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Changing device regulations in the European Union – impact on research, innovation and clinical practice

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Abstract:

Up until 2017, medical devices were placed on the European Union's (EU) single market in accordance to either Medical Device Directive 93/42/EEC for general medical devices or Medical Device Directive 90/385/EEC for active implantable devices. However, some devices that complied with these directives still failed catastrophically. In the orthopaedic device field these failures were most pronounced in metal-on-metal hip devices causing severe patient morbidity with increased need for revision surgery which had unpredictable outcomes. Subsequently, the newly introduced Medical Device Regulations 2017/745 are aimed at addressing patient safety based on previous experience and thorough device assessment prior to and post-release on the EU single market; to accommodate for this they are substantially different (and more stringent). This poses a greater challenge for manufacturers and regulatory bodies in terms of time and resources. This review provides the rationale behind this change and its potential impact on research, industry and clinical practice.

Key words

Medical Device Regulation

Medical Device Directive

Joint replacement

Introduction: The need for new medical device regulation

In the past two decades, medical devices have often been in the press for the wrong reasons. The incidence of reported safety alerts and field safety notices has significantly increased over the past couple of decades. This has contributed to the development of new regulations governing the introduction of medical devices to the European Union's (EU) single market.

Up until 2017 medical devices were placed on the EU single market in accordance to the regulatory framework for medical devices on Council Directives 93/42/EEC (1) for general medical devices, 90/385/EEC (2) for active implantable devices, and 98/79/EEC (3) for *in vitro* diagnostic medical devices which are collectively referred to as the Medical Device Directives (MDD). Under the MDD the introduction of new devices on EU single market did not always require rigorous testing. As stated in the MDD, the clinical data required for a medical device could be sourced from scientific literature for a similar device (Article 1 (iii) 93/42/EEC (1)). Based on these guidelines several devices were released which claimed to have equivalence to previously existing devices on the EU single and international markets. Unfortunately, some of these devices subsequently failed catastrophically when used *in vivo*. The most significant examples are metal-on-metal (MoM) hip replacements (4) and pelvic mesh failures (5), resulting in higher patient morbidity and in some cases mortality. These experiences have led to implant recalls, field safety notices, device alert calls, and a significant cost burden on patients, society, and health organisations.

Prior to 2009, hip resurfacing and total joint replacement devices could enter the EU market without any specific clinical investigation for that particular product. This was based on the assumed degree of the inherent risk of the device (6). Most (if not all) MoM hip replacements entered the EU economic market before the year 2009 and the majority were certified based on equivalence. As such, no post-market surveillance was required by the medical device regulatory authorities within the EU. At the time most of the devices were monitored by the National Joint Registries either within or outside of the EU single market area. Joint Registries were the first to report the high rates of revision and failures associated with MoM hips to the manufacturers. The most severe consequence reported was the release of metal ions into patients' blood stream or cerebral spinal fluid. The possible reasons for failures were both the surgical technique and implant design; the latter was ultimately shown to be

the main cause. To date, the failure of MoM implants either resurfacing or total hip replacement (THR) remain higher than for non-metal THRs (7).

In addition to the high-profile adverse incidents relating to medical devices highlighting the shortcoming of the EU regulatory framework prior to 2017, a number of other factors have contributed to the drive for change. Innovation and emerging technologies such as nanoscience, tissue engineering techniques, computer/robot assisted surgery, and minimally invasive surgical techniques have necessitated changes to be accommodated within the legally defined concepts of medical devices (8). Furthermore, the growth of the EU single market to 32 countries has led to increased variation in applications of the MDD. The MDD underwent a number of amendments between 1998 and 2007 to accommodate the emergence of new technologies and the increasing need for continued post-market surveillance to ensure satisfactory clinical outcomes. Ultimately the EU commission replaced the MDD with the 2017 introduction of the revised Medical Device Regulatory Framework (MDR) (9,10) for the EU single market.

In this paper we present an overview of the EU regulatory framework for medical devices and associated changes prior to April 2017 with a description of the associated route to market followed by an overview of the new regulations post April 2017. We then present a discussion analysing the prospective impact of the changes on research, innovation, industry and clinical practice.

Part 1: Timeline & schedule for MDR introduction:

Proposals for the revision of the regulatory framework for medical devices were published by the EU commission in 2012. In 2014 the EU parliament put forward a list of amendments and subsequent discussion between the EU commission, Council, and Parliament resulted in the agreed texts for the Medical Device Regulation (MDR) and In Vitro Diagnostic Regulation (IVDR) being published in June 2016 (11,12). The MDR and IVDR supersede the MDD. The MDR were formally adopted by EU parliament in April 2017 and became legally binding on 26th May 2017. However, the full implementation is scheduled for 26th May 2020. This means that before May 2020, new medical devices can still be placed on the EU market under the MDD. In the event where certificates were issued before May 2020, these will remain valid up until 27th May 2024 as of Article 120(2) MDR. After May 2024, the devices which were compliant to MDD before year 2020 (26th May), will still be allowed on the EU single market or be in service with no compliance certificate until 26th May 2025.

Part 2: Pre May 2017

EU Medical Device Directives

Up until 2017 medical devices were placed on the EU single market in accordance to the regulatory framework for medical devices on Council Directives 93/42/EEC (1) for general medical devices, 90/385/EEC (2) for active implantable devices and 98/79/EEC (13) for *In vitro* diagnostic medical devices which are collectively referred to as the Medical Device Directives (MDD).

Application to member state legal framework

Each member state of the EEA was required to include the directives into national law and appoint a “competent authority” which takes legal responsibility for the regulation of medical devices within that member state. The directives serve to form the basis of how the regulations are written into law but there remains some flexibility with regard to regulatory obligations allowing for national circumstances to be taken into account (8). Notified bodies responsible for conformity assessment are assigned within each member state by the designated competent authority, which in the UK is the MHRA.

CE Marking

Conformite Europeenne (CE) marking is a certification mark that indicates that a product conforms to health, safety, and environmental standards specified for products sold in the European Economic Area (EEA). Manufacturers need to demonstrate that the medical device meets the requirements by carrying out a conformity assessment. CE marking is attained through a process dependant on device classification, characteristics, and associated risk profile, which all determine the essential requirements for conformity assessment. Manufacturers can place a CE mark on the product to show that the medical device has met the requirements when it has passed the conformity assessment (14).

Medical Device Classification

The classification of the medical devices is based on the degree of inherent risk. Under the MDD, the degree of risk is determined by the duration of use, invasiveness, and whether the device is active.

Up until 2005 joint replacement devices could fall under either Class IIb or Class III as is the case for other implantable devices (Annex IX (2.4. 8.) MDD). In 2005 a new amendment to the directive was published by the EU Commission, 2005/50/EC, which set hip, knee, and shoulder total joint replacements to be classified as a Class III device; this amendment was fully applicable from 2009. For other orthopaedic implants to be Class III, they would need to have a biological effect, undergo change *in vivo*, or be in direct contact with central nervous system, heart or central circulatory system as per amendment 2007/47/EC.

Conformity assessment

The body responsible for the compliance of a product that goes on the EU single market is the original manufacturer of the device or the manufacturer of the fully refurbished device MDD Article 1(h). In some cases, compliance duties can be partially transferred to an authorised representative legally designated by the manufacturer. The manufacturer is obligated to register at least one person responsible for regulatory compliance. The clinical evaluation of the device must be conducted by medical practitioner. High-risk devices and Class II & III devices must be assessed by a third party, notified body, which is responsible for the conformity assessment before it is placed on the market.

Route to CE marking

An overview of the basic steps required of a manufacturer in placing a product on the market is presented below (8):

1. Define the scope of the product and identify the relevant regulations.
2. Classification: Identify the degree of inherent risk for the device in terms of patient safety, which determines whether the device is a Class I, Class IIa, Class IIb, Class III device.
3. Identify the essential requirements and associated conformity assessment route based on the above two points and manufacturer preference.
4. Compile relevant technical documentation in accordance with points 1-3.

5. Conduct conformity assessment based on the conformity route and device classification. The class of the device determines whether conformity assessment is internal or external by a notified body.
6. Issue the EU declaration of conformity and place a CE mark on a product.

Part 3: Post May 2017

The basic steps in placing a product on the market do not differ substantially between the MDD and MDR. The scope and topics, in general, are consistent with the previous directives with a few notable exceptions. However, additional rules and explicit requirements have been introduced for each of the steps and the compliance have been substantially extended in the MDR. Within the context of this article we highlight below a number of changes we feel are particularly relevant to orthopaedic implants and devices.

Change from directive to regulation:

The conformity assessment rules are no longer in the directive form but in regulations form. EU directives set out guidelines and objectives for member states in terms of developing or amending the existing regulations within the member state; EU regulation, on the other hand, is a binding legislation act, which must be obeyed by the member states without adaptation (14). Unlike directives, regulations do not need to be transposed into national law. The MDR and the IVDR will therefore limit discrepancies in interpretation across the EU market. The MDR incorporates both general medical devices and active medical devices and fully replaces the MDD (15).

Essential Requirements to General Safety and Performance Requirements:

In comparison to the directives, the MDR scope does not contain essential requirements (ER). Instead 'General Safety and Performance Requirements' were introduced. There were 29 essential requirements in the MDD (13 in the MDD93/42/EEC and 16 in 90/385/EEC) which have been replaced by are 23 'General Safety and Performance Requirements' (SPRs) in the new MDR (Annex I) (16). The scope of the SPRs remain similar to the ER however the overall text and requirements are expanded. Some topics (e.g. clinical evaluation and medicinal consultation) have moved from the requirements list into the articles, while other topics have been added (e.g. devices without a medical purpose and requirements for devices used by lay persons) (16). Several areas now have more explicit requirements aligning with harmonised standards and industry guidance (16).

Macomber & Schroeders white paper (16) gives an extensive overview of all 23 SPRs which is beyond the scope of this review. A notable change in relation to joint replacement safety is

the expansion of requirements related to biological effects and toxicity (MDR Annex I 10.6 and 12.2). Previously in MDD there was just one statement in relation to the choice of materials regarding toxicity and one statement on biocompatibility. Additionally, the MDR requires a risk assessment of the particles that might be released into the patient's body.

Classification

Under the new MDR 2017 Annex VIII section 5.4 Rule 8, all total and partial joint replacements and spinal disc replacements are a Class III device. The exceptions to this rule are the additional components such as screws, instruments, and other surgical tools. Importantly, the classification must be justified by the manufacturer according to MDR Annex II 1.1(f), which was not previously a requirement for MDD compliance.

Conformity:

The body responsible remains manufacturer as per as per MDR Article 2(30) or MDD Article 1(h). Under both MDD and MDR the manufacturer is obligated to register at least one natural or legal person responsible for regulatory compliance.

Changes to technical documentation:

Like other aspects, the technical documentation requirements submitted for assessment are substantially extended for the MDR in comparison to the MDD. Under the MDR there are now two Technical Documentation sections: Technical Documentation (MDR Annex II) and Technical Documentation on Post-Market Surveillance (MDR Annex III). The technical documentation outlined under the MDD had no strict rules or detailed guidelines (Annex VII (3)) and a design dossier was required for conformity assessment as per Annex II(4). In the MDR each technical documentation section is described in detail; these include among others device description, product verification, risk-benefit analysis, and more.

Equivalence:

In terms of clinical evaluation, recommendations under the MDD (93/42/EEC Annex X and 90/385/EEC Annex 7) are limited to successful performance under normal conditions only. This could be verified either through clinical investigations or scientific literature for an

equivalent device. For high-risk devices such as joint replacements, the concept of equivalence is now more strictly defined under the MDR. Firstly, in comparison to the MDD under the MDR it is now the responsibility of the notified body to assess the adequacy of the data submitted for conformity assessment whether it comes from scientific literature or clinical investigation (MDR Annex X (3)). Secondly, equivalence in the MDD is not clearly defined; to comply with MDR the equivalence of a medical device to another "on the market device" must be shown on three levels which are technical, clinical, and biological (Annex XIV Part A (3))

Clinical investigation:

According to the 2007 amendment to the MDD (93/42/EEC & 90/385/EEC) it is a legal requirement to report all serious adverse events to all competent authorities of the member states that deal with medical devices. Adverse events must be recorded in detail and reported immediately. In general, the requirements for clinical investigation processes did not undergo major changes with the introduction of MDR and are described in the harmonised standard ISO 14155:2011, which has been amended and will be soon replaced by ISO/DIS 14155 as stated by the ISO committee. The new rules for the clinical investigators and facilities have been added, including the requirement for the clinical investigator to produce a detailed critical evaluation of the data that has been gathered during the clinical investigation (MDR Annex XV (2.8)).

Post-market surveillance:

Under MDR, Annex III, the manufacturer is obliged to present a separate technical documentation for post-market surveillance (PMS) in relation to safety and success of the implant while *in vivo* when going through the conformity assessment. The post-market surveillance documentation must be continually updated throughout the life cycle of the device. The post-market surveillance plan is an obligatory part of the technical documentation under MDR, Chapter VII Section I. Chapter VII Article 83 on Post-market surveillance systems states that the "manufacturer must plan, implement and update a PMS system and the data it generates must be used to:

- Update benefit-risk determination and improve risk management
- Update the clinical evaluation

- Identify the need for preventative, corrective or field safety corrective action
- Identify the option to improve the usability, performance and safety of the device”

In addition, according to MDR Article 86, the manufacturer must provide periodic safety update reports (PSUR) concerning Class IIa and higher medical devices. The PSUR is an output of the post-market surveillance plan as detailed in Annex III. “The PSUR must:

• Draw conclusions of the benefit-risk determination

• Outline the main findings of the PMCF

• State the volume of sales, size of population using the device and if possible, the frequency of use

For Classes IIb and III a PSUR must be produced annually and for Class IIa this should be when necessary and at least every two years. Class III and implantable devices require the PSUR to be approved by a notified body.

Before the introduction of the MDR there were no specific rules for the EU single market on post-market surveillance. However, due to the severity of failures of some medical devices, independent expert panels were formed. Within the joint replacement community these panels took the form of national joint registries that collect data on the success and failure rates associated with implant type and design (17) . Prior to MDR these expert panels would inform manufacturers if a device had raised concerns using published and unpublished data. In the UK, manufacturers can apply for their product to be on the Orthopaedic Data Evaluation Panel Database (ODEP) (18). ODEP uses a rating system based on length of post-market surveillance and clinical outcomes of the implant, which allows for comparison between the designs and manufacturers. Both ODEP and national joint registries are not overseen by the government as such and operate on the voluntary basis in contrast to MDR.

EUDAMED and data transparency:

EUDAMED (European Database on Medical Devices) is a secure, web-based portal that acts as a central archive for the exchange of information between national competent authorities and the European Commission. This collection of data is not wholly new to the MDR. EUDAMED was established under the MDD (Article 14a) coming into force in 2011. EUDAMED aims to strengthen market surveillance and transparency with regards to medical

devices placed on the European market through providing European Authorities with fast, simple access to relevant regulatory information. The EUDAMED requirements have been expanded under the MDR. One of the most significant changes under the new MDR is the amount of data that will be stored. Depending on the classification of the product and applicable regulations, EUDAMED will include all or some of the following.

- The registration of manufacturers, their Authorized Representative and the devices in question
- Declaration of conformity
- A vigilance and traceability system (declaration or ISO certificate)
- Labelling and instructions (Artwork in English)
- Justification of the classification according to Annex IX
- A copy of ISO certificate/Proof of QMS
- Information on Clinical Investigations
- Additional documentations may be required, dependent on the special characteristics of the device.

Implant card:

The MDR General Safety and Performance chapter expands the MDD requirements on product labelling and instructions for use. The relevant new addition for medical devices is the Unique Device Identification (UDI), required for all devices. For Class III devices, including joint replacements, the UDI must be in place by 27th May 2021 (Annex VI Article 27(4) MDR). An additional requirement for the implantable devices is an 'implant card', which now must be provided for every patient (Article 18 Chapter 1).

The implant card will provide details on the device identification (e.g. name, serial number, Lot number, UDI, address & website of the manufacturer);– warnings, precautions, and measures to be taken by healthcare personal and patients;– details on the expected lifetime of the implant and necessarily follow up; and any information to ensure safe use of the device by the patient, including the information in point (u) of Section 23.4 of Annex I. This information is to be made available to the patient implanted with the device in lay terms understandable to them.

Under Article 32 a “Summary of Safety and Clinical Performance” must be submitted to the notified body with the documentation for validation who will then make it publicly available via EUDAMED for implantable devices and for Class III devices. The requirements for inclusion in the summary of safety and clinical performance are stipulated in Article 32 Section 2. Among these the intended purpose of the device and any indications, contraindications, device description including a reference to previous generation/variants, a description of the differences, and training for users.

Part 4: Impact

Challenges associated with transfer to medical device regulations:

In April 2019, the European trade organisation published an open letter to European Commission on the challenges associated with transferring from the European medical device directives (MDD & AIMDD) to the medical device regulations (MDR) (19). According to the open letter the major concern is an unavailability (or severe shortage) of the notified bodies for the conformity assessment. As MDR is not amending the MDD and AIMDD the existing notified bodies for those directives will have to be approved by the Competent Authority of the State to be a notified body under MDR (Chapter IV MDR). In the UK only one organisation was accredited to provide conformity assessment services under MDR, when previously 58 organisations in UK could provide those services.

It is thought that the introduction of the MDR will drastically decrease the release of the new products in European Single market. Firstly, for medical device manufacturers the re-certification of existing products with compliance to MDR will be a priority. This has led to substantial proportion of research and development activities within manufacturing organisations to be devoted to re-assessing the documentation for existing products. Secondly, the process in terms of time and cost for compliance procedures under MDR are uncertain. Harmonised standards have not yet been published (20) or approved. This will push companies / small-medium enterprises (SMEs), especially new ones or smaller ones, to select a product release market outside the European single market, where the procedures are well-established.

Changes for clinicians:

The scope MDR mainly concerns the obligations for manufacturers their representatives and competent bodies. However, for healthcare professionals and institutions, under MDR, no rules are set out other than recommendations to adequately inform patients on the medical devices being used (MDR Article 17).

With the introduction of new devices on a regular basis and without any clear demonstration of significant advantages with the use of a new device, clinicians, health authorities as well as patients are becoming increasingly more vigilant and conservative in their approach to adoption of a new device into routine clinical practice. In 2002, the Orthopaedic Data Evaluation Panel (ODEP) (18) was introduced in the UK to monitor the performance of an existing devices. The ODEP typically includes Orthopaedic Consultant Surgeons, representatives from NHS Supply Chain, independent Business Consultants and receives input from Northgate services. A rating system is applied based upon the availability of

reliable clinical data from various centres as well as over what duration. For example a 13A* ODEP rating for a THR would indicate that the panel has seen data for that particular device which included at least 500 patients at start with 400 patients at risk at 13-year mark and the revision rate was less than 8.5% and at least three surgeons have implanted that device. Similarly, a 3B ODEP rating for a TKR would suggest that at least 100 patients at start and 40 patients at risk were available for review of this device at the three-year mark with the revision rate less than 3.5% (data could be from a single surgeon series). These ratings have introduced some confidence amongst clinicians and although it is not legally allowed to stop sell (or usage) of a CE marked device in the UK, more and more surgeons (and hospital authorities) are restricting the adoption of new devices into clinical practice only when the device reaches a 7 or a 10 year acceptable rating. For new devices without ODEP rating, a detailed assessment of the existing evidence is carried out by a panel and if satisfactory, a Beyond Compliance certificate provided to allow the parent company to test the device and release it in a controlled manner. Additional information other than that collected routinely as part of National Joint Registry (NJR) can also be uploaded on the central system for review by independent assessors if the patients consent. This information (including clinical outcomes, implant retrieval data, radiographs) will help create a detailed analysis of all the relevant data.

Although a step in the right direction, these rules and regulations still do not consider the impact of patient and surgeon variables on the outcomes of a joint replacement. The outcomes are clearly closely interlinked with how the surgery is performed, what are the patient characteristics (e.g. high BMI, high impact activities, significant co-morbidities etc.) and of course the device.

Conclusions:

The change in legal requirements for the medical devices to be put on the EU single market ultimately leads to increased patient safety, which is supported by clinical professionals. The new requirements for data transparency, post-market surveillance and implant information availability increases the chance of catastrophic failure prevention.

However, the exact method of MDR implementation remains uncertain, as there are not enough notified bodies to perform a conformity assessment. In addition to this some essential rules on the data requirements for the MDR compliance have not yet been published by the EU. Many professionals in medical device feel these limitations will limit the availability of products on the market including withdrawal of existing devices and a decrease in new medical device innovation. It is speculated that lack of new technologies

within the medical device area can dramatically affect patient safety itself by not allowing potentially safer materials and methods on the EU single market, as the main focus for the manufacturer becomes the existing devices (19,21) [13, 15]. It is clear that at this juncture the future of device regulation is unclear, and, in part, we are heading into an unchartered territory.

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