



Congenius Whitepaper

# Overcoming the challenges of regulating combination products

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## Introduction

**Combination products have existed in both the EU and the US markets for several decades, but regulations for combination products are relatively recent, and in certain markets they do not yet exist. Regulatory submission formats specific to combination products have not yet been developed.**

The cross-sector collaboration among companies in the life sciences industry has increased over the years, leading to an ever-growing number of products combining medical devices, drugs and/or biologics.

Currently, regulations for medical devices, biotechnology and pharmaceuticals vary significantly. Navigating the regulation of these often unique products has long been a challenge for both regulators and industry that goes well beyond products consisting of either devices, drugs or biologics alone. And the degree of innovation and diversity involved in combination products is much greater still.

Some challenges for combination products are similar in the EU and the US, yet others are specific to the two markets. This whitepaper examines the regulatory challenges for combination products in the EU and the US, and the possible ways in which to manage them.



## Useful acronyms

**DDC** | Drug-Device Combinations, which consist of:

- **A Device component**
- **A Drug component**

**EMA** | European Medicines Agency

**EU MDR** | European Medical Device Regulation (EU) 2017/745

**MPD** | Medicinal Products Directive 2001/83/EC

**GSPR** | General Safety and Performance Requirements

**PMOA** | Principle Mode of Action

**OCP** | FDA Office for Combination Products





# Combination products and the FDA

## Definitions & Regulations

# Combination products and the FDA

## Definitions & Regulations

**A combination product as per the US Federal Food, Drug, and Cosmetics Act (21 CFR 3.2(e)) is a combination of a medical device, drug or biologic.**

The FDA groups combination products as follows:

### Single entity

Two or more regulated components that are combined or mixed into a single entity.

### Kits

Two or more separate products contained in one package.

### Cross Labelled

Products provided separately, but their labelling requires them to be used together to achieve their intended use.

The different components (device, drug, biologic) of a combination product are referred to as:

- **Device constituent part**
- **Drug constituent part**
- **Biologics constituent part**

In the US, 21 CFR contains a definition for combination products, as well as the procedure for how the FDA determines the assigning of an FDA centre for the review of a combination product. The FDA Office for Combination Products (**OCP**) ensures that the different centres involved with a combination product submission work together effectively.

**FDA is the only regulatory agency that deals with combination products in the US, and considers each combination product as a whole.**



# **Combination products and the FDA**

## **Determining the Responsible Centre & PMOA**

# Combination products and the FDA

## Determining the Responsible Centre & PMOA

FDA has three separate centres responsible for drugs, devices and biologics:



Combination products may require the collaboration and expertise of two or all three of these Centres, which normally work autonomously.

The **FDA Office for Combination Products (OCP)** is tasked with addressing the regulatory challenges for combination products. The OCP:

- Develops regulations, guidances and policies
- Helps assign the lead role for the review of a product to the appropriate centre
- Coordinates between the centres to ensure an efficient review
- Is a point of contact for manufacturers

# Combination products and the FDA

## Determining the Responsible Centre & PMOA

**Determining which FDA centre takes the lead in the review of their submission depends on the primary mode of action (PMOA) of the combination device.**

According to Section 503(g)(1)(C) and 21 CFR 3.2(m), the PMOA is the mode of action that provides the most important therapeutic action of the combination product, or makes the greatest contribution to the intended therapeutic effects.

The PMOA determines which FDA centre is responsible for the combination product in question, and in turn, which premarket submission is required:

PMOA	Lead Centre
Device constituent part (=> device-led combination product)	<b>CDRH</b>
Drug constituent part (=> drug-led combination product)	<b>CDER</b>
Biologic constituent part (=> biologic-led combination product)	<b>CBER</b>

For some devices, this approach may be relatively straightforward. For example, a combination product consisting of a pre-filled syringe and a drug, where the syringe is simply delivering the drug, and the drug provides the therapeutic effect, would likely be a drug-led combination product, therefore falling to the CDER.

However, determining the PMOA is often difficult, as it may not be clear which part (the device, the drug or the biologic), actually has the greatest therapeutic impact.

# Combination products and the FDA

## Determining the Responsible Centre & PMOA

### Overcoming the challenge

You can submit a **Request For Designation (RFD)** in order to receive help from the FDA to classify a combination product.

This is a formal process for determining how your combination product should be classified and which centre it should be assigned to. In this brief submission, as the manufacturer, you should explain your product to the OCP and provide a rationale as to which centre you believe your product should be assigned to. **Pre-RFD meetings** with the FDA are also available and can help to ensure a successful RFD submission.

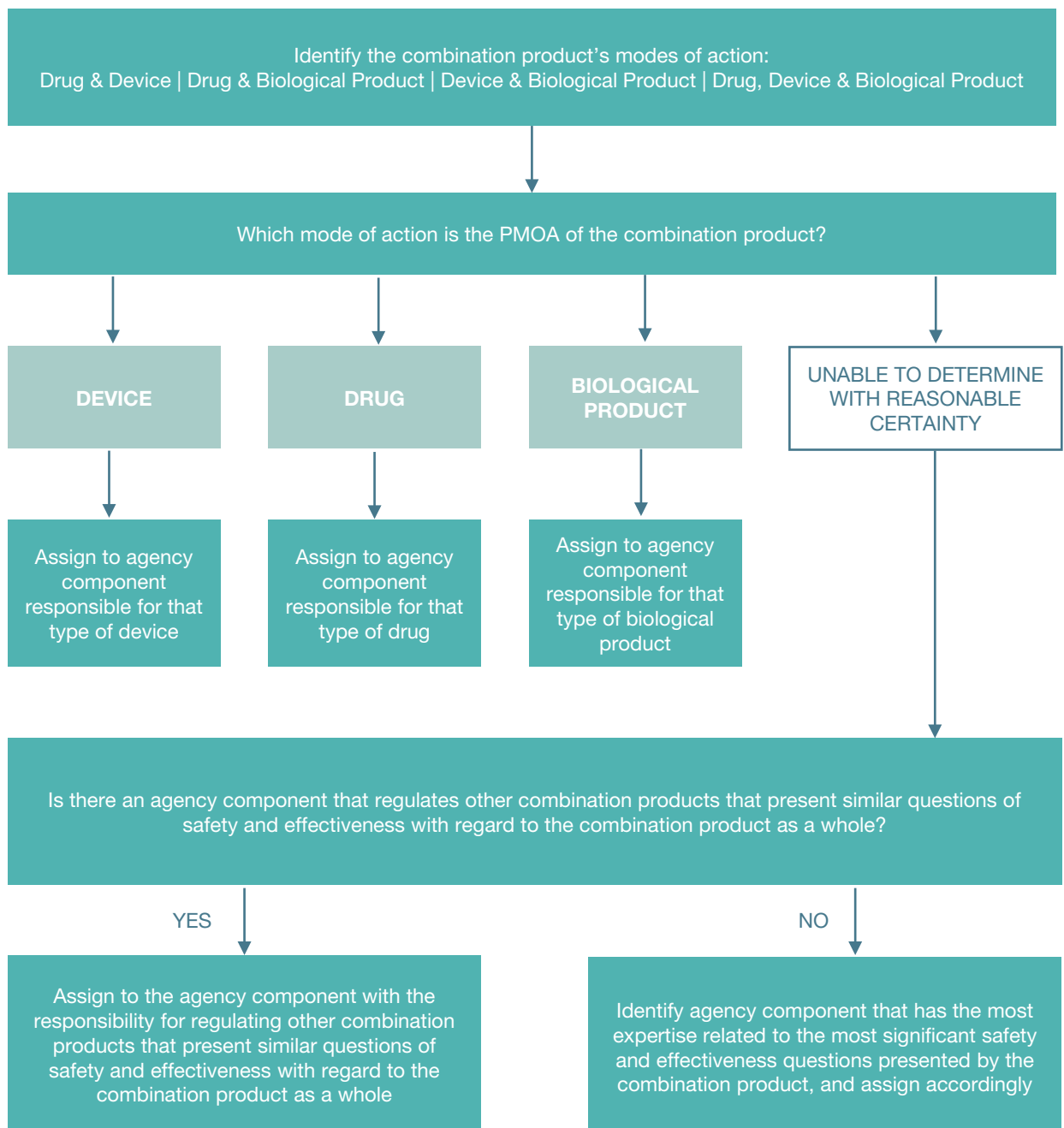
The OCP will then use an **assignment algorithm** to determine which centre should be assigned as the primary centre to review the submission. The algorithm takes into account aspects such as how similar products have been historically assigned, or which centre has the most robust expertise regarding the most significant question of safety and effectiveness posed by the combination product. **See overleaf for an illustration of this algorithm.**



# Combination products and the FDA

## Determining the Responsible Centre & PMOA

### Overcoming the challenge | The PMOA / Assignment Algorithm





# Combination products and the FDA

Finding the right pathway

## Combination products and the FDA

### Finding the right pathway

Another challenge for manufacturers of combination products is determining the appropriate regulatory submission path for their product.

The FD&C Act indicates that the FDA shall conduct the premarket review of a combination product under a *single* application where possible. The FDA finds that this approach avoids unnecessary duplication and proves more efficient.

The submission type is generally determined by the PMOA of the combination product. The [Principles of Premarket Pathways for Combination Products](#) is a useful resource from the FDA on this.

PMOA	PMOA-based submission pathway
Device constituent part	PMA (Premarket Approval Application)
	De Novo Classification Request
	510(k) (Premarket Notification Submission)
Drug constituent part	NDA (New Drug Application)
	ANDA (Abbreviated New Drug Application)
Biologic constituent part	BLA under 351(a) (Biologics License Application submitted under Section 351(a))
	BLA under 351(k) (Biologics License Application for Biosimilar and Interchangeable Biological Products submitted under Section 351(k))

## Combination products and the FDA

### Finding the right pathway

But even when only one submission is completed for a combination product, and the submission type is based on the lead constituent part as per the table on the previous page, the FDA will also require information that it would normally see in a submission of the non-lead constituent part.

Take a device-drug combination product for example, where the PMOA comes from the device, and therefore a [510\(k\)](#), [De Novo](#) or [PMA](#) is submitted. In this case, the FDA would **also require information for the drug-constituent part**, that would normally be submitted in an NDA. This could include nonclinical pharmacology, clinical pharmacology or CMC information, which would normally not be part of a medical device submission.

In addition, the information required for the non-lead part may not be the same information that would be required if that non-lead part were a device on its own. In our example of the device-led combination product that also contains a drug, the **information provided for the drug is different from information required if the drug were a device on its own and an NDA or ANDA were completed**. This is due to the fact that the drug is used differently in combination with the medical device, to if it were used on its own.

And in some (rarer) cases, the FDA may determine that it would not be possible to evaluate the combination product with the submission type that coincides with the PMOA. For example, take a combination product consisting of a drug and a biologic, where the PMOA is the drug, and based on this, an NDA or ANDA would be the submission. **If the bigger questions of safety and effectiveness come from the biologic, the FDA may decide that a BLA is actually the more appropriate submission type**. In this case, the submission type would then be determined not by the lead constituent part (drug), but by the non-lead constituent part (biologic).

# Combination products and the FDA

## Finding the right pathway

### Overcoming the challenge

**Reach out to the FDA early and take advantage of pre-submission meetings with FDA centres and the OCP.**

Liaising with the OCP can help determine which staff from which centre should be contacted for a particular topic. They can also help to resolve substantive issues, generally facilitate interactions with the centres, encourage collaboration within the FDA, and resolve disputes.

As a manufacturer, regardless of which submission pathway you use, the FDA will not only expect sufficient evidence to prove the safety and effectiveness of the lead constituent part of your combination product, but for *all* constituent parts.

**A submission can be easier if a part of the combination product has already been cleared on its own by the FDA in a previous submission.**

If a device-led combination product uses a drug that was already cleared by FDA, then the sponsor would only need to provide additional data for the drug that is specific to the use in the combination product.

**For cross-labelled combination products, separate premarket authorisations can be sought.**

For example, if the product consists of a drug constituent part and a device constituent part, an NDA can be sought for the drug and a 510(k) for the device.

In this case, it is important to still interact with the FDA through the lead centre, to ensure that the interactions with the two different centres are as efficient and coordinated as possible. The OCP can also help to coordinate the approach and communication.

And finally, when requesting meetings with the FDA, remember to communicate in advance the purpose and all topics to be covered, to give the FDA ample opportunity to ensure that the appropriate review staff from each centre attend the meeting.

The background is a solid teal color with a faint, semi-transparent wireframe globe centered in the middle. The globe is composed of a grid of lines forming a spherical shape, with some lines appearing thicker or more prominent than others, giving it a 3D effect.

# **Navigating EU regulations for medicinal product - medical device combinations**

**Defining Drug Device Combinations (DDCs) in the EU**

# Navigating EU regulations for medicinal product - medical device combinations

## Defining Drug Device Combinations (DDCs) in the EU

One of the first challenges with combination products in the EU, is that there is no single definition for them, and the definitions are not aligned:

The **Medical Device Regulation (EU MDR)**, defines them in Article 1(8) and 1(9) as:

*Any device which, when placed on the market or put into service, incorporates, as an integral part, a substance which, if used separately, would be considered to be a medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma.*

*Any device which is intended to administer a medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC.*

The **MEDDEV 2.1/3 Rev 3** outlines the following:

*Medicinal products, within the meaning of Article 1 of Directive 2001/83/EC incorporated, as an integral part, in a medical device and which are liable to act upon the body with action ancillary to that of the device.*

*Medicinal product constituents or medicinal products derived from human blood or human plasma, within the meaning of Article 1 of Directive 2001/83/EC, incorporated, as an integral part, in a medical device and which are liable to act upon the human body with action ancillary to that of the device.*

*A device that is intended to administer a medicinal product within the meaning of the MPD[...] governed by the MDD or by the AIMDD.*

# Navigating EU regulations for medicinal product - medical device combinations

## Defining Drug Device Combinations (DDCs) in the EU

The **MPD definition** is brief, in Part IV, 3.4.2:

*The medical device or the active implantable medical device may be an integral part of the active substance.*

In addition to the MPD, the **EMA guideline on quality documentation** defines combination products as either integral, co-packaged or referenced, similar to the FDA:

*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 principal,*

*Medicinal products placed on the market by the Marketing Authorisation Holder (MAH), where the medical device is packed together with the medicinal product, or*

*Medicinal products, where the product information refers to a specific medical device to be used with the medicinal product, and the medical device is obtained separately by the user of the medicinal product.*



# **Navigating EU regulations for medicinal product - medical device combinations**

**Complying with two regulations**

# Navigating EU regulations for medicinal product - medical device combinations

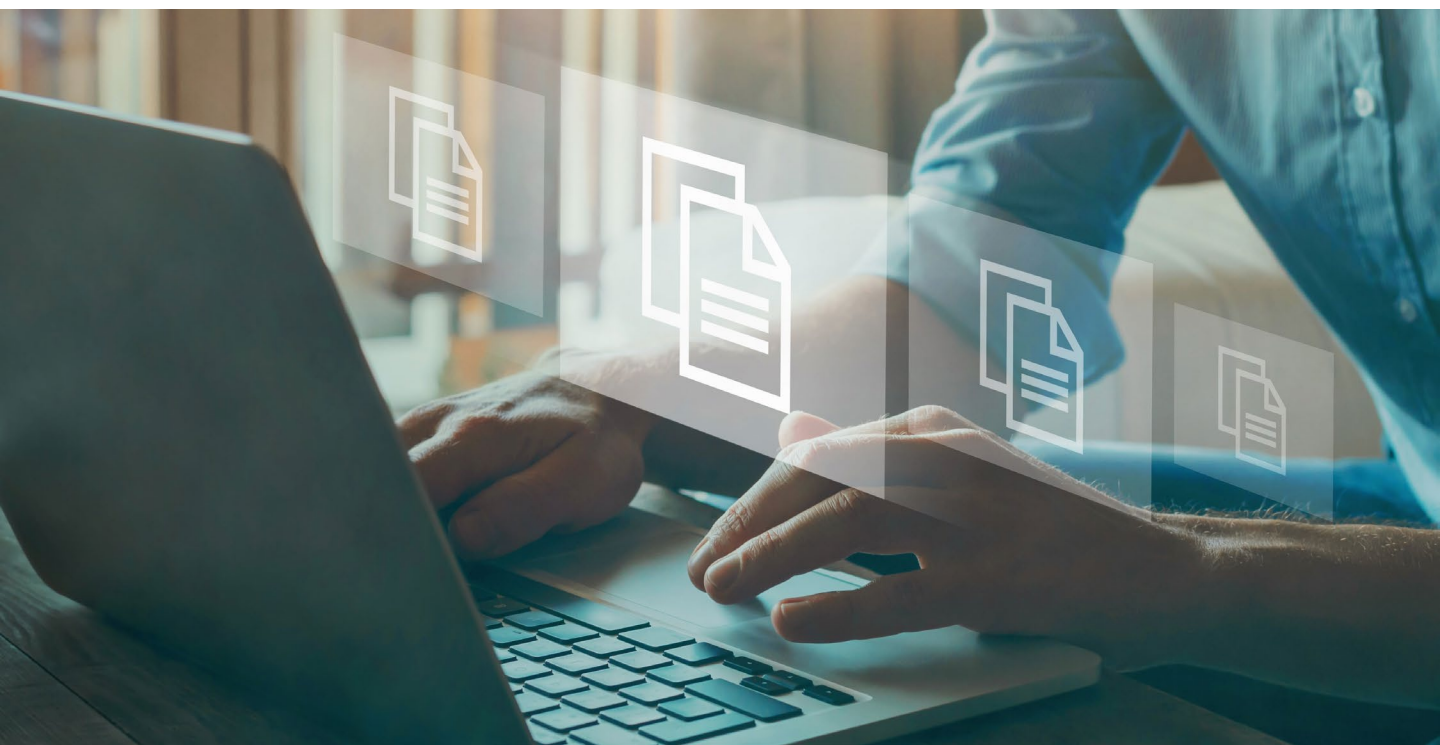
## Complying with two regulations

**In the EU, drug-device combinations (DDCs) are regulated either under Regulation EU 2017/745 (EU MDR) or Directive 2001/83/EC, depending on their principal mode of action (PMOA).**

Whilst some complex DDCs may not have a clear PMOA (which can also be the case in the US), in general, the EU takes quite a different overall regulatory approach to the US.

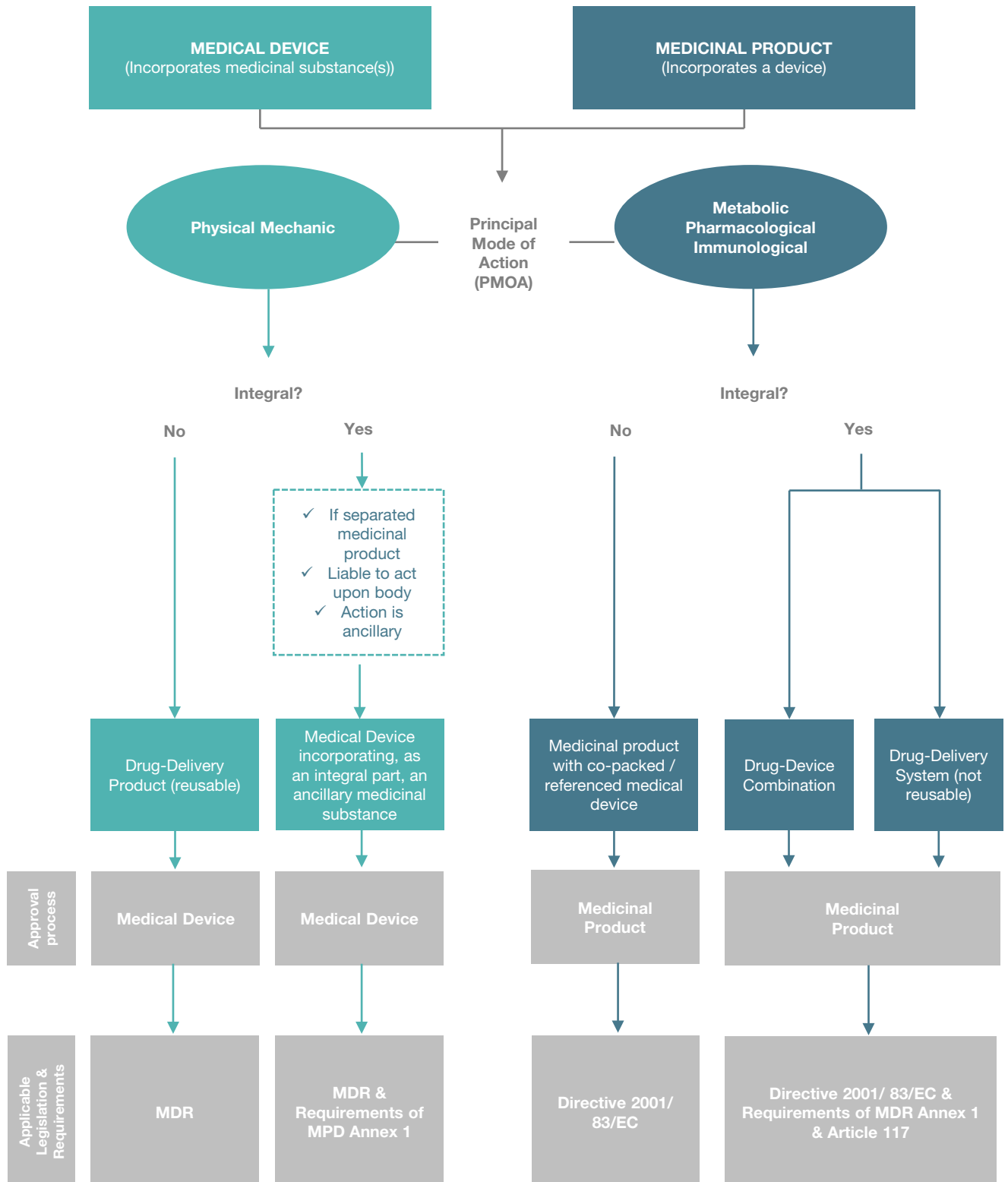
The EU separates DDCs into their different components, which are governed by different regulations. The PMOA determines which regulation is mainly applied, but other relevant requirements still apply.

For example, if the PMOA stems from the drug and Directive 2001/83/EC is the main regulation, some GSPR from the EU MDR will still apply. A big difference to the US, is that if devices are co-packed, each component, medicinal product and medical device are regulated separately under EU MDR and MPD.



# Navigating EU regulations for medicinal product - medical device combinations

## Complying with two regulations



# Navigating EU regulations for medicinal product - medical device combinations

## Complying with two regulations

Unlike the US, where the FDA will review the combination product as a whole, different actors are involved in the EU as shown in the diagram on the previous page.

The responsibility for the medical device component of the DDC lies with a **Notified Body**, selected by the manufacturer. Whereas the responsibility of substances as part of the product lies with the **EMA** or a **Competent Authority**, depending on the type of substance.

EU MDR has presented more challenges for regulating combination products in the EU, for example, raising questions about the application of the **importer and distributor definitions** regarding economic operators dealing with combination products, or the **applicability of labelling requirements**.

Let's take a look at how these types of challenges can be overcome.



# Navigating EU regulations for medicinal product - medical device combinations

## Complying with two regulations

### Overcoming the challenge

Concept and definition harmonization between different EMA guidelines, and between EU MDR and EMA guidelines is still somewhat lacking. However, there are guidances available which can help manufacturers to navigate the regulation of combination products in the EU:

- **MEDDEV 2.1/3 Rev 3** is helpful for obtaining clarity on procedures and definitions, however it hasn't been updated to address MDR.
- **EMA guideline on quality documentation for medicinal products when used with a medical device** helps to clarify the requirements of Directive 2001/83/EC and overcome the challenges presented by MDR.
  - **Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices** is helpful for manufacturers of borderline products who lack clarity on which regulation is applicable, and wish to determine the classification of their combination product.

### A note on new technology

The documents noted above do not address new technologies, so if you're a manufacturer looking to incorporate new tech into your product, you should engage with your Notified Body and Competent Authority or EMA directly.



# **Navigating EU regulations for medicinal product - medical device combinations**

## **Obtaining a Notified Body Opinion**

# Navigating EU regulations for medicinal product - medical device combinations

## Obtaining a Notified Body Opinion

According to Article 117 of EU MDR, a new combination product including a medical device needs to be CE marked under EU MDR before it is submitted for a Marketing Authorisation application, and proof of conformity to EU MDR has to be provided (either an EU MDR DoC or CE certificate).

If the device is not yet CE marked and a Notified Body is involved in the conformity assessment, it requires a Notified Body Opinion (NBOp) on the conformity of the medical device part with the GSPR of EU MDR.

A Notified Body opinion is also **required for certain changes to the medical device** part of a combination product.

Having to obtain an NBOp poses some challenges though:

- Issuing NBOps requires **more resources from Notified Bodies**
- Extra **time and money from medical device manufacturers** is needed during the conformity assessment process
- With **less Notified Bodies available under MDR**, pressure is further exacerbated
- Whilst many manufacturers plan to submit their NBOp request in parallel with their submission for the Marketing Authorisation Application, the NBOp itself actually **needs to be included within the Marketing Authorisation Application** for the drug

# Navigating EU regulations for medicinal product - medical device combinations

## Obtaining a Notified Body Opinion

### Overcoming the challenge

- ✓ Whilst it may be more difficult, under the EU MDR it is more important than ever to **have an active relationship with your Notified Body.**
- ✓ Make sure your **Notified Body is designated for the class of combination device you are developing**, and is experienced with NBOps.
- ✓ **Become familiar with the cost and timelines** for NBOps from your Notified Body.
- ✓ **Start communicating early with EMA via pre-submission meetings.** EMA recommends including the EU MDR DoC, CE certificate or Notified Body Opinion with the initial Marketing Authorisation Application for a DDC, whenever possible. EMA may, under certain circumstances, accept the absence of a Notified Body opinion in the initial submission, if the absence is justified, which should be discussed in a pre-submission meeting. The NBOp is required before EMA can issue an opinion on the medicinal product application.
- ✓ Create **water-tight supplier agreements** with any design / development / manufacturing subcontractors and implement robust supplier management. Ensure your agreement gives you full access to their documentation and states timelines for when information needs to be provided to you for your NBOp submission. If a supplier does not want to share certain information with you, work with your Notified Body to determine if the supplier can provide the information directly to them.



# **Navigating EU regulations for medicinal product - medical device combinations**

## **Handling Substantial Changes**

# Navigating EU regulations for medicinal product - medical device combinations

## Handling Substantial Changes

According to Directive 2001/83/EC, changes to a Drug-Device Combination product are categorised based on risk to public health and impact on a medicinal product's quality, safety and efficacy.

If a DDC undergoes significant change, it might require a new NBOp or Marketing Authorisation Application variation. An NBOp submission takes a lot of time and resources for both manufacturers and Notified Bodies, so bear this in mind during your project planning.

### Overcoming the challenge

- ✓ **Map out all of the upcoming changes** in the device constituent part, and when each change will occur.
- ✓ For each change, legal manufacturers need to **assess whether it will be significant or substantial** and whether it will require an NBOp.
- ✓ **Ensure supplier agreements are in place** to facilitate effective communication regarding device changes.
- ✓ If the medicine is affected by a change, **communicate early with EMA** to ensure that there is agreement on how the change will be assessed between yourself as the manufacturer, and EMA.
- ✓ **Consider whether changes to the medicinal product** (e.g. changes to volume, viscosity, etc.) **impact the performance of the device part**, which may require further verification and/or validation. Changes in the intended use or target population may require an additional usability study.



# **Navigating EU regulations for medicinal product - medical device combinations**

**A note on Managing Vigilance**

# Navigating EU regulations for combination products

## A note on Managing Vigilance

For essential DDCs regulated as a medicinal product, pharmacovigilance requirements apply but the medical device vigilance requirements of EU MDR are *not* required. However, it is advisable for DDC manufacturers to ensure their **QMS** can handle and investigate device-related complaints.

Additionally, **supplier agreements** regarding pharmacovigilance should address the device-related data on events and malfunctions that require collection.





# **Navigating EU regulations for medicinal product - medical device combinations**

**Overcoming the challenges with an  
Integrated Pathway**

# Navigating EU regulations for combination products

## Overcoming the challenges with an Integrated Pathway

The idea of having an **integrated pathway for the conformity assessment** of Drug-Device combination products aims to facilitate regulatory cohesion between Notified Bodies and medicine regulators.

EMA has begun to **collaboratively interact** with Notified Body working groups regarding MDR/IVDR implementation (e.g. Art 117 workshop, Companion Diagnostics Consulting WG and a Notified Body Opinion template), and has established **product specific procedures** such as provision of scientific advice and pre-submission meetings.

Since October 2021 however, the **work on an integrated pathway has been delayed** due to resource constraints relating to the implementation of MDR/IVDR.

And so, as the challenges for DDC products in the EU remain numerous and complex, making sure industry concern is heard and pushing for the furthering of solutions may therefore only be feasible on a larger scale - by **engaging in discussions and working groups that unite regulators and the industry**.

The background is a teal-tinted photograph of a laptop keyboard and a hand holding a smartphone. The text 'Useful resources' is overlaid in white on the left side of the image.

# Useful resources

## Useful resources

- [How to navigate EU regulations for drug-device combination products](#)
- [Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative](#)
- [The regulatory challenges of innovative customized combination products](#)
- [The Problem with Regulating Combination Products](#)
- [Combination Products: The Top Three Regulatory Challenges](#)
- [Challenges in Combination Product Regulation](#)
- [Combination Products Guidance Documents](#)
- [Regulatory perspectives of combination products](#)
- [How to navigate EU regulations for drug-device combination products](#)
- [Panel Discussion: Regulatory Issues for Combination Products](#)
- [Combination Products And the FDA: Issues and Answers](#)
- [European Medicines Agency mid-year report 2021](#)
- [Navigating the challenges of combination products](#)

**Should you have a Regulatory challenge,  
please do get in touch – our Regulatory  
team is ready and happy to help.**