Regulatory Pathways of Drug-Device and Device-Drug Combination Products in the EU

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So you have drug/device and device/drug combination products you want to get approved for the EU market? How do you go about this and how are these regulated? This article highlights how these products are defined in the EU market, what regulations apply and what agency authority is responsible for regulatory approvals.

Regulatory Framework for MDs in the EU – A Quick Guide

- Directive 93/42/EC
- Directive 98/79/EC In Vitro Diagnostic Devices
- Directive 90/385/EC Active Implantable MDs
- Essential Requirements (ER) (Annex 1 to 93/42/EC)
- MEDDEV Guidelines – not legally binding

Regulatory Framework for MPs in the EU – A Quick Guide

- Regulation 726/2004: establishment of European Medicines Agency (EMA)
- Amended by Directives: 2002/98/EC; 2004/24/EC; and 2004/27/EC

Comparison of MD vs MP

Medical Device
- Proportionality principle
- Technology-based
- Classified by risk
- Actions taken should be proportional to risks
- Primary intended purpose is achieved by physical or simple chemical means
- Large variety of products
- Inexpensive regulatory process

Medicinal Product
- Precautionary principle
- Science-based
- Primary intended purpose is achieved by physiological, metabolic or immunological means

Let’s first understand some simple definitions:

**Medicinal Product (MP)**
“Any substance or combination of substances which may be used in or administered to human beings either with 1) a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or 2) to making a medicinal diagnosis.”

**Medical Device (MD)**
“Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, intended by the manufacturer to be used for medical purposes for human beings, which does NOT achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means but which may be assisted in its function by such means.”
(Directive 93/42/EC)
• Limited number of products
• Expensive regulatory process

**Intended Primary Mode of Action (MoA)**
In deciding whether a product falls under Directive 2001/83/EC (MP) or Directive 93/42/EC (MD), take account of the primary mode of action of the product.

**Examples**

**Medical Devices**
- Wound dressing with antimicrobial agent
- Re-usable injector for use with insulin cartridge
- Separate application devices
- Heparin-coated catheters or stents

**Medicinal Product**
- Wound treatment product for delivery of antimicrobial agent
- Disposable pen injector integral with insulin cartridge
- Needle-free injector containing medicinal product
- Heparin

**Combination Products**
- Medicinal product and medical device kit
- In combinations which are classified as drugs, the device has, in most cases, a delivery function:
  - MP authorization by the competent authority (CA), application tool is MD (e.g. needle-free injector); if separate: CE mark required for the MD.
  - In combinations classified as devices, the MP has an ancillary function (must be proven): MD regulated by a notified body (NB), MP evaluated and approved via a consultation procedure with CA/EMA.

**Drug-Device Combinations I**
- Medicinal product has the primary action
- CA/EMA evaluates the application dossier
- Often administration devices only
- Separate administration devices must be CE marked; additional data might be required (compatibility, functionality, toxicological data, etc.)

**Drug-Device Combinations II**
- In case of blood products, EMA consultation is mandatory
- Contact EMA at least six months prior to procedure start
- Rapporteurs responsible for investigation and reporting to the EMA will be appointed
- Opinion is binding to NB; if an unfavorable opinion is given by EMA, the NB cannot issue a CE certificate
- Consultation is on quality, safety and usefulness (clinical risk/benefit) of the ancillary medicinal substance is required

**Consultation Procedure I**
The NB shall seek a scientific opinion from one of the competent authorities designated by the Member States or the EMA on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the substance into the device. (Essential Requirements 7.4)

**Consultation Procedure II**
Consultation procedure between any NB and any competent authority in any EU member state
Select NB with experience in combination devices
Careful selection of the CA
CA must complete evaluation and issue an opinion within 210 days upon receipt of a valid application
The scientific opinion of the CA must be included in the documentation concerning the device

Considerations for Device-Drug
Manufacturer is responsible for proper classification (case-by-case basis)
MoA must be clearly stated and confirmed by sufficient scientific data
Which legislation (MD vs MP) is applicable?
Interpretation by NB and CA/EMA might differ
Class III MD: full quality assurance and design examination – performed by the same NB

Dossier Requirements
Technical File & Design Dossier for MD – evaluated by NB
Consultation dossier for MP – evaluated by CA/EMA
Risk analysis/evaluation/control
Consider risk control for unacceptable hazards

Clinical Investigation I
Regulatory pathway determines the clinical trial regulation
Source of data: literature, clinical investigation or combination of both

MD clinical investigation:
Completely new device (components, method of action unknown)
Significant modification of an existing device which affects safety or performance
New indication, purpose or function

Clinical Investigation II
Medical Device
Annex X – Directive 93/42/EC
MEDDEV 2.7/1 rev 3 Clinical evaluation: Guide for manufacturers and notified bodies
National process
No EUDRACT number required
Evaluation by CA and EC
No paediatric investigation plan (PIP) required; no legal representative in EU required

Medicinal Product
Directive 2001/10/EC
National process
EUDRACT number required
Evaluation by CA and EC

Outlook
The Medical Device Directives are currently under revision. The European Commission proposed new rules on medical devices and issued a proposal for two regulations (MD and in vitro diagnostics MD) which should replace the current three directives. There are still some uncertainties about exactly what the new EU medical device regulations will contain and also when they will come into force in the EU. Unannounced inspections by your notified body and closer scrutiny of NB competence will certainly feature.

PIP required (legally binding, compliance check prior to MAA); legal representative in EU required

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Key Point Summary:

1. It’s critical to understand the main mode of action of your product as that will determine whether it will be regulated as a medical device or as a medicinal product (drug) in the EU.

2. Once you know what regulation applies to your product in the EU, you need to understand what you have to do get your product approved and on the market.

3. If the product is regulated as a medical device, it will be a faster and less expensive process than that of a medicinal product (drug). If your medical device product contains a medicinal agent as a secondary function, it is likely to be regulated as a Class III device (high-risk). In such a case, your notified body will have to consult with the competent authority (CA) about the safety, quality and usefulness of the medicinal agent in your product. As the CA is allowed 210 days after your submission to complete its evaluation and issue an opinion, this procedure is generally much slower than for lower-risk devices.

4. You need to choose a notified body with the competence and experience in assessing combination products and also to select a CA with the appropriate competence and experience.

5. The developing new regulations of medical devices in the EU will have more force than the existing EU directives which are currently used.