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All about Pre-Filled Syringe Systems

From Initial Development to Final Fill Finish

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Technical Aspects of Prefilled Syringes Regulatory and Pharmaceutical Aspects

Christa Jansen-Otten, Bernd Zeiss

23-24 October 2025

Vienna, Austria

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Agenda –
DAY 2

Technical Aspects of Prefilled Syringes
- Syringe meets formulation
- Physical performance
- Pharmaco-chemical performance

Regulatory and Pharmaceutical Aspects
- Short overview on regulatory guidelines and technical standards: EU / US / ISO / …
- Short overview and Introduction into Drug-Syringe Interactions

Manufacturing Aspects Regarding Filling, Finishing and Assembly
- Rod insertion and labeling
- Combi filling
- Robot filling
- New trends

Introduction into Autoinjectors

Questions and Answers

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Requirements towards Injections

and Ophthalmics

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

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

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

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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

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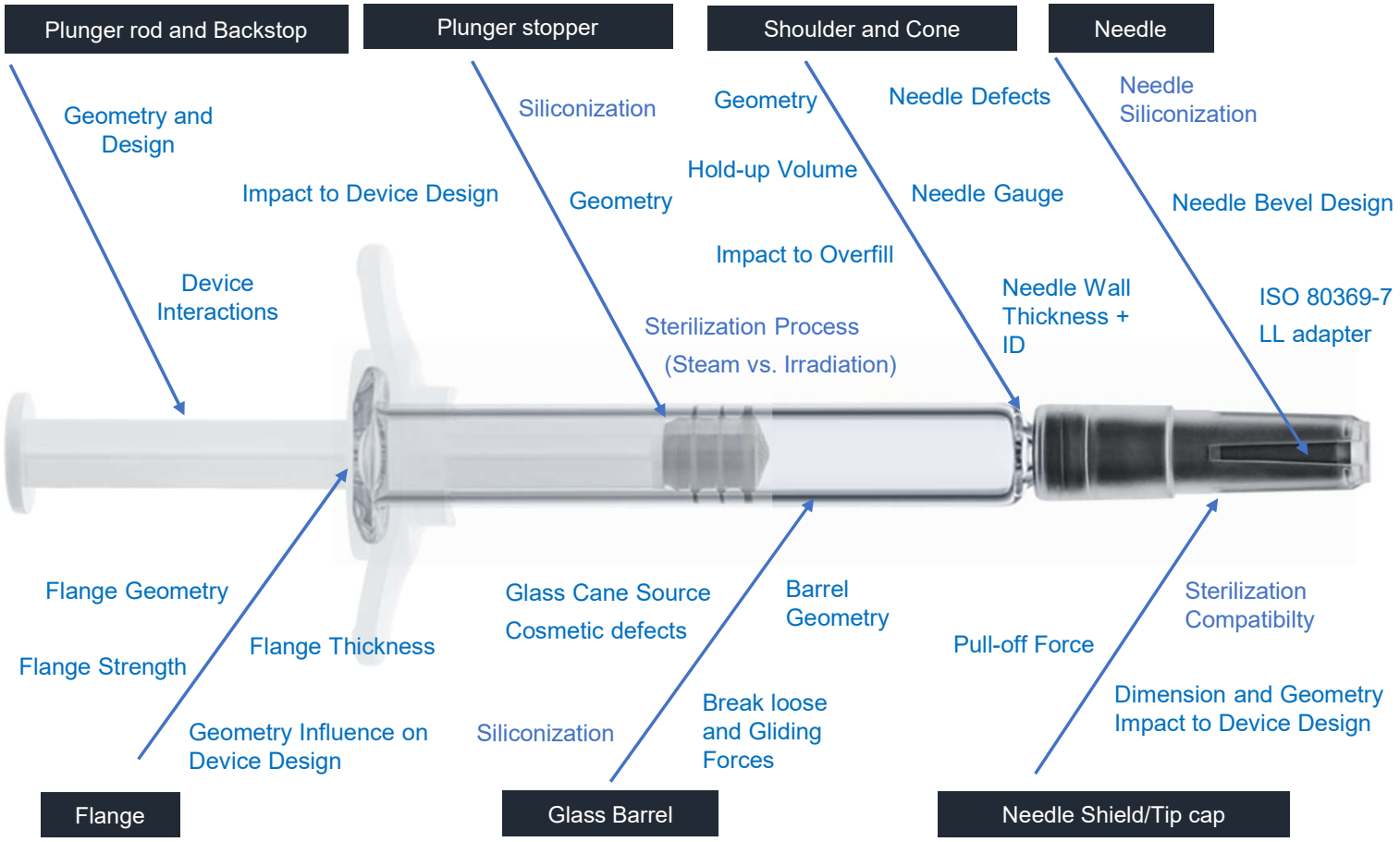
PFS components
Physical interfaces to the drug

Functionality: How do the components and drug substance work together



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

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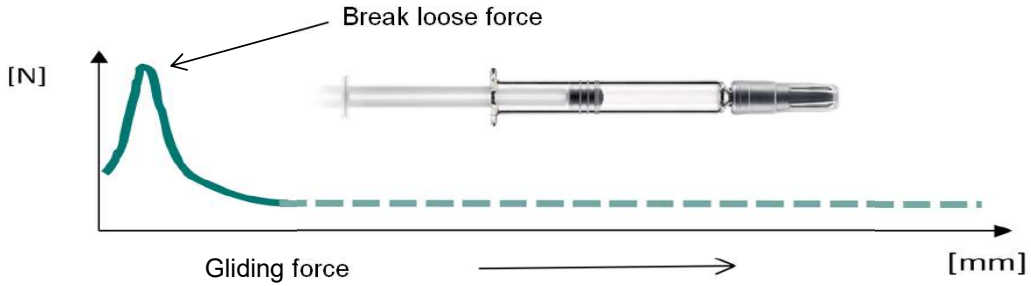
Break-loose and Gliding Force

Parameters influencing break loose and gliding forces:

- Syringe type (inner diameter, length)
- Stoppers used (rubber formulation, diameter, length, design, siliconization/coating)
- Plunger placement method
- Viscosity of the drug
- Needle diameter (gauge, inner diameter) and length
- Type and amount of syringe barrel siliconization
- Testing or application velocity
- Storage time and conditions



Hagen-Poiseuille equation:

$$F = \frac{8 * Q * \eta * L}{\pi * R^4 * A}$$

Formula valid for Newtonian fluids with F – frictionless travel force; Q – volumetric flow rate; η – fluid viscosity; L – needle length; R – needle inner diameter; A – cross sectional area of syringe plunger

Example: constriction of inner diameter of 10% leads to a reduction of throughput of 34%; a pressure raise of 52% would be needed to maintain original throughput

Gotthilf Hagen
1797-1884

Jean Marie Poiseuille
1797 - 1869

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Break-loose and Gliding Force

Empty syringe - ISO 11040-4

Lubrication test:

Annex E (informative)

Glide force test method to evaluate syringe lubrication

E.3.1 Universal tensile and compression testing machine complying with the following:

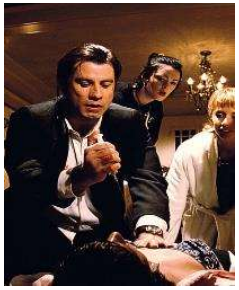
- test speed of 100 mm/min or as appropriate
- NOTE Definition of test speed and force range is subject to agreement between the manufacturer and the customer

Intended use examples:

Mass Vaccination?

or

Emergency Injection?



Filled Syringe - ISO 11040-8

No dedicated limits or rules for filled syringes

Placebo tests possible in R&D for device layout and syringe system verification:

- Reasonable test speed of 250-350 mm/min
- Basic parameters of liquid needed
- Integration into needle-based injection system (NIS)?

Break-loose and extrusion force testing shall be conducted with the final system as ***intended for use***. For the tests, the

- temperature same as for application
- forces might change over shelf life
- Test speed shall be defined based on the ***intended use*** (injection duration, content properties e.g. viscosity)

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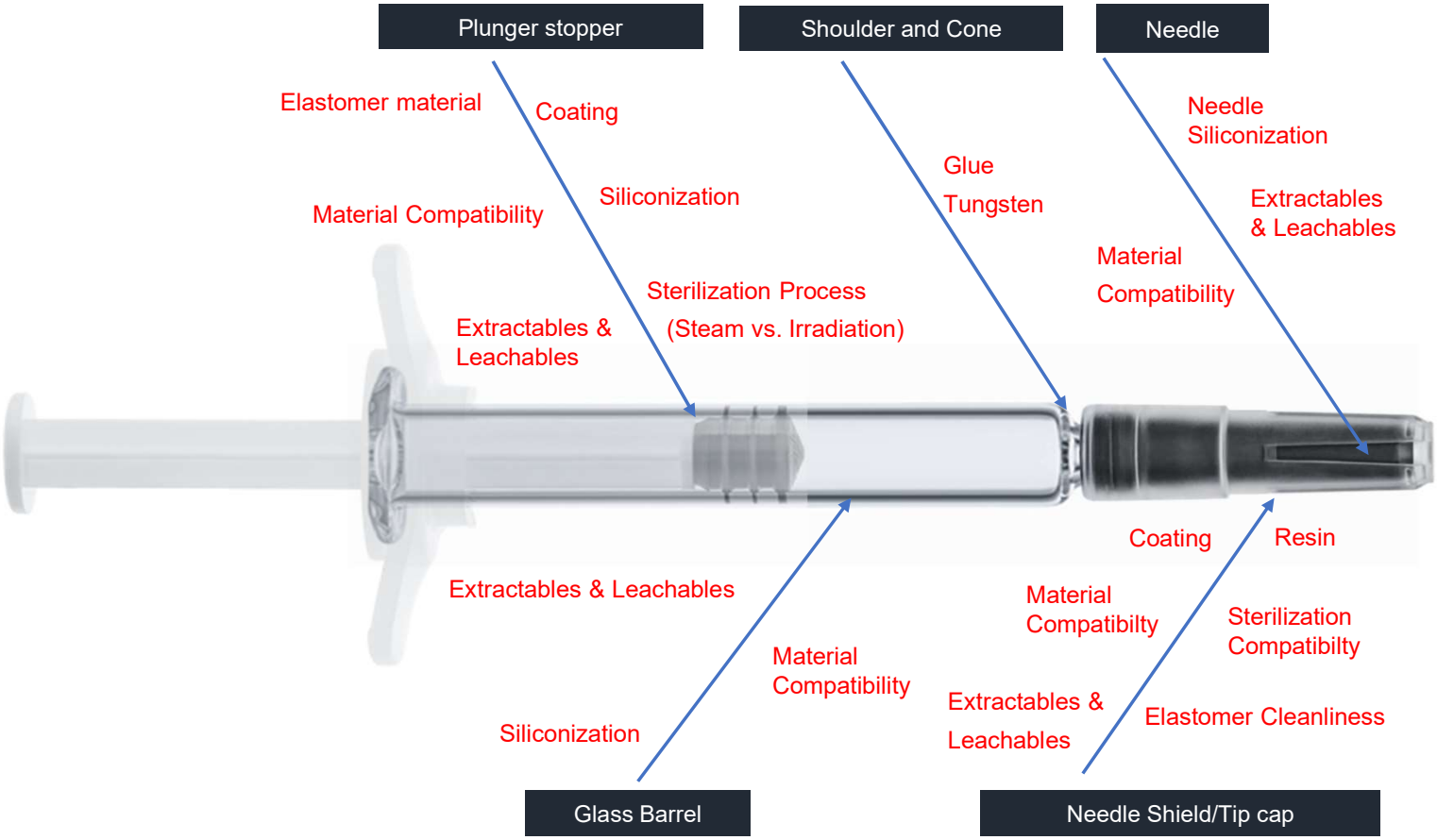
PFS components – Pharmaco-chemical interfaces to the drug

Interaction: How do components and drug substance influence each other



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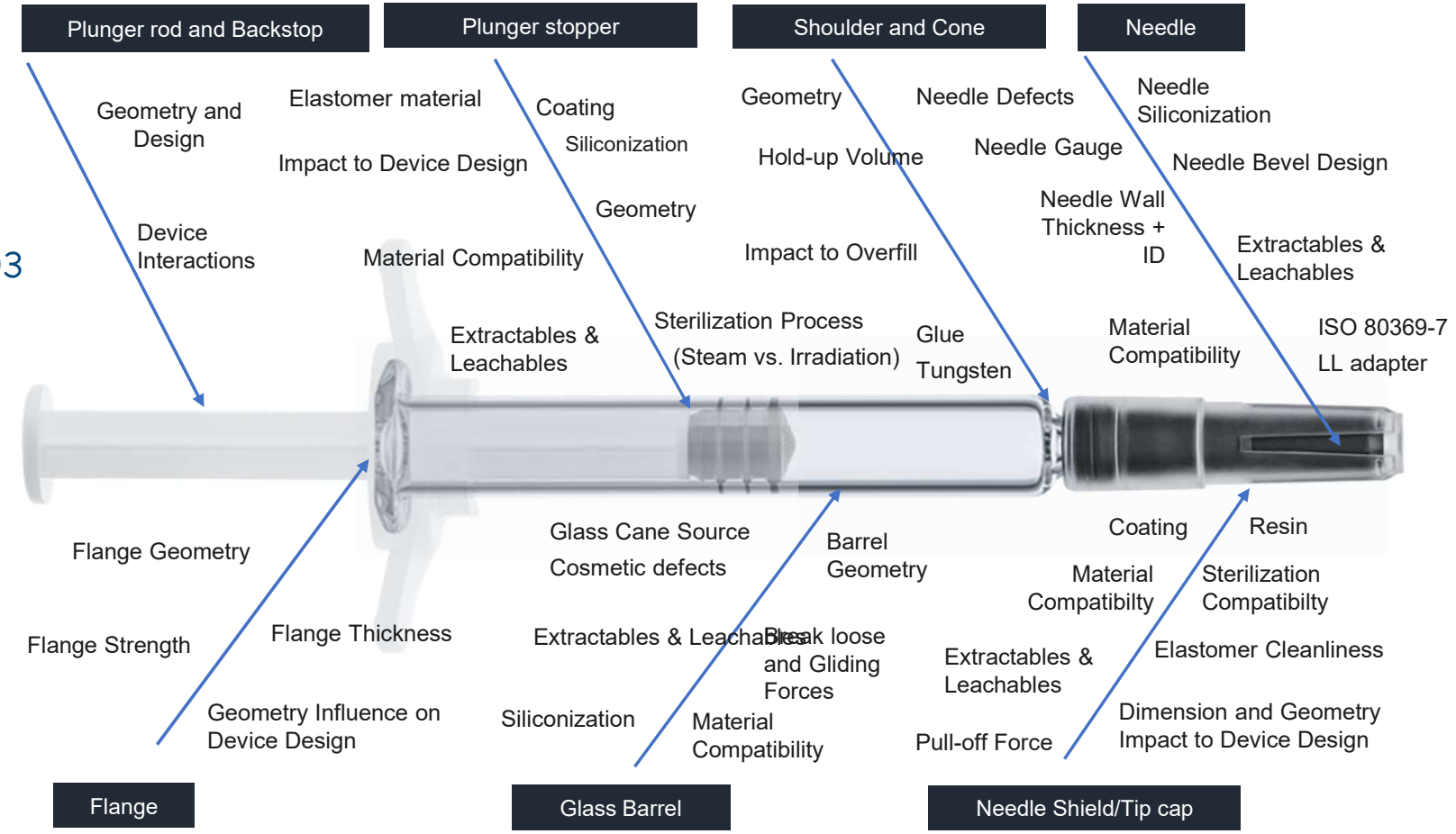
Finished Drug product

Material, Functionality, Drug contact

- ISO 11040-8
- BioComp - ISO 10993
- Sterilisation
- Sterility
- Stability
- Fill& Finish
- Shipping/Vibration Studies



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Syringe meets formulation

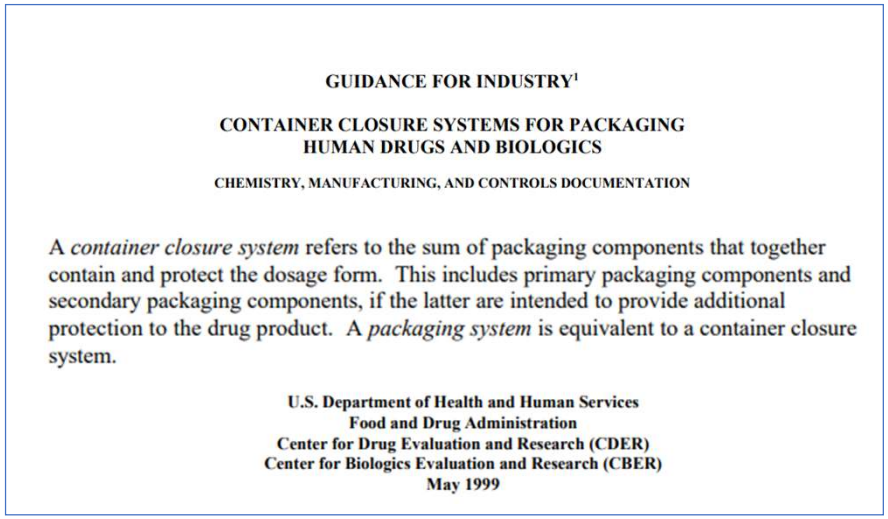
Preclinical
- no prefilled syringe

Phase I
- Selection of container closure system: vial, cartridge, syringe
- Compatibility study

Phase II
- Define commercial container closure system
- Transportation study
- Stability study

- **Phase III**
- Fill and Finish study
- Stability monitoring
- Extractables and leachables, photostability

Phase IV
- Supply chain
- Commercial line readiness



GUIDANCE FOR INDUSTRY[1]

CONTAINER CLOSURE SYSTEMS FOR PACKAGING HUMAN DRUGS AND BIOLOGICS

CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

A *container closure system* refers to the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A *packaging system* is equivalent to a container closure system.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1999

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Does the syringe perform well with the formulation?

Table 1
Roadmap for biologics drug product development.

Pre-clinical	Phase I	Phase II	Pivotal studies/Phase III	PPQ/ Commercial

• TPP developed by joint project team
• Develop initial QTPP and potential CQA's for Phase I
• Developability study (CMC stage) and/or pre-formulation studies
• Verify if platform formulation and analytical assays (if available) are suitable
• Early formulation study
• Non-GMP DP batch used for animal toxicology studies (Tox Batch): fill-finish, release testing
	• Lead lot stability for DS and DP from Tox Batch material
	• BDS Freeze-thaw and stability monitoring in representative containers
	• Confirm formulation for Phase I and Phase II clinical trials (fast to clinic/ not commercial ready)
	• Syringe and IV infusion in-use compatibility studies
	• Container/closure selection and compatibility for DS and DP
	• Establish the drug product manufacturing process (BDS to DP)
	• Initial definition of in-process control strategy
	• GMP DP batch: Fill-finish, release and stability monitoring
	• Development of matching placebo
		• Refine QTPP and confirm CQA's for DP (Late phase development and commercialization)
		• Define additional analytical methods based on QTPP
		• Oxidation and deamidation studies
		• Initial photostability under forced deg conditions (support Comm. Form Dev)
		• Define and develop formulation for Phase III and commercial use (liquid/ lyophilized/PFS)
		• Define commercial container/closure system
		• Comparison of Commercial Formulation to Phase I Formulation
		• Transportation/stability studies
		• Formulation Robustness (DOE) studies
		• Process Development of DP production
		• Formulation and concentration
		  • Freezing (rate and Tg')
		  • Thawing
		  • Mixing
		  • Filtration
		  • Filling
		• Update in-use stability to support Phase III
		• Microbial challenge studies to support Phase III (lyophilized/IV/syringe)
		• Device compatibility and definition of combination product pathway
			• Refine QTPP (for commercialization)
			• Establish pivotal study and commercial manufacturing site and ensure alignment of DP production with CDMO processes
			• Refine in-process control strategy
			• DP engineering run including mixing homogeneity study using placebo/active
			• GMP DP batch for pivotal clinical studies: Fill-finish, release and stability monitoring
			• Process risk assessment (Hazards or FMEA approach)
			• Process characterization studies
			• Photostability under ICH guidelines and confirmatory use conditions – Single Batch
			• Extractable and leachable risk assessment and studies
			• Expanded syringe and IV infusion compatibility studies
			• Transportation studies for product impact (IQ/OQ studies)
				• Finalize CQAs
				• Ensure alignment of DP characteristics with commercialization target
				• Manufacturing site risk assessment (FMEA) for commercial phase
				• Risk mitigation studies
				• Validation plan finalization
				• Finalize control strategy for DP process
				• Commercial manufacturing site readiness
				• Supply chain and raw material risk assessment and risk mitigation
				• Facilities and equipment qualification
				• DP Process Validation cGMP studies
				• DP PPQ runs at manufacturing site
				• DP Stability – 3 batches with at least one batch in secondary packaging
				  • Continuous process verification
				  • PPQ lot stability monitoring
				• Transport validation using actual shipping lanes
				• Microbial challenge studies
				• Preparation of BLA and Pre-Approval Inspection

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Regulatory Aspects

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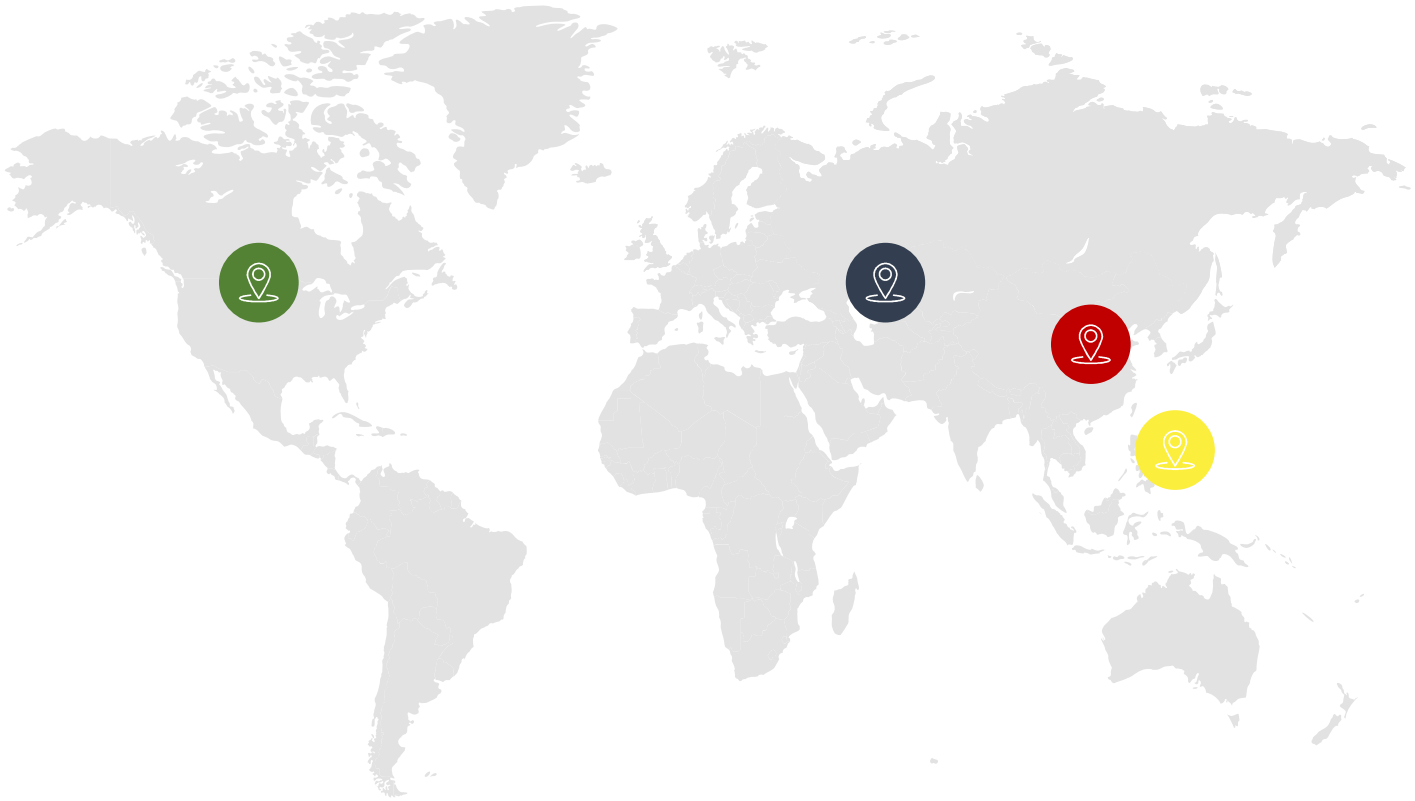
Global Pharmacopoeia



USP
U.S. Pharmacopeia

European Pharmacopeia
10th Edition

JP
Japanese Pharmacopeia

PHARMACOPOEIA
OF THE PEOPLE's REPUBLIC OF
CHINA

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Overview of Relevant USP Chapters

USP
U.S. Pharmacopeia

Glass Containers	Elastomer Components	Plastics Materials & Packaging	Polymer Manufacturing Components	Extractables & Leachables	Particles
660	381	661.1	665	232*	787
1660	1381	661.2	1665	233	1787
	382**	1661		1663	788
	1382**			1663	1788
					789
					790
					790

Biological Reactivity
87 *in vitro*
88 *in vivo*

Currently under revision, 1st December 2026 will be official

- *Chapters > 1000 informational*
- *Chapters < 1000 mandatory if required by monograph*
- *** will be official 01 December 2025*

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Overview of Relevant Pharmacopeia European Chapters

European Pharmacopeia 11th Edition

Glass Containers	Elastomer Components	Plastic Containers	Polymer Materials	E&L	Particles
3.2.1	**3.2.9**	**3.2.2 – 3.2.8** **3.2.2.1**	**3.1** **3.1.16** [new] **3.1.17** [new] **3.1.18** [new]	**5.20*** **2.4.20****	**2.9.19** **2.9.20** **5.17.2**

- **2.4.8 has been deleted replaced by 5.20*
- *** 2.4.35 creation of new chapters for Extractable Elements in Plastic Materials*

- *3.1.16. → COP*
- *3.1.18. → COC*

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Overview of relevant JP Chapters

JP
Japanese Pharmacopeia

Glass Containers	Elastomer Components	Plastic Materials	Polymer Manufacturing Components	E&L	Particles
7.01	**7.03**	**7.02**	**-**	**1.07**	**6.07** **6.08**

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Extract of relevant ISO Standards (1)

ISO

Glass Containers	Elastomers Components	Plastics Materials	Polymer Manufacturing Components	E&L	Particles	Needle Based Injection Systems [..AI, Pen]
719, 720	11040-2 11040-3 11040-5	11040-6 11040-7 11040-8	9113	8871-1 10993-18	8871-3	11608 series
4802-1 4802-2	8362-2 8362-3 8362-5 8362-6 8362-7		17855			
11040-1 11040-4 11040-7 11040-8 80369-7 80369-20			2898			
8362-1 8362-4	8871-2 8871-4 8871-5					
13926-1	13926-3					

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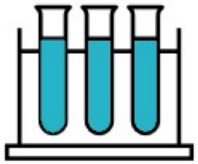
Biocompatibility

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



ISO 11040-8 Testing of Finished Prefilled Syringes at Pharma – under revision

Functional performance requirements and testing parameters depend on Intended use

1. Minimal configuration
- syringe barrel filled with the injectable product
- closed with a front-end closure and a plunger stopper

2. Additional components may need to be added to make it ready for administration by manual injection according to its intended use
- a needle for single use (for LL)
- assembly of a plunger rod or both)

3. Finished prefilled syringe may be combined with a device
- Needle-based injection system

- Design verification of the finished prefilled syringe's functional performance requirements to be in accordance with its design specifications. The test methods and testing are intended to verify the design at a confidence level of 95 %

- 30 test samples considered sufficient for DV

- Test to be carried out with finished drug product

- New tests and new procedures under revision

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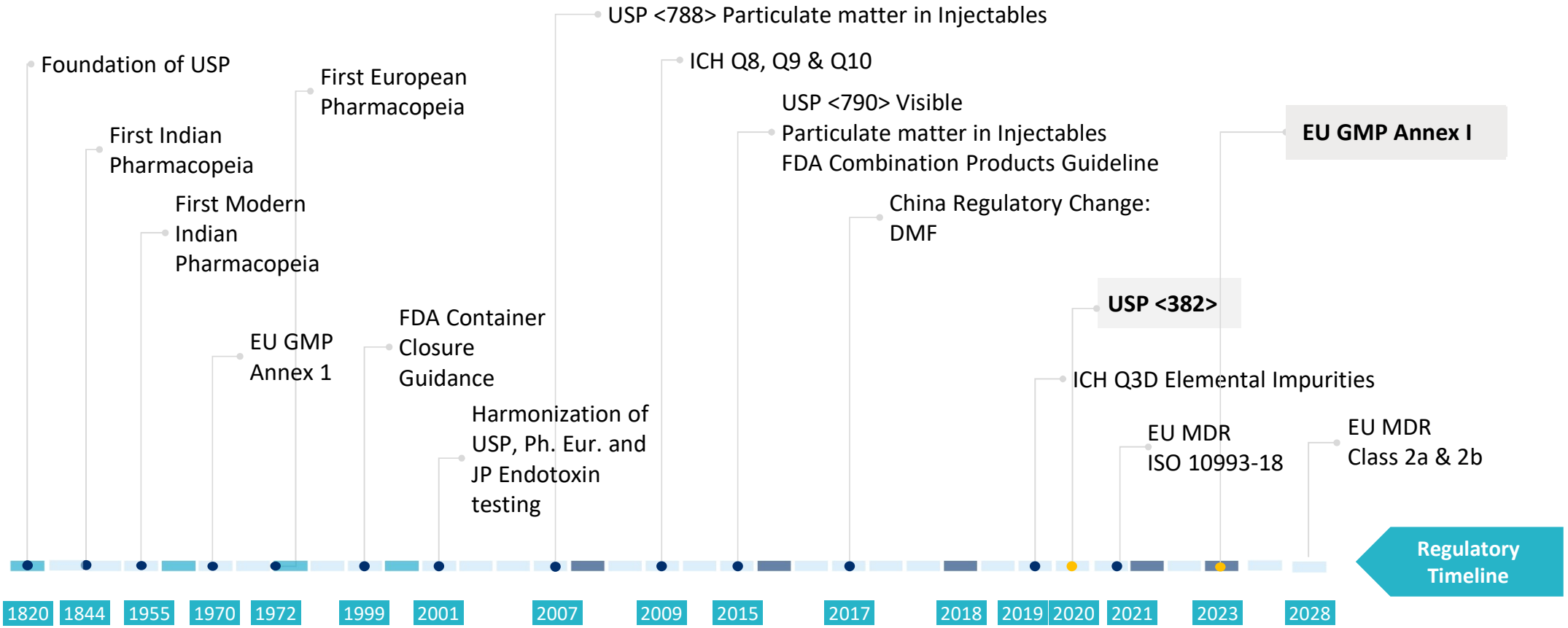
Regulations Over Time



EU: European Union; GMP: Good Manufacturing Practices; FDA: Food and Drug Administration; USP: United States Pharmacopeia; Ph. Eur.: European Pharmacopeia; JP: Japanese Pharmacopeia; ICH: International Council of Harmonization; PQRI: Product Quality Research Institute; MDR: Medical Device Regulation; ISO: International Organization for Standardization

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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

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Agenda Day 2

- Technical Aspects of Prefilled Syringes

  Syringe meets formulation • Physical performance • Pharmaco-chemical performance

- Regulatory and Pharmaceutical Aspects
  - Short overview on regulatory guidelines and technical standards: EU / US / ISO / …
  - **Short overview and Introduction into Drug-Syringe Interactions**
- Manufacturing Aspects Regarding Filling, Finishing and Assembly

  Rod insertion and labeling • Combi filling • Robot filling • New trends

- Introduction into Autoinjectors

- Questions and Answers

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Drug-Syringe Interactions

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Drug features and possible interactions with syringe components

- Viscosity, pH, concentration, ionic strength, buffer…
- Volume - contact surface of formulation to container
- Sensitivity towards
  - 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
- …

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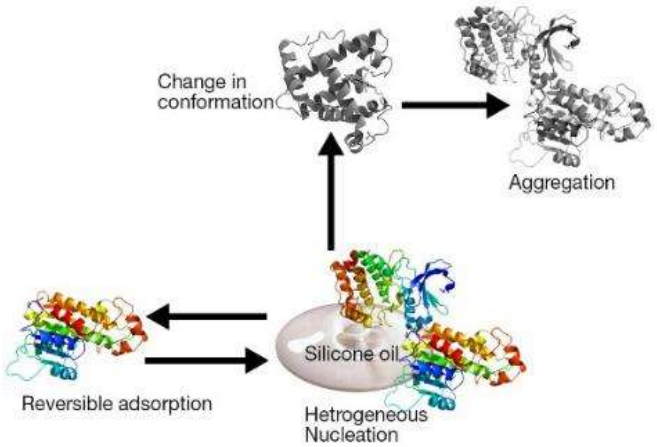
Drug-syringe Interactions - Introduction

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/no silicone oil
- Extractables profile of rubber components
- Coated plunger stoppers
- Reformulate or stay in vial

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Drug contact material vs container type

Contact material	Glass	Elastomer [Stopper, Plunger]	Elastomer [Lined-Seal]	Lubricant Silicone or other Coatings	Glue	Stainless Steal [Needle]	Tungsten
Primary Container	Ampoule 1						
	Vial 2						
	Cartridge			4			
	Prefillable Syringe with staked needle						7

Potential interactions with the drug: Extractables, Leachables, Particles, Delaminations (glass), Adsorption, Absorption, Aggregates

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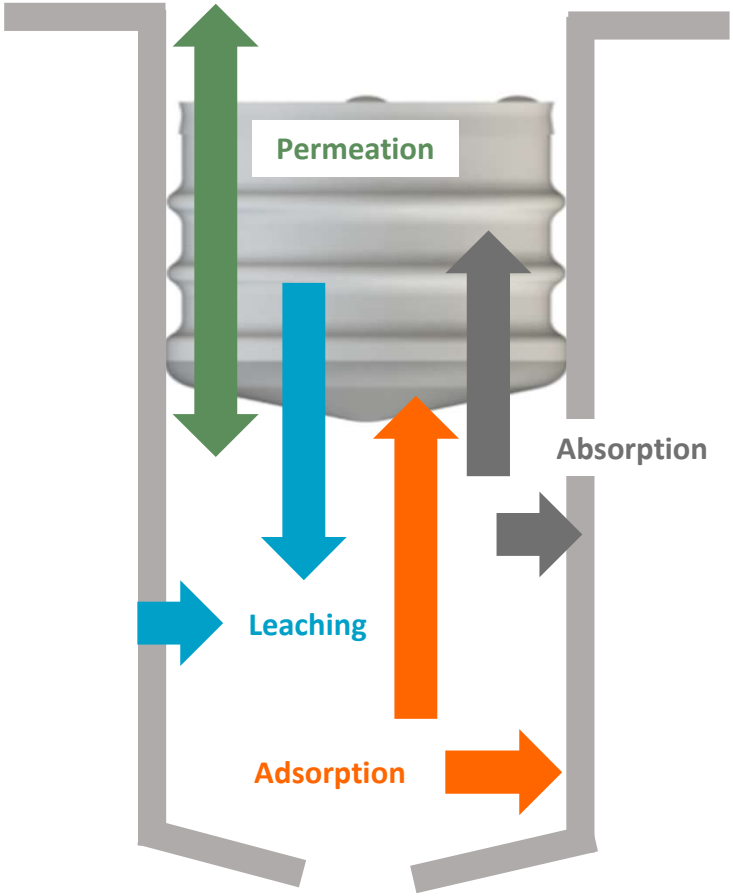
Possible Interaction of Drug Product and Elastomeric Closures

These four interactions generally occur at a low rate.



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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)

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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

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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

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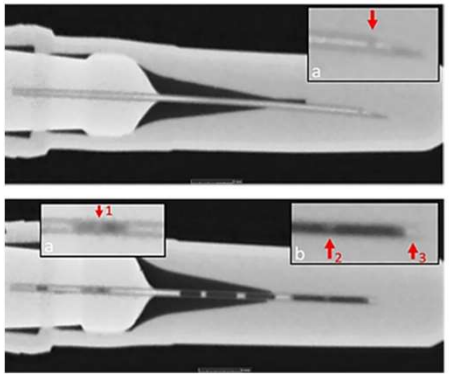
Drug-syringe Interactions II

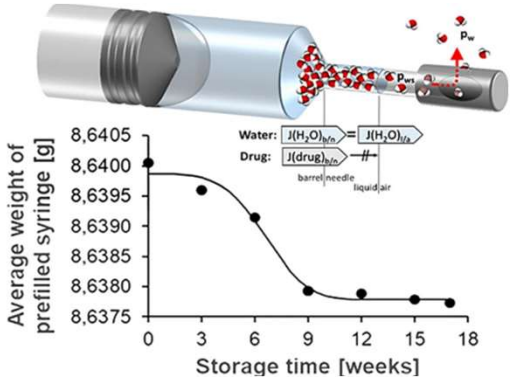
Needle clogging
- Cristallization of drug substance in needle

You see
- Blocked needle

Triggered by
- Drug formulation itself
- Evaporation through rubber cap/needle shield
- Liquid in the needle

What can be done?
- Stability testing
- Vacuum stoppering
- Gas tight cap (COP syringe)
- Dry needle (cartridge based Autoinjector
- Double chamber syringe (WFI filled or empty first chamber)





ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics

Volume 176, July 2022, Pages 188-198

Needle clogging of protein solutions in prefilled syringes: A two-stage process with various determinants

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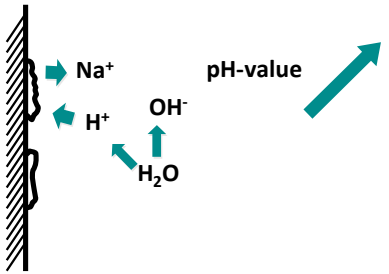
Drug-syringe Interactions III

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

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

What can be done?
- Surface treatment of vials (SiO2, Ammonium sulphate)
- Special high resistance glass vials, delamination tested
- COP vials
- Reformulate



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Drug-syringe Interactions IV

Particles in drug formulation
- Visible, subvisible
- extrinsic-intrinsic-inherent

You see
- Particle formation in
  - Light Obscuration (LO) and
  - Micro-Flow Imaging (MFI)

Caused by
- Drug formulation
- Process
- Siliconized barrel
- Plunger stopper

What can be done?
- Count, Stability testing
- Adapt formulation (e.g. buffer)
- Choose low silicone/baked-on siliconization/silicone-oil free systems

Table 1 Summary of particle compendial specifications as per Ph. Eur. and USP

Size range				Subvisible				Visible	
Method				LO		Microscopy		White and black double chamber	
Compendial guide				Ph. Eur.	USP	Ph. Eur.	USP	Ph. Eur.	USP
				2.9.19	788/789	2.9.19	788/789	2.9.20	790
Sample nominal volume	>100 mL [ppc]	Particle size [µm]	≥10 ≥25	25 3		12 2		2000 lux and 3750 lux 5 seconds in front of each background	
	≤100 mL [ppmL]		≥10 ≥25	6000 600		6000 600	3000 300		
	Ocular [ppmL]		≥10 ≥25 ≥50	50 5 2		50 5 2			

S.Messick, M. Saggu, A. Ríos Quiroz American Association of Pharmaceutical Scientists 2020 251-255. F. Jameel et al. (eds.), *Development of Biopharmaceutical Drug-Device Products*, AAPS Advances in the Pharmaceutical Sciences Series 35,https://doi.org/10.1007/978-3-030-31415-6_11

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Drug-syringe Interactions V

Change in BLGF/Particle formation

Caused by
- Siliconized barrel
- Vendor variability
- Storage prior to filling
- Plunger stopper
- Process
- Drug formulation

What can be done?
- Stability testing
- Choose low silicone/baked-on siliconization/silicone-oil free systems

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Rapid Communication

The Impact of Syringe Age Prior to Filling on Migration of Subvisible Silicone-Oil Particles into Drug Product

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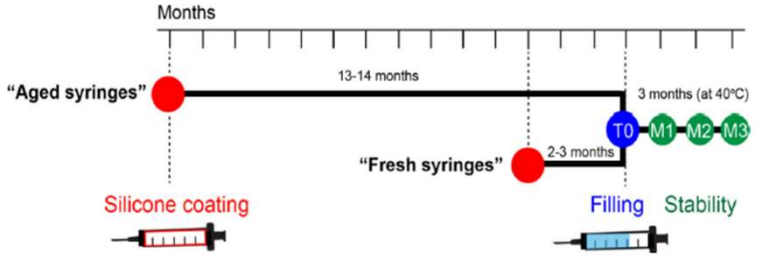

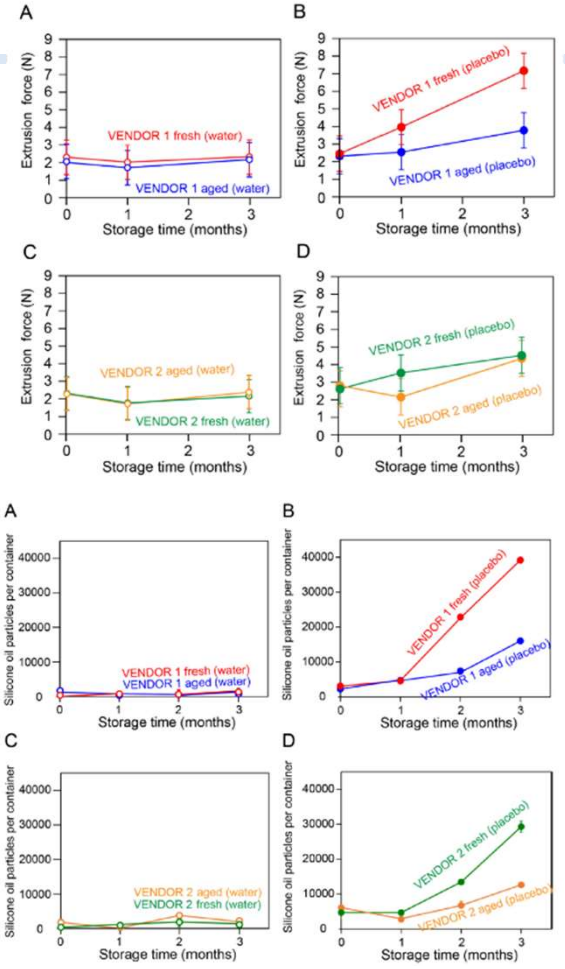

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Drug-syringe Interactions VI

Tungsten, steel, glue
- Residuals
- Ions

You see
- Stability issues
- Leachables

Caused by
- Glass forming process
- Steel cannula
- UV-cured glue

What can be done?
- Stability testing
- Tungsten-free syringes
- Tungsten reduced syringes (ask supplier)
- Luer lock syringes (glue free)

Syringe	Tungsten	Steel	Glue
Luer/luer lock Standard process	✓	-	-
Luer/luer lock tungsten free forming	-	-	-
Staked needle	✓	✓	✓
Source	Forming process	cannula	UV glueing
Alternative	tungsten reduced and W free syringe, ceramic pin	Luer/luer lock; extractables report	Luer/luer lock; extractables report
Interaction risk	moderate	low	low

Chemical background of the reactions with liquid formulations containing protein
Tungsten (W) oxidizes at high temperatures
$W + O_2 \Rightarrow WO_2$ (>400°C)
$2\,WO_2 + O_2 \Rightarrow 2\,WO_3$ (500-800°C)
$WO_3 \Rightarrow WO_4^{2-}$ (>1,100°C)
WO_4^{2-} (in acidic medium) => formation of complex W polyanions

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Common issues during development for different biologics DP presentations. Liquid formulations

Formulation and excipient related issues

- Design space not defined
- Conversion from frozen liquid to a refrigerated liquid
- pH shift during freezing
- Low concentration formulation (< 200 μg/mL formulation):
- adsorption and analytical challenges
- High concentration formulations: increased viscosity, higher rates of aggregation/self association, opalescence, liquid-liquid phase separation, increased color, . . .
- Polysorbate instability due to esterase activity resulting in subvisible and visible particle formation
- Metal contamination (His/Phosphate/Citrate), excipient degradation (polysorbates, His), nanoparticles (sucrose, trehalose), frozen state crystallization (sorbitol, trehalose), protein modification (citrate, succinate)
- Inconsistent raw materials impurities

Instabilities of the molecule: example protein

- Increased aggregation, subvisible and/or visible particle formation during FBDS storage and/or freeze-thawing
- Aggregation, subvisible or visible particle formation during DP manufacturing (stirring, tubing/pump compatibility), transportation, long-term storage, freezing during storage, In-use stability
- Post-translational modifications during storage, leading to decrease in potency, aggregation/particle formation, ADA response, reduced half-life, . . .
- Clipping/backbone hydrolysis – enzymatic and non-enzymatic
- Photosensitivity

Container closure and device-related issues

- Container incompatibility – glass lamellae formation and delamination due to formulation
- Extractables and leachables from container closure system
- Device compatibility and new surface interactions

Issues related to application to the patient

- Loss or aggregation during in-use stability studies, IV administration
- Injection site pain – switching from IV to SubQ (citrate present, pH)
- Reduced solubility at neutral pH (injection site precipitation)

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Common issues during development for different biologics DP presentations. Pre-Filled Syringes related issues (In addition to issues for liquid formulations)

Formulation and excipient related issues

- Polysorbate level is too low to prevent protein from binding the silicone oil droplets resulting in an increase in subvisible and visible particles
- Polysorbate level is too high resulting in emulsification of the silicone oil and polysorbate resulting in an increased silicone oil droplets level

Components of PFS that can induce instability

- Silicone-oil layer and droplets
- Tungsten remaining in the glass neck and potentially reacting with the protein to induce chemical changes, and form subvisible or visible particles
- Incomplete curing of the glue can result in PTM's of the protein, such as increased oxidation or adduct formation, for e.g. related to formation of methacrylate
- Needle shield or plunger components

Issues related to PFS functionality

- Air bubble size set during vacuum or mechanical stoppering
- Leakage of the solution around the plunger due to movement of the stopper/plunger rod during air transportation from reduced air pressure - breaking sterility
- Leakage of solution around the plunger due to freezing occurring during transportation
- Changes in break loose and glide force during storage - limit glide force to 20 N
- Sterilization related changes in surface chemistry of the syringes

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Test methods and Guidelines I

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

PDA Technical Report 73

ISO 11040-8

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, glueing, 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

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Test methods and Guidelines II

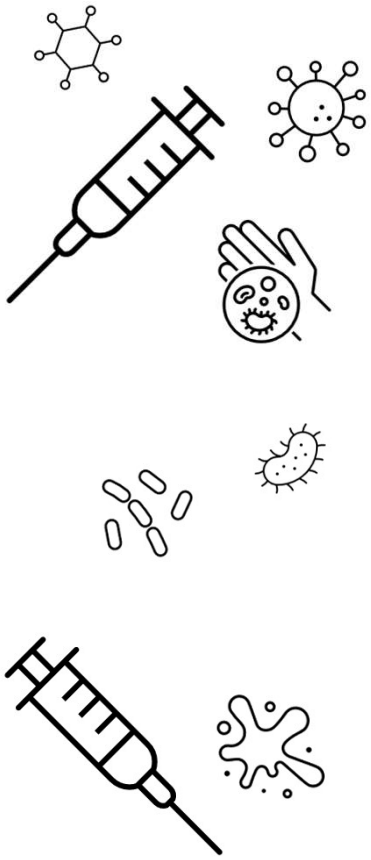
PDA Technical Report 73

ISO 11040-8

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 USP <788>, Pharm Eur. 2.9.19, USP <790>



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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