EUCROF - MEDICAL DEVICE WORKING GROUP

HOW TO DETERMINE THE REGULATORY PATHWAY FOR YOUR COMBINATION PRODUCT

In this article, we are going to discuss drug-device combination products. What is a combination product? How to determine which regulatory pathway is applicable to reach market access authorisation? Are clinical investigations needed to obtain your CE certificate? Once the investigation has started, what are the safety reporting requirements?

The objective of this article is to provide practical guidance and a direction to find the answers to these critical questions. At the end, an overview of references to various documents is provided, which can provide further detail on this complex matter. All answers in one place!

What is a drug-device combination product?

Let us first see what makes a product a medicinal product (drug) and what makes it a medical device.

Key is to define the primary mode of action. Products that achieve its primary mode of action by pharmacological, immunological, or metabolic means are considered a drug. Products where the primary mode of action is **not** achieved by pharmacological, immunological, or metabolic means, but may be assisted in its functions by such means, would be falling into the category of medical devices.

There are also products that combine a medicinal component with a medical device.

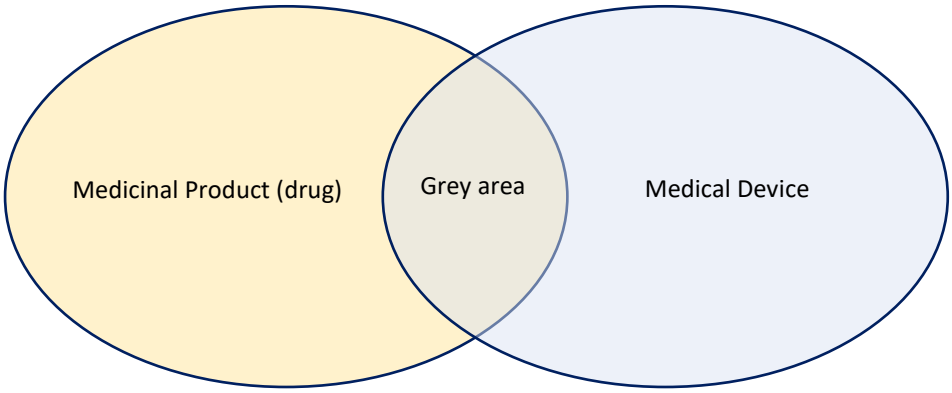
The examples of combination products below have a clear definition on what the intended purpose of the product is and what their primary mode of action is to achieve that purpose.

- *Primary mode of action – Medicinal Product*
    - Pills or capsules integrating a sensor where the drug has the primary mode of action and where the sensor is used to see if the capsule has reached the target position for instance.
    - Inhalers, where the drug has the primary mode of action, and the inhaler is the method to get the drug into the lungs.
    - Single-use pre-filled syringes, single-use pre-filled pens and single-use pre-filled injectors (including autoinjectors) used for the delivery of one or more doses of medicine and which are not intended to be re-used or refilled once the initial doses provided are exhausted, like insulin or vaccines.
    - Software as a medical device to dose drugs on specific timepoints.

- *Primary mode of action – Medical Device*
    - Catheter coated with an anti-inflammatory drug or anti-coagulant, where the catheter is used to transport a product from/into the body and the medicinal component is ancillary and used to reduce or prevent inflammation or blood clotting.

- Drug-eluting coronary stent, where the stent delivers the primary mode of action by widening the vessel lumen to support the blood flow and the drug is preventing blood clots forming in the stent.
- Bone cement with antibiotics. The bone cement is used for implant fixation, with the antibiotics preventing an infection from occurring.

Where the examples above have a clear intended purpose and the primary mode of action can be defined, there are also various products where this is not clear and where there is a "grey area" to what regulatory framework a manufacturer should comply.



For these so-called borderline products the MDCG has released a separate guideline (MDCG 2022-5).

Despite there not being an official definition in the EU, the term 'combination product' is commonly used in practice, which is described by the European Medicines Agency (EMA) as:

"*The medical device may be supplied as an integral component of the medicinal product (e.g. pre-filled syringe, auto-injector), or separately (co-packaged; e.g. oral syringe, pen-injector), as a non-integral combination with the medicinal product, or independently marketed (in cases where the device meets the requirements for the necessary delivery system stated in the Summary of Product Characteristics (SmPC) for the medicinal product)*."

The EMA has released a guideline on documentation for medicinal products when used in combination with a medical device and in there are terms introduced for three types of configurations:

1. *Integral Product* – Medicinal products where the medical device and/or device part and the medicinal product form an integral product that is not reusable and where the action of the medicinal product is primary.
2. *Co-packaged* – Medicinal products placed on the market by the Marketing Authorisation Holder, where the medical device is packed together with the medicinal product.

3. *Referenced* – Medicinal products, where the product information refers to a specific medical device (e.g. identified by its brand name and/or specific description) to be used with the medicinal product, and the medical device is obtained separately by the user of the medicinal product.

EU Regulatory Framework

When you have determined the primary mode of action of your product, the next step is to find the correct regulatory pathway for obtaining your market access authorisation.

As opposed to the US, the EU has no official definition in the legal framework for a product that combines a medicinal product with a medical device and the product is either regulated as a medicinal product or a medical device in the EU, with the primary mode of action governing the regulatory pathway.

In Europe, the agencies involved in these assessments include the EMA, the national competent authorities for the medicinal product part and the notified bodies for the device part.

Where the EMA and national competent authorities (NCA) are well-defined, there can be a higher challenge in identifying a notified body for your combination product, as the notified body must be designated to carry out the conformity assessment procedure for the particular medical device for which a certification or notified body opinion is sought. Applicants do so by visiting the EC NANDO website and clicking 'Legislation'. Here you can identify the designated notified bodies that can support in the conformity assessment procedure for your type of product.

The Regulations that apply are Directive 2001/83/EC or Regulation 726/2004 for medicinal products.

For medical devices it is Medical Device Regulation 2017/745 (MDR) or In-vitro Diagnostic Regulation 2017/746 (IVDR). In this article we will focus on the MDR and not on the IVDR. What is important to understand now, is that for in-vitro diagnostics the same principles apply for the determination of the regulatory pathway as for medical devices.

These regulations provide the responsibilities of EMA, NCA for medicinal products and medical devices plus notified bodies regarding combinations of medicinal products with medical devices as follows:

Integral Product – Primary mode of action = medicinal
An integral product with a medicinal primary mode of action is regulated under the medicinal products framework and the relevant General Safety and Performance Requirements (GSPRs), set out in Annex I, of the MDR apply to the device part (see MDR Article 117). This implies that for the device component of the integral product a CE certificate is required before the integral product can be approved by the EMA and placed on the market, i.e. you will still need to get a notified body involved for the device part of your combination product.

Integral Product – Primary mode of action = device
Where the primary mode of action is achieved by the device and the medicinal substance is ancillary, the product is regulated as a medical device (i.e. MDR, including Annex I on GSPR, applies) and therefore must be CE marked. However, the quality, safety and usefulness of the substance shall be verified by analogy with

the methods specified in Annex I of Directive 2001/83/EC. For that, a scientific opinion must be provided from a medicines authority before a notified body can issue a CE certificate for the combined product.

Co-packaged and Referenced Medical Devices
Where a medical device is co-packaged, it may be needed to include additional information about the medical device in the product information of the medicinal product. The extent of this additional information will depend on the specifics of the device, its intended use and the risks thereof to the quality, safety and/or efficacy, and hence overall benefit/risk determination of the medicinal product under consideration (e.g. compatibility, extractables and leachables, etc). These requirements do not apply in cases where reference is made in the product information of the drug to a general group of devices (e.g. "using a syringe" or "an infusion line", etc.).

With regard to these types of combination products, i.e. co-packaged or referenced, the device is regulated under the medical device framework (MDR, including Annex I on GSPR), as the medical device is not physically combined with the medicinal product and the device will need to be CE marked. In addition, the (separate) medicinal product must be licensed separately for use under the medicinal product directives.

Medical Device Incorporating a Medicinal Substance
Worth mentioning separately in this article, are medical devices that are composed of substances, or of combinations of substances, that are systemically absorbed by the body in order to achieve their intended purpose. These are **not** considered to be combination products.

Examples of these type of devices are:

- Active coal for oral administration
- Gels for vaginal moisturizing/vaginal lubricants
- Eye drops for hydration
- Ear drops

Although these substances are not considered to be combination products, they ARE products where there is a combination of authorities involved, as well in the assessment of conformity by notified bodies.

More specifically, MDR Annex IX 5.4 (b) states that for medical devices that are composed of substances, or of combinations of substances, the notified body shall seek a scientific opinion from one of the NCAs designated by the Member States in accordance with Directive 2001/83/EC or from the EMA.

Application to the Ethics Committee and Competent Authority

In case your clinical evaluation identifies a gap in available clinical data to support the conformity assessment of your medical device or combination, a clinical investigation or drug trial must be performed and a favorable opinion needs to be obtained prior to starting the clinical study activities.

At this point, there is no guidance available yet for the ECs/NCAs in Europe on how to handle the application of combination products, which makes it challenging for the EU Member States to harmonize their activities.

Chances are that multiple applications are needed (medicinal, as well as medical device), whilst a single point of application is preferred.

When submitting your application for a combination product to the EC/NCA(s), it is recommended to state specifically in the application letter that the product under investigation is a combination product and to include a description on background for the type of application pathway chosen. We also advice to include in the application letter a request to the reviewing body if the submission can be reviewed as a single application, instead of requiring multiple applications for the combination product.

As you may know, the expectation is that all modules in EUDAMED, including the one on clinical investigations, will go live in Q4 2023. At the time of writing this article, the specifications for submitting a clinical investigation involving a medical device or combination product for review to the EC/Cas through EUDAMED are not entirely clear. Please visit the EUDAMED website of the European Commission for the latest news.

Interesting to note is that the MHRA and HRA (UK) have launched their Combined Clinical Pilot Program, which may serve as a reference for Europe at one point.

Clinical data

By now you should know if your product is considered a medical device, a medicinal product or a combination product and which regulatory pathway is applicable. Whether a clinical investigation is required to comply with the GSPR of Annex I of the MDR, depends on the outcome of the clinical evaluation, which is driven by the classification of your device.

For drug-device combinations where the medicinal product is ancillary to the medical device, rule 14 of the classification rules in the MDR applies. This rule classifies the device part of your combination product as Class III.

As per Article 61 of the MDR, for Class III devices performing clinical investigations as part of your clinical evaluation is mandatory, except when sufficient clinical data is already available. Your Clinical Evaluation Plan (CEP) determines whether sufficient clinical data is already available or if a clinical investigation needs to be conducted to fill the missing gaps. If you would like to know more about clinical evaluation, please also have a look at our article on the differences between a clinical evaluation and clinical investigation.

The MDR also states that for class III devices manufacturers can seek scientific advice from an expert panel, as referred to in Article 106 of the MDR, prior to their clinical evaluation and investigations. The clinical development strategy proposed by the expert panel needs to be documented in the CEP accordingly.

Safety reporting for combination products

A non-CE marked component in a clinical drug trial, would implicitly have to be assessed for safety and performance and the study shall follow both MDR (Chapter VI) and the applicable legislation for clinical drug trials.

If a drug-device study (or a drug trial) is not undertaken to assess the safety or performance of a device used in the study, the reporting requirements of MDR Article 80 do not apply, as long as the device is CE marked and used within its intended purpose.

Do note that, while MDR Article 80 will not apply in these instances, the vigilance reporting provisions of MDR still apply in those situations, as for any commercially available device. Sponsors should make sure that the device manufacturer is notified about any incidents related to the device and the legal manufacturer of the device is responsible for the subsequent vigilance reporting.

Conclusion

High-level, determining the regulatory pathway to follow when trying to bring your drug-device combination product to market is not too complicated. The very first steps to take are to identify the indication or intended use of the combination product and to define what the primary mode of action is. It is essential to define your regulatory pathway well in advance.

The steps after determining your regulatory pathway can make things complicated and there are many considerations to be made. Two things to keep in mind. First, is that in case of a medical device or combination product, the sponsor must **always** comply with at least Annex I on GSPR from the MDR. Second, always check and confirm with the applicable agency how to submit your clinical trial application, as this will significantly support an efficient application process and increase the chances of shortening your regulatory timeline!

USEFUL LINKS

1. DIRECTIVE 2001/83/EC on the Community code relating to medicinal products for human use link
2. REGULATION (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency link
3. REGULATION (EU) 2017/745 on medical devices link
4. MDCG 2022-5 Guidance on borderline between medical devices and medicinal products under Regulation (EU) 2017/745 on medical devices link
5. Helsinki Procedure for borderline and classification under MDR & IVDR link
6. Drug-Device Combination Products Consultations National Competent Authorities link
7. Guideline on quality documentation for medicinal products when used with medical device link
8. Questions & Answers for applicants, marketing authorisation holders of medicinal products and notified bodies with respect to the implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746) 23 June 2021 Rev.2 link
9. MDCG 2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 link
10. Overview on designated notified bodies link
11. Expert panels in the field of medical devices and IVDs link

12. Consultation procedure for ancillary medicinal substances in medical devices link
13. Team-NB Position Paper on Documentation Requirements for Drug Device Combination Products Falling in the Scope of Article 117 of MDR 2017/745 link
14. EUCROF Medical Devices Workgroup – Understanding Medical Devices: Clinical Evaluation vs Clinical Investigation link
15. MHRA and HRA Combined Clinical Pilot Program link
16. European Medicines Agency - Medical devices link
17. European Commision - EUDAMED link

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