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Review Article

New regulations on Medical Devices in European Union

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Abstract

Due to the lack of sound approval process for medical devices in the EU people are suffered from many side effects. Some of the case studies which reflected mainly for the transformation of medical device regulations are PIP implants, MOM hip implants, COSTAR drug-eluting stent, and pleural seal, etc. To reflect the progress over the last 20 years, the EU revised the legal framework. Regulation (EU) 2017/745 on medical devices (MDR) introduces a major update of the regulatory framework in the European Union (EU). The modernization of the European regulatory system brings several changes compared to old directives which impact mainly manufacturers and SMEs. The new rules will fully be applied after the transitional period 3 years for MDR (up to 2020).

Keywords: MDR, Implants, Medical devices, CE mark, EU, FDA, MDD, 510(k) pathway

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1. Introduction

Medical devices and in vitro diagnostic medical devices are important to our health and quality of life which ranges from simple contact lenses and sticking plasters to sophisticated pacemakers and hip replacements.

People depend on these devices consistently and anticipate them to be safe and incorporate the recent advancements in science and innovation. The old directives on the safety and performance of medical devices in the European Union have been harmonized in the 1990s. To reflect the substantial technologies and scientific progress in this sector over the last 20 years, the European Union Commission proposed to update the rules to improve the safety of medical devices for EU citizens and create the conditions to modernize the sector and to consolidate its position as a worldwide pioneer.

Medical devices are crucial in diagnosing, preventing, monitoring, and treating illness and overcoming disabilities. They are additionally imperative to the economy, providing € 110 billion in sales and 6,75,000 jobs in the EU. The EU is a net exporter in this sector. (1, 2)

Regulatory framework (3)

Problems with diverging interpretation of the existing regulations as well as certain negative incidents. For example, breast implants, and metal hip implants - highlighted the weakness of the old system and damaged the belief of patients, consumers, healthcare professionals in the safety of medical devices. To address this, the commission proposed two regulations on medical devices and in vitro diagnostic medical devices in 2012. To make sure harmonized application of the rules throughout the EU, the two new regulations will replace the three directives on medical devices.

Existing directives on medical devices

Medical devices within the EU are regulated by three directives:

- Council Directive 90/385/EEC on Active Implantable Devices (AIMDD) (1990)
- Council Directive 93/42/EEC on Medical Devices (MDD) (1993)
- Council Directive 98/79/EC on In-vitro Diagnostic Medical Devices (IVDMD) (1998)

New regulations on medical devices

Two new Regulations on medical devices and in vitro diagnostic medical devices enter into force on 25 May

2017 and will progressively replace the existing directives after a transition period. These new regulations establish a modernized and more robust EU legislative framework to ensure better protection of public health and patient safety.

- Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices and repealing council directives 90/385/EEC and 93/42/EEC.
- Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on medical devices and repealing council directive 98/79/EC.

The new regulations create a robust, transparent, and sustainable regulatory framework, recognized internationally, which improves clinical safety and makes reasonable market access for manufacturers.

In assessment to directives, regulations do not need to be transposed into national law and are directly applicable. The MDR and IVDR will consequently decrease the risks of discrepancies in interpretation across the EU market.

New Regulations Incorporate a Sequence of Extremely Important Upgrades to Modernize the Current System. Among them Are (4)

- Stricter pre-market control of high-risk devices through a new premarket scrutiny involvement of professionals at the EU level.
- Implant cards are introduced which contains information about implanted medical devices for a patient.
- The reinforcement of the criteria for designation and processes for notified bodies' oversight.
- The reinforcement of the rules on clinical evidence, including an EU- wide coordinated process for authorization of multi-centre clinical investigations.
- Improve transparency via the established order of a complete EU database on medical devices and of a device traceability system based on UDI.
- Post-market surveillance requirements for manufacturers are strengthened.
- In the fields of vigilance and market surveillance, coordination mechanisms between EU countries are improved.

2. Background (5)

Unsafe and ineffective medical devices in the European market

In May 2012, the food and drug administration of the United States of America published an article regarding the unsafe and ineffective devices bearing a CE mark circulating on the EU market, which is not approved by the FDA in the United States.

This article contains a list of 12 devices that are unsafe and ineffective according to the FDA and include examples ranging from monitoring systems to implants. Most of these devices were ultimately withdrawn from the market but only after but thousands of patients were harmed according to the FDA. In many cases, the device's risks or ineffectiveness were only discovered as a result of studies conducted to support approval in the United States.

The differences between FDA approval and CE marking shows that limited information as evidence for safety is required for CE marking, while evidence of efficacy is needed to obtain FDA approval.

The net result is an advanced Marketplace introduction in Europe (CE marking takes 1-3 months on average) compared to the US (FDA approval takes 13- 22 months on average). The limited testing required in the EU fails to expect dangerous risks and lack of effectiveness in actual use.

List of Dangerous and Ineffective Devices Approved in the EU (6)

The following is a list of 12 devices that were approved in the EU and later discovered to be withdrawn from the market.

1. Pleura Seal to Seal Lung Incisions
2. Stent Grafts to Repair Aneurysms
3. Trilucent Breast Implants
4. Elbow Implant
5. Injected Dermal Fillers for Cosmetic Use
6. Cardiac Constraint Device Technologies for Treatment of Heart Failure
7. Pendra for Monitoring Blood Glucose Levels in Diabetes
8. PFO Occluders to Prevent Stroke
9. RoboDoc for Hip Surgery
10. Biofield Device to Detect Breast Cancer
11. Zephyr for Emphysema
12. CoSTAR Drug-Eluting Stent to Open Arteries

Brief Description of Twelve Unsafe and Ineffective Devices

- Pleura seal to seal lung incisions were approved in the EU with minimal testing, claiming that advanced stitches in preventing air leaks and subsequent lung collapse. These devices are withdrawn worldwide after a US study showed that 3 times as many as pleura seal patients had air leaks as compared to those with stitches.
- Stent grafts to repair aortic aneurysm made by many manufacturers were approved in the EU with limited testing. When US approval was sought, the FDA discovered that many devices approved in the EU possess severe risks to patients including blood clots, aneurysm rupture, and graft failure.
- Trilucent breast implants were approved in the EU without human testing and implanted in more than 8000 women. The implants are withdrawn after the Soybean fillers were found to break down into toxic compounds, causing rupture, disfigurement, potentially cancer, and birth defects.
- Elbow implant was approved in the EU after the FDA told the manufacturer that it had been inadequately tested and was prone to fracture. Once marketed in the EU, many reports about fractures caused the manufacturers to withdraw from the market.

- In the EU, 160 injected dermal fillers containing poorly tested substances are approved. Causing nerve damage and severe allergic reactions.
- Cardiac constraint devices in the EU were approved based on limited testing. Testing to support US approval showed that the devices had been no better than prescription drug therapy, but subject patients to invasive surgery, a higher risk of operative death, and necessary bypass surgery for patients.
- Pendra glucose monitor sensor was the first non-invasive blood glucose monitoring system approved in the EU. These devices are withdrawn after studies showed that these devices are inaccurate and did not warn about dangerous blood sugar levels.
- PFO occluders implanted in the heart to prevent strokes were approved in the EU. Studies conducted for US approval shows that the device marketed in the EU is no more effective for stroke. It causes heart perforations and other serious complications.
- RoboDoc is used to drill the femur for hip replacement and was approved in the EU with limited data. Later studies showed that the device caused serious complications; including tendon rupture, nerve injury, and hip implant failure.
- The Biofield devices were approved in the EU with limited testing. Claim to detect breast cancer better than mammography. FDA review showed that the company's studies failed to demonstrate that the device did, or even could, work. It was not marketed in the EU.
- Zephyr, a valve implanted in the lung to treat emphysema, was approved in the EU to replace surgery. A later study for US approval showed that Zephyr was no more effective than surgery, but resulted in deaths and serious complications.
- The CoSTAR drug-eluting stent, approved in the EU with limited testing, was withdrawn from the EU when a study for US approval showed that patients more often need repeat procedures and suffered heart attacks with COTAR than another similar available stent.

Reasons for Unsafe and Ineffective Devices on the European Market (7)

Table 1 includes a few bottles on why the chance of unsafe and ineffective devices increases in the EU compared to the US. Apart from that, there are some bottlenecks as follows:

- The risk level of devices is determined by the developer and not determined by notified body experts.
- Notified bodies are commercial companies that are subjected to competition.
- Notified bodies do not have personnel expertise with each type of medical device.
- To make mort profit notified bodies do not reject requests of device developers.
- The CE mark is granted to the device even though there are no clinical investigations with a high level of clinical evidence.
- Finalized devices are seen by a notified body only one year after the CE mark is granted. Moreover, the description of the device on paper is sufficient for CE mark granting by notified bodies.
- Recall medical devices does not make sense as similar devices will still be circulating on the EU market. Even though original devices are banned, but similar devices are still circulating on the market
- There is no current overview of which medical devices are circulating on the EU market.

Table 1. The FDA report compares the Regulation of high-risk devices in the US and EU (8, 9)

Features	United states	European union
Standard for approval	Safety Effectiveness: proof of actual benefit to patients.	Safety technical performance, not benefit patients.
Evidence required	• Valid clinical trials- generally randomized and controlled.	• Limited data, which may be laboratory testing, literature reviews, or small scale clinical trials.
Approval granted by	• Central regulatory authority: Food and drug administration.	• Notified bodies: Private, profit organizations chosen and hired by the manufacturers. Approval by any notified body authorizes marketing throughout the EU.

Transparency of approval decisions	• FDA has almost all the regulatory processes public-accessible with several mechanisms like "Summary of Safety and effectiveness Data" could provide justification and discussion of adverse events for the approval of high-risk devices. • Approvals and their evidentiary basis are disclosed to the public.	• The relevant review data only circulate within the involved organization like Competent Authorities and NBs. • Neither approvals nor evidentiary basis disclosed to the public
Post-approval reporting requirements and transparency	• Side effects and recalls must be reported to the FDA and are publicly disclosed on its website.	• Reported Side effects and recalls are not publicly disclosed.
Post-market surveillance	• The low adverse events notification rate was one essential pain.	• Coordination and analysis vary widely in the EU. Only several countries were notified of adverse events rather than the whole EC.
Access	• Higher patient's accessibility to new devices like the clinical premarketing testing of devices, institutional review boards, and typically post-approval studies evaluating outcomes were asked by the FDA. • Higher patient's accessibility to new devices like the clinical premarketing testing of devices, institutional review boards, and typically post-approval studies evaluating outcomes were asked by the FDA.	• There were 23 of 42 devices confirmed to be approved by both the US and EU and the approvals from the EU were received averagely 3.5 years earlier than the US. • Less rigorous proof of the effectiveness of the fast-accessible devices in the EU could lead to some issues that not showed up in the premarket review.
Funding	• The funding of the FDA consists of federal appropriations (80%) and user fees (<20%). • The changes in federal funding should affect the FDA.	• The financial support for the Competent Authorities in the EU is variable among countries, and the NBs are paid directly by manufacturers. • The interest conflicts with industry clients could emerge for NBs.
Mandate	• Mandatory to provide reasonable assurance on the medical devices concerning safety and effectiveness because of the public's sensitiveness on the adverse events. • The severity of the disease and the availability of alternative treatments were seriously considered for the evaluation of high-risk devices.	• The system was initially directed by the "Single Market"- concept framework for streamlining trade and harmonizes the standards within the EU (Council of the European Union, 2008). • Compared with reducing the trade barriers, the protection of public health was not the primary goal. • Concerns might arise from the cooperation with industry clients as well as the balance between effectiveness and risk of safety.
Centralization	It is easier and simpler to achieve the standardization and coordination of premarketing and post-marketing evaluation because of the central system in the US.	The processes are carried out by Competent Authorities and NBs without any public, searchable system.

Data requirements	The device's performance data was regarded as less important than clinical effectiveness.	• The device's performance data was regarded as more important than clinical effectiveness. • It is impossible to conduct the study on the premarket features of the intended to be recalled devices in the EU where the insights on the clinical endpoints of high-risk devices are limited.

Based on the comparison above, the problems in the medical devices regulation in the EU are evident and clear to understand.

3. Regulatory Approval Process of Medicals Devices in US and EU

The approval process of medicals devices in the United States (10)

In the US for Class, I and a small amount of Class II devices may apply for exemption with the FDA. If the exemption is granted, no pre-market review is required, but the FDA still controls the labeling and information provided to the consumer. These devices are then referred to as "FDA registered" or "FDA listed" devices once they make it to the market.

If an exemption is not appropriate, the device is low to moderate risk, and there is a device predicate already on the market, the 510(k) pathway is then utilized. A company must prove how the new device is equivalent to the marketed device and provide preclinical data, but clinical trial data is usually not required for the 510(k) pathway unless mandated by the FDA. Devices that successfully go through the 510(k) pathway are then referred to as "FDA cleared" devices.

For high risk, Class III devices, or for devices that do not have a market equivalent, the pre-market approval (PMA) pathway is required. This requires the company to apply for an Investigational Device Exemption (IDE) from the FDA. Once the IDE is obtained, the company can start the collection of data via a clinical trial in addition to pre-clinical data to provide in the eventual PMA submission. Devices that follow this pathway and are determined safe and effective, receive the "FDA approved" label. For devices that are low to moderate-risk, but do not have predicate on the market, the medical device company can work with the FDA to explore alternative pathways to bring the device to market if clinical trial data is not warranted. Alternative pathways include the De-Novo pathway, Humanitarian Device Exception, Product Development Protocol, and Custom Device Exemption, but these pathways are less common than the 510(k) and PMA pathways.

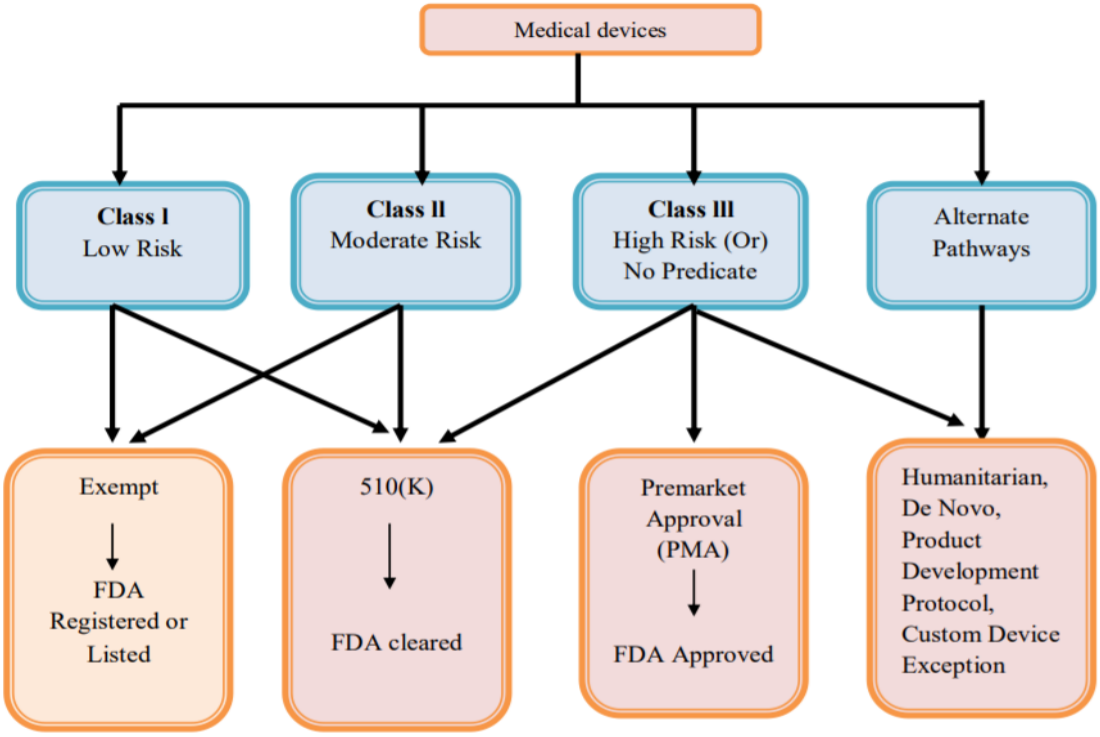

Figure 1. Medical device approval process (US)

The approval process of medicals devices in the European Union (11, 12)

Medical devices must conform to the regulations before marketing and/or put into service in the EU. At the EU level, there is no centralized approach similar to that in the United States.

The European Medicines Agency of the EU, unlike the Federal Drug Administration in the United States, is not involved in the approval process of medical devices. Manufacturers, before placing their devices in the market, are required to determine the classification of a device, based on the risk factors associated with each device, and then to apply the appropriate conformity route. Medical devices are assessed for efficacy and safety by notified bodies, which are private organizations, staffed by experts, and certified by the EU Member States. The affixing of a CE marking on medical devices, which is the last stage in the approval process, indicates that those medical devices conform to the requirements provided in the legislation. The legal value of the CE marking lies in its proof that the medical device concerned is in full compliance with applicable legislation. On the other hand, the CE marking does not represent quality, even though consumers often assume that products bearing the CE marking are of better quality than others.

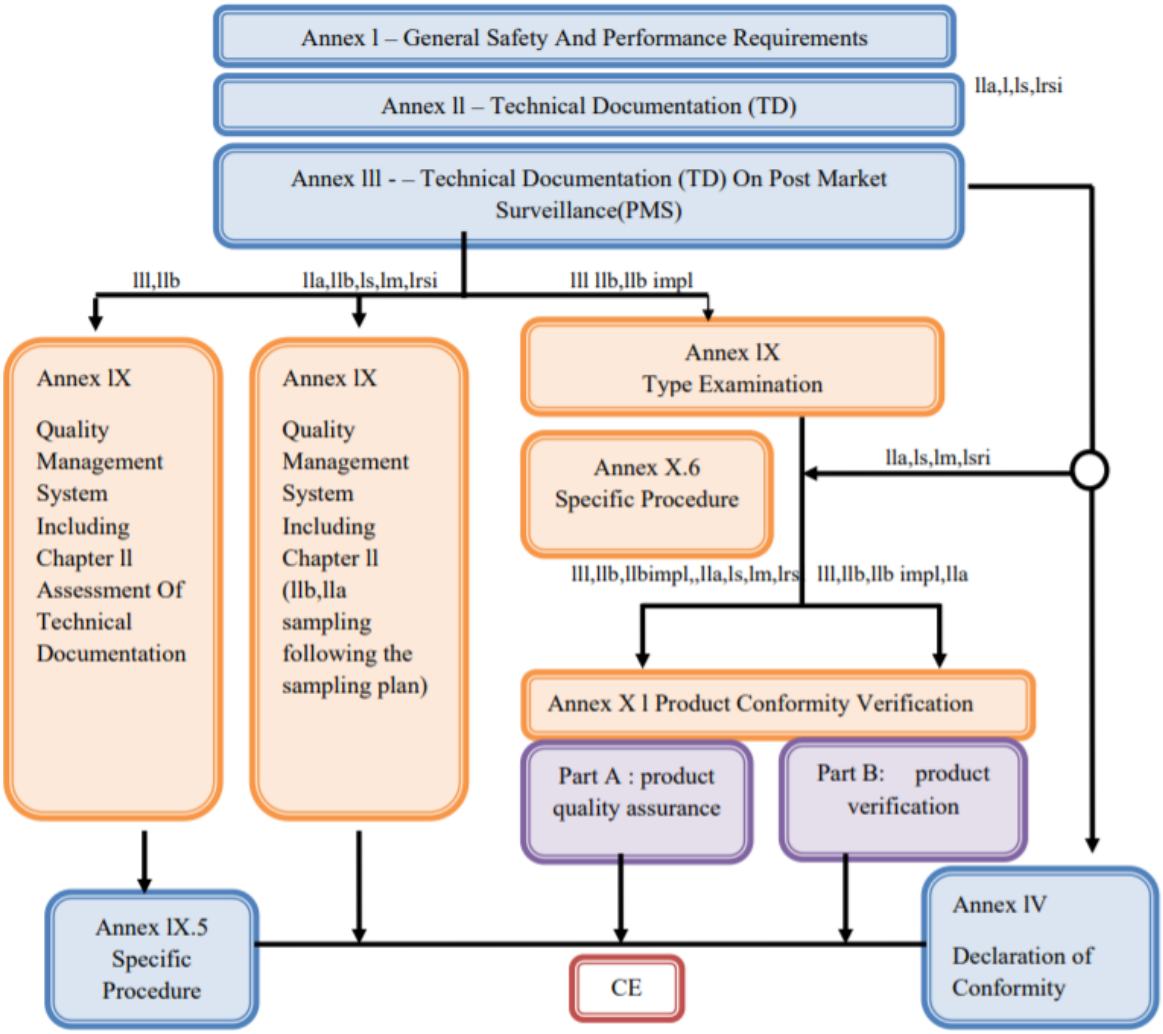

Figure 2. Approval process of medical devices (EU)

A Brief Overview on Dates of the MDR (13, 14)

- 2008: EU Commission begins consultation on 'framework' for Directive revision
- 2012: EU Commission publishes proposal for MDR
- 2014: EU parliament and council reviews the draft and proposes additional changes
- 2015: the Member States agree on 'general approach' to revision
- 2017: Member State representatives agree to adopt regulations to replace AIMD, MDD, and IVDD
- 5 May 2017: Publication of MDR (to replace AIMD and MDD) and IVDR (to replace IVDD) but dated 5 Apr 2017
- 26 May 2017: First entry date of 'application' of MDR with transition period 3 years for MDR.

4. Impact of New Regulations on Medical Devices (15, 16)

- The EU's new medical device regulations apply to all devices sold or marketed within the EU, regardless of where they are manufactured. For that reason, the regulations will have many significant impacts on manufacturers, importers, and distributors of medical devices.

Impact of medical device regulations

- For the Medical Device Regulation (MDR), this regulation aims to ensure the smooth functioning of the internal market regarding Medical Devices, taking as a base a high level of protection of health for patients and users. At the same time, this regulation sets high standards of Quality and Safety for Medical Devices to meet common safety concerns as regards such products.

Wider, Clearer scope of the products covered

- The scope of the products will become broader to include Medical Devices that may not have the intended medical purpose or include devices for the prognosis of the disease or any other health condition due to the impact of the Medical Device Regulation (MDR) on the scope of the products.

Changes in the Clinical Investigation

- For class III and implantable medical devices, as part of the requirements of the clinical evaluation, the Medical Device Regulation (MDR) will put in place a European regimen for clinical investigations that will replace the diversity of member state regulations in the EU. It will introduce many new concepts relating to clinical evaluation and clinical investigation, as well as a mandatory Post-Market Clinical Follow-up (PMCF) and Periodic Safety Update Reports (also known as PSURs). This will require a thorough review of the manufacturer's Clinical strategy and PMCF plans and require manufacturers to conduct clinical performance along with providing evidence of Safety and Performance following the risk associated with the device and to collect Post-Market Clinical Data. With the new rules; the Medical Device manufacturers will need to perform a gap analysis to identify gaps in Clinical Evidence under new rules for devices currently on the market and perform the required update since the compliance to current MEDDEV 2.7.1 rev 4 without an update to the Clinical Strategy and performing the gap analysis may not be sufficient.

Unique device identification (UDI)

- To improve the ability of the authorities and manufacturers to trace the specific devices through the supply chain and to smooth the recall process of Medical Devices that have been found to present a safety risk, the proposed Medical Device Regulation (MDR) mandates the use of Unique Device Identification (UDI) mechanisms.

- Provisions regarding registration of devices and economic operators, in particular, those governing the Unique Device Identification system have been complemented and clarified. They should lead to the establishment of a more functional system related to the Identification and Traceability of devices while maintaining alignment with international principles and practices in this field.

- Besides, the European Databank on Medical Devices (Eudamed) is expected to be expanded to provide more efficient access to information such as clinical investigations, Post-Market Surveillance (PMS), Vigilance on approved medical devices.

Classification and Conformity Assessment

- There will be an impact on the classification for certain medical devices; reclassification of the medical devices to a higher risk class is possible such as for some reusable surgical instruments. However, the MDR reclassification is mainly impacting class II implants (class III if they come into contact with the spinal column (rule 8)) and substance-based medical devices.

- The review of the lower risk devices will be highly enforced on Clinical Evaluation so the manufacturer should revisit the content of the current Technical Documentation as there will be an impact on the existing Quality Systems and to take into account the changes in the conformity assessment rules, the Regulation will feature new essential Safety and Performance requirements for example.

Impact on the Post Market Activities

- The major change in this process is mainly driven by the request of real-life data for the Post-Market Clinical Performance Evaluation. Its results must be taken into account for Clinical Evaluation and Risk Management update.

- The manufacturer will need to review their current Post-Market Surveillance (PMS) and Vigilance procedures with evaluation linked to the review of the Risk Management (RM) and Clinical Evaluation. The authority of the Notified Body will be increased with emphasis on Unannounced Audits (UAs), along with product sample checks and product testing. Annual Safety and Performance reporting by device manufacturers will also be required in many cases.

Common Specifications

- The Medical Device Regulation (MDR) plan to allow the EU Commission or expert panels (to be defined) to publish Common Specifications which shall then be taken into account by manufacturers as well as Notified Bodies. These Common Specifications shall exist in parallel to the Harmonized Standards and the State of the Art. These specifications provide a means to comply with the General Safety and Performance requirements and the requirements for Performance Studies and Performance Evaluation and/or Post-Market Follow-Up.

Identification of Qualified Person (QP)

- At least one person must be assigned within the organization that should be responsible for all aspects of compliance with the requirements of the Medical Device Regulation (MDR). The qualifications of this individual must be documented and be available upon request. The qualifications of this person can be demonstrated by evidence of formal qualification awarded on the completion of a university degree or of a course of study recognized as equivalent by the Member State concerned. The Qualified Person must also have at least one year of professional experience in Regulatory Affairs or Quality Management Systems (QMS) related to Medical Devices.

5. Comparison of Medical Devices Directive (93/42/EEC) and Medical Devices Regulation ((2017/745) (17)

The MDR is significantly more comprehensive and detailed compared to the MDD. While the MDD comprises 23 articles and 12 annexes over 60 pages, the MDR has 123 articles and 17 annexes over 175 pages. This table describes the differences between MDD and MDR.

Table 2. Difference between MDD and MDR.

Topic	Medical Devices Directive (93/42/EEC)	Medical Devices Regulation ((EU) 2017/745)
Scope inclusion	Article 1 • The scope of the MDD covers medical devices and their accessories, including devices: • Incorporate an ancillary medicinal product. • Are derived from non-viable animal material.	Article 1 • The scope of the MDR covers medical devices for human use and their accessories including: • Active implantable medical devices(AIMDs), • Devices incorporating an ancillary medicinal product, including a medicinal product derived from human blood or human plasma, • Devices incorporating ancillary non-viable tissues or cells of human origin or their derivatives, • Devices manufactured utilizing tissues or cells of animal origin, or their derivatives, which are non-viable or are rendered non-viable, • Products specifically intended for the cleaning, disinfection, or sterilization of devices, • Aesthetic products without an intended medical purpose listed in Annex XVI.
Post-market surveillance	• PMS is mentioned in Annex X of the MDD as being the source of clinical data to update the clinical evaluation and clinical evaluation report. If PMCF is not deemed necessary as part of the PMS plan, this has to be justified and documented. • Additionally, the Annexes for conformity assessment require the manufacturer to: • Institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase; and, • Implement appropriate means to apply any necessary corrective action. • This is a PMS system	Articles 83 – 86 • For each device, the manufacturer has to plan, establish, document, implement, maintain and update a post-market surveillance (PMS) system that is proportionate to the risk class and appropriate for the type of device. The PMS system is required to be an integral part of the manufacturer's QMS. • The PMS system actively and systematically gathers records and analyses data on the quality, performance, and safety of a device throughout its entire lifetime. Data gathered by the manufacturer's post-market surveillance is used: • To update the benefit-risk determination and to improve risk management; • To update the design and manufacturing information, the instructions for use, and the labeling • To update the clinical evaluation; • To update the summary of safety and clinical performance • To identify the need for preventive, corrective, or field safety corrective action • To identify options to improve the usability, performance, and safety of the device • To contribute to the post-market surveillance of other devices; and • To detect and report trends • APMS plan is required and details of the PMS plan are provided in Annex III.

		• Post-market clinical follow-up (PMCF) is a continuous process that updates the clinical evaluation. It is conducted under a PMCF plan that is an element of the overall PMS plan. • PMCF can include: • Gathering Of clinical experience • Collecting feedback from users; • Screening of scientific literature and other sources of clinical data; • Evaluation of suitable registers conducting PMCF studies. • Manufacturers of class I devices have to prepare a PMS report which is updated when necessary and made available to the competent authority upon request. Manufacturers of class IIa, Class IIb, and Class III devices have to prepare a periodic safety update report (PSUR) for each device or each category or group of devices. The PSUR for class IIb and class III devices is updated at least annually and for class IIa devices when necessary and at least every two years. • For class III devices or implantable devices, the PSURs are submitted to the notified body, who reviews the report and prepares an evaluation. The PSUR and notified body evaluation are made available to the competent authority.
Declaration of conformity and CE-marking	Articles 11 and 17 • The manufacturer has to draw up a declaration that the device conforms to the MDR and add a CE-mark to the product. • The format of the CE mark is given in Annex XII.	Articles 19 and 20 • The manufacturer has to draw up a declaration that the device conforms to the MDR and add a CE-mark to the product. • The declaration has to be kept up to date and available in the official language or languages required by the Member State(s) in which the device is made available. • The information to be included in the declaration of conformity is detailed in Annex IV and the format of the CE mark is given in Annex V.
Vigilance	Article 10 Competent authorities have to record and evaluate centrally device recalls or reports of events which might lead to or might have led to the death of a patient or user or a serious deterioration in their state of health due to: • Malfunction or deterioration in the characteristics and/or performance of a device. • Inadequacy in the labelling or the instructions for use. • The requirements for manufacturers to report are included in the conformity assessment procedures in the Annexes to the MDD. A significant amount of guidance on the responsibilities of manufacturers and competent authorities is included in MEDDEV2.12-1revision 'Guideline on a medical devices' vigilance system.'	Articles 87 – 92 Manufacturers have to report: • Serious incidents, and • Field safety corrective actions • A serious incident is associated with: • The death of a patient, user, or another person, • The temporary or permanent serious deterioration of a patient's, user's or other person's state of health, or, • A serious public health threat. • Additionally, there is a requirement for trend reporting of incidents that are exempt from reporting; that is to report any statistically significant increase in the frequency or severity of incidents that do not meet the reporting criteria but could have a significant impact on the risk-benefit analysis and present unacceptable risks to the health or safety of patients, users or others. The timelines for reporting events that are: • Considered serious public health threats in two days; • Death or unanticipated serious deterioration in is ten days; and, • All other events are15days.

6. Impact on Manufacturers (18)

Broader applicability of regulatory requirements - The number and type of medical devices that fall under the provisions of the new regulations are significantly greater than those covered under the former medical device framework.

Increased scrutiny for high-risk devices - The new regulations describe requirements in greater detail and provide for increased scrutiny for high-risk devices. The old device directive already has Common technical specifications for high-risk devices detailing specific safety and performance criteria to be met. Under the new regulations, there are requirements for common specifications (CS) for specific high-risk medical devices and in vitro diagnostic devices. CS will be compiled by the MDCG, which includes competent authority experts who may also select to oversee the review of new or high-risk devices that do not have a CS.

Greater provisions for traceability and transparency - The adoption of a UDI system, and single registration numbers (SRN) and the expansion of the Eudamed device database will make it easier for the market to quickly identify products in the EU market, as well as the economic operators responsible for those products.

No exemptions for devices that are currently CE-marked - Medical devices are already authorized under the medical device directives are not exempt from the requirements of the new regulations. They will be required to meet the new requirements according to their prescribed transition timeline (three years for medical devices and active implantable medical devices and five years for in vitro diagnostic devices). An extension in this timetable is unlikely, and devices that fail to comply with the new regulations according to the prescribed schedule will no longer be able to be legally sold or distributed on the market.

The three-year transition period for medical devices will expire in May 2020. Given the investment of time and resources required to bring new medical devices to market, manufacturers are well-advised to thoroughly investigate the potential impact of the new EU regulations on their current and planned product lines and to identify the steps necessary to achieve compliance with the new requirements within the stated transition timeframes.

Small and Medium-Sized Enterprises (19, 20)

Small and medium-sized enterprises (SMEs) are the backbone of Europe's economy. They represent 99% of all businesses in the EU. In the past five years, they have created around 85% of new jobs and provided two-thirds of the total private sector employment in the EU. The European Commission considers SMEs and entrepreneurship as key to ensuring economic growth, innovation, job creation, and social integration in the EU.

Challenges of SME's

- To meet the new EU rules, the SME's have to spend a huge amount to full fill the organizational and financial requirements.
- Producers of medical devices, especially SME's, will have to re-adapt the products, documents, and processes to ensure compliance with the changes and innovations in MDR.
- As described in the previous chapters, there are some completely new, but also several old, revised manufacturer requirements.
- Producers have to explicitly consider whether their product must have a new product classification or conformity assessment.
- The UDI also offers an extraordinary impact. If there is no UDI, manufacturers must implement a complete UDI system. Besides, post-market surveillance is relevant as it is necessary to check if there is a monitoring system or whether anyone needs to be developed. Due to the new requirements of the technical documentation, a considerable effort is also created here. To meet these requirements, many companies need to increase their quality management staff. It will take lots of time to review all specifications of all products to verify their conformity.
- An important factor is the power of SMEs, which is often improperly estimated, e.g. overestimated, by public authorities, which is expected to be not beneficial for SMEs.
- Another problem facing manufacturers of class IIa, IIb, and III products is that it is not yet clear when the first notified body will be accredited according to the MDR. The notified body will have to spend much more effort, as they will have to work with a panel after the new MDR and have to apply the quality so that they can certify companies. Thus, this situation represents another hurdle for small and medium-sized companies, because only the big companies are certified first.
- If a medical product company does not have a suitable notified body, it does not have many options. Either the company will be closed, sold, or the company specializes in other things.

7. Conclusion

Comparing and contrasting regulatory differences between the existing MDD and the new MDR is important. As it is highly likely for most legacy devices that a review of MDR requirements will identify regulatory issues that will need to be addressed for every device. To assess the impact of these changes on the business and its commercial and R&D operating models, organizations will need to build a robust business case and strong project management capability with effective cross-functional stakeholder management. Especially small and medium-sized companies have to manage intense MDR induces resource and financing problems. Also, new qualified personnel must be hired to meet future demands. The resulting financing problem will lead to more expensive products on the market. As a result, the portfolio of medical devices is expected to be reduced dramatically. As the transitional period is only three years for MDR, manufacturers, and especially SMEs, should promptly begin to address the new MDR. However, it is too late now, because it will be difficult for small companies to implement all requirements on time.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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