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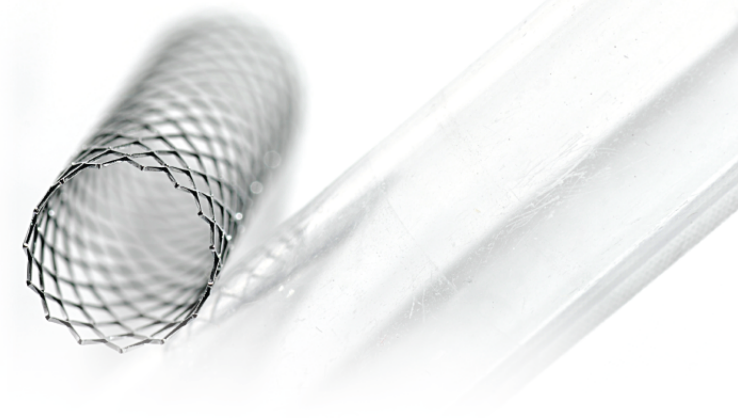

Regulatory Pathways of Drug-Device and Device-Drug Combination Products in the EU

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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.

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."

(Directive 2001/83/EC as amended by Directive 2004/27/EC)

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)

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)
- Directive 2001/83/EC: medicinal products for human use
- 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

- 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 Requirements

- Clinical trial authorization
- Marketing authorization
- GMP manufacturer´s license
- Strict dossier format (common technical document (CTD))
- Demonstration of safety, quality and efficacy
- MD: data requirements of pharmaceutical directives and ER; CTD section 3.2.P.1, 3.2.R
- Variations need to be approved prior to implementation

Device-Drug Combinations I

- Main authority is the NB:
  - ♦ Monitor manufacturer´s (quality) system to produce declaration of conformity
  - ♦ Check if manufacturer follows the declared procedures and ER
- Manufacturer has responsibility for safety and product liability (through declaration of conformity)
- Device-drug combinations are usually Class III MD (highest risk)
- Usefulness (clinical benefit/risk) of ancillary medicinal substance must be evident (NB report required for submission to CA); rationale/justification for using the MP in the device

Device-Drug 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

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- 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.

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