All about Pre-filled Syringe Systems

From Initial Development to Final Fill Finish

Technical Aspects

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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

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

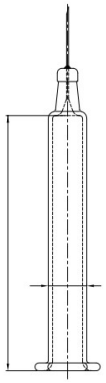
Relevant standards and regulations

- 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

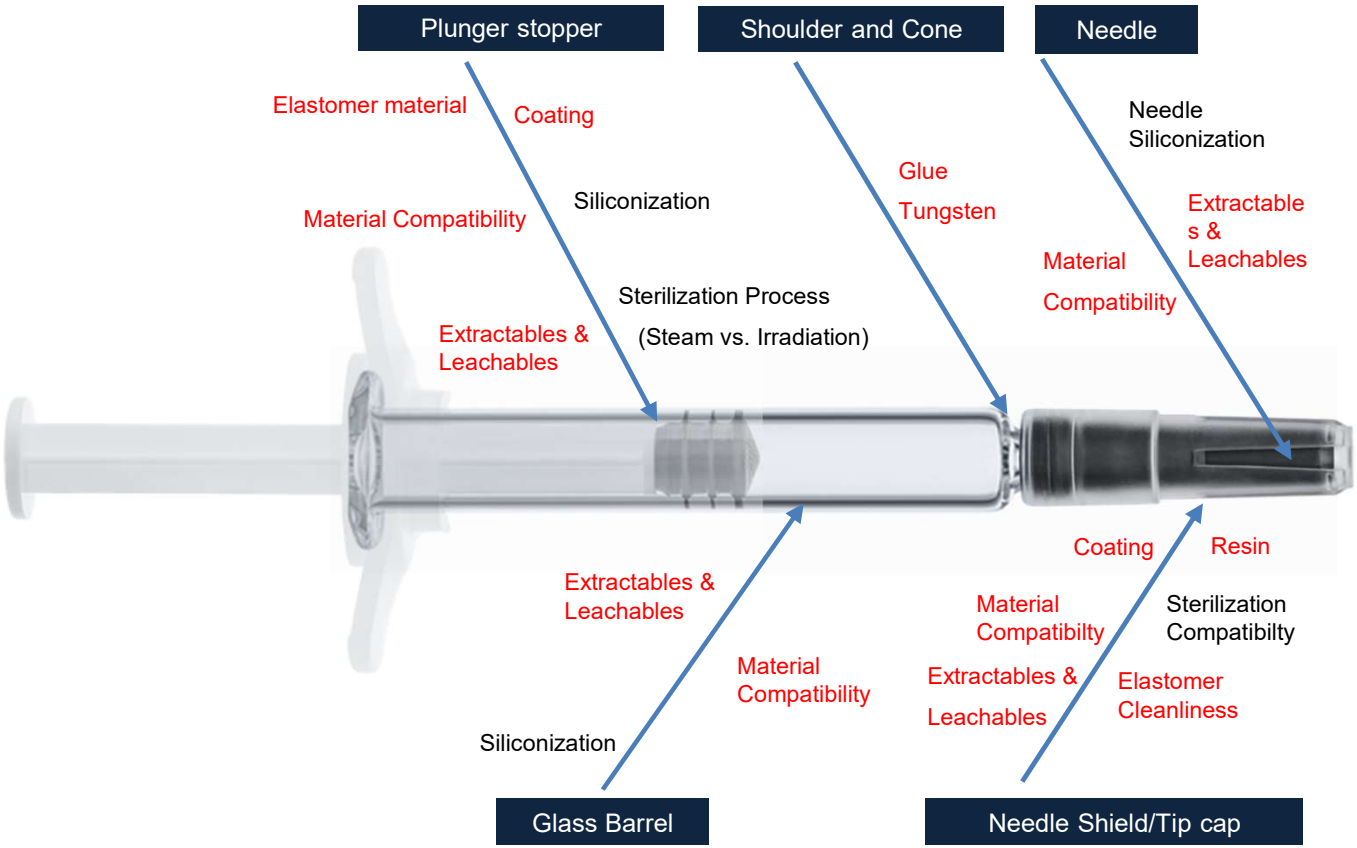
- ISO 9001: Quality management
- ISO 15378: GMP Primary packaging
- 21 CFR 211 Subpart E – Control of Components and Drug Product Containers and Closures
- DMF Type III
- Ph. Eur. USP and JP

- 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



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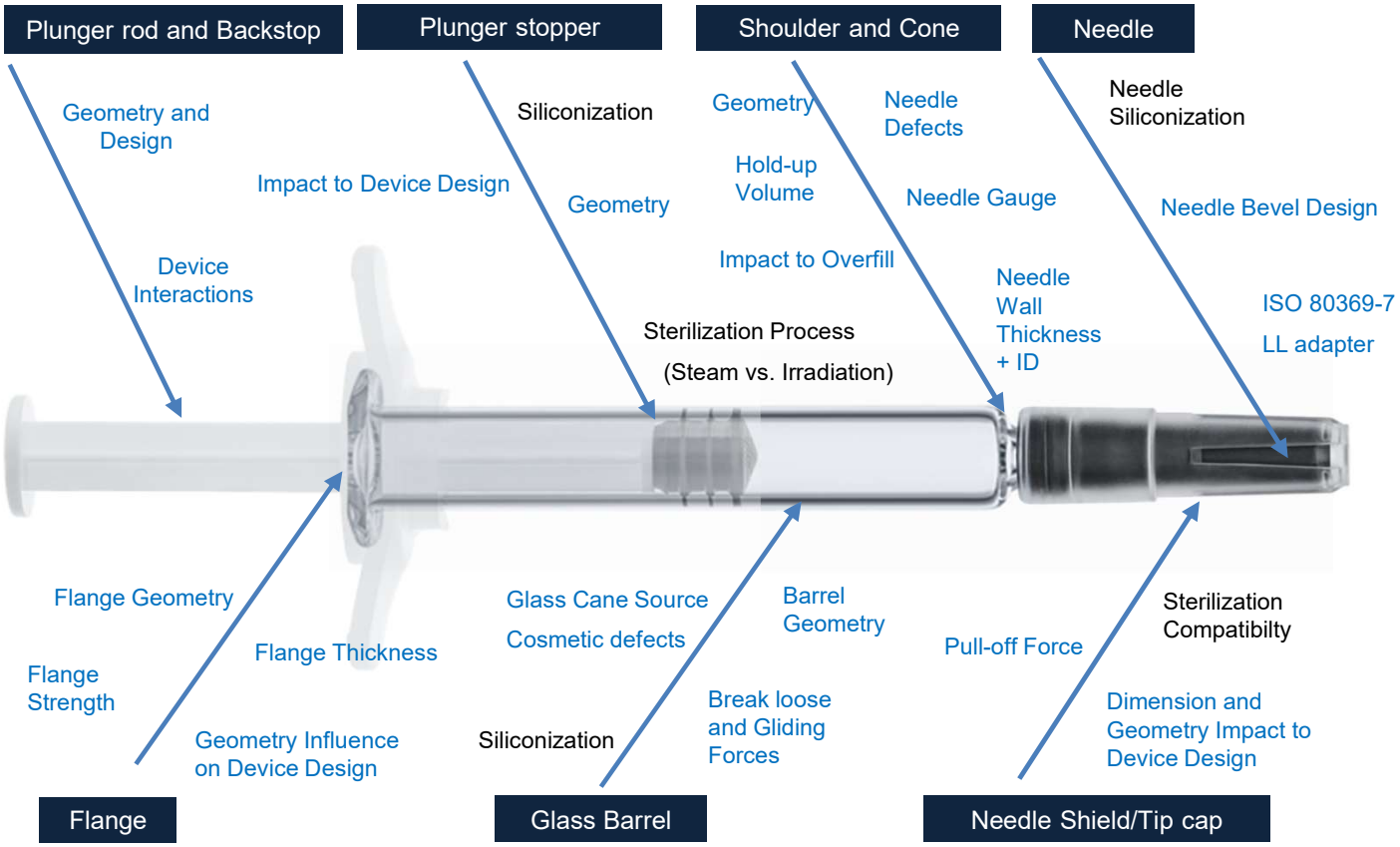
PFS components: Physical interfaces to the drug



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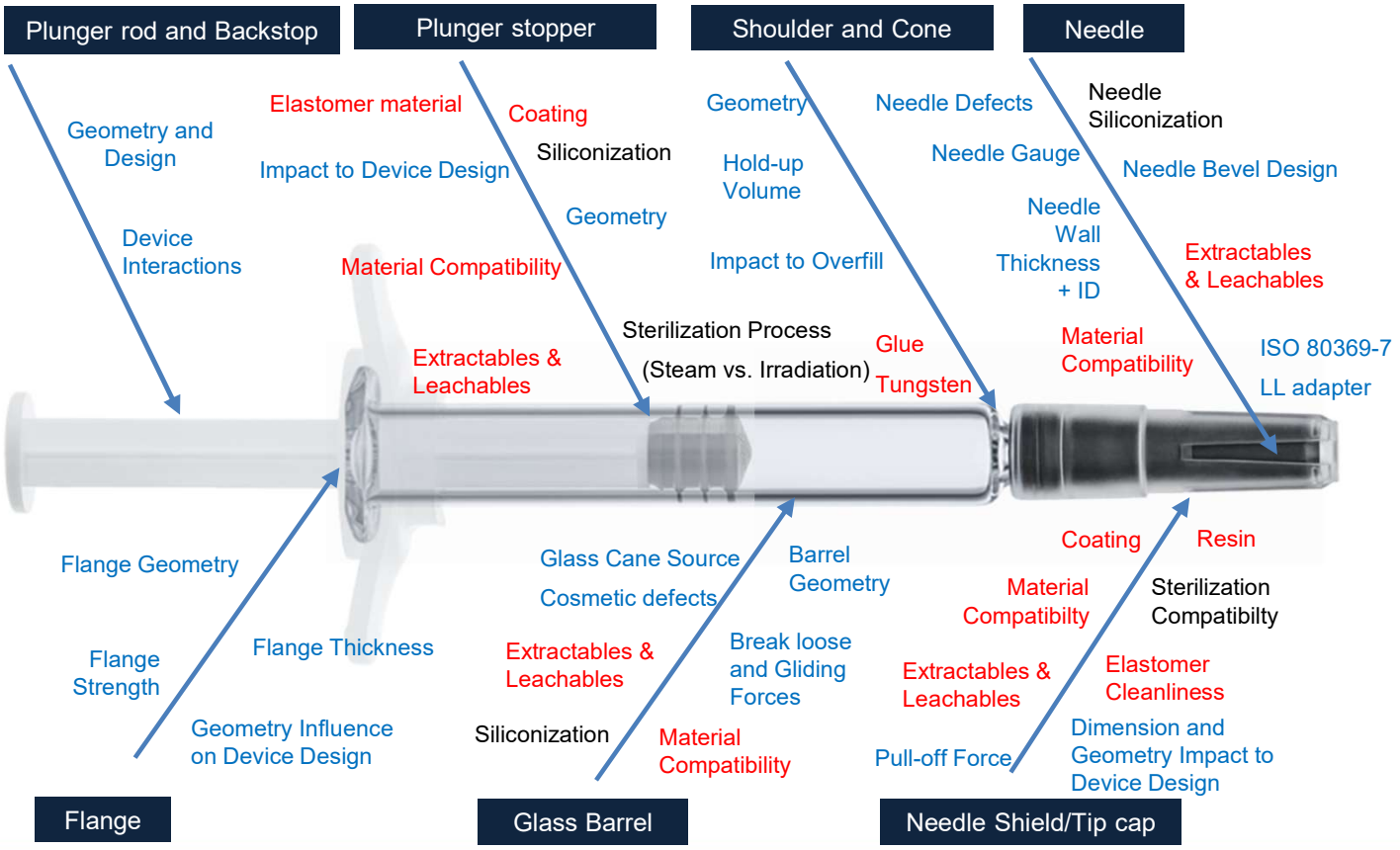
Does the syringe perform well with the formulation?

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

ISO 11040-8 is a good starting point



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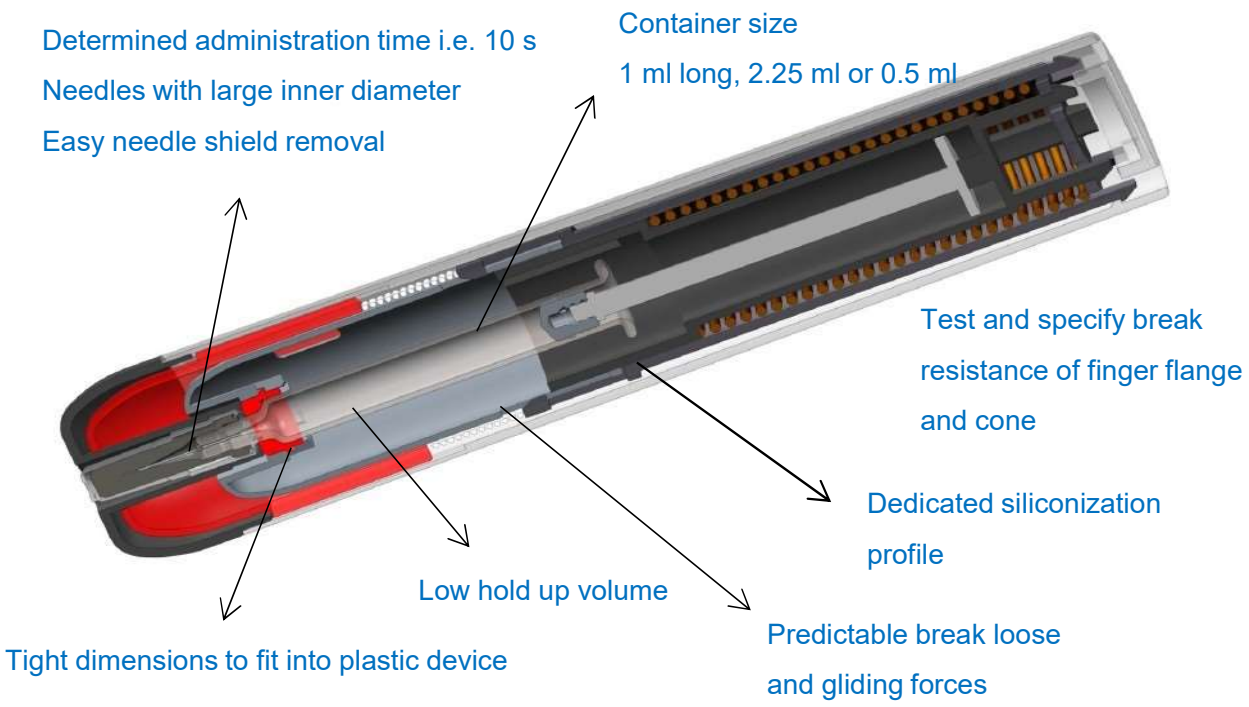
How suppliers can support ISO 11040-8

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

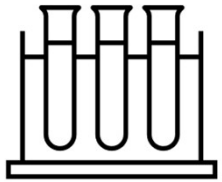
- Intraveneous (vial + disposable syringe)
- home use limited

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

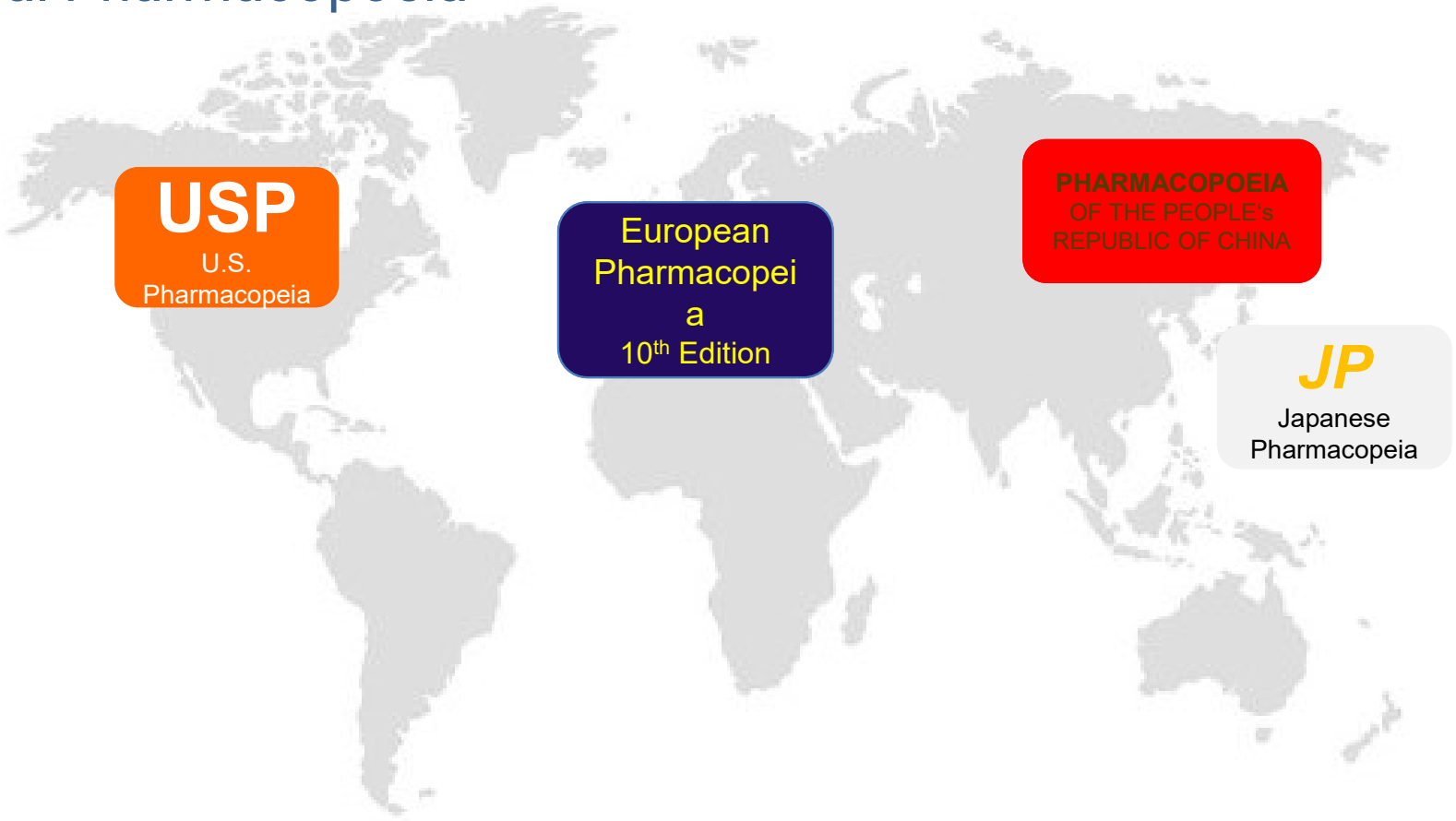
Regulatory Guidelines

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

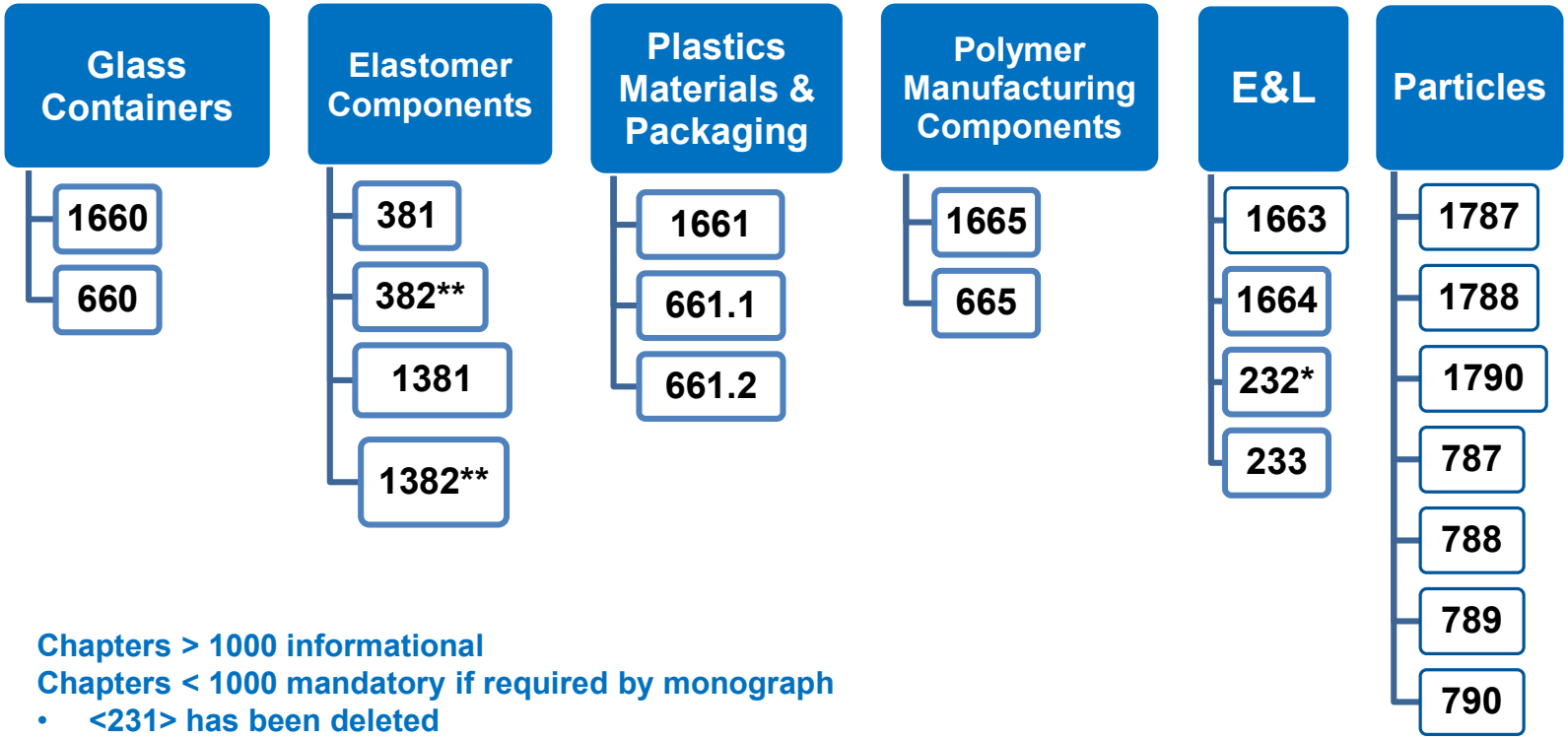


Global Pharmacopoeia



Overview of Relevant USP Chapters

USP
U.S. Pharmacopeia



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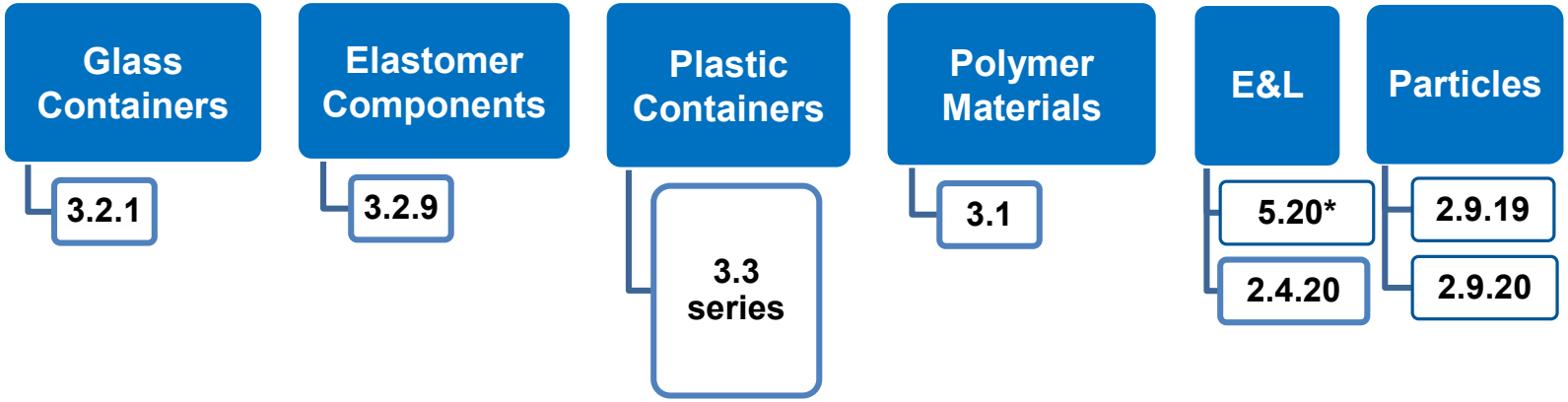
** will be official 2025

Overview of Relevant Ph Eur Chapters

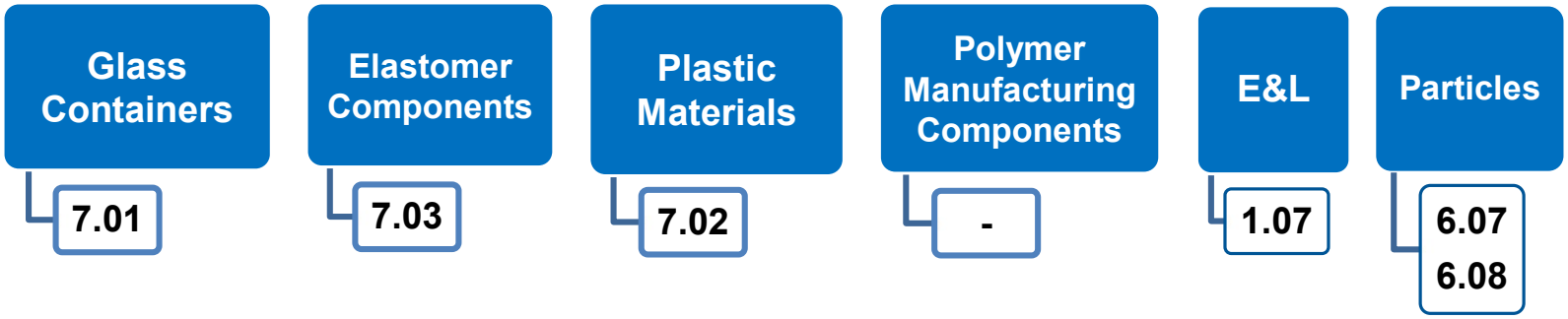
European Pharmacopeia 10th Edition



* 2.4.8 has been deleted

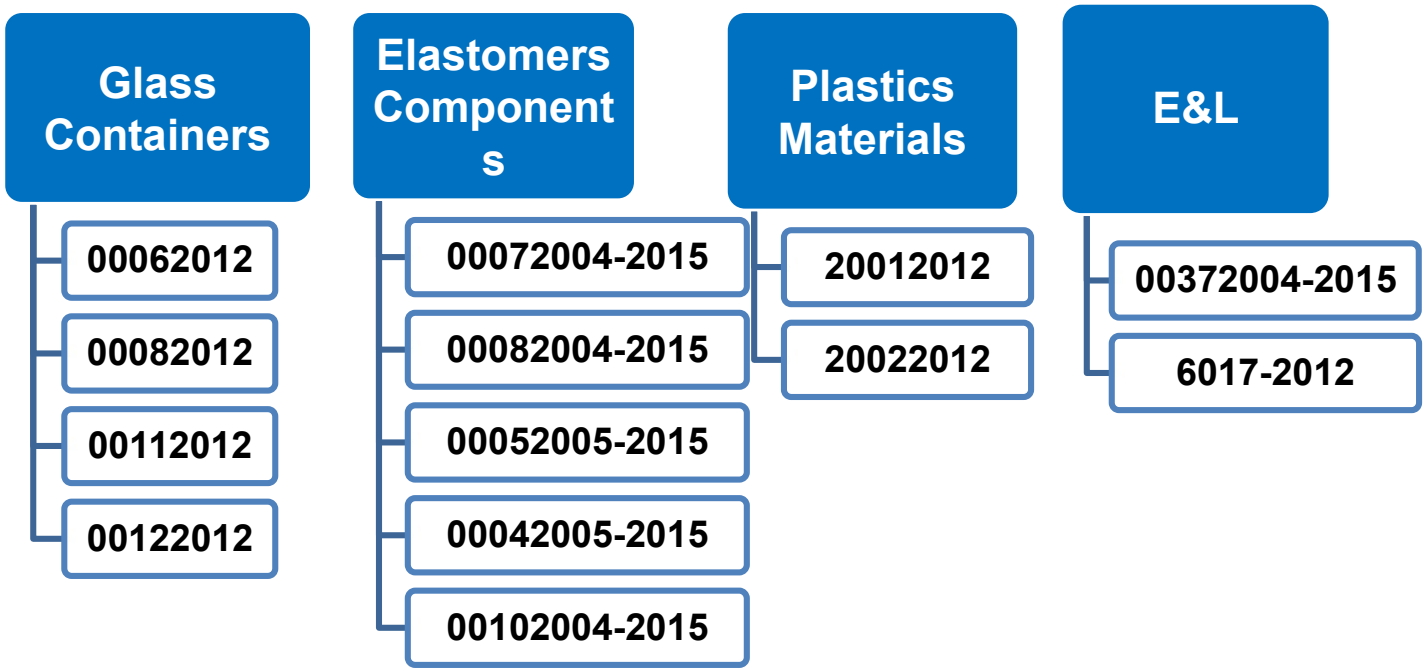
Overview of relevant JP Chapters

JP
Japanese Pharmacopeia



Examples of relevant YBB Standards

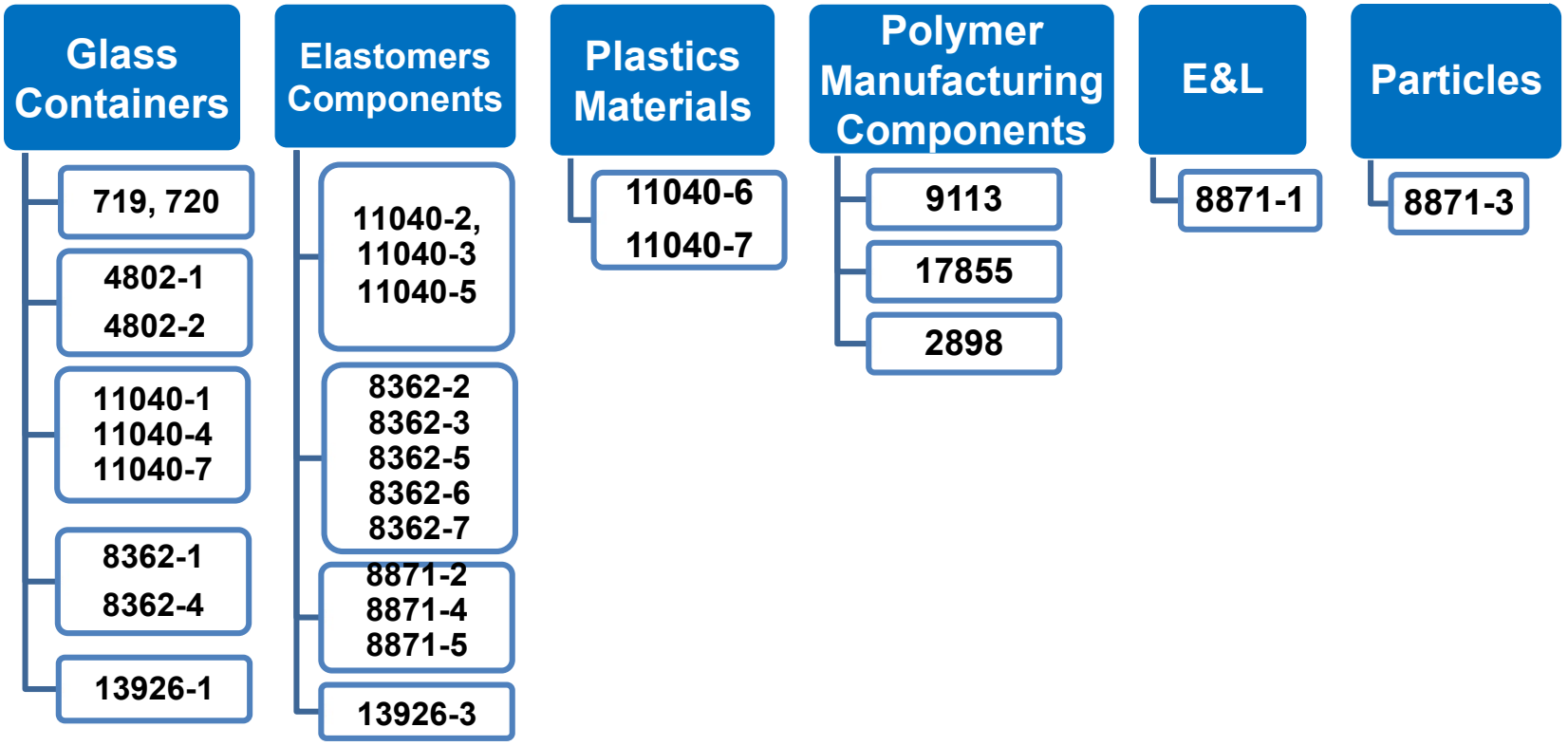
YBB



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



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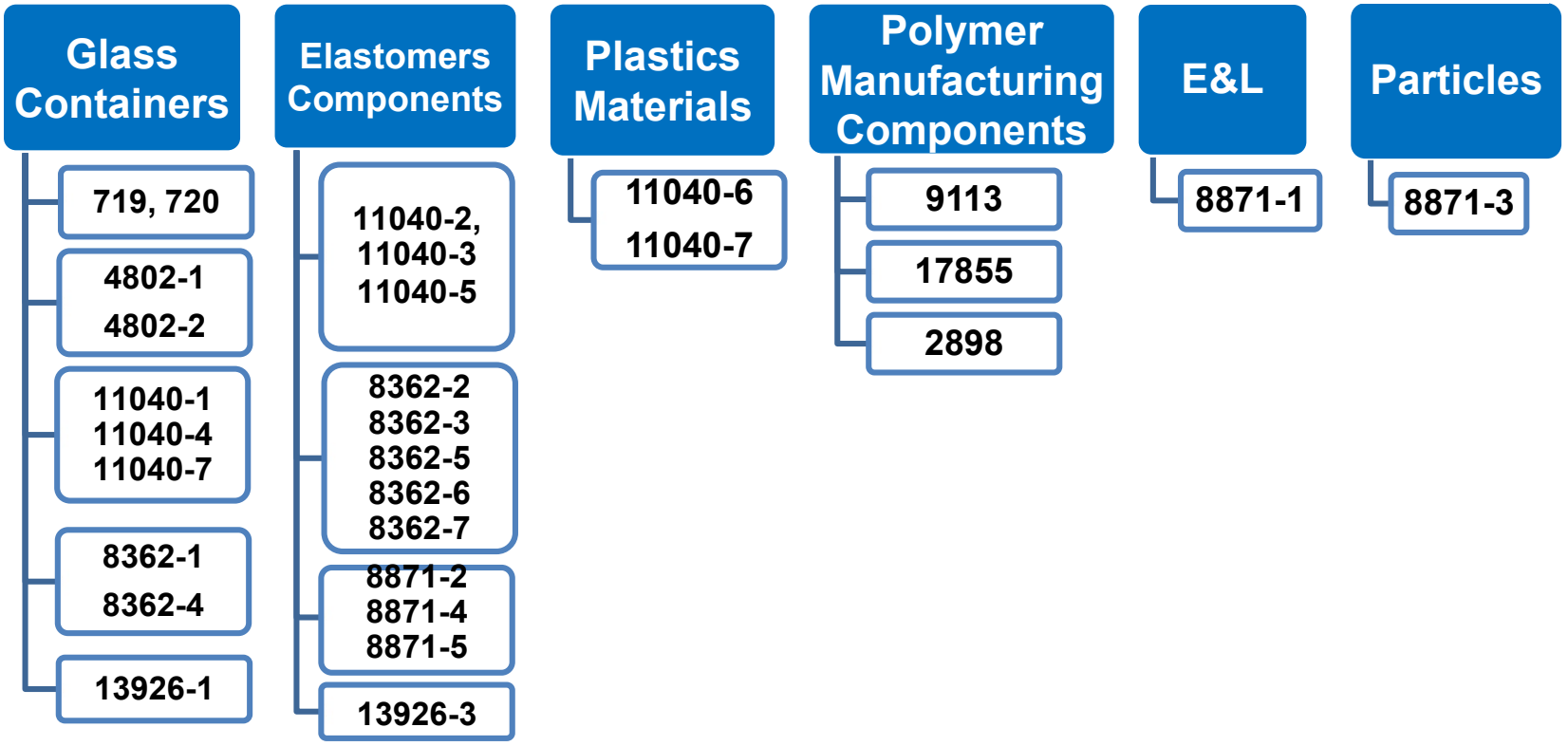
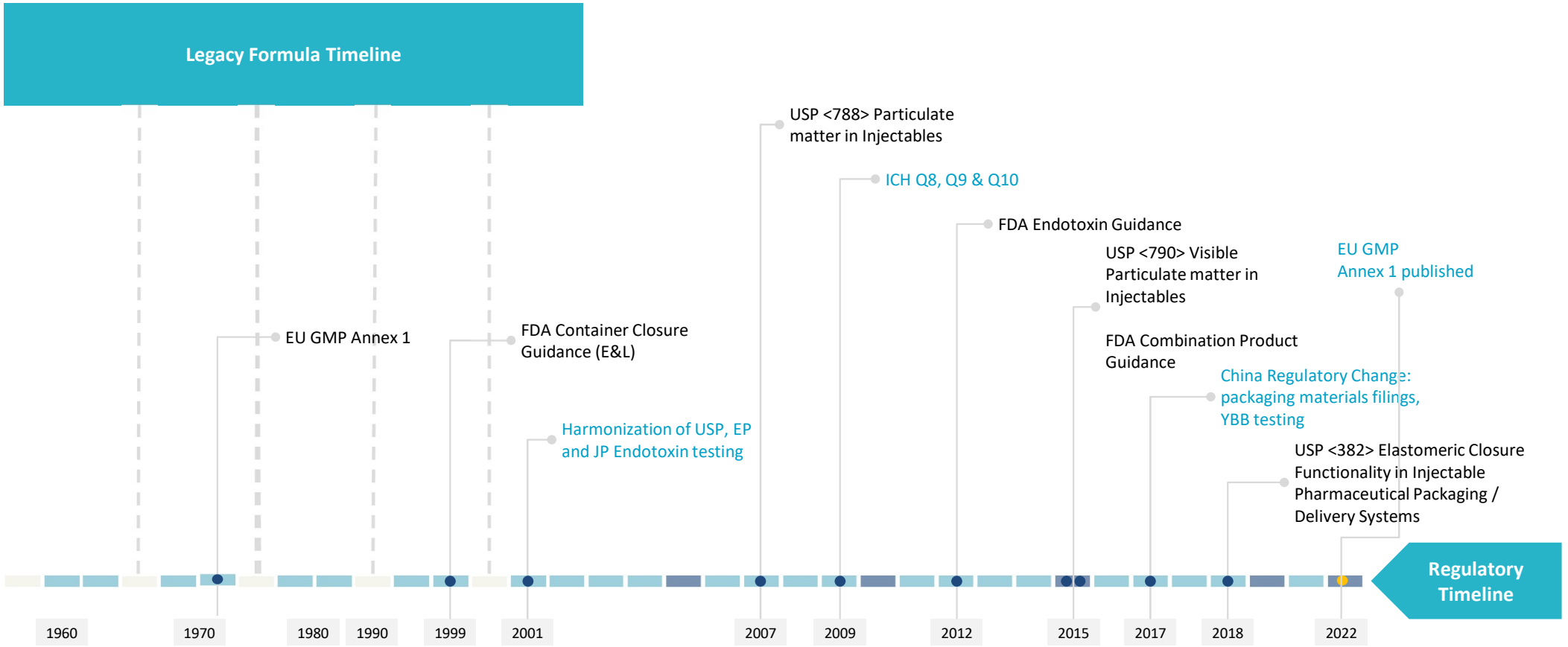


Regulations Are Evolving



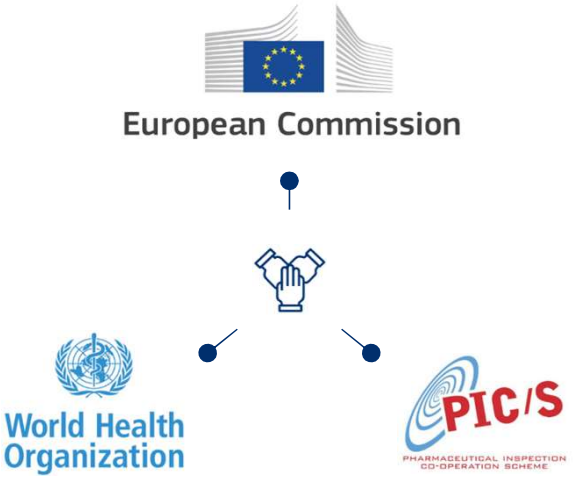
EU GMP Annex I: at a glance

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
  - Regulations are evolving, two main topics Annex 1 and MDR
- 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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- 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)