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Review

The combination of medical devices and medicinal products revisited from the new European legal framework

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ABSTRACT

Medical devices and medicinal products have many similarities in their nature, scope or specific medical purposes, and despite the differences in their principal means of action, they are often used in combination. Indeed, many medicinal products depend on medical devices for their administration, and it is increasingly common for medical devices to contain medicinal substances to support their action. Therefore, the combination of medicinal products and medical devices provides additional benefits for patients. However, their higher technical complexity requires a strengthening of their authorisation and certification requirements.

In this regard, more comprehensive requirements and classification rules are introduced by a new European regulation on medical devices that fully applies from May 26th 2021. On account of their therapeutic significance, this review aims at gaining insight into the borderline between medical devices and medicinal products in this new 2021 regulatory framework. For the first time, any item containing a medical device and a medicinal product will have both parts evaluated. Through exemplification of both marketed and investigational devices incorporating medicinal substances and drug-device combinations, the new European requirements and their implications are thoroughly illustrated herein.

1. Introduction

The last European Medicines Agency (EMA) Annual Report, published in 2019, showed that approximately one in four centrally-approved medicines included a medical device component (EMA, 2019). This is concurrent with the evolution of materials science which, combined with medicinal products, has fuelled the development of more sophisticated therapies (Alvarez-Lorenzo and Concheiro, 2019; Cohn et al., 2019; Sadeghi et al., 2021). Increasing collaboration between pharmaceutical companies and medtechs to provide better products that incorporate both medical devices and medicinal products in the same item has led to an increase in complex hybrid products that can range from drug-administering (e.g. pre-filled pens and injectors) to drug-eluting (e.g. drug-eluting stents (DES)) medical devices (Cyphert and Von Recum, 2017; Quarterman et al., 2021). However, the use of these hybrid products has come with its own regulatory difficulties, especially

Abbreviations: ALBC, Antibiotic-Loaded Bone Cement; AFSSAPS, Agence Française de Sécurité Sanitaire et des Produits de Santé; AIMDD, Active Implantable Medical Devices Directive (Council Directive 90/385/EEC); CE, Conformité Européenne (European Conformity); CEAR, Clinical Evaluation Assessment Report; CHMP, Committee for Medicinal Products for Human Use; CMDh, Coordination Group for Mutual Recognition and Decentralised Procedures - Human; COVID-19, Coronavirus Disease 2019; CPAR, Consultation procedure Public Assessment Report; DES, Drug-Eluting Stent; DDC, Drug-Device Combination; EC, European Community; EEC, European Economic Community; EMA, European Medicines Agency; EU, European Union; Eudamed, European Database on Medical Devices; GSPR, General Safety and Performance Requirements; HbA1c, Glycated Hemoglobin; IUD, Intrauterine Device; LNG-IUD, Levonorgestrel-Releasing Intrauterine Device; MDCG, Medical Device Coordination Group; MDD, Medical Devices Directive (Council Directive 93/42/EEC); MDR, Medical Devices Regulation (Regulation (EU) No 2017/745); MPD, Medicinal Products Directive (Council Directive 2001/83/EC); PJI, Prosthetic Joint Infection; PMCF, Post-Marketing Clinical Follow-up; PSUR, Periodic Safety Update Report; SCENIHR, Scientific Committee on Emerging and Newly Identified Health Risks; SSCP, Summary of Safety and Clinical Performance; TJA, Total Joint Arthroplasty; UDI system, Unique Device Identification system; WET, Well-Established Technology; WHO, World Health Organization; WPBC, Working Party on Borderline and Classification.

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in the form of uncertainty with regards to whether they should be marketed as medicinal products or as medical devices *(see Graphical abstract)*. Accordingly, the legal boundaries and requirements for these items needed to be revisited.

Following the thalidomide disaster of the late 1950s, the first European Council Directive aimed at harmonising the different Member States' legal frameworks with regards to medicinal products was approved in 1965 (Council Directive 65/65/EEC) (Feldschreiber and Breckenridge, 2015; Vargesson, 2015). A number of regulations have been passed ever since, until the establishment of the current EU legal framework, composed of Council Directive 2001/83/EC (EC, 2001) (MPD), relating to medicinal products for human use, and Regulation (EC) No 726/2004 (EC, 2004b), laying down procedures for the authorisation of medicinal products and establishing the European Medicines Agency.

By comparison, the first directives related to the marketing of medical devices were approved by the European Economic Community (EEC) in the early 1990s. Active implantable medical devices and regular medical devices were covered, respectively, under Council Directive 90/385/EEC (EEC, 1990) and Council Directive 93/42/EEC (EEC, 1993) (named Active Implantable Medical Devices Directive (AIMDD) and Medical Devices Directive (MDD), in that order), whereas *in vitro* diagnostic medical devices were covered under Directive 98/97/EC (EC, 1998). The aim of these directives was the approximation of Member States legislation to have a similar legal framework with regards to technical requirements, ensuring patient safety and minimizing risks associated with the use of medical devices. These directives set goals that all Member States had to achieve, and they required transposition into each national legal framework.

However, in 2010, medical devices had their own "thalidomide disaster". Member States were informed by French authorities, via the Medical Devices Vigilance System, of an increase in reported rupture incidents and local complications related to the use of silicone-filled breast implants of a certain manufacturer (Bachour et al., 2018). The incident was caused by the fact that most breast implants were filled with a silicone gel different from the one described in the CE (Conformité Européene/European Conformity) marking and batch manufacturing files (AFSSAPS, 2010a; SCENIHR, 2012). The recall, withdrawal from the market and cease of distribution, export, as well as use, of silicone-filled breast implants manufactured by that company was enforced (AFSSAPS, 2010b). This fraud acted as an accelerant to highlight the need for a significant strengthening of the legal framework existing at the time for medical devices to ensure high standards of quality and safety, along with reinforced post-market surveillance, as well as a smooth functioning of the internal market.

Since these objectives cannot be sufficiently achieved by the Member States on their own but can rather, by reason of their scale and effects, be better achieved at Union level, the European Union (EU) adopted the new Regulation (EU) No 2017/745 of the European Parliament and of the Council on medical devices (EU, 2017a) (MDR), which was scheduled to be fully implemented by May 26th 2020. However, the COVID-19 outbreak and the associated public health crisis has led to an unprecedented demand for additional resources, such as medical gloves, surgical masks, equipment for intensive care and other crucial medical devices (Emanuel et al., 2020; Kirkpatrick et al., 2020; Laventhal et al., 2020; Worby and Chang, 2020). Therefore, to prevent shortages during the ongoing COVID-19 pandemic, due to the limited capacity of national competent authorities and/or notified bodies for ensuring the proper implementation of the MDR, a one-year extension of the transitional period was approved, thus postponing its full application to May 26th 2021 (EU, 2020). Unlike the previous council directives, the new regulation is legally binding, meaning it must be applied in its entirety across all Member States, without having to be transposed to each national legal system. Additionally, this regulation unites under the same legislative act, for the first time, all medical devices other than *in vitro* diagnostic medical devices. Instead, *in vitro* diagnostic medical devices will remain to be covered by a specific regulation (i.e., Regulation (EU) No 2017/746) (EU, 2017b).

On account of their therapeutic relevance, the present work focuses on analysing the definitions and legal requirements of the distinct types of combinations of medical devices and medicinal products in the remit of the new European regulatory framework. First, the differences in nature, specific medical purposes and means for achieving their principal intended action of both medical devices and medicinal products are highlighted through an analysis of their definitions to assist in the classification of borderline cases. Then, the definitions and legal requirements of hybrid presentations where medical devices and medicinal products are used jointly, are reviewed through a thorough exemplification of both medical devices with an ancillary medicinal substance and medicinal products containing a medical device part (i.e., drug-device combinations). (Table 1)

2. The borderline between medical devices and medicinal products

2.1. Comparison of the definitions of medical devices and medicinal products

The major difference between medical devices and medicinal products stems from a comparison between their definitions.

On the one hand, according to its first article, for the purposes of the MPD, "a medicinal product is any substance or combination of substances which may be used in or administered to human beings with a view to treating or preventing disease, to making a medical diagnosis or to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action" (EC, 2001).

On the other hand, according to its second article, for the purposes of the new MDR, "a medical device is any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment, alleviation of, compensation for, investigation, replacement or modification of a disease, an injury or disability, the anatomy or of a physiological or pathological process or state,
- providing information by means of *in vitro* examination of specimens derived from the human body, including organ, blood and tissue donations,
- control or support of conception,
- cleaning, disinfection or sterilisation of medical devices and their accessories, and products without an intended medical purpose but

Table 1
Examples of medical devices with an ancillary medicinal substance and of drug-device combinations.

Item		Examples
Medical devices with an ancillary medicinal substance		– Drug-eluting stents – Antibiotic-loaded bone cements – Haemostatic matrixes with human thrombin – Medicated condoms – Drug-impregnated dressings
Drug-device combinations	Integral	– Levonogestrel-releasing intrauterine devices – Non-refillable inhalers – Pre-filled syringes – Transdermal patches
	Non-Integral	– Intrathecal pumps – Reusable inhalers – Insulin pumps – Oral administration devices (cups, spoons, syringes…)

based in a technology similar to that of analogous devices with an intended medical purpose (as listed in its annex XVI),

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means" (EU, 2017a).

Furthermore, medical devices are divided into four classes based on the vulnerability of the human body and taking into account their intended purpose as well as their inherent risks based on duration of use (transient, short term or long term), invasiveness (non-invasive, invasive with respect to body orifices, surgically invasive or implantable), energy source (active or non-active) and the part of the body where the device is intended to be used. From low to high risk, any device falls under one of four classes: class I, class IIa, class IIb or class III. The MDR has not modified the principle of the medical device categories; however, some classification rules have been revised and four new rules have been added to the eighteen already existing under the previous directive (Martelli et al., 2019). This phenomenon may be responsible for the movement of certain devices from one class under MDD to a higher-risk class under the new MDR regime, with the corresponding regulatory consequences.

According to their definitions, neither the nature nor the medical purposes of an item are relevant in the medical device – medicinal product delineation, as both definitions use terms as "material" or "substance", which overlap with each other, and so do their disease-related purposes. Therefore, the means for achieving their principal intended action is the major difference between medical devices and medicinal products, since the specific medical purposes of a medical device cannot be achieved by "pharmacological, immunological or metabolic means". Accordingly, the applicable legislation with regards to any specific item will be based on its action mechanism and on how it achieves its specific medical purpose. However, it is possible that the principal intended action of a medical device is assisted in its function by pharmacological, immunological or metabolic means, on an ancillary basis.

2.2. Classification of borderline products

EMA defines "borderline products" as "complex healthcare products for which there is uncertainty over which regulatory framework applies" (EMA, 2021).

National competent authorities classify borderline products either as medicinal products or medical devices on a case-by-case basis. Applicants who are unclear on the classification of their product may consult a national competent authority by providing information on its composition, mode of action and intended purpose. Furthermore, the MDR stipulates that the European Commission may consult EMA on items that borderline with medicinal products. Moreover, to ensure consistent qualification decisions across all Member States, the European Commission is allowed to consult the Medical Device Coordination Group (MDCG), whose creation is established by Article 103 of the new MDR. A not legally binding manual that allows for consultation of how various borderline examples have been handled has been developed and is updated on a regular basis by a working party on borderline and classification (WPBC), chaired by the European Commission and composed of representative experts from all Member States and other stakeholders (EC, 2015; WPBC, 2019). Furthermore, a new guideline specific to the medical device – medicinal product borderline is under development and is planned to be endorsed in 2021 (MDCG, 2021).

The classification of borderline products as either medicines or as medical devices determines the applicable regulatory framework, which is especially relevant during its certification for making it available on the market and/or putting it into service. Furthermore, even when classified as medical devices, their conformity may be evaluated through different routes depending on their risk class: for low-risk medical devices (namely, class I devices placed on the market in non-sterile conditions, without measuring functions or non-reusable surgical instruments) this procedure is carried out under the sole responsibility of manufacturers, whereas an appropriate level of involvement by a notified body is required for all other classes, to ensure a high level of health and safety protection.

When in doubt, and after taking into account all its characteristics, for any product that may fall within the definition of a "medicinal product" and the definition of a product covered by other EU legislation (including that of medical devices), the provisions of the medicinal products directive shall apply (MPD Article 2(2), as amended by Directive 2004/27/EC) (EC, 2004a).

3. Medical devices with an ancillary medicinal substance

3.1. Definition of medical device with an ancillary medicinal substance

As stated by the MDR, medical devices can be assisted in their principal intended actions by medicinal substances on an ancillary basis. Indeed, any medical device which incorporates, as an integral part, a substance which, if used separately, would be considered a medicinal product (including blood products), and that has an action ancillary to that of the device, shall be assessed and certified in accordance with the MDR. Therefore, in medical devices with an ancillary medicinal substance the principal intended action is achieved by the device part.

3.2. Examples of medical devices with an ancillary medicinal substance

Among the most well-known devices in this category are *drug-eluting stents*, which have completely replaced the use of bare-metal stents in the treatment of coronary artery diseases, given their lower risk of failure due to in-stent restenosis (AbuRahma et al., 2019). In fact, it was observed that coating the stent with some medicinal substances, such as sirolimus, everolimus or paclitaxel, could significantly reduce the appearance of complications (Limeres et al., 2019; Palmerini et al., 2015), and this became the driving force behind the development of DES (Borhani et al., 2018; Kommineni et al., 2018; Piccolo et al., 2019; Tomberli et al., 2018). Nonetheless, in all cases the pharmacological action of the medicinal substance is always ancillary to the principal intended action of the device, which is achieved by physical or mechanical means. These medicalized stents are constantly improving, as in-stent restenosis has not completely disappeared with their use (Singh et al., 2020a).

Moreover, many implantable medical devices are susceptible to bacterial adherence and biofilm formation (Arciola et al., 2018). Therefore, patients tended to require systemic antibiotic treatments for extended periods of time, putting them at a higher risk of developing antibiotic-resistant infections (Riau et al., 2019). This could ultimately result in the need to remove the medical device in order to eradicate the infection, resulting in a deterioration of the patient's condition (Schwarz et al., 2019; Singh et al., 2020b). As a result, many manufacturers have begun introducing antibiotic drugs in their devices so that, while the medical device is still responsible for the principal intended action, the ancillary medicinal substance can be delivered at its site of action, increasing both efficiency and safety (Bhusal et al., 2016). An example of this are *antibiotic-loaded bone cements* (ALBC), widely used in orthopaedic surgery as bone void fillers, since a common complication during total joint arthroplasty (TJA) is the occurrence of prosthetic joint infection (PJI) caused by opportunistic microorganisms introduced by site seeding during surgery (Kapadia et al., 2016; Koh et al., 2017; Price et al., 2018; Shah et al., 2020; Wall et al., 2021). For this reason, ALBC provides localized antibiotic prophylaxis allowing for higher dosage and minimal adverse reactions as there is no need for the use of systemic antibiotic drugs, resulting in a lower risk of infection following TJA and a higher safety profile (Li et al., 2019; Sebastian et al., 2020). Even though the benefits outweigh the risks, efforts are being taken to prevent

the appearance of antibiotic resistance among microorganisms causing PJI (Schmitt et al., 2020).

Another medical device with an ancillary medicinal substance intended to be used during surgery are *haemostatic matrixes with thrombin* (CHMP, 2012). For these devices, both components (the gelatine matrix and the enzyme) serve the same purpose: to control the bleeding when that is not possible through ligation or conventional procedures. However, the gelatine matrix, which is usually composed of cross-linked bovine gelatine granules, is the agent achieving the principal intended action; while the action of the medicinal substance, thrombin, is only ancillary in supplementing the haemostatic function of the device. While in the past these devices tended to use bovine thrombin, current haemostatic matrixes replace this enzyme with its human analogue in order to reduce the risk of developing antibodies and increase the safety with regards to bovine pathogen transmission (Minkowitz et al., 2019; Olson and Ornstein, 2017; Sanabrias Fernández de Sevilla and Sánchez Guerrero, 2019).

Apart from these devices intended to be used during surgery, other medical devices including ancillary medicinal substances are targeted at the end-user. This is the case of *medicated condoms*, whose principal intended action of preventing pregnancy, as well as the transmission of sexually transmitted infections, is achieved by the physical barrier provided by the device, while the action of the medicinal substance (palliating the effects of premature ejaculation) is ancillary to that of the device (Beksinska et al., 2020; Derefinko et al., 2020). Even though their efficacy in comparison with regular condoms has not been tested in controlled trials, the theoretical benefits of incorporating an anaesthetic drug, such as benzocaine, have been enough to promote the use of these devices (Butcher et al., 2020). Moreover, when compared with other therapeutic alternatives for premature ejaculation (be it oral or topical anaesthetics), medicated condoms have a higher safety profile (Porst and Burri, 2019). However, potential side effects can range from decreased strength of erection, sensitivity and/or pleasure, to contact dermatitis, even when the dosage is limited (Caminati et al., 2019; Ljubojevic Hadzavdic et al., 2018).

Other common medical devices with an ancillary medicinal substance are *drug-impregnated dressings*, which have replaced traditional gauzes, bandages and dressings in almost every situation. The main problem with these traditional medical devices was that, when treating common wounds, burns, pressure ulcers, or catheter-related complications, among others, they had to be frequently changed (even on a daily or more frequent basis) due to the wound swelling, which posed a great burden to both the patient and the caregiver (Gupta et al., 2017; Liu et al., 2017). Furthermore, the appearance of infections or the chronification of the wound were also commonplace, leading to the development of chronic non-healing wounds (Derakhshandeh et al., 2018). However, the incorporation of medicinal substances such as chlorhexidine to dressings has significantly improved the healing process (Graça et al., 2020; Wei et al., 2019).

Moreover, the incorporation of medicinal substances in medical devices is gaining momentum thanks to 3D printing (Sun et al., 2019). As a matter of fact, with the advent of this technology, common medical devices also used by laypersons can become safer with the introduction of medicinal substances into their composition. This is the case of devices currently under research such as *3D-printed antibiotic-loaded hearing aids* (Vivero-Lopez et al., 2021). Even though more than 65% of people over 60 years of age have some degree of hearing loss and nearly 25% of people in this group suffer from disabling hearing loss (WHO, 2021), the use of hearing aids can introduce debris to the ear canal as well as alter its microbiota, resulting in the appearance of infection (Jung et al., 2017; Orji et al., 2014). This has led to the use of topical, or even systemic, antibiotics, contributing to the adverse reactions or potential errors associated with polypharmacy in an already polymedicated population (Pérez-Jover et al., 2018; Turgeon et al., 2017). Therefore, the incorporation of substances that could prevent the formation of biofilms, thus preventing the appearance of infection in the ear canal, could mitigate many problems associated with the use of hearing aids.

3.3. Summary of legal requirements for medical devices with an ancillary medicinal substance

The incorporation of medicinal substances in medical devices is an ever-growing trend. When taking the regulatory perspective, any device that incorporates a substance which, if used separately, would be considered a medicinal product, and that has an action ancillary to that of the device, shall be assessed and certified in accordance with the MDR, as established by the first sub-paragraph of its Article 1(8). Furthermore, as opposed to its old analogous MDD Rule 13 (MDD Annex IX), with the introduction in the MDR of Rule 14 (MDR Annex VIII), these devices are now considered class III medical devices, regardless of whether the medicinal substance acts directly on the body or not (MDCG, 2020). Therefore, even if their invasiveness or duration of use would not qualify them as such, the incorporation of a medicinal substance to a device puts it at the highest risk class possible, and thus, a more comprehensive conformity assessment procedure will be required for making it available in the market and/or putting it into service.

From a clinical perspective, a major novelty introduced by the MDR is that for medical devices with an ancillary medicinal substance (as for all other class III devices) clinical investigations are needed to prove clinical benefit. To prevent unnecessary duplication of clinical investigations, an electronic system covering clinical trials performed in the EU is to be created. Therefore, manufacturers have to justify the level of clinical evidence necessary to demonstrate conformity with MDR requirements, which has to be appropriate to the characteristics and intended purpose of the device (Melvin and Torre, 2019).

Moreover, a post-market surveillance system, in accordance with their highest risk class, should be planned as an integral part of the manufacturer's quality management system in order to be able to report serious incidents and field safety corrective actions, should they be needed (Micläuş et al., 2020). On the one hand, a post-marketing clinical follow-up (PMCF) should be implemented to actively monitor devices and improve clinical information regarding them. On the other hand, a Periodic Safety Update Report (PSUR) summarising the results of the analyses of the data gathered on the post-market surveillance plan shall be prepared by manufacturers, who will have to update it at least annually. To aid in this, a new international Unique Device Identification system (UDI system) to identify any medical device placed in the European Union internal market has been implemented, and a European database on medical devices (Eudamed) has improved its functionality in order to increase both traceability and transparency (Fraser et al., 2018; Migliore, 2017; Tracol, 2016). Furthermore, for medical devices with an ancillary medicinal substance, a summary aimed at the intended user will also be available at Eudamed. Under the name of Summary of Safety and Clinical Performance (SSCP), it will list the main safety and performance aspects, as well as the outcome of the clinical evaluation.

Furthermore, when it comes to the information supplied by the manufacturer, a requirement introduced by the MDR is that devices containing or incorporating a medicinal substance, including a human blood or plasma derivative, must indicate so on the label. In this regard, the regulation allows this information to be provided by a harmonized symbol, which is especially convenient when a manufacturer markets its device in multiple Member States with different official languages. However, as an harmonised ISO standard with regards to symbols for medical devices is not available, MedTech Europe, the European trade association representing the medical technology industries, has published a guide of validated symbols in order to be able to comply with this requirement (MedTech Europe, 2019). (Fig. 1)

In addition, for medical devices containing human blood or plasma derivatives the manufacturer shall inform the notified body of the release of the batch of devices and send an official certificate concerning the release of the batch of human blood or plasma derivative used in the

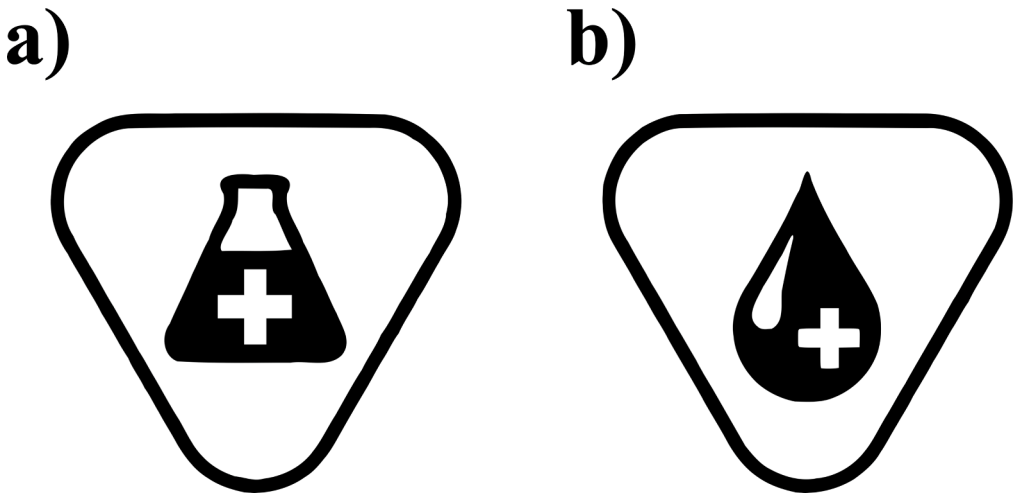

Fig. 1. MedTech Europe's symbols to indicate compliance with the MDR: a) Contains a medicinal substance; b) Contains human blood or plasma derivatives.

device, issued by a Member State laboratory in accordance with Article 114 (2) of the MPD (MDR Annex IX Section 6). This process is known as "batch verification".

Therefore, to certify compliance with the new requirements in the MDR, manufacturers of medical devices with an ancillary medicinal substance must follow a series of steps (Fig. 2):

First of all, manufacturers have to draw up the technical documentation of the device (MDR Annexes II and III), which includes: i) the General Safety and Performance Requirements (GSPR) (MDR Annex I), in order to ensure that the device achieves its intended purposes in a safe and effective manner and that any risks which may be associated with its use are acceptable when weighted against the benefits (Vasiljeva et al., 2020); ii) a system for risk management covering the entire lifecycle of the device, including risk-management plans, post-market surveillance systems and risk-control measures, among others, aimed at reducing the risks without adversely affecting the benefit-risk ratio; and iii) the appropriate clinical evaluations, including post-marketing clinical follow-ups (PMCF).

Subsequently, after compiling all clinical and technical data, the compliance of the device with the requirements laid down in the MDR is proven by undertaking a conformity assessment procedure (MDR Article 52). Therefore, as with any class III medical device, manufacturers of medical devices with an ancillary medicinal substance have to apply for a conformity assessment procedure based on a quality management system and an assessment of the technical documentation for every device (MDR Annex IX). Alternatively, manufacturers may apply for a conformity assessment procedure based on type examination (MDR Annex X) and the subsequent product conformity verification, either by ensuring quality during production or by a verification of the product (MDR Annex XI). (Table 2)

In addition, the MDR introduces a new system for assessing the clinical evaluation carried out for class III implantable medical devices, including those with ancillary medicinal substances: the clinical evaluation consultation procedure, also known as "the scrutiny procedure". For this, the notified body must prepare a Clinical Evaluation Assessment Report (CEAR), which puts forward its conclusions concerning: i) the clinical evidence summarized by the manufacturer on a clinical evaluation report and a draft SSCP; ii) the consistency of that evidence with the intended purpose; and iii) the PMCF plan submitted by the manufacturer (Fraser et al., 2020). Following this, an expert panel independent from the manufacturer, the notified body and the national health authorities will scrutinize this CEAR submitted by the notified body and give its opinion.

The notified body should consider the views expressed by the expert panel, and even though the final decision on the approval of a certain device is theirs to make, if the expert panel's opinion is unfavourable, it will be publicly available on Eudamed, along with the notified body's justification. Therefore, even though expert panels do not have any sanctioning power, Member States' health authorities do, and weighing up all this information could lead to the withdrawal from the market of any devices under dispute.

Once compliance with the requirements has been demonstrated following the applicable conformity assessment procedure, manufacturers assume their responsibility in complying with all EU legislation applicable to a device by drawing up an EU declaration of conformity, which should be continuously updated.

Finally, a CE marking of conformity is affixed to the device before its placing on the market, thus certifying that it is in conformity with MDR requirements. As class III devices, medical devices with an ancillary medicinal substance require the intervention of a notified body for their conformity assessment, and therefore, their CE marking shall be followed by the identification number of the notified body responsible for the conformity assessment procedure.

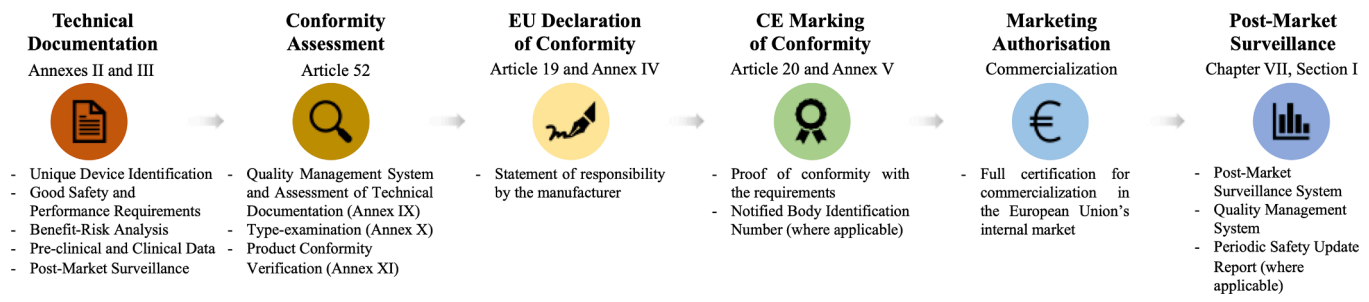

Fig. 2. European certification procedure for medical devices under the new MDR.

Table 2
Certification routes for medical devices with an ancillary medicinal substance under the new MDR. When more than a certification route for a given subclass of medical device exists, they are separated by intervening lines in the columns related to the conformity assessment procedure. The notified body opinion column refers to the conformity of the device part of integral DDCs with the relevant GSPRs issued by a notified body in the remit of the Article 117 of the MDR. It is an abbreviated route in comparison with the EU Certificate of Conformity issued by a notified body after a complete conformity assessment procedure that ultimately allows the CE mark to be affixed on the device.

Medical devices with an ancillary medicinal substance																
Class	Type	General Safety and Performance Requirements	Conformity Assessment						Summary of Safety and Clinical Performance	Post-Market Clinical Follow-up	Periodic Safety Update Report	Notified Body Opinion	Medicinal Products Authority Scientific Opinion	UE Declaration of Conformity	CE Marking of Conformity
			Quality Management System	Technical Documentation	Type-Examination	Product Conformity Verification		Scrutiny Procedure							
						Production Quality Assurance	Product Verification								
III	Non-implantable	✓	✓	✓ For every device	✓	✓	✓		✓ Updated annually	✓ Updated annually	Updated annually		✓	✓	✓
	Implantable	✓	✓	✓ For every device	✓	✓	✓	✓	✓ Updated annually	✓ Updated annually	Updated annually		✓	✓	✓

3.3.1. *Highlights on medical devices with an ancillary medicinal substance under the new European legal framework*

Since the principal intended actions of medical devices with an ancillary medicinal substance are achieved by the device part, whereas the medicinal substance only supports these actions, they shall be certified under the new MDR. However, for medical devices with an ancillary medicinal substance, notified bodies shall seek a scientific opinion from a medicinal products authority regarding the quality, safety and usefulness of the substance, including the benefit or risk of its incorporation into the device. This requirement applies to all devices that incorporate a medicinal substance regardless of whether said substance exerts its action on the human body or not. Therefore, for all those devices where the "liability to act upon the body" was used by the manufacturer as a justification not to follow the consultation to medicinal products authorities under the MDD, the consultation must always take place under the MDR (MDCG, 2020). The competent medicinal products authority issuing the scientific opinion may vary depending on the type of medicinal substance: if it is a biological medicinal product derived from human blood or plasma or any other medicinal product that may fall under the scope of the centralized procedure, the scientific opinion can only be given by EMA, and it shall be compiled in a Consultation procedure Public Assessment Report (CPAR), whereas for all other medicinal products, any competent authority designated by a Member State, as well as EMA, may provide the scientific opinion.

Therefore, although these items are considered medical devices, if the consulted medicinal products authority emits an unfavourable scientific opinion, the notified body will not be able to issue an EU technical documentation assessment certificate, even when they meet all the requirements laid down by the MDR.

4. Drug-device combinations

4.1. *Definition of drug-device combination*

A 2019 draft guideline on quality requirements for "drug-device combinations" (DDCs) that was scheduled to be finalised before the entry into force of the MDR on 26th May 2021 defines them as "medicinal products which contain one or more medical device(s) as an integral part of the composition, as well as medicinal products for which one or more medical device(s) and/or device component(s) are necessary for use of the medicinal product" (CHMP, 2019).

Therefore, drug-device combinations can be divided into two categories: integral DDCs and non-integral DDCs. However, as opposed to medical devices with an ancillary medicinal substance, which are considered class III medical devices in virtue of MDR Rule 14, all other classification rules may apply to the device part of DDCs, and thus, DDCs may not necessarily be composed of exclusively class III medical devices.

4.2. *Integral drug-device combinations*

4.2.1. *Definition of integral drug-device combination*

Integral drug-device combinations are medicinal products that incorporate one or more medical devices in their composition. They are physically united during manufacture, and therefore have to be supplied and used jointly. As established by the second sub-paragraphs of both Article 1(8) and Article 1(9) of the MDR, integral DDCs form a single product intended exclusively for use in the given combination and not reusable, and for which either the medicinal substance it incorporates has an action that is principal and not ancillary to that of the device, or the device is intended to administer the medicinal product. Therefore, they are considered medicinal products and, as such, will be covered by the MPD.

4.2.2. Examples and summary of legal requirements for integral DDCs with a class III medical device part

An example of integral drug-device combinations are *levonorgestrel-releasing intrauterine devices* (LNG-IUD). In addition to contraception, this technology is starting to be used for the treatment of some diseases and ailments such as heavy menstrual bleeding, for which it has demonstrated to be more effective than oral therapies in reducing blood loss and improving quality of life (Bofill Rodriguez et al., 2020), reduction of pain in dysmenorrhea, adenomyosis and endometriosis (Song et al., 2020), as well as protection against atypical hyperplasia or low-risk endometrial cancer (Adeyemi-Fowode and Bercaw-Pratt, 2019; Pal et al., 2018). LNG-IUD are integral drug-device combinations, given that their principal intended action is achieved by the medicinal substance, and the device part solely acts as its support or mode of administration. As a result, LNG-IUD are marketed as medicinal products (covered by the MPD).

Since IUDs are long term invasive devices whose principal intended action is contraception, the device part of these DDCs will be a class III medical device (MDR Annex VIII Rule 15). Therefore, manufacturers have to apply for the same conformity assessment procedure for the device part as the ones explained above for devices with an ancillary medicinal substance, except those related to the substance itself, since they are all class III medical devices. (Table 3)

4.2.3. Examples and summary of legislative requirements for integral DDCs with a class IIa or a class IIb medical device part

One of the most well-known examples of integral DDCs are *non-refillable inhalers*, which have revolutionized asthma and chronic obstructive pulmonary disease treatment. These drug-device combinations have allowed local delivery of the medicinal product. There are various types of devices available depending on the patient's cognitive status, dexterity, ability to coordinate inhaler actuation and inhalation, and disease severity (Chandel et al., 2019; Rogliani et al., 2017). Taking into account the particularities of these DDCs, the new MDR has revised their risk class by adding a new classification rule which states that "all inhalers invasive with respect to body orifices are class IIa devices, unless their mode of action has an essential impact on the efficacy and safety of the administered medicinal product or they are intended to treat life-threatening conditions, in which case they are classified instead as class IIb" (MDR Annex VIII Rule 20).

Manufacturers of DDCs where the device part is a class IIa or IIb device have to compile the technical documentation (MDR Annexes II and III), including a PMCF and a PSUR, updated at least every two years for class IIa devices and at least annually for class IIb devices. Then, they apply for a conformity assessment procedure based on a quality management system and an assessment of the technical documentation for at least one representative device for each category of devices for class IIa devices, and for at least one representative device per generic device group for class IIb devices (MDR Annex IX), in order to certify compliance with the requirements laid down by the MDR.

Alternatively, if the device part is a class IIa device, manufacturers may apply for a conformity assessment procedure based on ensuring that devices are manufactured in conformity with their technical documentation for at least one representative device for each category of devices, together with a product conformity verification, either by ensuring quality during production or by a verification of the product (MDR Annex XI). On the other hand, if the device part is a class IIb device, manufacturers may apply for a conformity assessment procedure based on a type-examination coupled with a product conformity verification, either by ensuring quality during production or by a verification of the product (MDR Annexes X and XI).

Furthermore, if the device part is a class IIb implantable device not considered a well-established technology (WET) as specified in Article 52 of the MDR (i.e., sutures, staples, dental fillings and braces, tooth crowns, screws, wedges, plates, wires, pins, clips and connectors), manufacturers following the first procedure will have to apply for an assessment of the technical documentation for every device. However, if they are indeed WET, an assessment of the technical documentation per generic device group will be enough.

4.2.4. Examples and summary of legislative requirements for integral DDCs with a class I medical device part that is sterile, has a measuring function and/or is a reusable surgical instrument

Another example of integral DDCs are *pre-filled syringes*. In this case, the medical device part acts only as a drug-administering device, and therefore, the principal intended action is achieved by the medicinal product that it administers. These products promote a more active role of patients in their own medication regime, thus minimizing the burden on the healthcare system; and they allow for more individualized and precise dosing, increasing both the efficacy and safety profiles (I'Ons, 2020). Nowadays, medications available in pre-filled syringes can range from vaccines (e.g., recombinant hepatitis B, quadrivalent human papillomavirus or conjugate 13-valent pneumococcal), to treatments for cancer (e.g., adalimumab or etanercept), rheumatoid arthritis (e.g., tocilizumab), or deep vein thrombosis (e.g., enoxaparin) (Ludwin et al., 2021; Sacha et al., 2015).

Since the device part of pre-filled syringes that do not carry the needle pre-assembled is a non-invasive device intended for channelling liquids for the purpose of eventual infusion, they are considered class I medical devices (MDR Annex VIII Rule 2). Furthermore, as they are supplied in sterile conditions and have a measuring function, they are part of the sub-group of class I medical devices that require the involvement of a notified body during their conformity assessment. However, for these pre-filled syringes, the involvement of a notified body shall be limited to any aspects relating to the conformity of the device with the metrological requirements and to any aspects relating to the establishment, securing and maintenance of sterile conditions (MDR Article 52(7)). Therefore, manufacturers will have to compile technical documentation (MDR Annexes II and III) similar to that of other devices but whose PMCF will not require annual updates. Another difference is that instead of preparing a PSUR, manufacturers of these device parts will have to compile a post-market surveillance report (that will only need updating when necessary, instead of periodic updating as with PSUR). Then they will apply for a conformity assessment procedure based on either a quality management system (MDR Annex IX), or a product conformity verification by ensuring quality during production (MDR Annex XI), in order to certify compliance with the requirements laid down by the MDR.

4.2.5. Examples and summary of legislative requirements for integral DDCs with a class I medical device part that is non-sterile, does not have a measuring function and/or is not a reusable surgical instrument

Another example of integral DDCs whose medical device part is a class I device are *transdermal patches*, a pharmaceutical dosage form that circumvents most of the caveats observed for oral medicinal products like drug hydrolysis by digestive fluids or first-pass hepatic metabolism (Lee et al., 2018). Transdermal patches can provide a sustained drug delivery profile, which makes them convenient, especially for long-term treatments. For instance, the range of ailments treated with these integral DDCs has increased over the years: from smoking cessation (Lindson et al., 2019), to contraception (Galzote et al., 2017), pain relief (Nalamachu and Gudin, 2020), motion sickness (Pastore et al., 2015) or cardiac disorders (Al Hanbali et al., 2019). Transdermal patches are integral drug-device combinations, given that the principal intended action is achieved by the medicinal substance, and the device only acts as its support or mode of administration. Therefore, as the device part is non-invasive and no other rules apply, transdermal patches are class I medical devices (MDR Annex VIII Rule 1) (CHMP, 2014). However, since these class I medical devices are placed on the market in non-sterile conditions, without measuring functions and are not reusable surgical instruments, they do not require the intervention of a notified body, and only the technical documentation (MDR Annexes II and III)

Table 3
Certification routes for the device part of integral drug-device combinations under the new MDR. When more than a certification route for a given subclass of medical device exists, they are separated by intervening lines in the columns related to the conformity assessment procedure. The notified body opinion column refers to the conformity of the device part of integral DDCs with the relevant GSPRs issued by a notified body in the remit of the Article 117 of the MDR. It is an abbreviated route in comparison with the EU Certificate of Conformity issued by a notified body after a complete conformity assessment procedure that ultimately allows the CE mark to be affixed on the device.

Integral Drug-Device Combinations															
Class	Type	General Safety and Performance Requirements	Conformity Assessment						Summary of Safety and Clinical Performance	Post-Market Clinical Follow-up	Periodic Safety Update Report	Notified Body Opinion	Medicinal Products Authority Scientific Opinion	UE Declaration of Conformity	CE Marking of Conformity
			Quality Management System	Technical Documentation	Type-Examination	Product Conformity Verification		Scrutiny Procedure							
						Production Quality Assurance	Product Verification								
III	Non-implantable	✓	✓	✓ For every device	✓	✓	✓		✓ Updated annually	✓ Updated annually	✓ Updated annually	✓		✓	
	Implantable	✓	✓	✓ For every device	✓	✓	✓	✓	✓ Updated annually	✓ Updated annually	✓ Updated annually	✓		✓	
IIb	Non-implantable	✓	✓	✓ Per generic device group	✓	✓	✓			✓	✓ Updated annually	✓		✓	
	Implantable non well-established technologies	✓	✓	✓ For every device	✓	✓	✓		✓ Updated annually	✓ Updated annually	✓ Updated annually	✓		✓	
	Implantable well-established technologies	✓	✓	✓ Per generic device group	✓	✓			✓ Updated annually	✓ Updated annually	✓ Updated annually			✓	

(*continued on next page*)

Table 3 (*continued*)

Integral Drug-Device Combinations														
Class	Type	General Safety and Performance Requirements	Conformity Assessment					Summary of Safety and Clinical Performance	Post-Market Clinical Follow-up	Periodic Safety Update Report	Notified Body Opinion	Medicinal Products Authority Scientific Opinion	UE Declaration of Conformity	CE Marking of Conformity
			Quality Management System	Technical Documentation	Type-Examination	Product Conformity Verification	Scrutiny Procedure							
						Production Quality Assurance / Product Verification								
						✓								
											✓			
	Active intended to administer medicinal substances	✓	✓	✓ Per generic device group			✓		✓	✓ Updated annually			✓	
					✓	✓								
						✓								
											✓			
IIa	Non-implantable	✓	✓	✓ Per device category					✓	✓ Updated biannually			✓	
					✓	✓								
						✓								
											✓			
	Implantable	✓	✓	✓ Per device category				✓ Updated annually	✓ Updated annually	✓ Updated biannually			✓	
					✓	✓								
						✓								
											✓			
I	Non– Sterile, measuring or reusable surgical instruments	✓		✓ No Notified Body intervention						✓ Post-Market Surveillance Report			✓	
	Sterile, measuring or reusable surgical instruments	✓	✓	✓					✓	✓ Post-Market Surveillance Report			✓	
					✓	✓								
											✓			

has to be drawn up in order to certify compliance with the GSPR laid down by the MDR.

4.2.6. Examples of investigational integral DDCs

Moreover, in addition to marketed DDCs, a number of investigational integral DDCs are currently under development, including 3D printed DDCs where the device part action is ancillary to that of the medicinal product. As a matter of fact, progress is being made for almost any mode of administration, such as oral (Jeong et al., 2020), subcutaneous (Stewart et al., 2020), topical (Goyanes et al., 2016), vaginal (Tiboni et al., 2021) or intrauterine (Sivasankaran and Jonnalagadda, 2021), to boost the development of more precise drug delivery profiles (Elbadawi et al., 2020).

4.2.7. Highlights on integral drug-device combinations under the new European legal framework

Despite integral drug-device combinations being regulated as medicinal products under the MPD or under the Regulation (EC) 726/2004, their marketing authorisation dossiers have to include the results of the conformity assessment for the device part with regards to the relevant GSPR contained in the manufacturer's EU declaration of conformity, or the relevant certificate issued by a notified body that would allow it to affix a CE marking, as amended in the MPD by the new Article 117 of the MDR. Manufacturers of integral DDCs can affix a CE marking of conformity to the device part, but this should not be included on the product's package, as it could lead to the misinterpretation that it is certifying the product as a whole. In fact, the integral DDC must follow the labelling requirements for medicinal products. As integral DDCs are primarily governed by the MPD, then MDR obligations related to unique device identifier (UDI) are not required and neither should they be applied to the labelling of the integral DDC. For integral DDCs with a CE mark on their device part, the UDI may be assigned to the device itself but should not appear on the labelling or outer package of the integral DDC (CMDh, 2019).

Alternatively, whatever the risk class may be (except for class I medical devices placed on the market in non-sterile conditions, without measuring functions or not being reusable surgical instruments, since those do not require the intervention of notified bodies), when the aforementioned documentation is not available, an opinion from a notified body on the conformity with the MDR's relevant GSPR is enough to be granted certification (CMDh, 2019). Nonetheless, for the first time, a notified body's intervention in the marketing authorisation becomes crucial with the introduction of Article 117 in the MDR.

As a result, even though a CE marking of conformity will not be necessary for these items as the device part is indissolubly united to the medicinal product, when compared with the MDD, the MDR is more efficient at ensuring the safety of these items, as manufacturers of integral DDCs will need to have the device part evaluated by a notified body before it can be made available in the market and/or put into service. This will entail an increase in the safety and performance of these items, as drug-device combinations will meet the requirements laid down by both MPD and MDR. (Table 4)

For integral DDCs, the EMA and national competent authorities strongly recommend submitting the EU certificate, declaration of conformity or notified body opinion already as part of the dossier of the initial marketing authorisation application for the medicinal product, to facilitate a smooth running of the procedure. The absence of this documentation may result in additional clock stops during the procedure as it is necessary for the adoption of a favorable opinion by the Committee for Medicinal Products for Human Use (CHMP).

4.3. Non-integral drug-device combinations

4.3.1. Definition of non-integral drug-device combination

Non-integral drug-device combinations are those for which two or more separate components (medicinal product and medical device) are not physically united during manufacture but need to be combined for administration. The medical device part can be supplied either co-packaged with the medicinal product or in a separate packaging. In the latter case, the medicinal product package leaflet will include a reference to the medical device, because it is inextricably needed for its administration.

Moreover, any device which is intended to administer a medicinal product shall be governed by the MDR, as established by the first subparagraph of its Article 1(9). In this case, the medicinal product and its medical device part are placed on the market separately, and as such, even though they are used jointly, they will each have to meet their respective regulatory requirements.

Table 4
Integral drug-device combination's authorisation similarities and differences between MDD and MDR's regimes.

Regime	Under MDD	Under MDR
Consideration	Medicinal Product	Medicinal Product
Rule	Directive 2001/83/EC or Regulation 726/2004	Directive 2001/83/EC or Regulation 726/2004
Requirements	Relevant essential safety and performance requirements of Annex I of Council Directive 93/42/EEC (MDD)	Relevant general safety and performance requirements of Annex I of Regulation (EU) n°. 2017/745 (MDR)
Notified Body	No intervention required	Article 117: – Conformity assessment results with regards to GSPR for EU declaration of conformity or – Conformity assessment results with regards to GSPR for CE marking certificate or – Notified Body opinion on the conformity with the relevant GSPR

4.3.2. Examples and summary of legislative requirements for non-integral DDCs with a class III medical device part

As life-prolonging treatments improve, cancer survivorship increases, shifting the focus of pain management therapy from short-term analgesia to chronic pain relief (Bruel and Burton, 2016; Siegel et al., 2020). In this context, *intrathecal pumps* provide an effective technique for the treatment of cancer-related pain.

The main advantage of these drug-device combinations, consisting of a refillable reservoir (typically of morphine or ziconotide) attached to a small catheter threaded upward into the spinal fluid space, is that they deliver the medicinal products directly into the central nervous system, allowing for the administration of lower doses in their site of action, which translates into fewer systemic adverse effects and better control of the analgesia (Deer et al., 2019; Fallon et al., 2018). Subsequently, the pump is programmed to regularly release a specific dose and, depending on the pump size, concentration and dose, it will have to be refilled every couple of months using a syringe and a needle. However, even though the benefits outweigh the risks, their incorporation into clinical practice has been limited, in part due to the added complexity of implantation surgery when compared with oral or intravenous administration (Dupoiron, 2019). When classifying the implantable device part of intrathecal pumps, they qualify as class III medical devices for three different reasons: i) they are intended to be used in direct contact with the central nervous system; ii) they are intended to administer medicinal products; iii) they are active implantable devices (MDR Annex VIII Rule 8). Therefore, manufacturers of these non-integral DDCs must follow the same steps previously described for all other class III medical devices. (Table 5)

4.3.3. Examples and summary of legislative requirements for non-integral DDCs with class IIa or class IIb medical device parts

Contrary to non-refillable inhalers, which are integral DDCs as the

Table 5
Certification routes for the device part of non-integral drug-device combinations under the new MDR. When more than a certification route for a given subclass of medical device exists, they are separated by intervening lines in the columns related to the conformity assessment procedure. The notified body opinion column refers to the conformity of the device part of integral DDCs with the relevant GSPRs issued by a notified body in the remit of the Article 117 of the MDR. It is an abbreviated route in comparison with the EU Certificate of Conformity issued by a notified body after a complete conformity assessment procedure that ultimately allows the CE mark to be affixed on the device.

Non-Integral Drug-Device Combinations															
Class	Type	General Safety and Performance Requirements	Conformity Assessment						Summary of Safety and Clinical Performance	Post-Market Clinical Follow-up	Periodic Safety Update Report	Notified Body Opinion	Medicinal Products Authority Scientific Opinion	UE Declaration of Conformity	CE Marking of Conformity
			Quality Management System	Technical Documentation	Type-Examination	Product Conformity Verification		Scrutiny Procedure							
						Production Quality Assurance	Product Verification								
III	Non-implantable	✓	✓	✓ For every device	✓	✓	✓		✓ Updated annually	✓ Updated annually	✓ Updated annually			✓	✓
	Implantable	✓	✓	✓ For every device	✓	✓	✓	✓	✓ Updated annually	✓ Updated annually	✓ Updated annually			✓	✓
IIb	Non-implantable	✓	✓	✓ Per generic device group	✓	✓	✓			✓	✓ Updated annually			✓	✓
	Implantable non well-established technologies	✓	✓	✓ For every device	✓	✓	✓		✓ Updated annually	✓ Updated annually	✓ Updated annually			✓	✓
	Implantable well-established technologies	✓	✓	✓ Per generic device group	✓	✓	✓		✓ Updated annually	✓ Updated annually	✓ Updated annually			✓	✓
	Active intended to administer medicinal substances	✓	✓	✓ Per generic device group	✓	✓		✓		✓	✓ Updated annually			✓	✓

(*continued on next page*)

Table 5 (*continued*)

Non-Integral Drug-Device Combinations														
Class	Type	General Safety and Performance Requirements	Conformity Assessment					Summary of Safety and Clinical Performance	Post-Market Clinical Follow-up	Periodic Safety Update Report	Notified Body Opinion	Medicinal Products Authority Scientific Opinion	UE Declaration of Conformity	CE Marking of Conformity
			Quality Management System	Technical Documentation	Type-Examination	Product Conformity Verification	Scrutiny Procedure							
						Production Quality Assurance / Product Verification								
IIa	Non-implantable	✓	✓	✓ Per device category	✓ / ✓ / ✓				✓	✓ Updated biannually			✓	✓
	Implantable	✓	✓	✓ Per device category	✓ / ✓ / ✓			✓ Updated annually	✓ Updated annually	✓ Updated biannually			✓	✓
I	Non– Sterile, measuring or reusable surgical instruments	✓		✓ No Notified Body intervention						✓ Post-Market Surveillance Report			✓	✓
	Sterile, measuring or reusable surgical instruments	✓	✓	✓	✓				✓	✓ Post-Market Surveillance Report			✓	✓

medicinal product and the medical device are physically united, *reusable inhalers* are non-integral DDCs, as the inhaler and the cartridges can be obtained separately. Even though they can be sold in different secondary packages, the cartridge product information will contain a reference to the inhaler, because it will be inextricably needed for its administration. Nevertheless, no matter if co-packaged or not, the same new classification rules introduced with the MDR will apply for all inhalers which are invasive with respect to body orifices (MDR Annex VIII Rule 20). Therefore, according to their risk class, reusable inhalers will have to follow the same conformity assessment procedures that have been previously explained for non-refillable inhalers.

Moreover, the MDR includes a set of especial requirements for class IIb active devices intended to administer and/or remove a medicinal product (MDR Annex VIII Rule 12). An example of a non-integral drug-device combination with this type of device part are *insulin pumps*. Continuous subcutaneous insulin infusion offers a more physiologic insulin replacement profile than multiple daily insulin injections. However, insulin pump efficacy in young adults with type 1 diabetes remains uncertain (Pickup, 2019), and results vary widely when compared to multiple daily insulin injections: from a lower risk of severe hypoglycaemia and ketoacidosis and better glycaemic control (Karges et al., 2017), to a modest reduction in HbA1c (Benkhadra et al., 2017), or even an increased risk of ketoacidosis (probably due to malfunction of the pump and/or catheter occlusion) (Pala et al., 2019). Despite this controversy surrounding efficacy, psychosocial benefits, such as motivation, adherence to treatment, increased quality of life or decreased caregiver burden, especially in newly diagnosed patients and in children, may have contributed to the increase in insulin pump adoption (Mueller-Godeffroy et al., 2018). This has driven the constant innovation of manufacturers with ever more sophisticated pumps (Sharma et al., 2021; Sora et al., 2019; Zimmerman et al., 2019), and even the development of systems that combine a pump and a monitor for automated insulin delivery (Beck et al., 2019). As the medical device part of insulin pumps is a class IIb active device intended to administer and/or remove a medicinal product, in addition to the conformity assessment procedure for any class IIb medical device, manufacturers will have to carry out the scrutiny procedure explained above for class III implantable devices, by which a notified body has to elaborate a CEAR that will be assessed by an independent expert panel. Moreover, it is worth noting that software, in its own right, when specifically intended by the manufacturer to be used for a medical purpose, like the one used in last generation automated insulin pumps, also qualifies as a medical device under the MDR, and therefore shall be subject to risk classification and the appropriate conformity assessment procedures before it can be made available in the market and/or put into service (Beckers et al., 2021; Minssen et al., 2020; Muehlematter et al., 2021).

4.3.4. Examples and summary of legislative requirements for non-integral DDCs with a class I medical device part that is sterile, has a measuring function and/or is a reusable surgical instrument

Finally, *oral administration devices*, such as cups, spoons, or syringes, that are generally supplied along with liquid medicinal products, are non-integral DDC for which the medical device is a class I device with a measuring function. For these devices, the involvement of a notified body shall be limited to the aspects relating to the conformity of the devices with the metrological requirements. Therefore, manufacturers of these devices will have to follow the same procedures previously discussed for integral DDCs with class I medical devices placed on the market in sterile conditions, with measuring functions or that are reusable surgical instruments.

4.3.5. Highlights on non-integral drug-device combinations under the new European legal framework

As opposed to integral DDCs, for which a notified body's opinion on the compliance with the relevant GSPR may be sufficient if the conformity assessment of the device part is not available, manufacturers of non-integral DDCs must pass the appropriate conformity assessment procedure to draw up an EU declaration of conformity.

Moreover, unlike integral DDCs, medical devices constituting non-integral DDCs must be affixed with a CE marking of conformity in accordance with the MDR before making them available in the market and/or putting them into service.

5. Concluding remarks

A succession of safety issues, most notably the thalidomide disaster and the breast implant rupture incident, have motivated regulators, stakeholders and patients alike to promote an ever more comprehensive European legal framework for both medicinal products and medical devices. In this context, a new European regulation on medical devices, which fully applies from May 26th 2021, aims at ensuring the smooth functioning of the internal market and setting high standards of quality and safety for these items.

In the remit of this new European regulation (MDR) the main difference between medical devices and medicinal products is the means of achieving their principal intended action. For manufacturers of borderline products, obtaining marketing authorisation as a medical device or as a medicinal product may pose a huge difference in the entry to the market, and thus, in profit returns after the initial investment. The MDR constitutes a major asset to clearly set the basis for the regulatory framework under which a product incorporating both a medicinal product and a medical device falls.

In this regard, for devices incorporating medicinal substances where the action of the medicinal substance is ancillary, the product is primarily regulated as a medical device and must be CE marked. However, a favourable scientific opinion must be provided by a medicinal products authority before a notified body can issue an EU certificate for the device. Unlike the MDD, the MDR states that the notified body may not deliver the certificate if the opinion is unfavourable. Furthermore, for the first time, the MDR also states that clinical investigations are mandatory for these medical devices with an ancillary medicinal substance (as for all other class III devices) to prove clinical benefits. The new regulatory requirements applicable to medical devices that incorporate an ancillary medicinal substance show that the legislative model is moving towards convergence with the legislative approach required for the authorisation of medicinal products, based on a high level of health protection for patients and users. Alternatively, for devices incorporating a medicinal substance where the action of the medicinal substance is principal, the integral drug-device combination is primarily regulated under the medicinal products framework, although, for the first time, the relevant general safety and performance requirements of the MDR regarding the quality, safety and efficacy of the medicinal product apply to its device part.

Moreover, the regulatory framework for administration devices is also clarified with the MDR. If the administration device is marketed as a single integral product intended exclusively to be used in the given combination and it is not reusable, the integral drug-device combination is primarily regulated under the medicinal products framework, although, for the first time, the relevant general safety and performance requirements of the MDR have to be demonstrated for the device part. In this case, CE marking is not necessary. However, if the device part has CE marking, it may be included on the device itself but not on the labelling for the drug-device combination, as it may be misinterpreted as referring to the combination as a whole. Alternatively, for all other administration devices not physically united to the medicinal product (either co-packaged or not), the administration device is primarily regulated under the MDR. Accordingly, for these non-integral drug-device combinations, the device part has to be CE marked.

Altogether, the core precept of the new European legal framework is that medicinal products authorities evaluate the specific aspects related to the quality, safety and efficacy of the medicinal product, and that notified bodies assess the relevant general safety and performance

requirements of the medical device. As a result, the full application of this new framework from May 2021 onwards will have a great impact on regulatory agencies.

In fact, with the introduction by the MDR of more comprehensive requirements for notified bodies, the number of qualified notified bodies and their scope will inexorably decrease. In particular, Article 117 of the new MDR introduces a new requirement for the involvement of notified bodies in the European market authorisation of integral drug-device combinations. Analogously, the MDR has also introduced more rigorous procedures for the evaluation of class III implantable devices and class IIb active devices intended to administer and/or remove a medicinal product by notified bodies through the implementation of the scrutiny procedure. Moreover, the movement of certain devices to a higher risk class under the MDR will demand more involvement of notified bodies in their evaluation of conformity. Taken together, the MDR will doubtless increase the notified bodies' workload for the evaluation of both medical devices with ancillary medicinal substances and drug-device combinations (either integral or non-integral).

The MDR also lays down new responsibilities for EMA and the national competent authorities for medicinal products. As a result, before a notified body can issue a CE certificate for a medical device with an ancillary medicinal substance, it must seek the scientific opinion of a medicinal products authority on the quality and safety of the ancillary substance. Moreover, the MDR allows the European Commission to consult EMA when deliberating on the regulatory status of borderline products involving medicines. Finally, national competent authorities or EMA must lead the marketing authorization process of drug-device combinations (either integral or non-integral). As a result, medicinal products authorities will also increase their workload noticeably upon full application of the MDR.

Therefore, an increase in collaboration between notified bodies and medicinal products authorities is to be expected. In particular, to ensure a consistent procedure, the assessment report of notified bodies containing the requested opinion for integral drug-device combinations and the scientific opinion provided by the medicinal products authority on medical devices with an ancillary substance should be designed in such a way that each half can rely on the other for the final marketing authorisation or certificate of conformity, respectively. However, despite the positive increase in quality standards through the implementation of the MDR, this joint assessment will also translate into prolonged times for certification and authorisation.

Overall, the new European perspective contributes to the understanding of the companionship between medical devices and medicinal products, defining their boundaries and requirements and providing the necessary regulatory framework to enable European healthcare to benefit from the new arising collaboration between medtechs and pharmaceutical companies.

CRediT authorship contribution statement

Pau Antich-Isern: Writing – original draft. **Julia Caro-Barri:** Writing – review & editing. **Juan Aparicio-Blanco:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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