



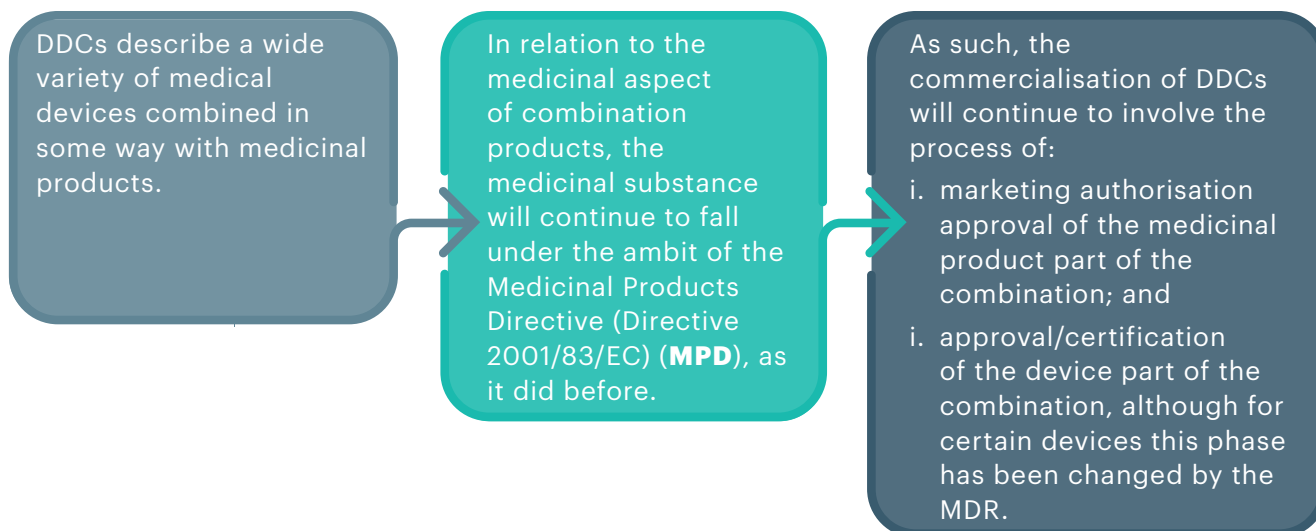
Drug-Device Combination Products: where do they fall within the new Medical Devices Regulation?

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With innovation leading to the increasing integration of drugs and devices, traditional boundaries between medicines and medical devices are often blurred. As a result, determining the correct regulatory pathway for drug-device combination products (**DDCs**) can prove challenging. The development of these products involves interaction between EU and national regulations, one of which, the Medical Devices Regulation (**MDR**), is set to become fully applicable on 26 May 2021.

Prior to the publication of updated guidance on DDCs from the European Commission and the Health Products Regulatory Authority (**HPRA**) (which is due to be published prior to 26 May), we have examined the MDR's impact on the regulatory pathway for DDCs.

WHAT REGULATORY FRAMEWORK APPLIES TO DDCs?



INTEGRAL DDCs AND NON-INTEGRAL DDCs

For regulatory purposes DDCs are categorised as **Integral DDCs** and **Non-Integral DDCs**.

1. INTEGRAL DDCs



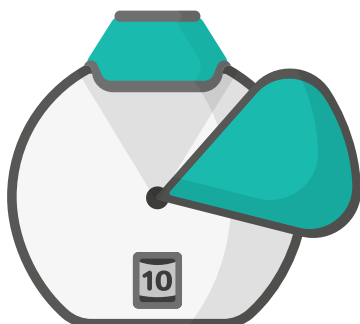
Under the MDR there are different categories of Integral DDCs.

Draft [guidance](#) released by the European Medicines Agency (**EMA**) in May 2019 treats devices that are subject to the second sub-paragraphs of Article 1(8) and Article 1(9) of the MDR as **Integral DDCs**.

- Devices that incorporate (as an integral part), a **substance** (including a medicinal product derived from human blood or human plasma), which if used separately would be considered a medicinal product and the action of that substance is **principal** and not ancillary to that of the medical device (Article 1 (8) 2nd para.);

› Examples of these integral DDCs:

- mouthpiece on the top of spray cans for throat sprays
- an implant whose primary purpose is to release the medicinal product inside (i.e. the ancillary device simply releases the medicinal product)



- Devices intended to administer a medicinal product, marketed as a **single integral product**, intended **exclusively for use** in the given combination and is **not reusable** (Article 1 (9) 2nd para.);

› Examples of these integral DDCs:

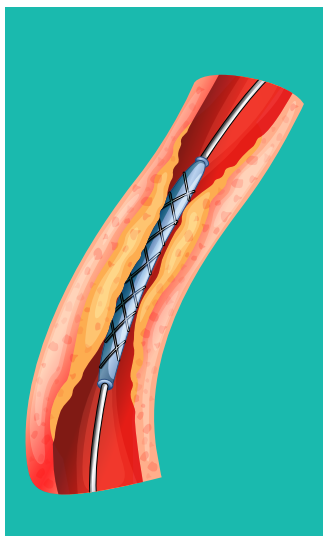
- a single dose pre-filled syringe/pen
- patches for transdermal drug delivery
- drug-releasing intra-uterine devices
- dry powder inhalers

These two categories of Integral DDCs are regulated as follows:

Type of DDC	MPD (or Regulation (EC) No 726/2004, as applicable) Apply?	MDR Apply?
i. DDC - action of the medicinal substance is principal (Art. 1 (8) 2nd para.)	Yes, applies to full DDC	Yes, relevant general safety and performance requirements (Annex I) applies to the device part only
i. DDC - 'single integral product' (Art. 1 (9) 2nd para.)	Yes, applies to full DDC	Yes, relevant general safety and performance requirements (Annex I) applies to the device part only

WHAT'S NEW? ARTICLE 117 NOTIFIED BODY REVIEW

- > Article 117 of the MDR (amending Annex I to the MPD, point 12 of section 3.2) requires that the marketing authorisation dossier for these DDCs include, where available, the results of the assessment of conformity for the device (i.e. the declaration of conformity or the relevant certificate issued by a notified body).
- > If this documentation is not available, then an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to the MDR from a notified body, must be provided.
- > Pharmaceutical manufacturers need to be aware of these new obligations when planning their product development activities.
- > **Integral DDCs** currently authorised for sale in the EU or those whose applications will be submitted prior to the MDR operable date, will not be impacted by Article 117 requirements, according to the EMA. However, this will not be the case if after the granting of the market authorisation, substantial changes are made to the device's design or intended purpose, or to replace/add device components to the products.



• Devices that incorporate (as an integral part), a **substance** (including a medicinal product derived from human blood or human plasma) which if used separately would be considered a medicinal product and the action of that substance is **ancillary** to that of the medical device (Article 1 (8) 1st para.). These Integral DDCs are subject to slightly different rules to those set out above.

- › Example of these integral DDCs:
 - Drug eluting stents

These Integral DDCs are regulated as follows:

Type of DDC	MDR Apply?	Requirements
DDC – action of the medicinal substance is ancillary (Art. 1 (8) 1 st para.)	Yes, applies to DDC	<p>Scientific opinion must be provided from a national competent authority or the EMA before a notified body can issue a certificate</p> <p>*Where the device incorporates a human blood or human plasma derivatives or a substance falling exclusively under the Annex I to Regulation (EC) No 726/2004 (the centralised procedure), the EMA must provide the scientific opinion</p>

ARE THESE REQUIREMENTS NEW?

Under the 'old' Medical Device Directive (93/42/EEC), scientific opinion had to be provided from a medicines authority before a notified body could issue a certificate. The objective of the consultation procedure with the competent authority for medicinal products is to verify the safety and quality of the medicinal substance, taking account of the intended purpose of the device.

In Ireland, the HPRA is the competent authority for medicinal products and the National Standards Authority of Ireland (**NSAI**) is the notified body. Applicants have to consult with the HPRA before the NSAI can approve the DDC.



Although the MDR replaced the Medical Device Directive (93/42/EEC), to date this consultation procedure does not appear to have changed. The HPRA are still accepting applications for consultation. The HPRA's official guidance is expected to be released before full implementation of the MDR on 26 May 2021 and should clarify any changes to this process.

2. NON-INTEGRAL DDCs



Non-Integral DDCs are those DDCs for which two or more components i.e. medicinal products and devices, are not physically integrated during manufacturing, or where the medicinal product and the specific devices are combined for administration (Article 1 (9) 1st para.). These 'administrative products' fall outside of Integral DDCs, and accordingly have different regulatory requirements.

EMA draft Guidance states that these devices are either:

- a. co-packaged and supplied along with the medicinal product; or
- b. the product information (summary of product characteristics (**SmPC**) and package leaflet) refers to the device to be used with the medicinal product, but the device is obtained separately.

› Examples of these Non-Integral DDCs:

- oral administration devices (e.g. cups, spoons, syringes)
- injection needles
- filter needles

These **Non-Integral DDCs** are regulated as follows:

Type of DDC	MDR Apply?	Requirements
DDC – Non-Integral administration devices (Art. 1 (9) 1 st para.)	Yes, applies to DDC	Administrative devices co-packaged with medicinal substances are treated differently to those obtained separately. Guidance from the EMA as to the requirements can be found here .

**** Advanced therapy medicinal products and *in vitro* diagnostic devices are excluded from the scope of this briefing.

CONTACT US

For more information, please contact Charleen O’Keeffe or your usual William Fry Healthcare contact to discuss any questions about your combination products, or concerns you have in relation to the MDR.



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