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REVIEW

New European Regulation for Medical Devices: What Is Changing?

Nicolas Martelli[1,2] · Déborah Eskenazy[2] · Carole Déan[3] · Judith Pineau[1] · Patrice Prognon[1] · Gilles Chatellier[4] · Marc Sapoval[3,5,6] · Olivier Pellerin[3,5,6]

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Abstract
Introduction The Medical Devices Regulation (MDR) 2017/745/EU will fully apply from May 2020. Interventional radiologists use medical devices on a daily basis and so must be aware of the impact that this new regulation will have on their daily practice.
Materials and Methods In this paper, we describe the major transformation that the MDR brings to the medical devices sector, with a focus on clinical evaluations and clinical investigations.
Results This regulation significantly tightens controls to ensure that devices are safe and effective. In addition, equivalence to already existing devices, which allowed an accelerated access to the market, will now be possible only in some cases. Furthermore, post-marketing clinical follow-up is extended under the MDR and is required for all devices. These new requirements will probably lead to a dramatic increase in the number of clinical investigations and also to a delay in the availability of certain devices on the market.
Conclusions In the coming years, interventional radiologists are likely to be affected by these changes in their daily practice, in terms of medical device availability and/or in terms of increased involvement in clinical investigations.

Keywords Medical device · Regulation · Clinical investigation · CE mark

Introduction

Interventional radiologists typically use many implantable and non-implantable medical devices during interventions. Such products are defined in Europe as "*any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: (i) diagnosis, prevention, monitoring, treatment or alleviation of disease; (ii) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; (iii) investigation, replacement or modification of the anatomy or of a physiological process; (iv) control of conception*" [1]. Safety and marketing of medical devices in the European Union (EU) are regulated by three directives, collectively known as the Medical Devices Directives (MDDs), which are: the

✉ Nicolas Martelli
nicolas.martelli@aphp.fr

1 Pharmacy Department, Assistance Publique - Hôpitaux de Paris, Hôpital Européen Georges Pompidou, 20, rue Leblanc, 75015 Paris, France

2 University of Paris-Sud, Université Paris-Saclay, EA7358 GRADES, 5 rue Jean-Baptiste Clément, 92290 Châtenay-Malabry, France

3 Vascular and Oncological Interventional Radiology Department Assistance Publique - Hôpitaux de Paris,, Hôpital Européen Georges Pompidou, 20, rue Leblanc, 75015 Paris, France

4 Clinical of Research Unit (URC), Assistance Publique - Hôpitaux de Paris, Hôpital Européen Georges Pompidou, 20, rue Leblanc, 75015 Paris, France

5 Faculté de Médecine, Université Paris Descartes - Sorbonne - Paris - Cité, Paris, France

6 INSERM U970, Paris, France

Active Implantable Medical Devices Directive (AIMDD) 90/385/EEC published in July 1990 [2], the Medical Devices Directive (MDD) 93/42/EEC published in July 1993 [1], and the In Vitro Diagnostic Medical Devices Directive (IVDMD) 98/79/EC published in December 1998 [3]. To be launched onto the European market and according to the MDDs, a medical device needs a CE mark (CE for *Conformité Européenne*—European Conformity) [4]. The CE mark is required to prove both the device safety and that it achieves the performance intended by the manufacturer [1]. MDDs will be replaced by two new regulations published and entered into force in May 2017 [5, 6]. Medical Devices Regulation (MDR) 2017/745/EU [5] will replace AIMDD and MDD in May 2020, and In Vitro Diagnostic Medical Devices Regulation (IVDR) 2017/746/EU [6] will replace IVDMD in May 2022. In the present paper, we chose to focus on Regulation (EU) 2017/745 because this will more greatly affect interventional radiologists. Throughout the paper, we will use MDR to refer to the new Regulation (EU) 2017/745 and MDDs to refer to the "old" Directives.

The major difference between an EU regulation and an EU directive is that a regulation is immediately applicable and enforceable by law in all EU Member States, whereas a directive sets out goals that EU Member States must achieve [7, 8]. However, the individual countries are free to decide how to reach these goals, which may cause discrepancies in the application of a directive [7]. This difference means that the introduction of the MDR should thus contribute to harmonization of medical device legislation in Europe, but this is not the only goal of the MDR. In fact, the MDR significantly tightens the controls to ensure that devices are safe and effective [5]. Indeed, the MDR introduces the concept of effectiveness, which was not covered by the MDDs. The MDR also implements many new requirements for manufacturers and authorities, which have a short transition period (until May 2020) to ensure compliance with these. This transition period of only three years could add another layer of complication for adopting this very thorough new regulation. Evaluation of medical devices will be dramatically impacted and these dramatic changes may strongly affect the availability of medical devices, by extension of evaluation times or market withdrawal of certain devices [9]. In the present paper, we focus on the main differences between the MDR and the MDDs in terms of clinical investigations, both because these changes are important for those involved (or those involved in the future) in clinical investigations and because all interventional radiologists should be aware of these changes, which may have consequences for their daily practice.

Background

Four categories of medical devices are defined in the MDD: class I, class IIa and class IIb, and class III [1]. These classifications are based on the intended purpose of the device, as well as the duration of contact with the body, the local versus systemic effect and the degree of invasiveness [4]. In the CE marking process, the manufacturer must determine whether their device falls within the scope of one of these four categories using the classification rules listed in Annex IX of the MDD [1]. The category determines the conformity requirements, with higher-risk devices (class III ranks as the highest) undergoing higher levels of assessment [4]. The MDR does not modify the principle of the medical device categories, but classification rules and conformity requirements have been revised [5]. It should be noted that the MDR introduces the reclassification of some categories of devices to class III. For example, surgical meshes have been reclassified as class III, and clinical investigations are still mandatory for class III devices (for which exemptions have been changed). Moving from one class to a higher-risk class has a great impact on the CE marking process, because it can change the conformity assessment procedure. For example, if a device moves from class IIb to class III, clinical investigations, which are optional for class IIb, become mandatory, and the manufacturer has a more limited choice of conformity assessment routes (see Table 1).

In the CE marking process, a manufacturer must prove that the device complies with the essential requirements of the MDD [1]. This demonstration is based on a conformity assessment procedure, which differs according to the classification of the device (Table 1). Except for class I devices that are not supplied in sterile conditions and/or do not have a measuring function, a third party must ensure that conformity assessment procedures are completed according to the MDD criteria [1]. This is the role of the "notified body", which is an organization designated by a Member State. As explained above, the manufacturer initially determines the classification of their device. However, where the manufacturer and the notified body disagree on the classification of a device, either party can refer the case to the competent authority that the notified body is subject to for a final decision [1]. The MDR does not modify the principle of the notified bodies at all, but more rigorous procedures for these organizations have been introduced for class III and implantable devices, and these procedures require a process of clinical evaluation [5].

Table 1 Assessment routes according to the medical device classification

Medical device class	Level of risk	Example	Type of assessment	Application to a notified body to approve the declaration
Class I *Excluding sterile products and/or those with a measuring function*	Low	Non-sterile gloves	Technical documentation + EC Declaration of conformity (Annex VII of the MDD)	No (Self-certification)
Class I *Sterile products and/or those with a measuring function*	Low	Thermometers	Same requirements as Class I non-excluding sterile products and/or those with a measuring function + manufacturer's choice from the following options: 1. Examination and testing of each product or homogenous batch of products (Annex IV of the MDD) 2. Audit of the production quality assurance system (Annex V of the MDD) 3. Audit of final inspection and testing (Annex VI of the MDD) 4. Audit of the full quality assurance system (Annex II of the MDD)	Yes
Class IIa	Moderate	Sterile needles	Audit of the full quality assurance system (Annex II of the MDD) or Same requirements as for Class I devices excluding sterile products and/or those with a measuring function + either option 1, 2 or 3 above	Yes
Class IIb	Moderate	Surgical meshes	Audit of the full quality assurance system (Annex II of the MDD) or Type examination (Annex III of the MDD) + either option 1, 2 or 3 for Class I sterile products and/or those with a measuring function	Yes
Class III	High	Peripheral stent	Audit of the full quality assurance system (Annex II of the MDD) or Type examination (Annex III of the MDD) + either option 1 or 2 for Class I sterile products and/or those with a measuring function	Yes

EC: European conformity; MDD: Medical devices Directive

Clinical Evaluation and Clinical Investigations

The MDR outlines the difference between a clinical investigation and a clinical evaluation. A clinical investigation is defined by the MDR as "*any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device*". Most of the time, it refers to "clinical trials" as a source of clinical data. According to the MDR, a clinical evaluation is a wider source of data, because it takes into account all relevant scientific data available (technical data, preclinical data, etc.) in addition to the clinical data from a clinical investigation.

Article 61 of the MDR states for all medical devices that "*a clinical evaluation shall follow a defined and methodologically sound procedure based on the following: (a) a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, […]; (b) a critical evaluation of the results of all available clinical investigations, […]; and (c) a consideration of currently available alternative treatment options for that purpose, if any*" [5]. In other words, the MDR states that a clinical evaluation is now not only based on a clinical investigation and that critical review of the relevant data from the scientific literature may be sufficient for most devices (Fig. 1) [5]. For example, a class IIa device, e.g., an introducer sheath, does not require a clinical investigation, and technical data or preclinical data collected would be enough to constitute the clinical evaluation. By contrast, for implantable devices and class III devices, clinical investigations are mandatory. This means, for example, that a manufacturer should demonstrate through a clinical investigation that its new peripheral stent achieves the performances intended, is safe and provides the expected clinical benefit. However, the MDR introduces three exceptions:

1. The device is already CE-marked according to the MDDs. In this case, clinical investigations are not mandatory if the manufacturer can provide sufficient clinical data and can prove conformity to applicable

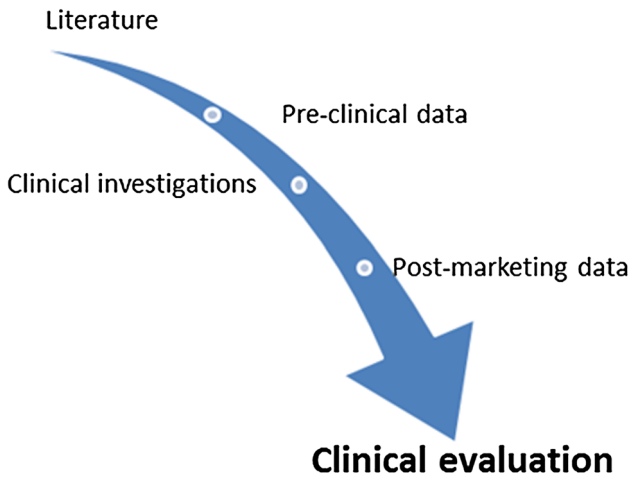

Fig. 1 Sources of data for clinical evaluations according to the Medical Devices Regulation (MDR) 2017/745/EU

common specifications. For example, the clinical data can be issued from a post-market surveillance study. It should be noted that MDD CE certificates have an extended validity period until May 2024 [5].

2. The device has been designed as a "modification" of a device produced by the same manufacturer and is already CE-marked according to the requirements of the MDR. In this case, the new device is deemed a non-substantial modification of the existing device. The manufacturer has demonstrated that the modified device is equivalent to the previously marketed device, and this demonstration has been endorsed by the notified body. The modification can be considered non-substantial if it does not change the performance, safety or effectiveness of the device. For example, a modification of the device packaging would not be considered a substantial modification. In contrast, for a peripheral stent using an eluting drug, a change of the drug could be seen as a substantial modification, because it could modify its effectiveness and tolerability.
3. The device is equivalent to a device produced by another manufacturer and already CE-marked according to the MDR. The modified device has been demonstrated by the manufacturer to be equivalent to the previously marketed device and this demonstration has been accepted by the notified body. In this case, three additional conditions should be met: (1) the two manufacturers should now have a contract that explicitly grants the manufacturer of the new device full access to the technical documentation on an ongoing basis; (2) the original clinical evaluation must have been performed in compliance with the requirements of the MDR; (3) the manufacturer of the new device must provide clear evidence thereof to the notified body. For example, a manufacturer has designed a new detachable coil for embolization of peripheral vasculature, and this coil is equivalent to another device already CE-marked but produced by another manufacturer. In this scenario, the second manufacturer must reach an agreement with the original manufacturer to obtain full access to the technical documentation of the detachable coil.

Clinical investigations are not only required for the CE marking process, but they are also required for post-marketing clinical follow-up (PMCF) [10]. PMCF is needed to confirm existing clinical data on the device and to update the clinical evaluation after the device is launched onto the market. PMCF was already required under the MDDs but is extended in the MDRs and is required for all medical devices, whatever the class of medical device. PMCF is a continuous process aiming to generate data for the clinical evaluation, and PMCF studies are generally device registries containing data on large samples of patients [11]. This will lead to more clinical investigations for high-risk medical devices (class III and implantable), because, according to the MDR, the PMCF evaluation report will now be updated at least annually for such devices.

Finally, the MDR also introduces a comprehensive EU database on medical devices, by extending the existing database EUDAMED. With the aim of enhancing transparency, the new version of EUDAMED will contain a lot of information on the device (economic, technical, and clinical information); almost all information will be accessible by competent authorities and the European Commission, and some will also be made publicly available. The MDR states that data from clinical investigations should be entered into EUDAMED (although this will not be publicly available), as should data from PMCF studies.

Demonstration of Equivalence

For demonstrating equivalence between two devices, the MDR defines new and stricter criteria [5]. Thus, the device to which the manufacturer claims equivalence must share the same technical, biological, and clinical characteristics (Table 2). For example, if the device to which the manufacturer is comparing its own device has the same technical and clinical characteristics but uses different materials (biological criterion) without a justified rationale, this will be not enough to demonstrate equivalence. According to the MDR, considerations of equivalence must be based on a suitable scientific justification [5]. Consequently, the manufacturer must gather sufficient evidence about the other device on every feature claimed as equivalent; this will be a big challenge without the agreement of the first

Table 2 Criteria for the demonstration of equivalence

Technical	Clinical	Biological
Similar design	Same clinical condition or purpose, including similar severity and stage of disease, at the same site in the body, in a similar population (age, anatomy and physiology)	Same materials or substances in contact with the same human tissues or body fluids for a similar kind and duration of contact and similar release characteristics of substances, including degradation products and leachables
Similar conditions of use	Same kind of user	
Similar specifications and properties including physicochemical properties such as intensity of energy, tensile strength, viscosity, surface characteristics, wavelength and software algorithms	Similar relevant critical performance in view of the expected clinical effect for a specific intended purpose	
Similar deployment methods		
Similar principles of operation and critical performance requirements		

manufacturer. This will have consequences for clinical evaluation and/or clinical investigations, because more clinical data will be needed to demonstrate equivalence. For example, a manufacturer of a new inferior vena cava filter would like to compare their device to another inferior vena cava filter available on the market, and there are no substantial modifications. The manufacturer must prove, among other things, that the devices have the same design (e.g., a conical shape), the same indication of use (e.g., short-term contraindication of anticoagulation) and are made using the same material (e.g., nitinol). Nevertheless, to do so, the manufacturer of the new inferior vena cava filter will not be able to demonstrate equivalence, in a relevant way, without full access to the technical documentation of the already CE-marked device.

Definition of the Expert Panel

The MDR also introduces new procedures involving an expert panel. The MDR states that "expert panels consist of advisors appointed by the European Commission on the basis of up-to-date clinical, scientific, or technical expertise in the field" and, in accordance with the requisite needs, it is the European Commission which will determine the number of members of the panel [5].

Thus, for all class III devices and some class IIb devices, the manufacturer may consult the expert panel, with the aim of reviewing the manufacturer's intended clinical development strategy and proposals for clinical investigations [5]. This must be done prior to the clinical evaluation and/or investigation of the device. For the manufacturer, it is an opportunity to obtain early scientific advice on its clinical development strategy. Although this is an entirely voluntary approach, the MDR underlines that the manufacturer should give due consideration to the views expressed by the expert panel [5]. For example, we envision that the expert panel would be able to provide some guidance on the patient population to study, or the number of patients to be included in the clinical study. One important point is that, although it will take a considerable effort on the part of manufacturers to comply with these new requirements, given that the regulation is immediately applicable by law in all EU Member States, it is worth the investment to access a very large market in one single go.

According to the MDR and during the CE marking process, a notified body will be obliged to request that the expert panel scrutinizes the clinical evaluation assessment report for class III implantable devices and class IIb active devices intended to administer and/or remove a medicinal product [5]. This is called the "scrutiny procedure" [10]. The expert panel will then decide whether it will give its own opinion within 60 days. If no opinion is given, the notified body can continue with the certification process. As in the case of voluntary early advice, the notified body must consider the views expressed by the expert panel. In the case of divergent views between the notified body and the expert panel, a comprehensive statement of reasons is requested. In cases of unfavorable opinions, the MDR does not indicate any power of sanction from the expert panel [5]. However, all relevant documents regarding the opinion of the expert panel and the final decision of the notified body will be available in EUDAMED, which may well deter notified bodies from ignoring the opinion of the expert panel. It will also give competent authorities of Member States the possibility of being informed about devices that have been cleared despite an unfavorable opinion of the expert panel, and consequently to enforce

potential sanctions. This could occur, for example, in cases where the expert panel considers that the clinical evaluation is not adequate to determine the acceptable risks claimed by the manufacturer. Ultimately, one could imagine that a competent authority informed thanks to EUDAMED could restrict the access of the device onto the market or eventually withdraw the device from the market.

Discussion

The MDR will lead to significant transformations in the field of medical devices. As we have seen, the MDR will impact the risk classification of many devices and certain devices will be moved into a higher class. This could result in significant costs and important delays for recertification that could discourage manufacturers from continuing to market some of their own devices, especially those that are not compliant with the MDR after moving to a higher risk class. Consequently, this reclassification is likely to lead to a reduced availability of certain devices, which will directly impact interventional radiologists in their daily practice. This is reinforced by another major modification in the MDR, relating to the need for access to technical documentation to demonstrate equivalence between two devices from two different manufacturers. Allowing another manufacturer to access technical documentation will be a very difficult step for manufacturers, especially in a competitive environment. One can hypothesize that it might be impossible for the manufacturers to reach an agreement in some cases and the ability to demonstrate equivalence would therefore disappear. It could also tighten the market of certain devices; without recourse to the use of equivalence, it is possible that fewer manufacturers will launch devices for which equivalent devices exist on the market. For interventional radiologists, this may therefore reduce the supply of devices and the variety of products available. Because demonstrating equivalence will be more challenging, it is likely there will be an increase in clinical investigations on implantable devices and class III medical devices. We think that this is the most critical consequence of the MDR and is going to dramatically change the development plans or market access strategies of numerous manufacturers. On the one hand, this will be likely to delay the launch of implantable and class III medical devices onto the market and discourage some manufacturers from marketing certain new devices. This will impact interventional radiologists by reducing the devices available on their shelf. On the other hand, because of the probably increase in clinical investigations, interventional radiologists will potentially be increasingly involved in clinical studies on new medical devices. This will also be reinforced by the fact that post-marketing registries will become increasingly common due to the new requirements for PMCF. For these reasons, the involvement of interventional radiologists in clinical investigations on medical devices is going to be essential in the years to come, and those who until now did not participate regularly in such investigations are likely to become involved in some way. Another, separate, impact of the MDR is the uncertainty around the scrutiny procedure. According to the MDR, the aim of the consultation is to harmonize the evaluation of high-risk medical devices.

In conclusion, the MDR transforms the regulation of medical devices in Europe with the aim of launching more effective and safer medical devices onto the market. For interventional radiologists, this means better devices and increased safety for their patients. In addition, a lot of information, such as the results of clinical investigations, will be available on EUDAMED, and this will contribute to greater transparency on the marketing of medical devices. This point is important for all health professionals in Europe and may also ensure better selection among medical devices available on the market. However, some of the new requirements of the MDR will potentially delay the availability of certain medical devices or lead to discontinuation of the marketing of others. The real impact is difficult to measure at the present time, but we cannot exclude the possibility that interventional radiologists will experience difficulties in obtaining some devices used in their daily practice in the coming years.

Compliance with Ethical Standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices. Official Journal of The European Communities L 169, 12.7.1993; 1–43. n.d. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A31993L0042 Accessed 21 Oct 2018.
2. Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices. vol. OJ L. 1990.
3. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices. vol. OJ L. 1998.
4. French-Mowat E, Burnett J. How are medical devices regulated in the European Union? J R Soc Med. 2012;105:S22–S28. https://doi.org/10.1258/jrsm.2012.120036.
5. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. vol. 117. 2017.
6. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices

and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. vol. 117. 2017.
7. Miller V, Clark E. The European Union: a guide to terminology, procedures and sources. SN/IA/3689. House of Commons Library; 2010.
8. Article 288 of the Treaty on the Functioning of the European Union, Official Journal C 326, 26.10.2012; 1–390.
9. Migliore A. On the new regulation of medical devices in Europe. Expert Rev Med Devices. 2017;14:921–3. https://doi.org/10.1080/17434440.2017.1407648.
10. Bianco S, Nunziata A, Pozzoli G. Clinical investigations on medical devices, after the new European regulation (2017/745). Clin Trial Pract Open J. 2017;1:10–4.
11. Gliklich RE, Dreyer NA, Leavy MB. Registries for medical devices. Agency for Healthcare Research and Quality (US); 2014.