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EU Regulatory Roadmap for Class III Medical Devices with Ancillary Medicinal Substances under MDR Rule 14

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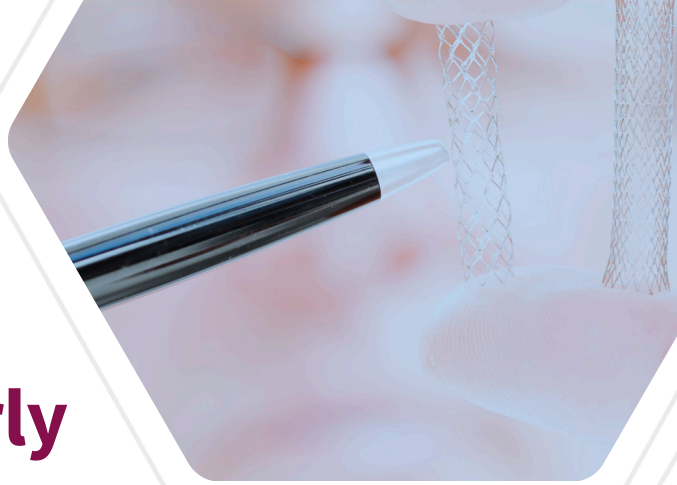
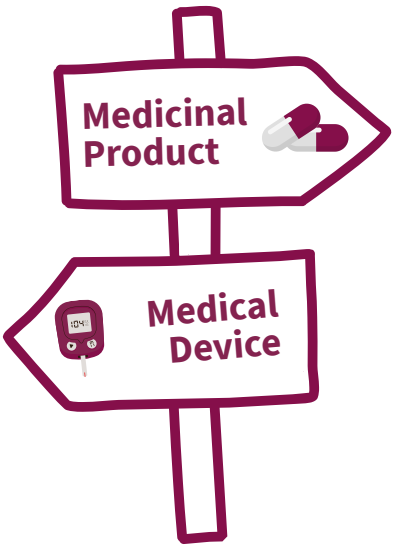


The Importance of Early Product Qualification

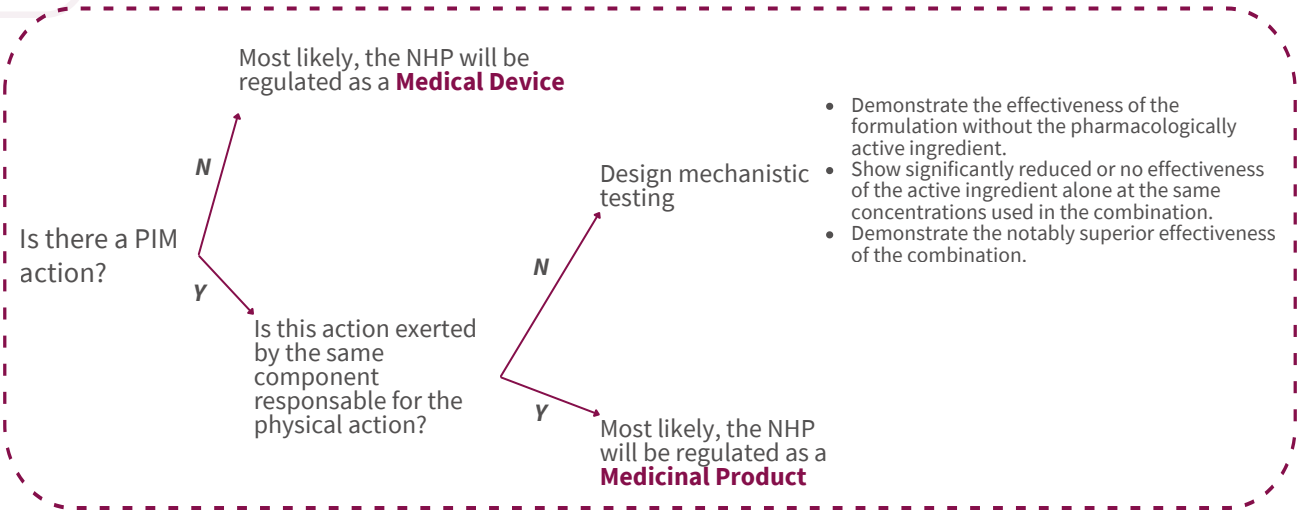
Determining the correct regulatory pathway for a product with a medical intended purpose at an early stage is one of the most critical steps in the development of the technology.

The product's principal intended action is determined as being either mechanical/physical (device) or pharmacological/immunological/metabolic (medicinal). Under Medical Device Regulation (UE) 2017/745 (MDR) Article 1(6), if the primary effect is medicinal, the product falls under pharmaceutical law (Directive 2001/83/EC relating to medicinal products for human use).



The principal mode of action shall be documented and scientifically justified. If a drug device combination's intended effect is achieved by the incorporated medicinal substance, then, the whole combination is a medicinal product. This hierarchy (device vs. medicinal) is reinforced in the MDCG 2022-5 guidance.

Attention is needed with certain exceptions, for example, in vivo diagnostic agents (contrast media, MRI enhancers) are classified by definition as medicines. The EU borderline guidance provides examples of the classification rationale for borderline products, as applied by experts designated by the European Commission.



PIM: pharmacological , immunological or metabolic action

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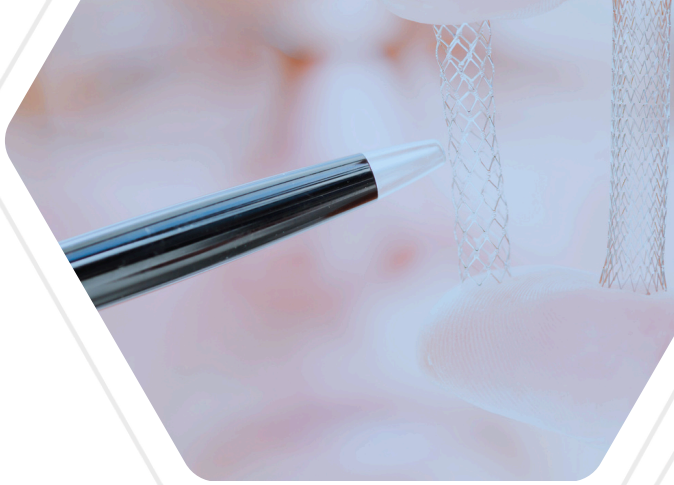
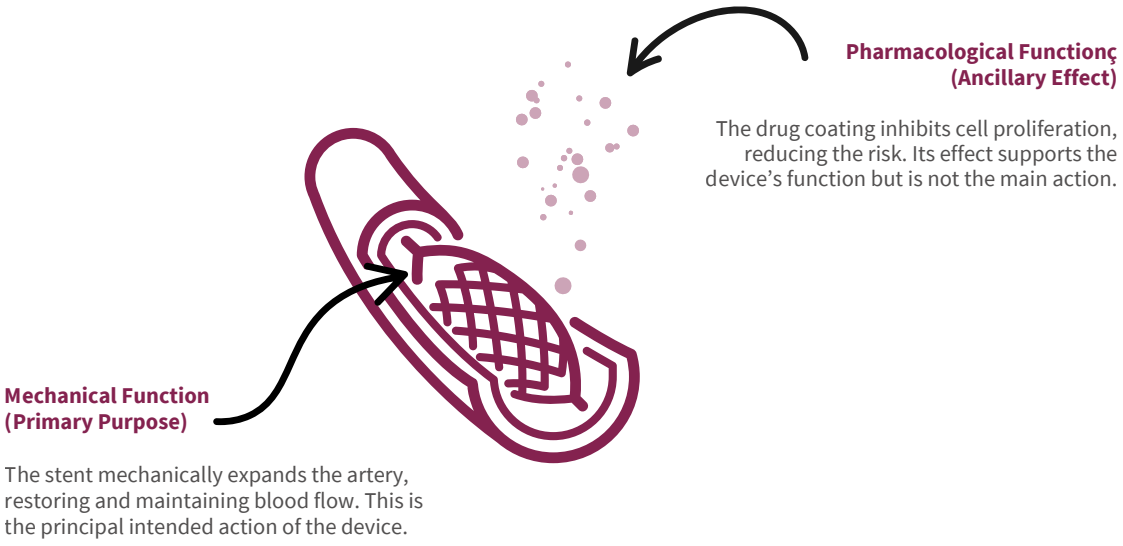


Rule 14 Explained

Rule 14 (MDR Annex VIII): All devices incorporating an integral substance that, if used separately, is a medicinal product with an ancillary action, are Class III. The main intended effect of a medical device is generally obtained through physical modes of action. These may include mechanical effects, the formation of a barrier such as a protective film, lubrication, transfer of heat, application of radiation or ultrasound, or the substitution for, or assistance to, organs and body functions. In addition, changes in hydration status or in pH can also serve as mechanisms by which a device achieves its principal action. If the medicinal substance achieves the principal intended action, the product is regulated as a medicinal product.

Key Principle: The integrated drug's effect must be supportive, not the device's main function. Competent authorities (CAs) emphasize the hierarchy: "where a technology may be regarded as a medicinal product, it is classified as a medicinal product".

Example:



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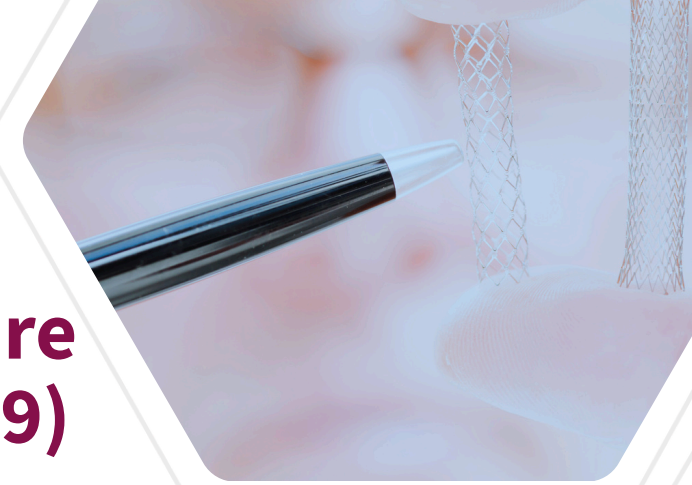


Consultation Procedure under MDR Article 52(9)

MDR Consultation (Art. 52(9) & Annex IX 5.2):

- **Obligation:** In Europe, for a class III medical device with an ancillary medicinal product, the manufacturer needs to satisfy a conformity assessment procedure and, as with other medical devices, the notified body (NB) will issue the CE mark that allows product commercialisation throughout the European Economic Area. During this conformity assessment procedure, NBs must must seek a scientific opinion from a medicines authority (national CA or EMA) on the ancillary substance's quality, safety and benefit–risk before certification.

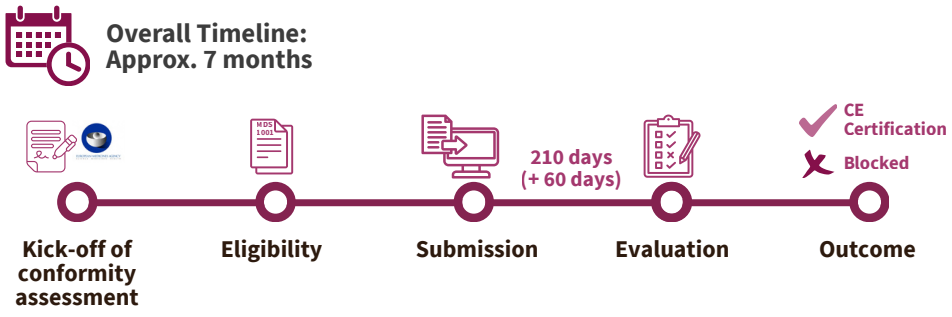
- **Be aware:** Notified Body must be designated under the MDR code MDS 1001 – Devices incorporating medicinal substances.

- **Process:** NB submits the complete ancillary-substance dossier to the chosen authority (any national competent authority, NCA, or the EMA in the case of medicinal substances derived from human blood or human plasma or that fall under the scope of a centralised procedure). The authority has 210 days to provide the initial opinion (and 60 days for any major changes/supplementary review).

- **Outcome:** A negative opinion from the competent authority blocks CE certification. Only if the authority finds the substance safe and useful can the NB finalize the MDR CE mark.

- **Timeline:** A review period of approximately seven months is foreseen. Include previous consultation opinions and a clear list of changes since any prior review.

- **Roles:** The NB organizes submission; the Medicines NCA/EMA (with pharmacology expertise) evaluates the medicinal product data; the manufacturer addresses any queries and incorporate the opinion into the technical documentation.



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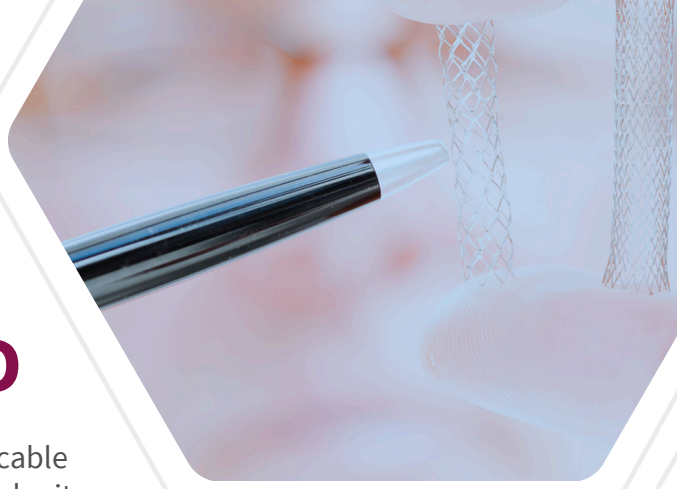
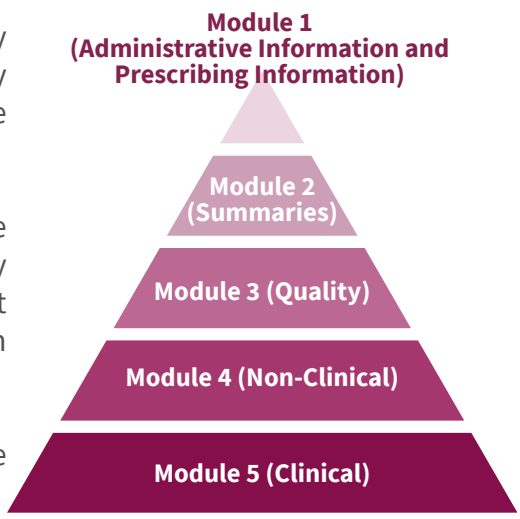


Preparing the Medicinal Dossier: CTD

CE marking requires that a medical device meets the applicable General Safety and Performance Requirements (GSPRs) under its intended use (Annex I of the MDR). Compliance is documented in the Technical Documentation (TD) and ensured through the manufacturer's Quality Management System (QMS) across design, manufacture, and the product's lifecycle. Additionally, for medical devices incorporating an ancillary pharmacological substance, a separate medicinal dossier must be prepared, including information on the quality, safety, and usefulness of the substance that is integrally combined with the device

Ancillary Substance Dossier – CTD Modules (1–5):

- **Format:** Prepare a Common Technical Document (CTD) for the medicinal substance. Medicines authorities expect pharma-style dossiers. Organize content into Modules 1–5 as for a drug.
- **Module 1 (Administrative Information and Prescribing Information):** General device description and justification of the medicinal substance. Include the substance's risk–benefit evaluation in context. Provide a signed GMP declaration for the substance's manufacture. Attach labelling/IFU extracts.
- **Module 2 (Summaries):** Overview of Quality, Non-Clinical and Clinical data. Include a Quality Overall Summary and critical analysis, and a Clinical Summary emphasizing the substance's utility and safety in the device.
- **Module 3 (Quality):** Full quality data on the Drug Substance (source, API manufacturing, control tests) and Drug Product (composition of the device-integrated drug, manufacturing method, specifications). Reference any CEPs or ASMFs. Include GMP certificates for substance production sites. Include device-specific excipients (e.g. coating materials).
- **Module 4 (Non-Clinical):** Relevant pharmacology/ toxicology studies on the substance, including local/systemic toxicology and biocompatibility related to device use. Include literature or testing data on the integrated product as needed.
- **Module 5 (Clinical):** Summary of clinical data and literature on the substance's effect and safety. The manufacturermay reference the device's Clinical Evaluation Report, but highlight the risk–benefit of the drug addition. Conclude on the additive value and safety of the substance.
- **Tips:** Keep files concise (zip modules, ~<100MB). Provide Tabulated changes and letters of access to DMFs.



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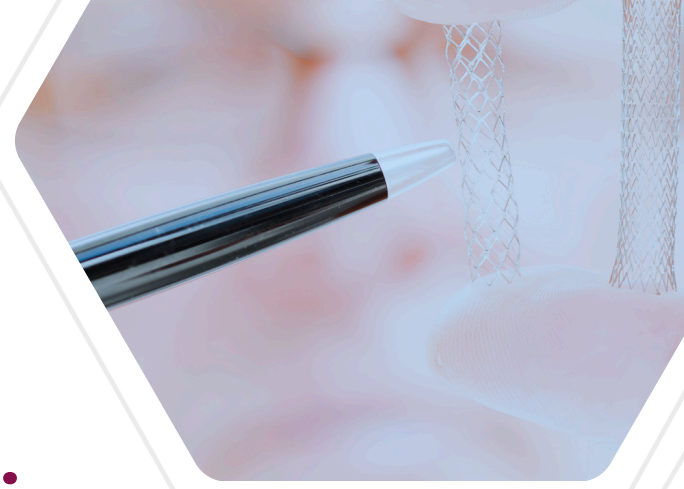

Case Study: Drug-Eluting Coronary Stent

Practical Example – Drug-Eluting Stent:

- **Product:** A coronary stent with an antiproliferative drug coating (e.g. sirolimus). Primary function: mechanical vessel support. Ancillary effect: drug preventing restenosis.
- **Classification:** Rule 14 applies. The stent is Class III because the drug is integral and ancillary.
- **Regulatory Steps:** Manufacturer prepares the device TD and a parallel CTD for the drug. The NB confirms ancillary status and initiates an a consultation procedure with a competent authority as per point 5.2 of Annex IX of the MDR.
- **Consultation:** Full drug dossier (Modules 1–5) and device overview are sent to the NCA or EMA. The authority reviews (~210 days) and issues a scientific opinion. For legacy devices, previous MDD opinions can be referenced but a full MDR submission is required.
- **Outcomes:** A positive opinion allows the NB to grant CE marking. A negative opinion stops certification and triggers redesign or additional data. This ensures patient safety by vetting the medicinal component.

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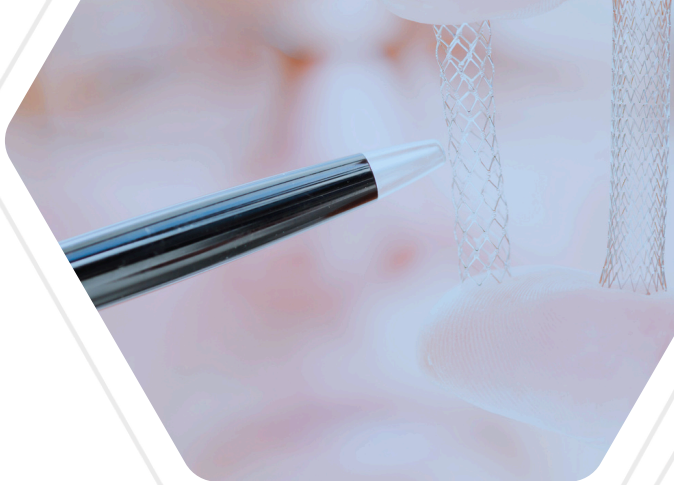
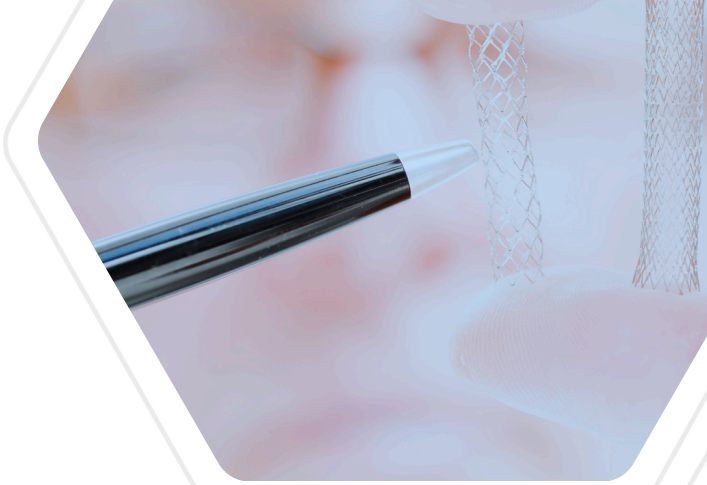


Final Reflections and Recommendations

Recap: Lessons & Recommendations

- **Start Early & Justify MoA:** Determine device vs. medicinal status during R&D. Use MDCG 2022-5 and EU guidance to scientifically justify the primary action.
- **Prepare CTD for the medicinal substance:** Develop the ancillary substance dossier in parallel. Secure GMP compliance, and robust quality data for the drug. Ensure the device CER discusses the drug's usefulness.
- **Engage Regulators:** Involve your NB early to agree on classification and consultation strategy. Agree with the NB on the appropriate NCA/EMA, and compile any previous opinions or data as supporting info.
- **Plan for Timing:** Account for the 210-day review conducted by the competent authority in your timeline as part of the complete conformity assessment process for obtaining the CE mark. Provide a complete submission (with consolidated change list) to avoid delays.



References

- Regulation (EU) 2017/745 on medical devices (MDR)
- Directive 2001/83/EC on the Community code relating to medicinal products for human use
- MDCG 2022-5 Rev.1: Guidance on borderline between medical devices and medicinal products
- Manual on borderline and classification for medical devices under Regulation (EU) 2017/745 and (EU) 2017/746
- Manual on borderline and classification in the community regulatory framework for medical devices, Version 1.22 (May 2019)
- MDCG 2020-12: Guidance on transitional provisions for consultations of authorities on devices incorporating a substance
- EMA/CHMP/578661/2010 Rev.1: Recommendation on the procedural aspects and dossier requirements for the consultation to the EMA
- BSI guidance: “Medicinal Substance Dossier – Content and Format”

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