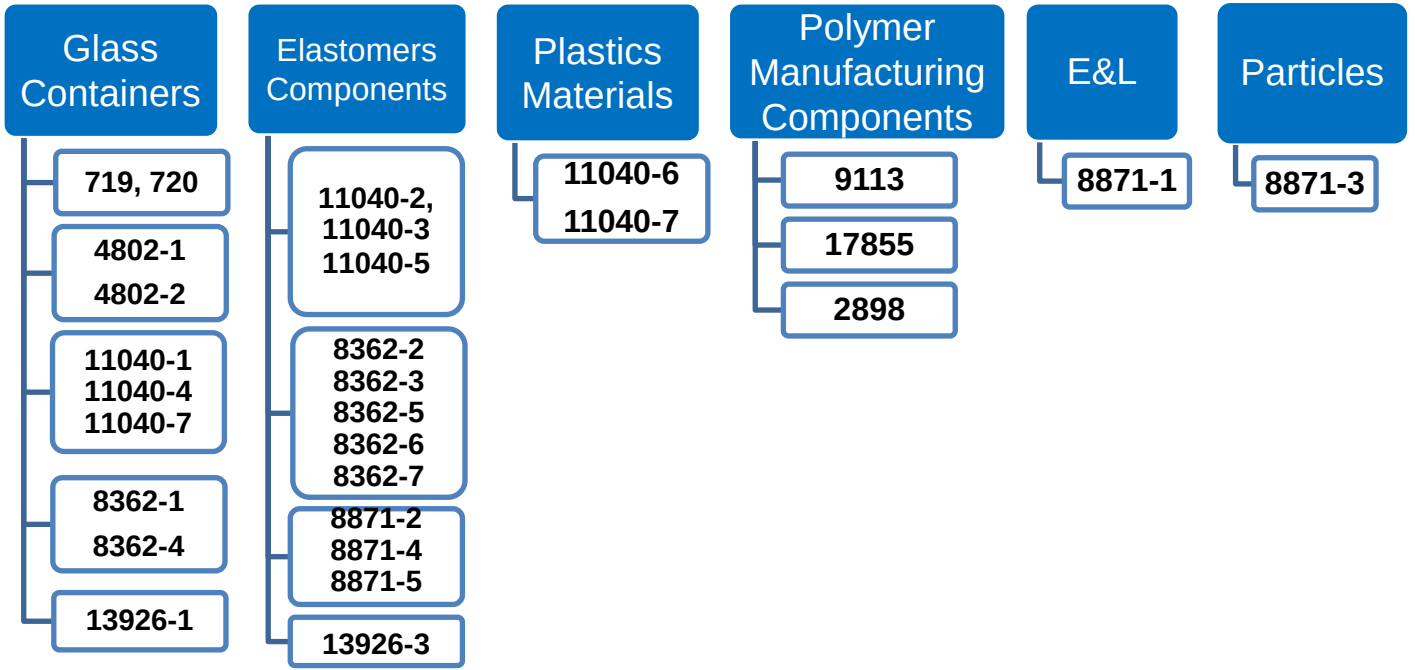
PHARMACOPOEIA OF THE PEOPLE's REPUBLIC OF CHINA



YBB standards are subsequently integrated into ChP for packaging material;
16 already became obsolete when ChP2020 became effective Dec 2020

Extract of relevant ISO Standards

ISO



EU GMP Annex I: at a glance

Background

- Revision of Annex I *Manufacture of Sterile Medicinal Products* of the EU *Guidelines for good manufacturing practices for medicinal products*
- Will be endorsed globally
- Focus on Contamination Control Strategy
- Introduced & strongly recommended RABS & Isolators
- Focus on assurance of Container Closure Integrity
- Knowledge and Experience of the Container Closure System
- Primary Packaging components are also in scope

What does this mean for you

- Need to prove compliance
- Need to have a contamination control strategy document
- Information from suppliers is part of this

16 pages 58 pages

Medical Device Regulation: At A Glance

Background

- Revision of Regulation 2017/745 on medical devices (MDR)
- Prefilled Syringe is a medical device
- MAA needs a Notified Body Opinion (NBOp)
- Need to fulfill Annex I General Safety and Performance Requirements (GSPRs)
- GSPRs have been expanded significantly
- Knowledge and Experience of the Container Closure System
- Primary Packaging components are also in scope

What does this mean for you

- Need to obtain a NBOp
- Information from suppliers is part of this

EMA
&
Notified Bodies

Opinion
GSPRs

GSPR: General Safety and Performance Requirements
NBOp: Notified Bodies Opinion
MAA: Marketing Authorization Applicant

Summary – Technical aspects

- Many physical and chemical factors to consider
- PFS is both drug delivery device and primary packaging container
- Component suppliers become system suppliers
- Regulation for prefilled syringes is complex – start with ISO standards
- Comprehensive documentation and testing necessary
- Risk management:
- Start with ISO standards - finish with risk assessment
- Closer cooperation with component manufacturers necessary in future

Sources

- FDA Guidance Container Closure Systems for Packaging Human Drugs and Biologics
- ISO 11040-4: Glass syringes ready for filling
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- ISO 11040-5: Plunger stoppers
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- Ph. Eur. USP and JP
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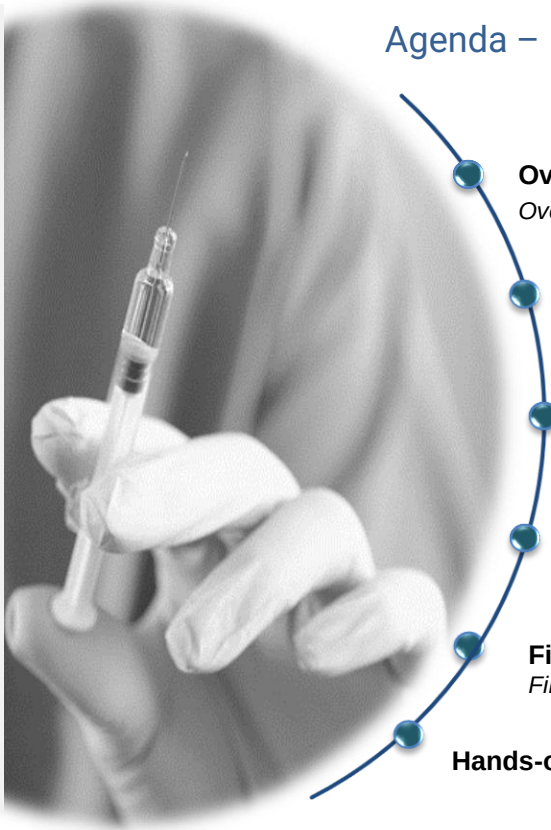
- Subcutaneous Delivery of High-Dose/Volume Biologics: Current Status and Prospect for Future Advancements: Advait V Badkar, Rajesh B Gandhi, Shawn P Davis & Michael J LaBarre (2021), Drug Design, Development and Therapy, 15:, 159-170, DOI: 10.2147/DDDT.S287323
- Structure of Technical Documentation (Medical Devices) (mdc-ce.de)



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

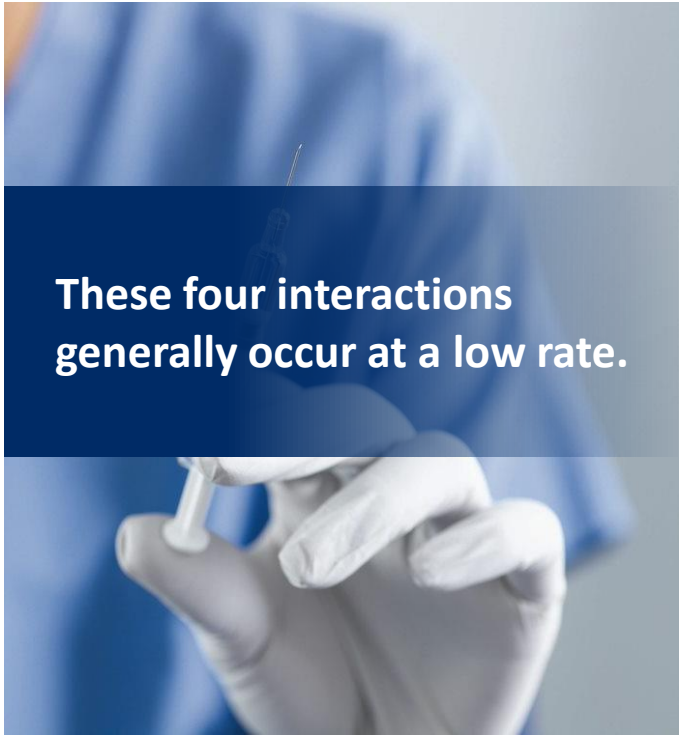
Drug features and possible interactions with syringe components

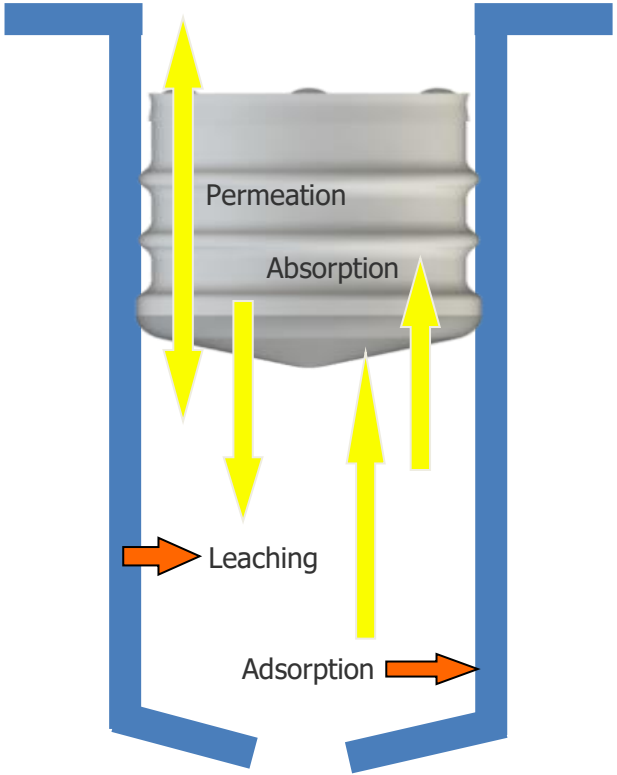
- Viscosity, pH, concentration, ionic strength, buffer…
- Volume - contact surface of formulation to container
- Sensitivity
  - Light
  - Oxygen
  - Temperature
  - Particles
  - Silicone oil
  - Storage
  - Vibration
  - Shear forces
  - Rubber components
  - Tungsten, glue, steel…
  - Terminal Sterilization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

- Interact with API
- Interact with excipient
- Interfere in drug assays
- Increase impurity level
- Be a safety concern
- Alter pH
- Cause precipitate
- Interfere with medical diagnostic tests

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

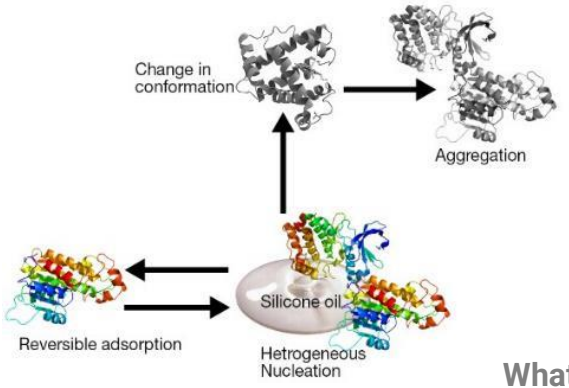
- Expansion and plunger movement risk in air transport (CCI harmed)
- Air means oxygen

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



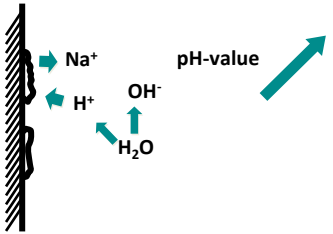
What can be done?
- Stability testing
- Low tungsten
- Low silicone oil
- Extractables profile of rubber components
- Coated plunger stoppers
- Reformulate or stay in vial

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

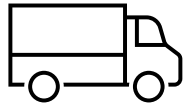
ISO 10040-8

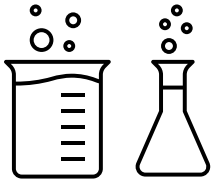
ICHQ1A

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

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ISO 10040-8

ICHQ1A

Drug-container interaction

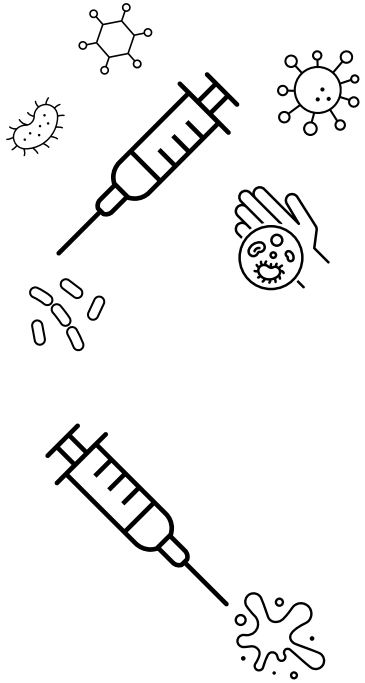
7. The container closure system shall maintain **sterility** throughout its shelf life including transportation

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