All about Pre-filled Syringe Systems

Technical Aspects

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Venice, April 20st and 21st 2023

PDA Parenteral Drug Association

West

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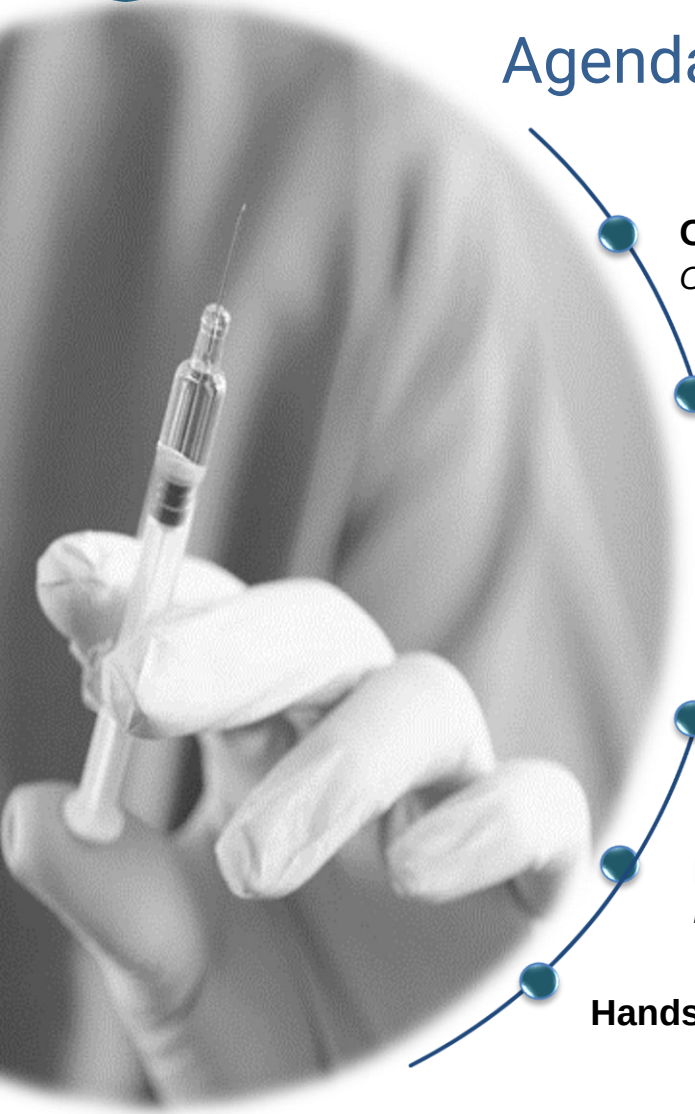
Agenda – DAY 1



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

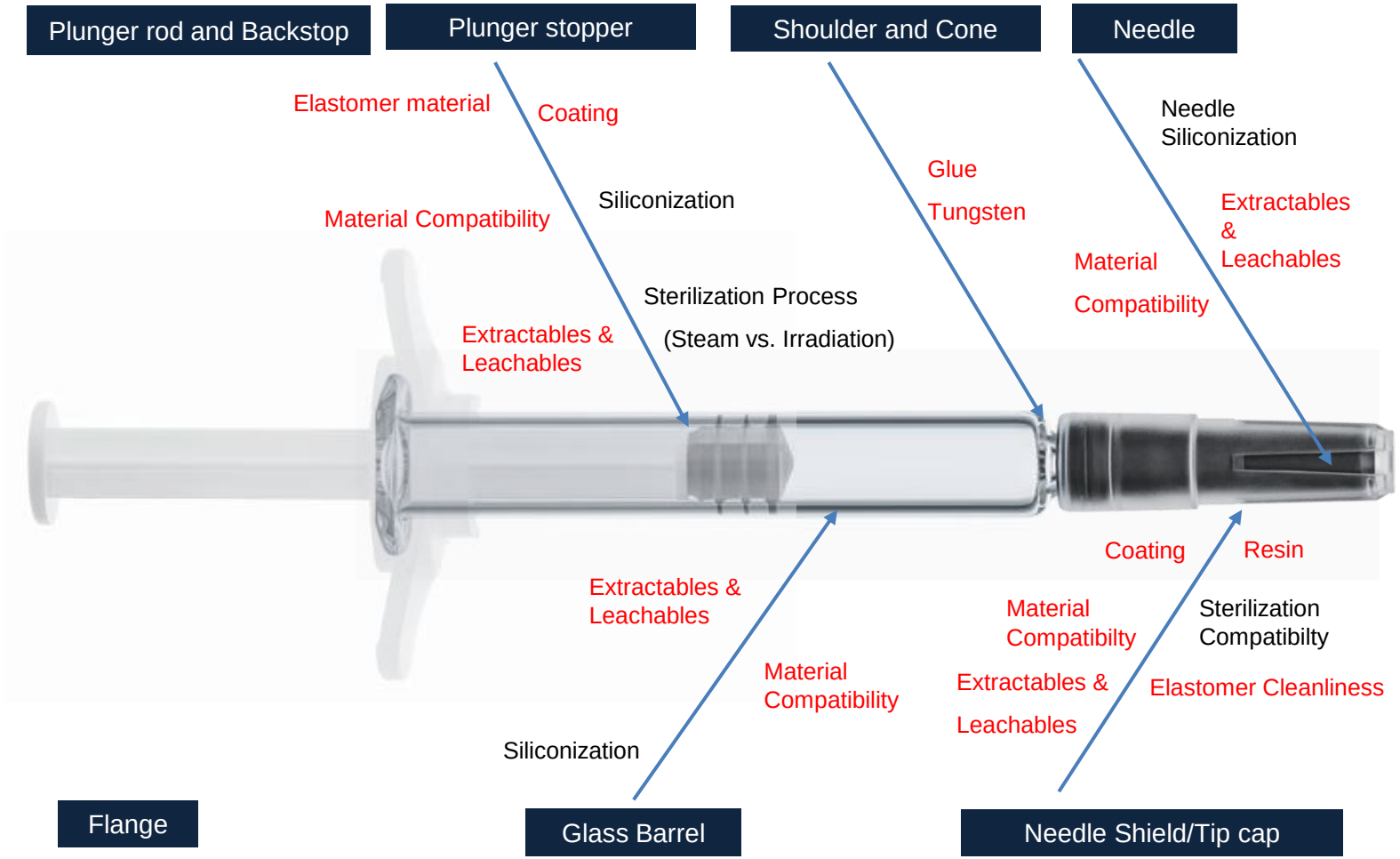
Overview & Introduction into Drug-Syringe Interactions
Aggregation • Degeneration • Oxidation • Viscosity • Bubbles

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

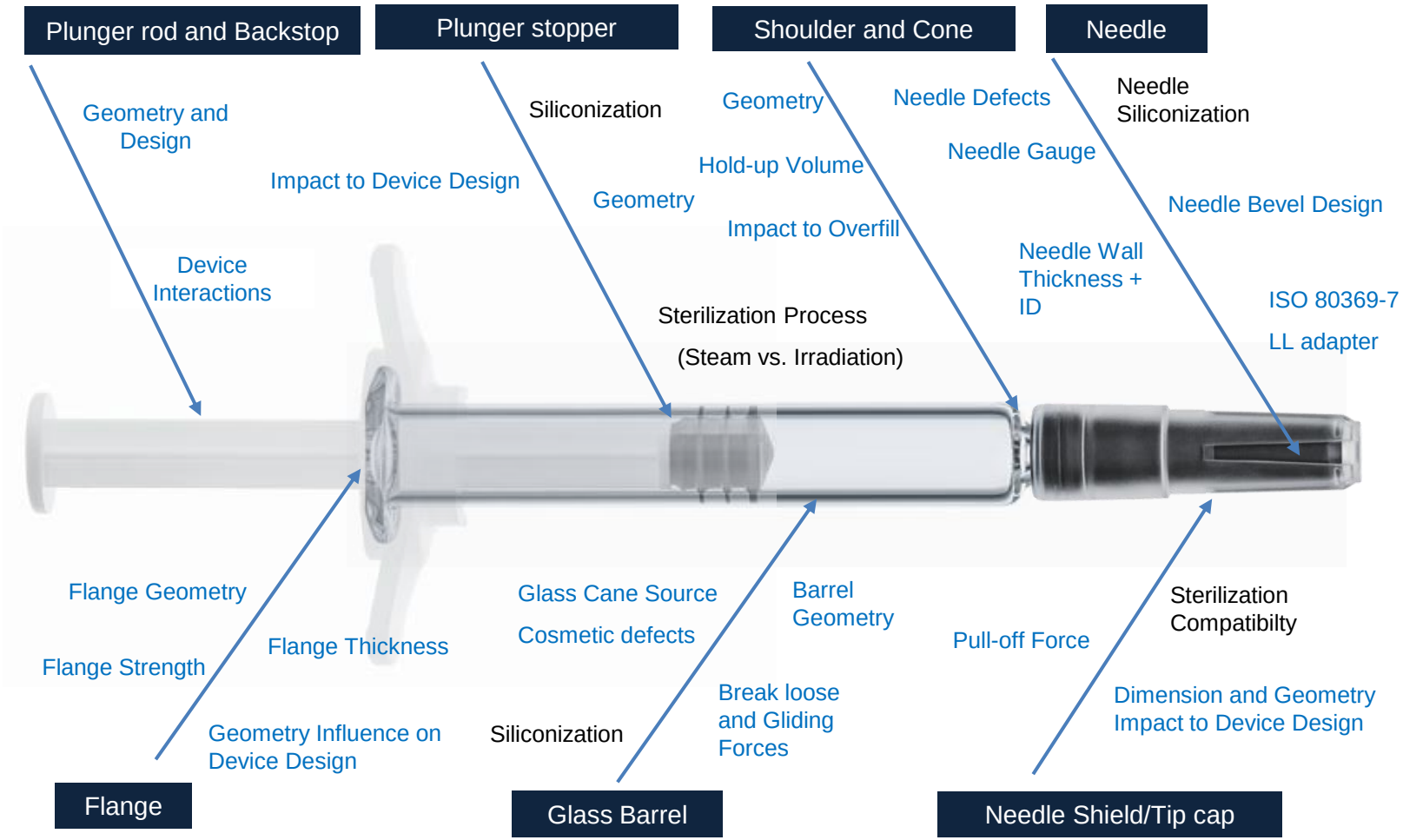
Hands-on Session 1

Pharmaco-chemical parameters



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

Physical parameters



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Pharmaco-chemical and physical parameters

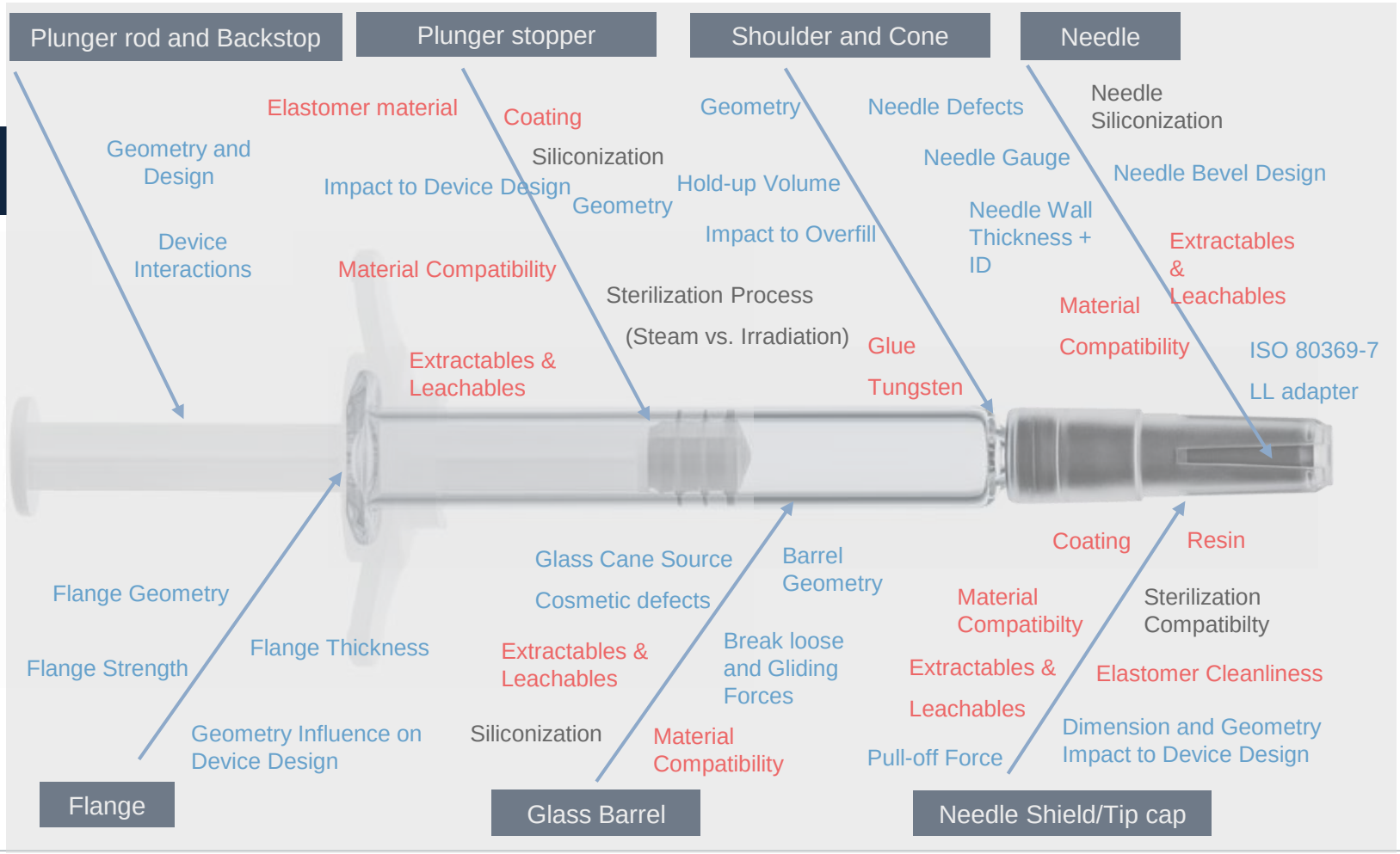
Final Drug Product

Container Closure Integrity

Accuracy of Delivery Dose

Drug Product Stability

Shipping/ Vibration Study



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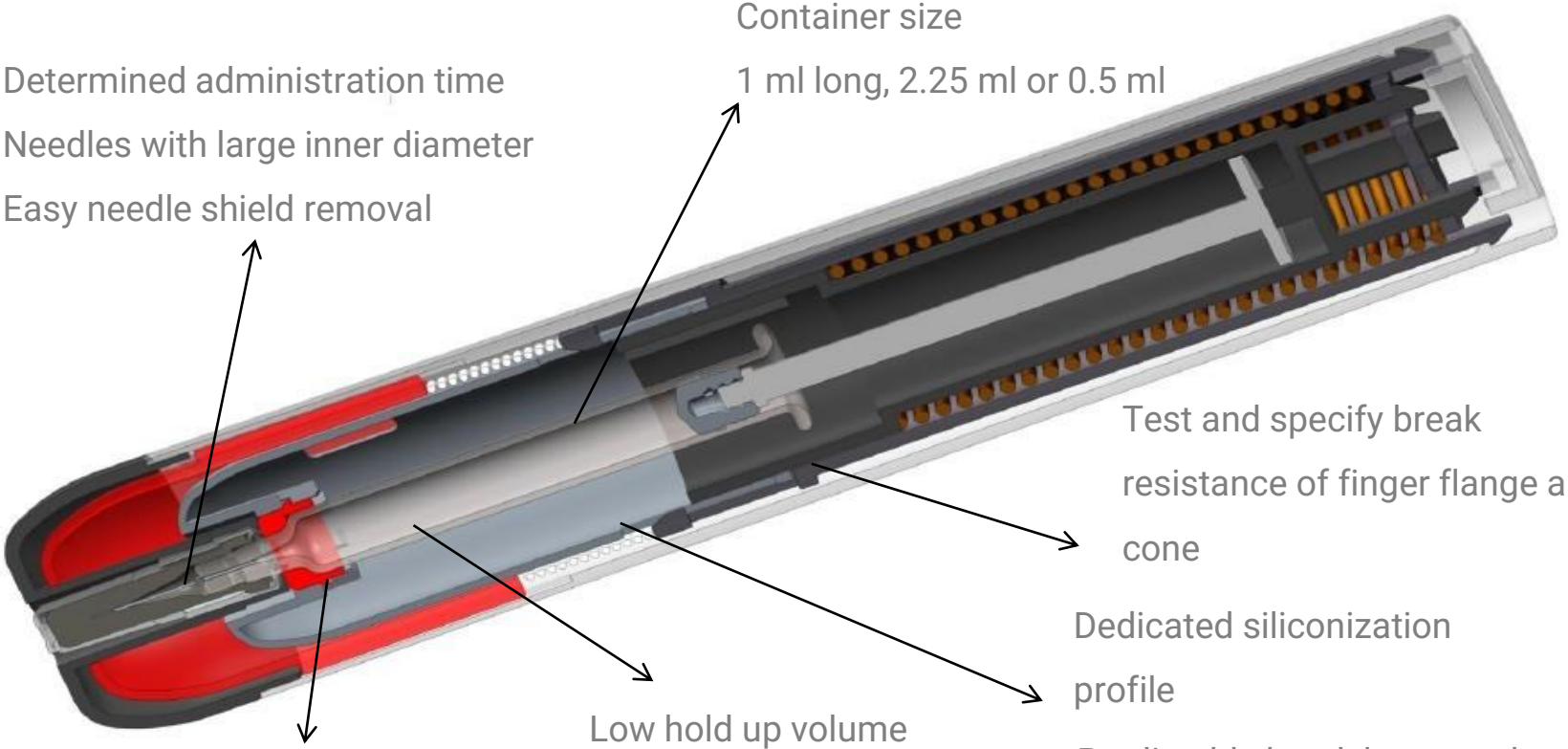
Syringe system with Autoinjector



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 13926-1: Pen cartridges
- ISO 9187-1: Ampoules
- ISO 8362-1: Vials from tubular glass

- 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 -> very complex, see next slides

0.5 ml	47.6	6.85	4.65	1/2
1.0 ml long	54.0	8.15	6.35	1/2
1.0 ml standard	35.7	10.85	8.65	1/2 | 5/8
1.5 ml	43.2	10.85	8.65	1/2 | 5/8
2.25 ml	54.4	10.85	8.65	1/2

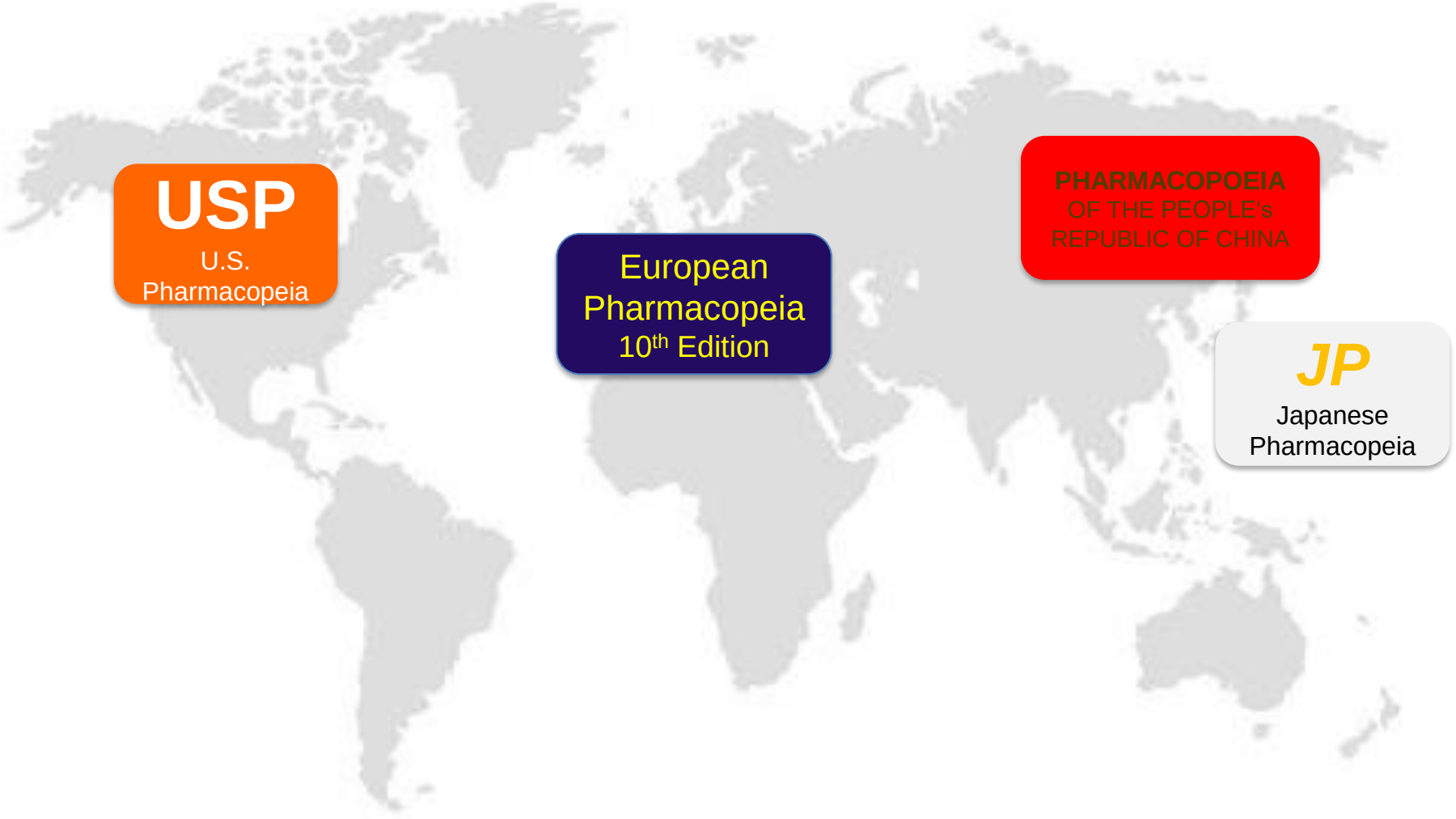
Regulatory Guidelines

Biocompatibility: Biological evaluation of medical devices

ISO 10993:

- 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

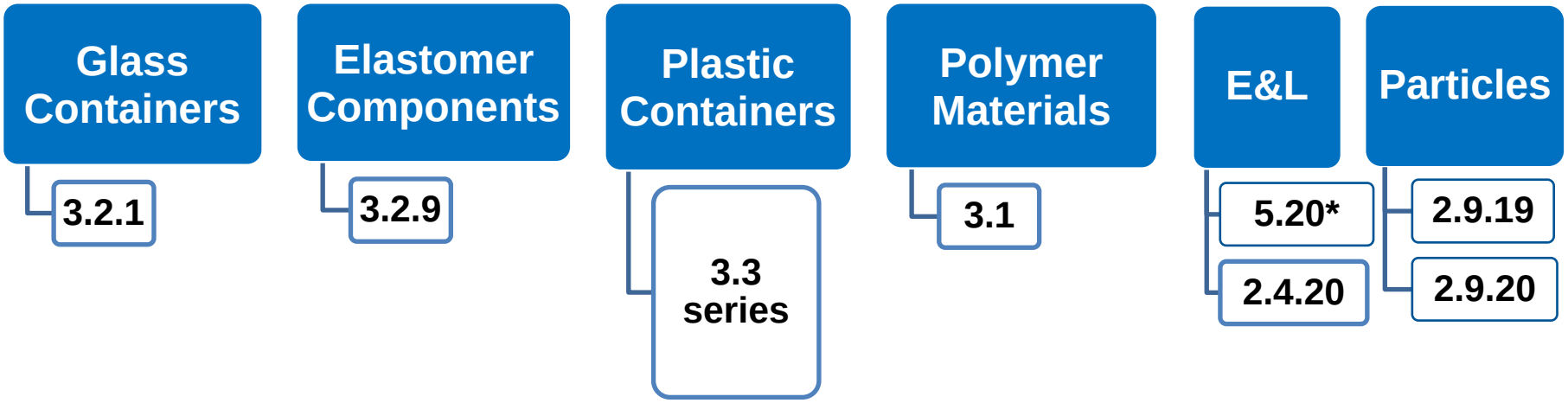
- **Glass Containers**
  - 1660
  - 660
- **Elastomer Components**
  - 381
  - 382**
  - 1381
  - 1382**
- **Plastics Materials & Packaging**
  - 1661
  - 661.1
  - 661.2
- **Polymer Manufacturing Components**
  - 1665
  - 665
- **E&L**
  - 1663
  - 1664
  - 232*
  - 233
- **Particles**
  - 1787
  - 1788
  - 1790
  - 787
  - 788
  - 789
  - 790

Chapters > 1000 informational
Chapters < 1000 mandatory if required by monograph
- **<231> has been deleted**

**** will be official 2025**

Overview of Relevant Ph Eur Chapters

European Pharmacopeia 10th Edition



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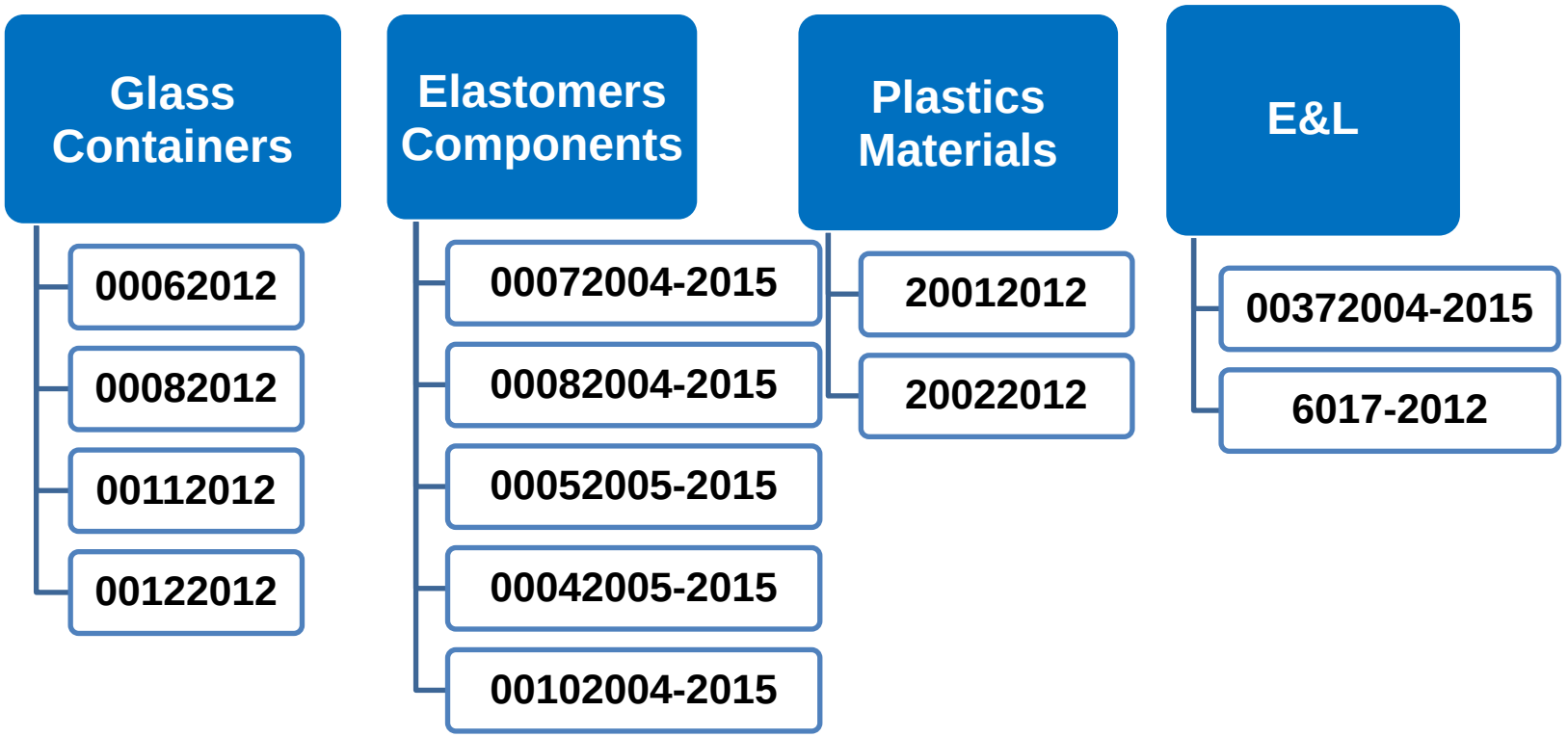
Overview of Relevant JP Chapters

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

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

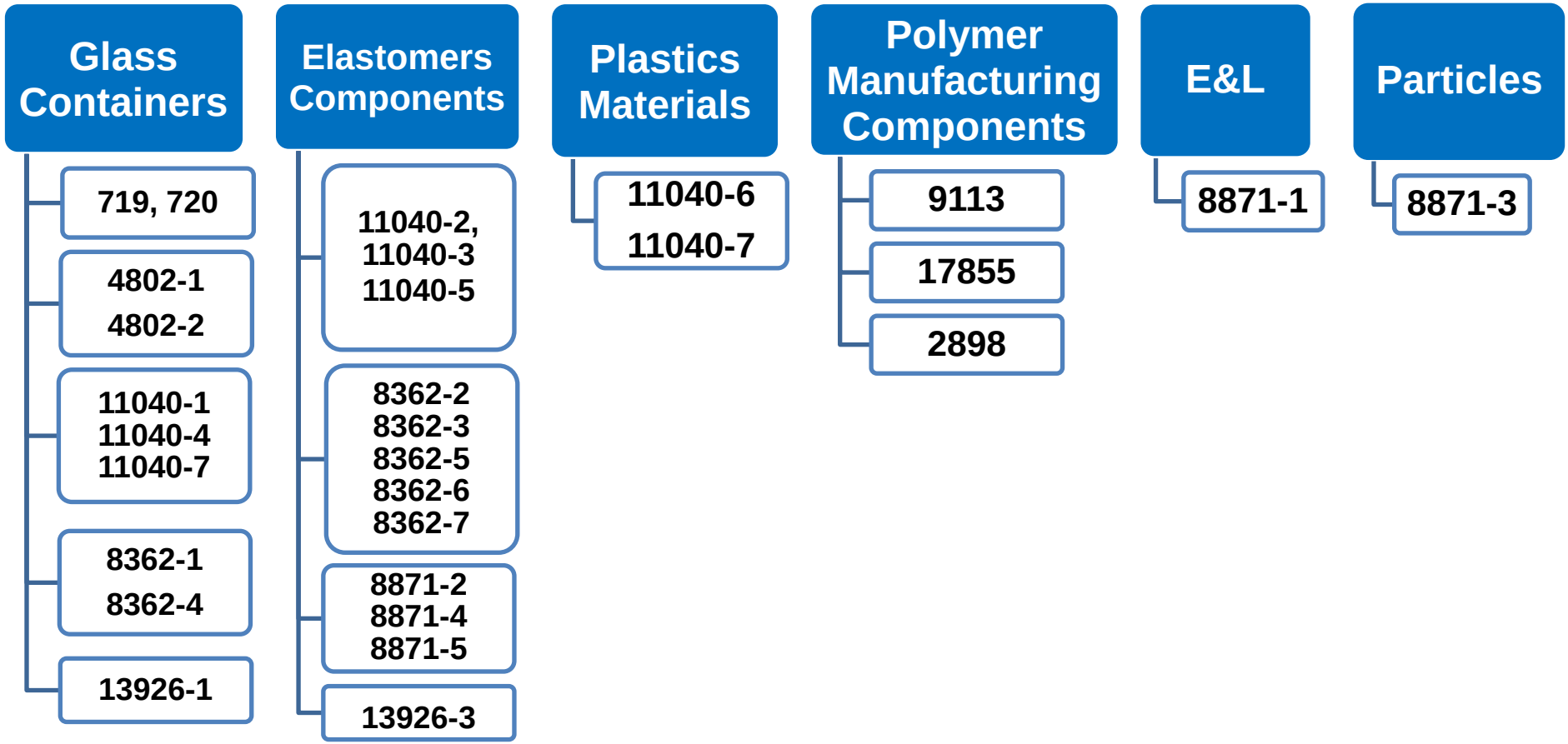
Extract of Relevant ISO Standards

ISO

Glass Containers	Elastomers Components	Plastics Materials	Polymer Manufacturing Components	E&L	Particles
719, 720	11040-2, 11040-3 11040-5	11040-6 11040-7	9113	8871-1	8871-3
4802-1 4802-2	8362-2 8362-3 8362-5 8362-6 8362-7		17855		
11040-1 11040-4 11040-7	8871-2 8871-4 8871-5		2898		
8362-1 8362-4	13926-3				
13926-1					

Extract of Relevant ISO Standards

ISO



Prefilled Syringe Regulation in USA and Europe

No direct comparison between US and EU regulation possible. Different approaches

- Code of Federal regulation - CFR: "Depending on the primary mode of action, prefilled syringes can be classified as either a drug-delivery device (Class II) or a drug-device combination product (Class III).“

- Medical Device Regulation - MDR: "Prefilled syringes are generally classified as Class IIa or IIb devices, depending on the intended use and the degree of invasiveness. No classification as “Medical Device”. A judgement from authorities with statement from Notified Body is required.

Separate Regulatory Workshop recommended

EU: Prefilled Syringe is a Medicinal Product

EU MDR 2017/745, Article 1(8)

Drug delivery system and container closure - in case of PFS:

- ***Prefilled syringe is a single integral medicinal product***
- ***Inteded exclusively for use in the given combination***
- ***Non reusable***

EU MDR 2017/745 Article 1(9)

To be considered:

1. General safety and performance requirements (GSPR) - EU MDR Annex 1 Chapter 1
2. Directive 2001/83/EC or Regulation (EC) No 726/2004, Annex 1 (GSPR) to be applied (EU MDR 2017/745 Article 1(9))
3. A marketing authorisation dossier shall include
   - the results of the assessment of the conformity of the device part with the relevant general safety and performance
   - manufacturer's* EU declaration of conformity or
   - Certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device
   - If the dossier does not include the results of the conformity assessment referred, the involvement of a notified body is required acc. (EU) 2017/745 ARTICLE 117, AMENDMENT TO DIRECTIVE 2001/83/EC

ARTICLE 117, AMENDMENT TO DIRECTIVE, 2001/83/EC

*Pharma company, not packaging manufacturer

MDR - Article 1 - Subject matter and scope - Medical Device Regulation (medical-device-regulation.eu)

USA: Prefilled Syringe is a Combination product

21 CFR
Part 3.2
Part 4
Part 210
Part 211

- ***Consists of drug + device* = Drug delivery device***
- ***PFS is a single entity product***
- ***Syringe in AI or pen *****

*21 CFR Part 3.2 Combination of two or more regulated components out of drug, device and/or biological products (21 CFR Part 3.2)

**21 CFR Part 4 – co-development of drug and device e.g. pen, AI. General cGMP requirements

21CFR Part 210, Part 211: syringe (or cartridge) only

Good arguments needed for choosing a fitting, protective primary container needed (consider volume, formulation, viscosity…)

No „off the shelf device“ possible

Vendor data can help, but will not be sufficient for approval at FDA/EMA

Justify device selection based on design, stability testing, therapeutic area, patient profile, assembly and manufacturing risk, performance, supply chain, sustainability…

Shipping study e.g. acc. ASTM D4169

Design control, design history file (supportive data from primary packaging manufacturer)

Risk management in Design control process - FMEA

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
- Comprehensive documentation and testing necessary
- Risk management required
- Closer cooperation with component manufacturers necessary in future

EU: MDR article 1 (8) and (9)

EU MDR 2017/745, Article 1(8)

EU MDR 2017/745 Article 1(9)

ARTICLE 117, AMENDMENT TO DIRECTIVE, 2001/83/EC

8. *Any device* which, when placed on the market or put into service, incorporates, as an integral part, a substance which, if used separately, would be considered to be a medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma as defined in point 10 of Article 1 of that Directive, and that has an action ancillary to that of the device, *shall be assessed and authorised* in accordance with this Regulation

- However, if the action of that substance is principal and not ancillary to that of the device, the *integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004* of the European Parliament and of the Council, as applicable. In that case, the relevant *general safety and performance requirements set out in Annex I to this Regulation shall apply* as far as the safety and performance of the device part are concerned.

9. *Any device* which is intended to administer a medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC *shall be governed by this Regulation*, without prejudice to the provisions of that Directive and of Regulation (EC) No 726/2004 with regard to the medicinal product.

- However, if the device intended to administer a medicinal product and the medicinal product are placed on the market in such a way that they form a *single integral product* which is intended exclusively for use in the given combination and which is *not reusable*, that single integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable. In that case, the relevant *general safety and performance requirements* set out in *Annex I* to this Regulation *shall apply* as far as the safety and performance of the device part of the single integral product are concerned.

- 2017/745 ARTICLE 117, AMENDMENT TO DIRECTIVE 2001/83/EC

MDR - Article 1 - Subject matter and scope - Medical Device Regulation (medical-device-regulation.eu)

EU: Article 117 - Amendment to Directive 2001/83/EC

EU MDR 2017/745, Article 1(8)

EU MDR 2017/745 Article 1(9)

ARTICLE 117, AMENDMENT TO DIRECTIVE, 2001/83/EC

‘(12) Where, in accordance with the second subparagraph of Article 1(8) or the second In Annex I to Directive 2001/83/EC, point 12 of Section 3.2. is replaced by the following:

‘(12) Where, in accordance with the second subparagraph of Article 1(9) of Regulation (EU) 2017/745 of the European Parliament and of the Council (*1), a product is governed by this Directive, the *marketing authorisation dossier shall include*, where available, the *results* of *the assessment* of the conformity of the device part with the relevant *general safety and performance requirements* set out in Annex I to that Regulation contained in the manufacturer's EU declaration of conformity or the relevant certificate *issued by a notified body* allowing the manufacturer to affix a CE marking to the medical device.

If the *dossier does not include the results* of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the *involvement of a notified body is required* in accordance with Regulation (EU) 2017/745, the authority shall require the applicant to provide an *opinion on the conformity of the device part* with the relevant general safety and performance requirements set out in Annex I to that Regulation issued by a notified body designated in accordance with that Regulation for the type of device in question.

MDR - Article 1 - Subject matter and scope - Medical Device Regulation (medical-device-regulation.eu)