Combination Products in the EU

From Regulatory Compliance to Clinical & Market Acceleration

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12.05.2026

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Provides a broad range of technologies and services for reliable and user-friendly injection systems for self-medication

- Founded in 1984, scope insulin pumps
- Based in Switzerland
- First pen marketed in 2010
- First autoinjector in 2018
- 10+ developed platforms:
  - **Pen Injectors** -> disposable & reusable
  - **Autoinjectors** -> disposable
  - **Connected devices** -> reusable
  - **On body delivery devices** -> disposable

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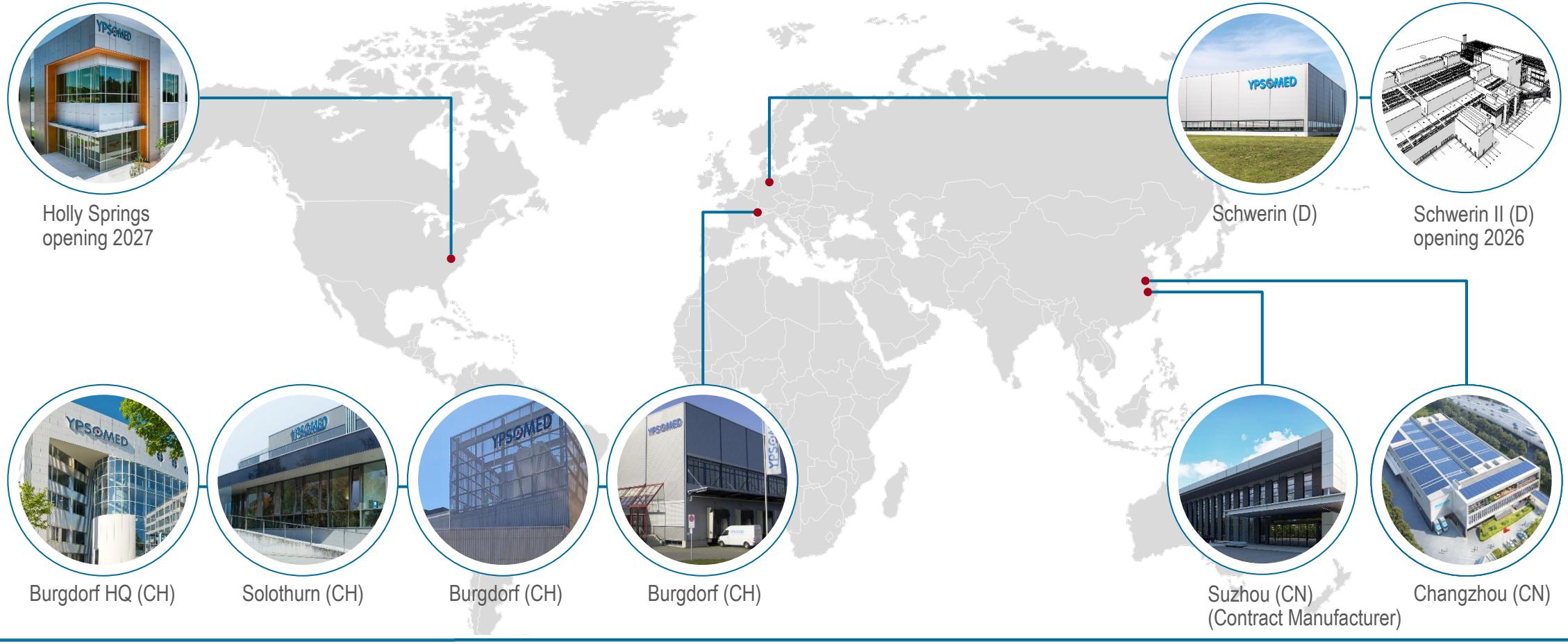
Ypsomed: Global manufacturing footprint



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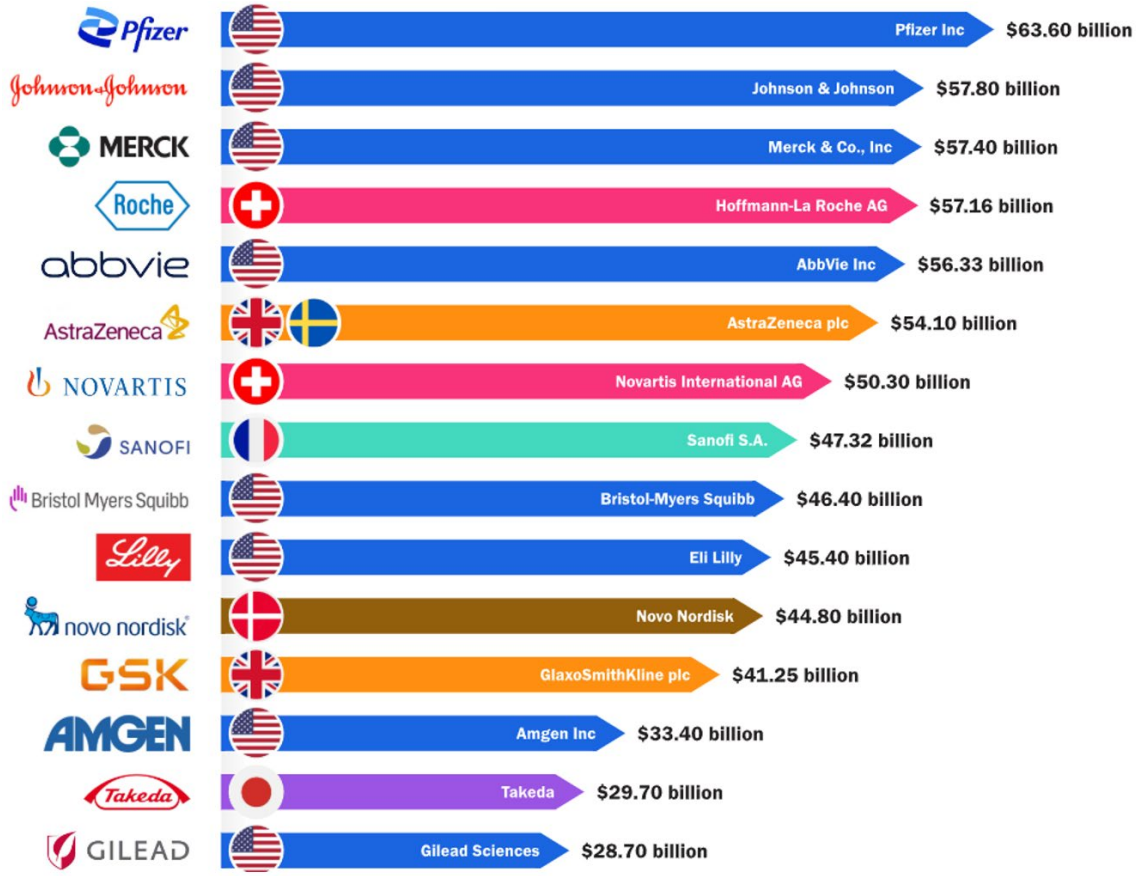
Top 15 largest Pharmaceutical Companies in the world 2025

They are all customers of Ypsomed



Source: GetReskilled, based on company annual reports (2024)

Agenda

1. Definitions
2. Regulatory Landscape
3. Self-Injection Devices
4. Pharma Responsibility
5. Platform Approach
6. Clinical Bridging Approach

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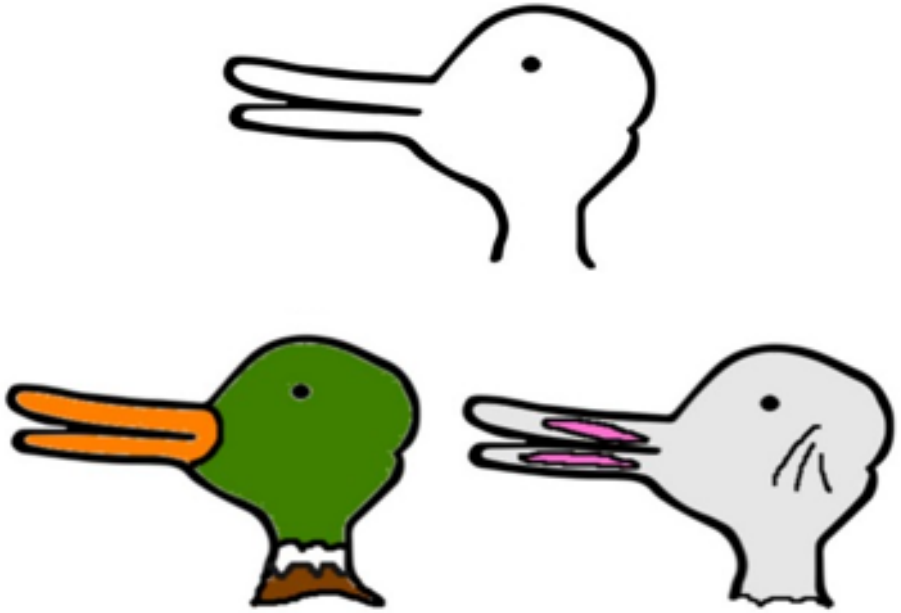
1.
Definitions

General Challenge

What animal is this?



Bringing definitions and criteria
from Medicinal Product Regulations and Medical Device Regulations
together

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Terminology Differences – Helpful to Understand

Master Project Plan	Design & Development Plan
Target Product Profile	User Needs & Design Inputs
Specifications, Drawings, MBR	Design Outputs
CMC Stage Gate Reviews	Design Reviews
Characterization / Suitability	Design Verification
Clinical Studies	Design Validation
Guidance on Medication Errors	Human Factors
Technology Transfer / MBR	Design Transfer / Medical Device File
Product Dossier & Dev. Reports	Device & Development File
Master Batch Record	Medical Device File
Risk Analysis, Controls & Residuals	Risk Analysis, Controls & Residuals
eCTD	MDF, TD, STED
Pharmacopoeia (Ph.Eur., USP, JP)	ISO Standards, EN ISO Standards

Source: Amended based on presentation from Susan Neadle at PDA, 2018 on Product development challenges for drug/device combination products

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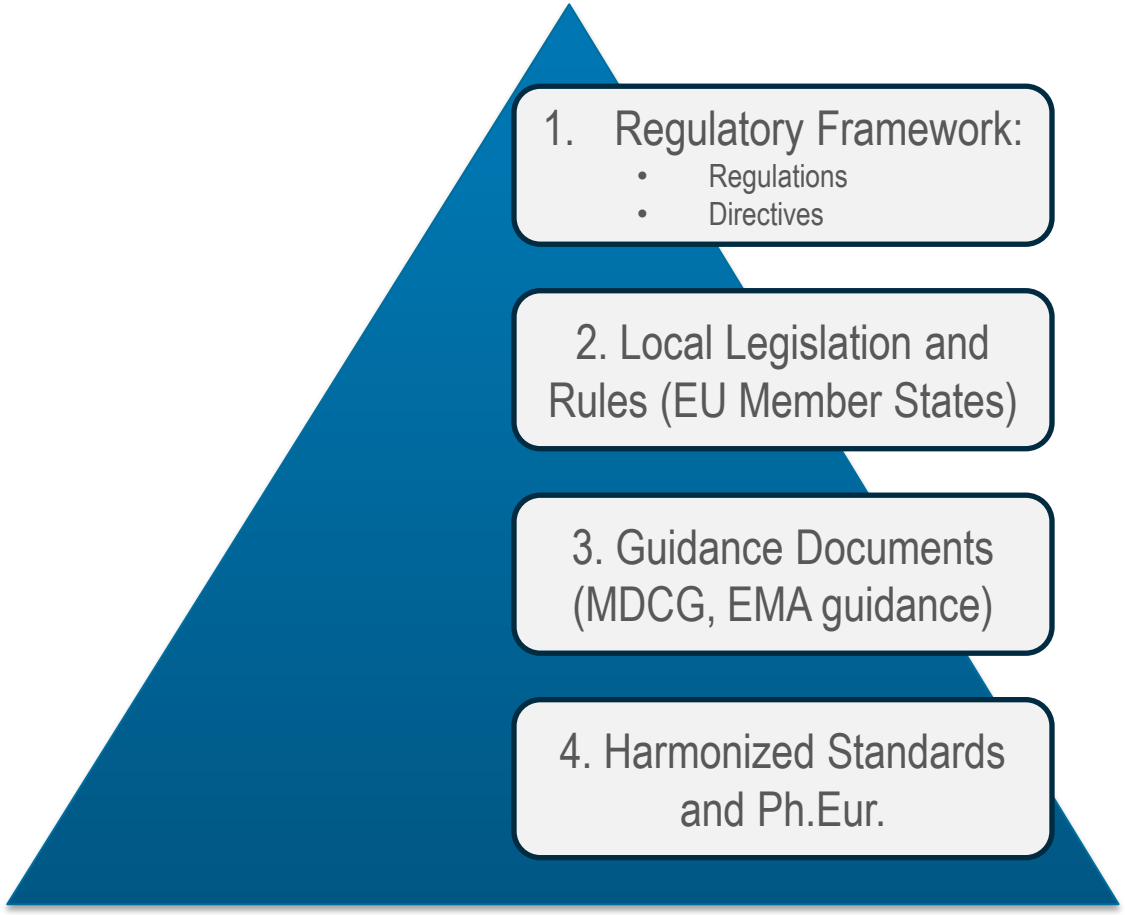
Refresher: Legal Hierarchy (EU)



- Regulations set the mandatory framework: MDR, MPD.
- National rules adapt and enforce locally.
- Guidance explains expectations.
- Standards and CS provide the technical route to conformity.

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Medical Device Definition

MDR Regulation (EU) 2017/745, Article 2(1)

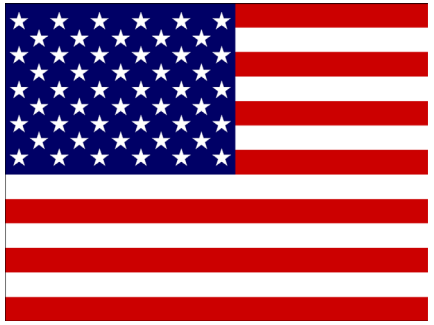
…**any instrument, apparatus, appliance, software, implant, reagent, material or other article…**

intended by the manufacturer for human use for one or more specific medical purposes, including:

- diagnosis, prevention, monitoring, **prediction, prognosis**, treatment or alleviation of disease or injury or **disability**;
- investigation, replacement or modification of anatomy or of a physiological or **pathological process or state;**
- and certain related purposes such as **supporting/sustaining life, control/support of conception,** and **cleaning/disinfection/sterilisation of devices…**

… and which **does not achieve** its principal intended **action by pharmacological, immunological, or metabolic** means, **in or on human body but which may be assisted in its function by such means.**

Combination Product Definition



US 21 CFR 3.2(e)

- **Clear legal definition** of a combination product.
- **Two or more regulated components** (drug, device, biologic) combined as a **single entity**.
- **Separate products packaged together** in one package.
- Products **packaged separately** if **cross-referenced** via labeling and intended only for use in a given combination.

EU MDR & MPD

- **No single overarching legal definition** in the legislation.
- Regulatory path depends **on configuration** and **principal mode of action (PMOA)**:
  - **Medicinal product with an ancillary device** → Directive 2001/83/EC / Reg. 726/2004 + **MDR Annex 1 (GSPRs)** → **NBOp**
  - **Device with an ancillary medicinal substance** → **Full MDR + Opinion from CA**

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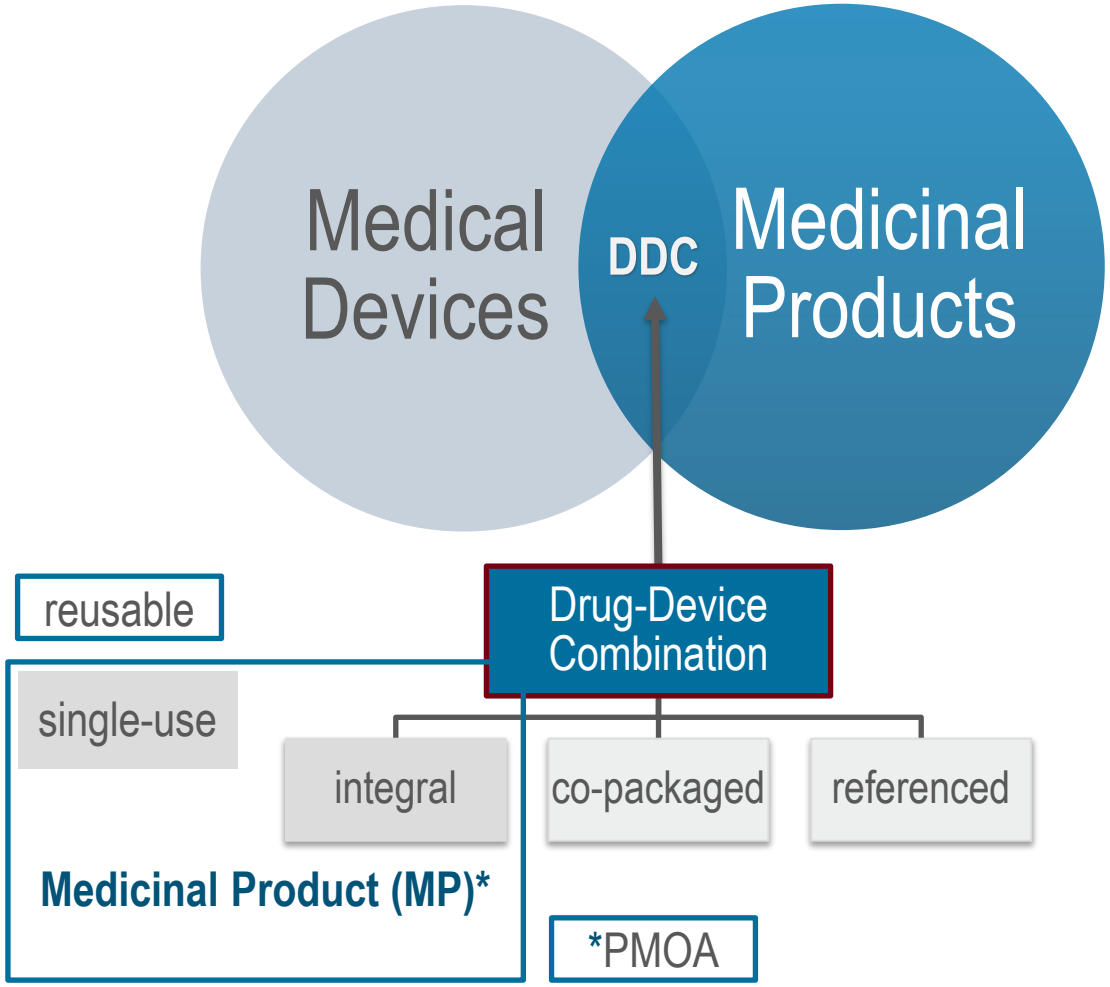
EU: Drug-Device Combinations (DDC)



Drug-Device Combinations – Some Examples

DDC - Single integral

Pre-Filled Syringe

Pre-Filled Pen

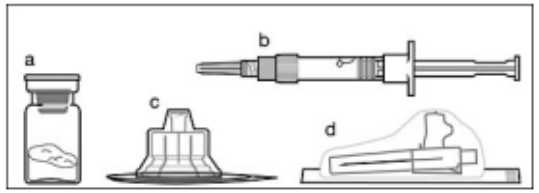
Pre-Filled inhaler

Integral DDC (iDDC)

DDC – cross labeled DDCs

- Product label referring to specific device/drug to be used with
  - Drug label referring to specific injector

DDC – co packaged



Not DDCs

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2.
Regulatory Landscape in the EU

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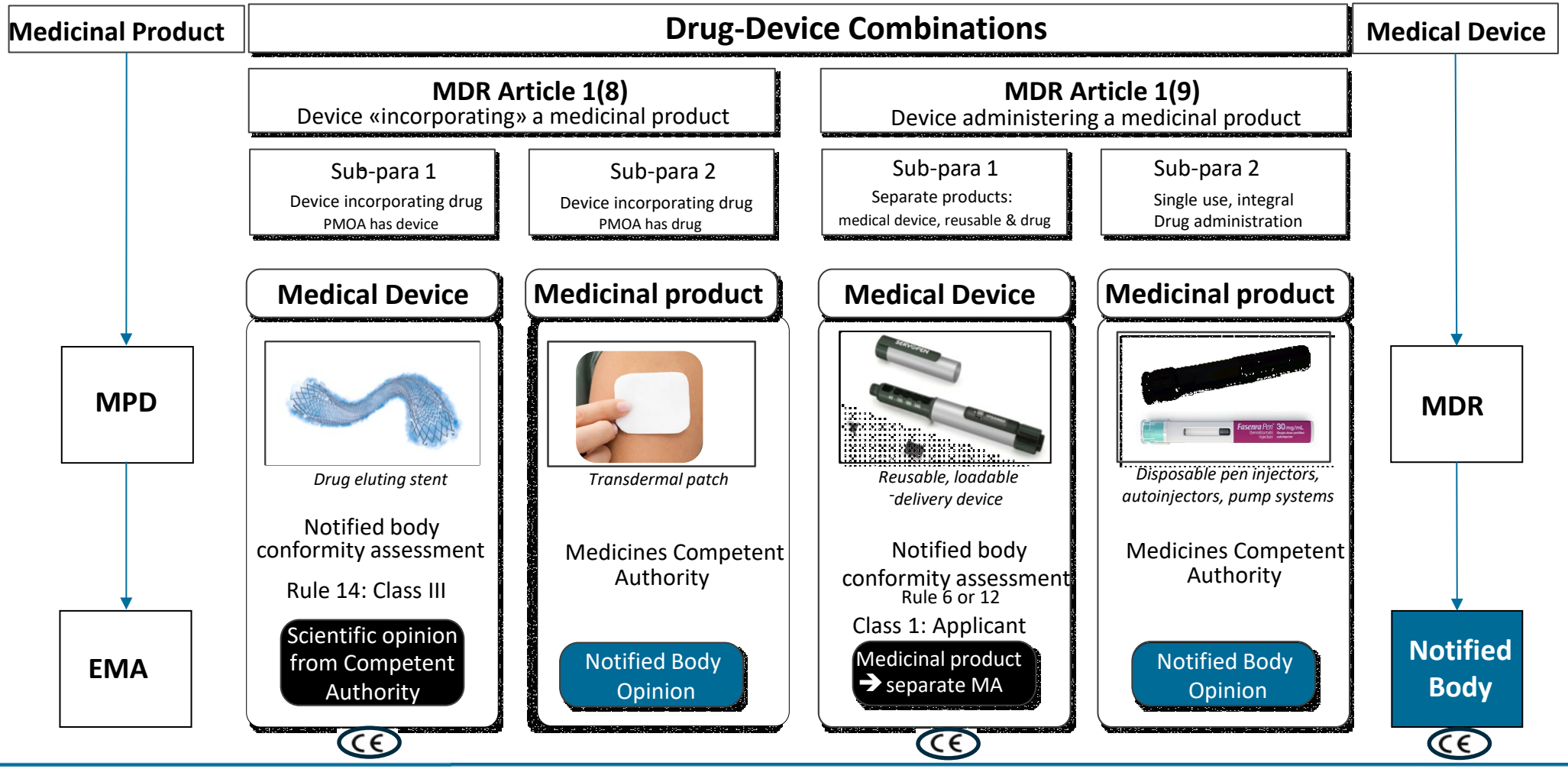
EU Regulatory Paths



Source: Adapted from: Marc Chipperfield @TOPRA/RAPS Inter-regulatory and stakeholder workshop, 20/11/2018

Integral DDC – MDR Art. 1(8) and 1(9) Second Sub-paragraph

Device intended **to administer** a medicinal product

MDR Art. 1(9), 2nd subparagraph

Device **incorporating** a medicinal substance

MDR Art. 1(8), 2nd subparagraph

Single & Integral

Medicinal substance: **PMOA***

2001/83/EC Medicinal Products Directive

+

Art.117 EU 2017/745

May 26 2021

* PMOA Principal Mode of Action

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Integral DDC - MDR Art. 117: amendment to MPD

"If the MA dossier does not include the results of the conformity assessment **[....]** and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required [...] 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 [...]

If the device constituent part product has no:

- EU Certificate and Declaration of Conformity
- Self-Declaration of Conformity (Class I)

and has a theoretical risk class:

- **Higher than Class I**

then:

- **Notified Body Opinion (Assessment based on GSPR)**

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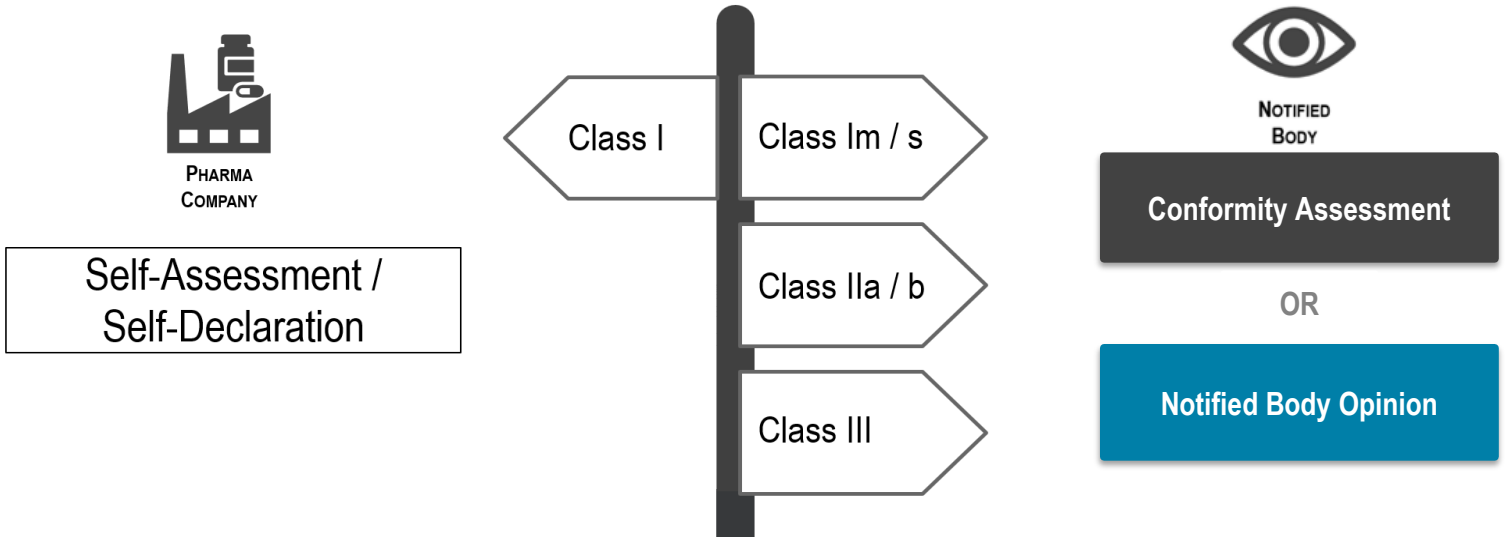
Integral DDC - Theoretical Risk Classification

Risk Class – decision point on NB involvement

- **MDR: Annex VIII**
- **MDCG 2021-24**: Guidance on classification of Medical devices



Declaration of Conformity vs Notified Body Opinion

MDCG 2019-15 Guidance

Declaration of Conformity	Notified Body Opinion
MAH becomes Medical Device Manufacturer fulfilling all applicable obligations and requirements of MDR	No obligations as Medical Device Manufacturer
Affixing a CE mark to the medical device part	No CE mark of medical device required
Put in place a quality management system and draw up the technical documentation According to Annex II and Annex III + Surveillance activities	Quality Management according to the requirements of Medicinal Product Directive
Conduct a clinical evaluation in accordance with Article 61, as established in Article 10(3) and Annex XV.	Clinical Data based on performance
Assign to the device a UDI which will allow identification and traceability.	Labeling requirements following Medicinal Product Directive requirements

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Role of a Notified Body (NB)

Who is it: Independent third-party designated under the EU MDR.

What it checks: Device (parts) compliance with MDR / relevant GSPRs.

What it reviews: Technical Documentation and Supporting documents.

What it provides: EU certificate or Notified Body Opinion (NBO)

NANDO: EU database to find notified bodies

Notified Bodies' Map

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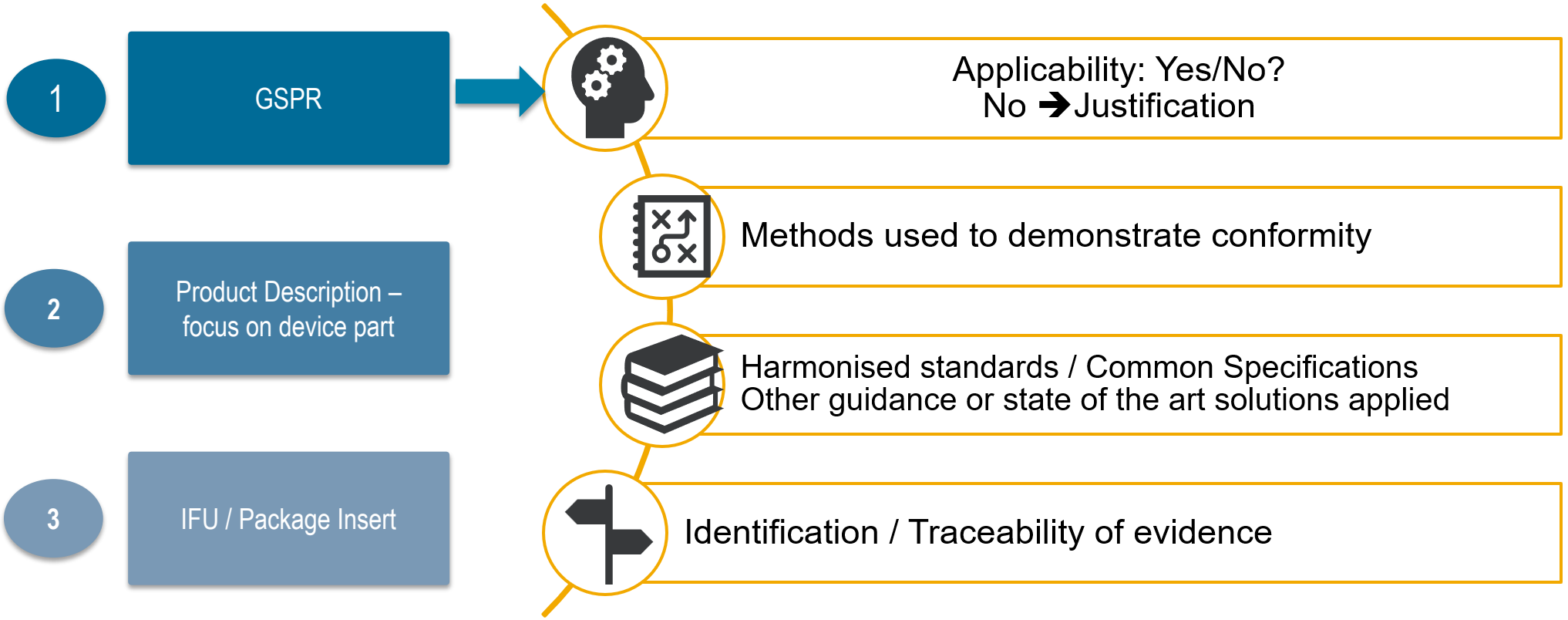
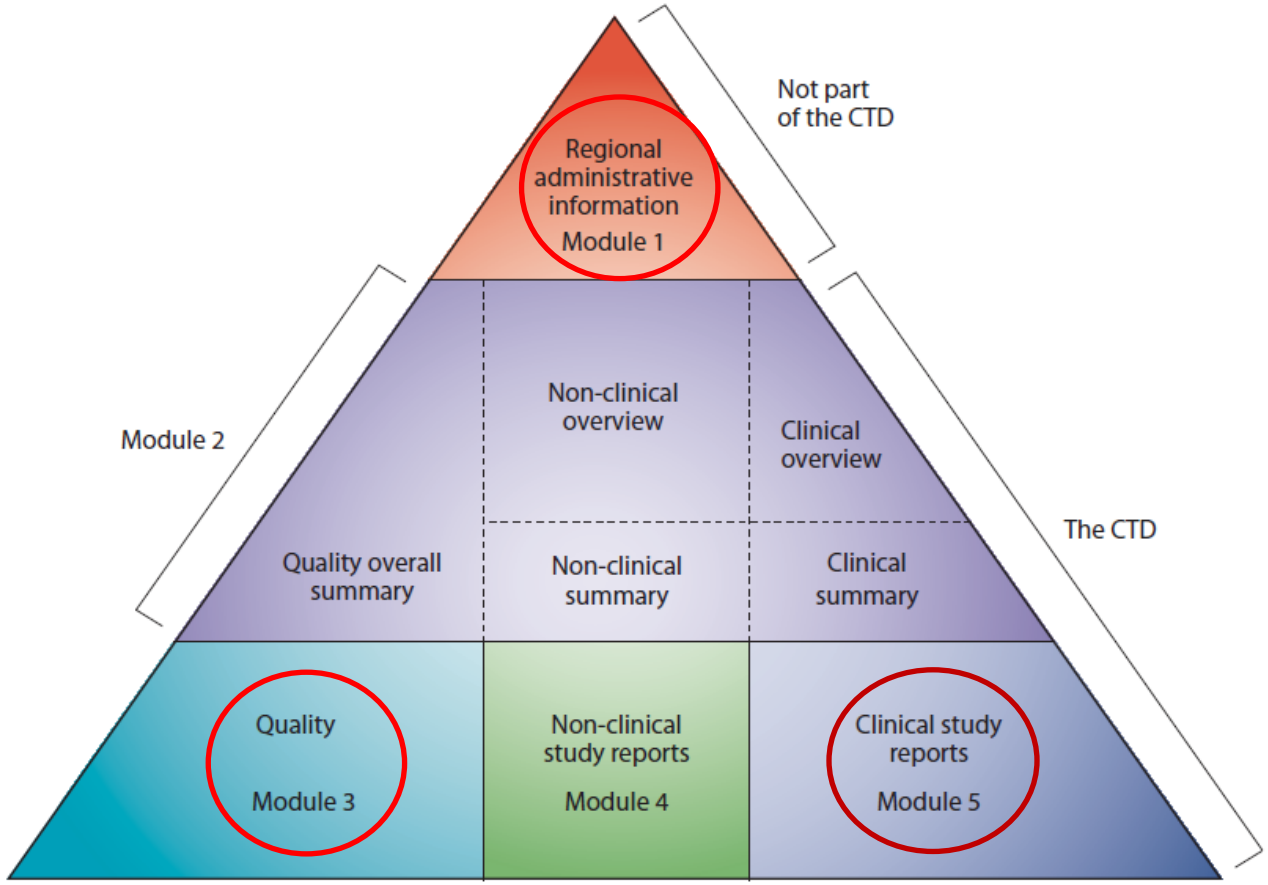
Integral DDC – content of Technical Documentation



MDR: Annex I (GSPR)

MDR: Annex II (Technical Docmentation)

Information on the Device in eCTD



Information on the device provided in el. **Common Technical Document (eCTD)** format:

- **Module 1** – CE evidence or NBOp
- **Module 3** - specific **quality aspects related to the device**
- **Modul 5 -** validation summary report form **Human Factors** study.

Source: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf

3.
Self-Injection Devices

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Primary Drug Container and Self-Injection Devices

Vial & syringe

Pre-filled syringe

Cartridge

Auto-injector

Typically, single injections, non-preserved formulations

Pen Injector

Typically, multiple injections, preserved formulations

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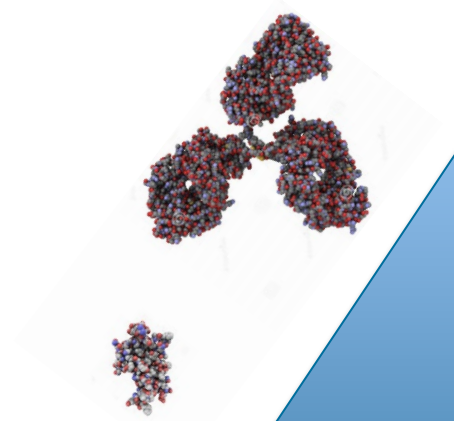
Injection Devices – Segmentation by Injection Volume



10-50 mL
Biologics

Biologics 2-10 mL

Biologics <2.25 mL

Small molecules and biologics <1.0mL

Small molecules, hormones and biologics
in small, preserved doses <0.5mL

20+mL injectors

Patch injectors 5-10 mL

Autoinjectors 2-5 mL

Autoinjectors for 2.25 mL PFS

Autoinjectors for 1 mL long PFS

Pen injectors for 3mL cartridges

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Injection Devices – Segmentation by Therapy Areas

Indications for pens

- Diabetes (insulin, GLP-1)
- Obesity (GLP-1)
- Growth disorders (hGH)
- Fertility (FSH)
- Osteoporosis (PTH)
- Parkinson's (Apomorphine)

Indications for autoinjectors

- Diabetes and Obesity (GLP-1)
- MASH (metabolic dysfunction-associated steatohepatitis)
- Autoimmune disorders
- Asthma, respiratory diseases
- Immuno-oncology
- Migraine
- Psoriasis

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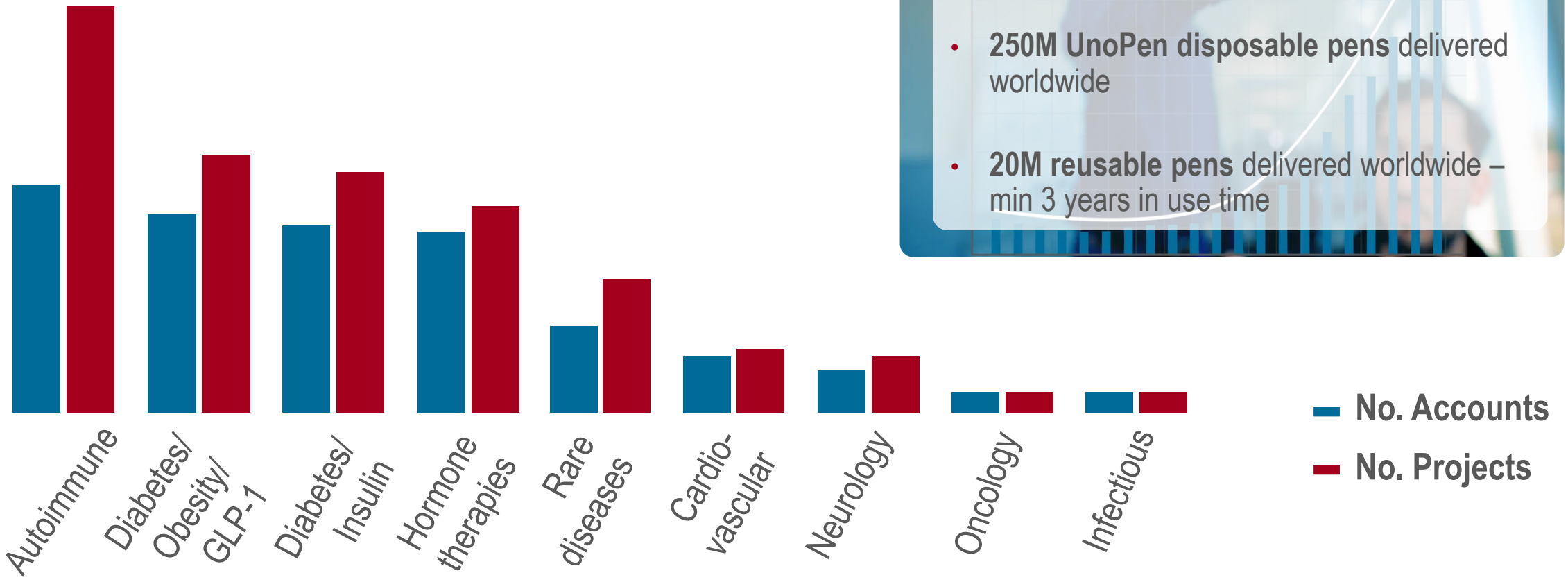
Disease Areas Reflected in Our Projecs



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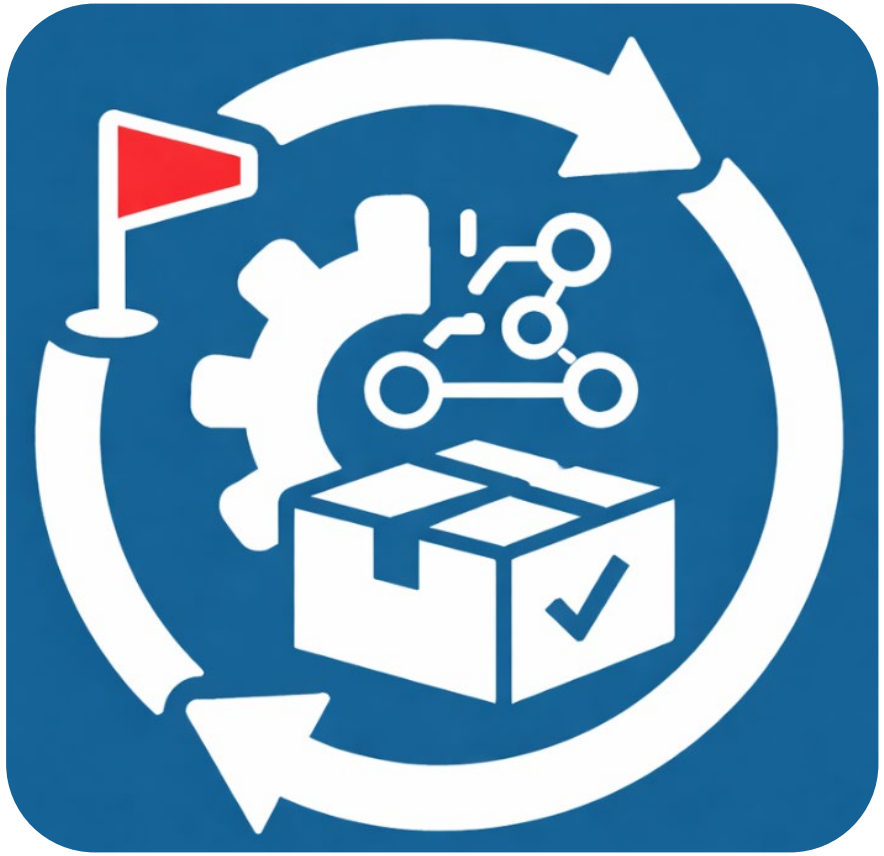
4.
Pharma Responsibility



Integral DDC: Release Specification and Control of Device Performance

What a pharma QP should check

Medicinal Product

Critical Quality Attributes

- Identity & Strength
- Purity
- Potency
- Stability
- Sterility
- Container Closure Integrity
- E&L
- Compatibility with the Drug

Device Constituent

Critical Functional Parameters

- Primary Functions (ISO 11608): Dose Accuracy, Needle extension, Injection time
- Further essential parameters: Pen Cap Removal, Feedback Functions, Needle Retraction Distance, Lock out Force,
- Final Assembly: CoA from CMOs
- (Shelf-Life)

Integral DDC: pharma QP must ensure both critical parameters are verified before releaase

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Responsibilities of Device Manufacturer and Pharma

Medical device Manufacturer

- Device Biocompatibility
- Formative Usability Study
- Risk assessment of design, manufacturing and shipment of the subassembly unit
- Device Design Verification (including aging and device transport verification)

Pharma (MAH)

- Clinical Assessment
- Extractables/Leachables
- Summative Usability Study
- Final product risk assessment
- Final product stability and transport verification
- Final Assembly
- Packaging and labeling of the final product.

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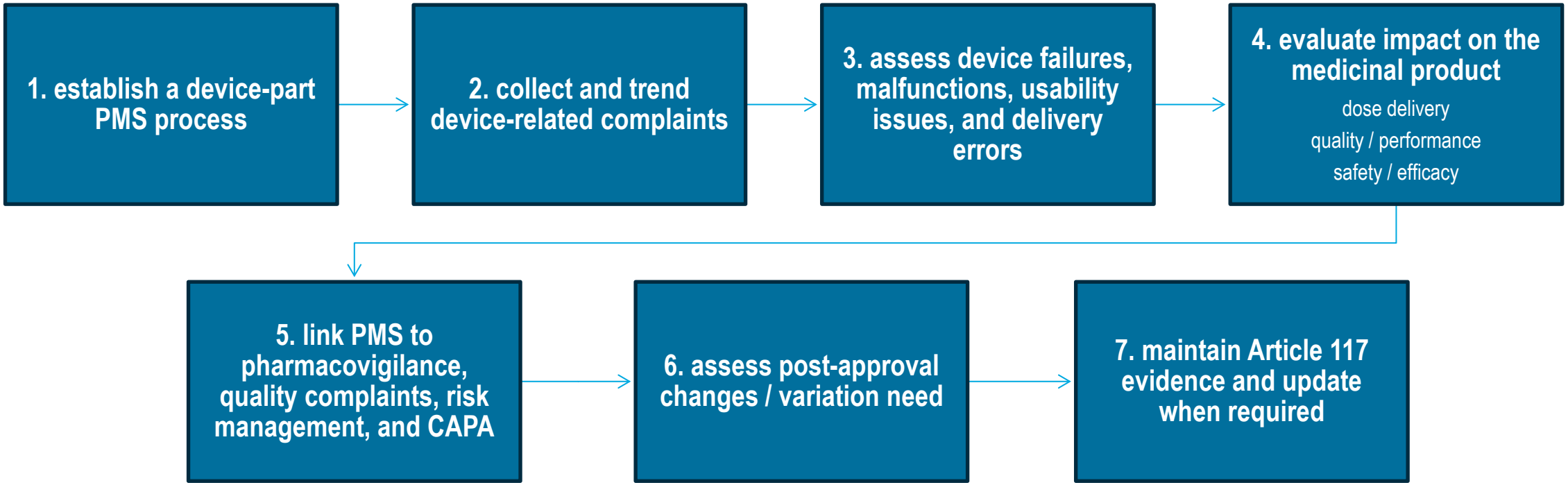
Post Market Surveilance - Obligations of the pharma company

For the integral DDC, the MAH should:



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5.
Platform Approach

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Definition of Platform Approach and Platform Technology

Platform Approach

When a technology (drug constituent, biologic constituent or device technology or software) is used as a base upon which other applications, processes, or products are supported or developed.

Platform Technology

1. Medical device or medical device system that may be suitable for use with various medicinal products and whose pre-existing device data or information, or both can be leveraged in whole or in part to support such use,

2. Medicinal product formulation that may be suitable as a platform for use with various medical devices.

Source: Combination Products Handbook, A Practical Guide for Combination Products and Other Combined Use Systems from Susan W. B. Neadle

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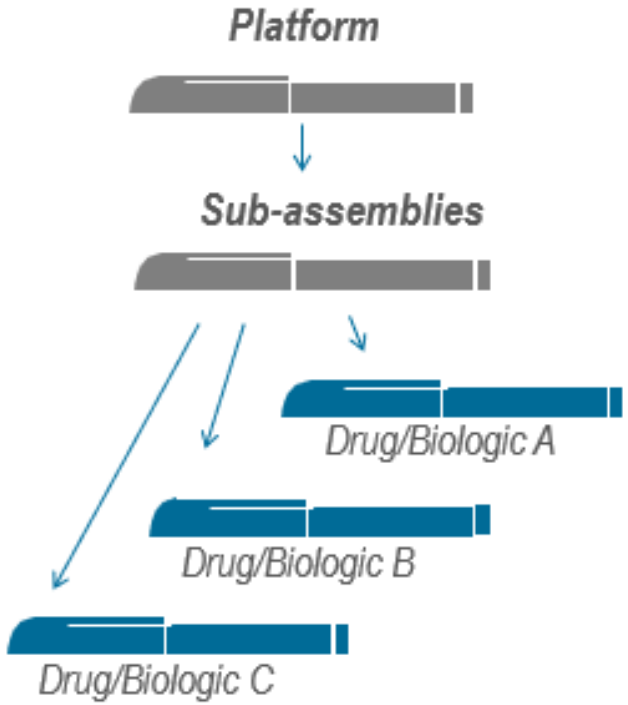
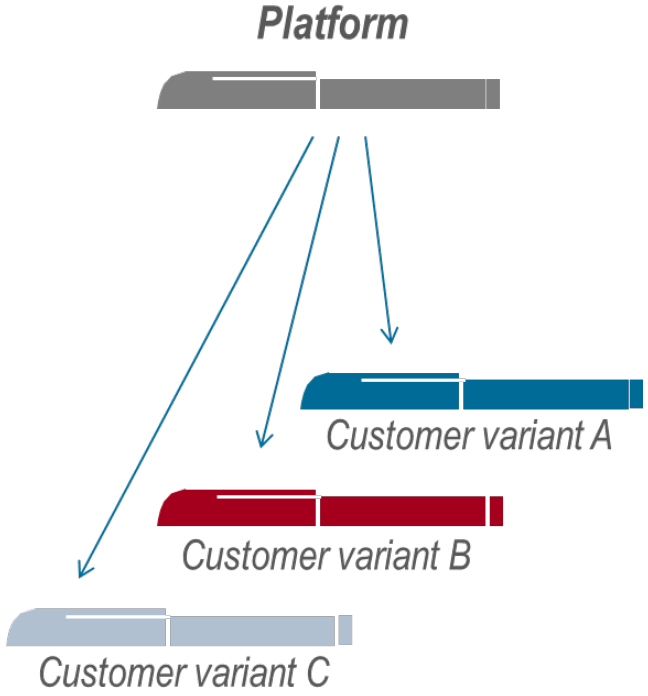
Platform strategies

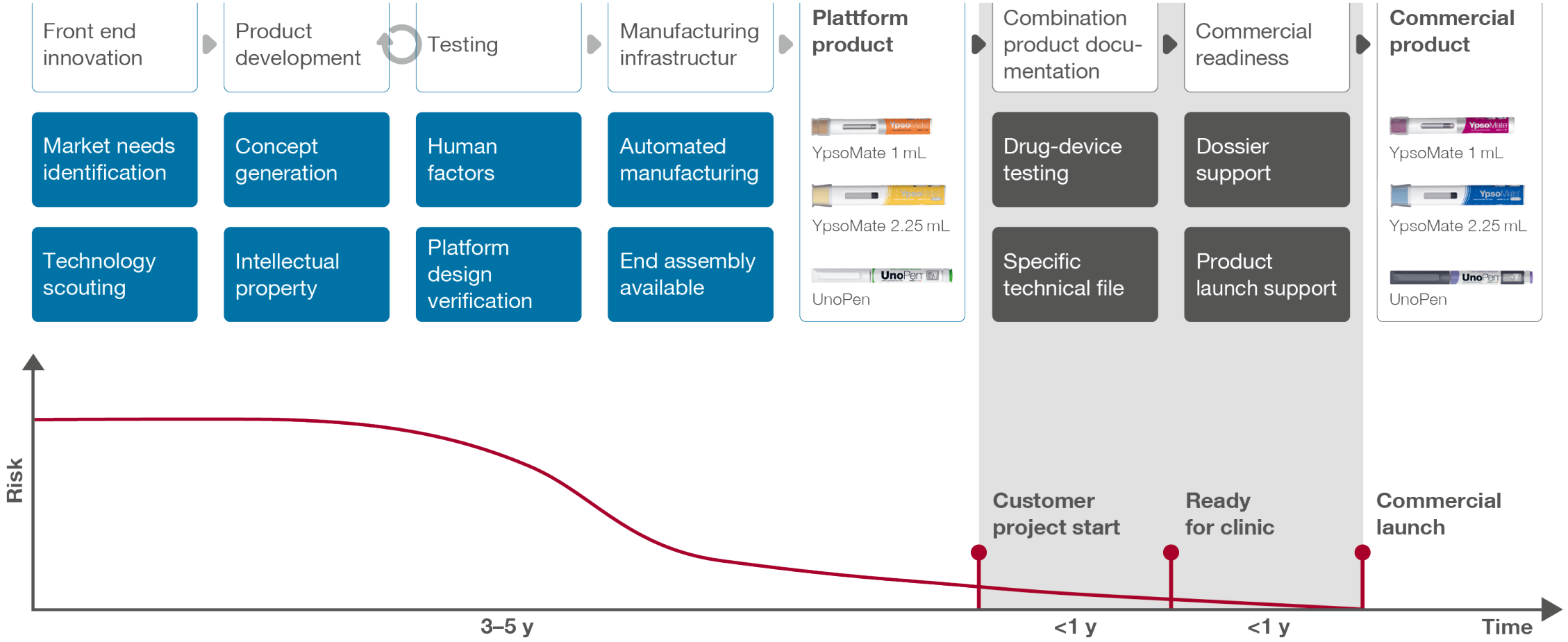


Platform-to-Platform: based on pre-configurated devices with limited customization options



Modular Approach: Platform for development purpose and further customization

1) Modular Platform and Conventional Variant Development Strategy



2) Platform-to-Platform Approach

Drug development program

Study protocol IIb/III

SUBMIT

Clinical study IIb/III with autoinjector

SUBMIT

PK bridging study

Market launch

Submission with Ypsomed's clinical documentation

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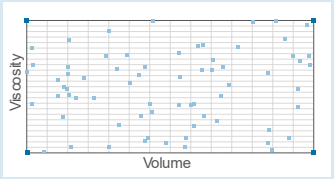

Robust platform performance data

Rapid supply of clinical devices and DV data

Short and coordinated supply path < 6 months

Customized commercial devices

Bridging to clinical device + commercial product documentation

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Platform Benefits

SHORTER TIME TO CLINIC/MARKET

DECREASED DEVELOPMENT COSTS

REDUCED DESIGN RISK

STREAMLINED VERIFICATION AND DOCUMENTATION

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6.

MIDBA – EMA Approved Clinical Bridging Approach

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MIDBA: simple explanation

Molecule-**I**ndependent **D**evice **B**ridging **A**pproach

Approach to support a switch from manual / PFS injection to an autoinjector without repeating a new PK bridging study for every eligible mAb.

What changes

manual / PFS

→

What MIDBA uses

existing PK data from reference mAbs

→

AI switch

Who collaborated

- **Roche proposed the methodology to EMA**
- Validated AI set-up: YpsoMate 1.0 and 2.25 mL with Ypsomed
- Reference mAbs: omalizumab and gantenerumab

What EMA approval means

- **It is a qualification opinion for a method — not a product approval**
- CHMP adopted it on 26 Feb 2026
- EMA published it on 20 Mar 2026

MIDBA can reduce repeated PK device-bridging work for an eligible manual / PFS → autoinjector switch

But only when the product stays inside the qualified MIDBA scope.

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MIDBA: simple explanation

To use MIDBA, what must stay the same?

Must be the same / identical

- ✓ **Same mAB**
  including the product used for manual and autoinjector presentation
- ✓ **Same dose**
- ✓ **Same formulation**
  including identical excipients at the same concentrations
- ✓ **Same injection volume**
  within the qualified range of 0.5–2.0 mL
- ✓ **Same injection site(s)**
  use only sites already supported for manual injection

Must also fit MIDBA scope

Not identical — but still required

- Exposed needle length: 4–8 mm
- Slow absorption after SC injection
- Physicochemical properties similar to at least one reference mAb
- If the AI device or key specs change, extra data / justification are needed

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KEY TAKEAWAY

Key Takeaways

The EU pathway is defined by product configuration and principal mode of action.

Platform approaches can accelerate development when reuse stays within clearly defined limits.

For integral combinations, Art. 117, risk classification, and Notified Body expectations should be addressed early.

Clinical bridging can be streamlined, but only within a qualified and justified scope.

Self-injection is expanding across volumes, indications, and device formats.

Combination products require **stronger control of interfaces** — especially between **drug and device requirements**, **outsourced** activities, and **QP / MAH oversight.**

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Thank you & happy to stay in touch!

Questions?

Topics I'm always happy to exchange on.

- Combination product and medical device registration strategies
- Platform approaches and self-injection devices
- Pragmatic development and commercialization pathways
- …

Always happy to continue the discussion - on LinkedIn or after the session.

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