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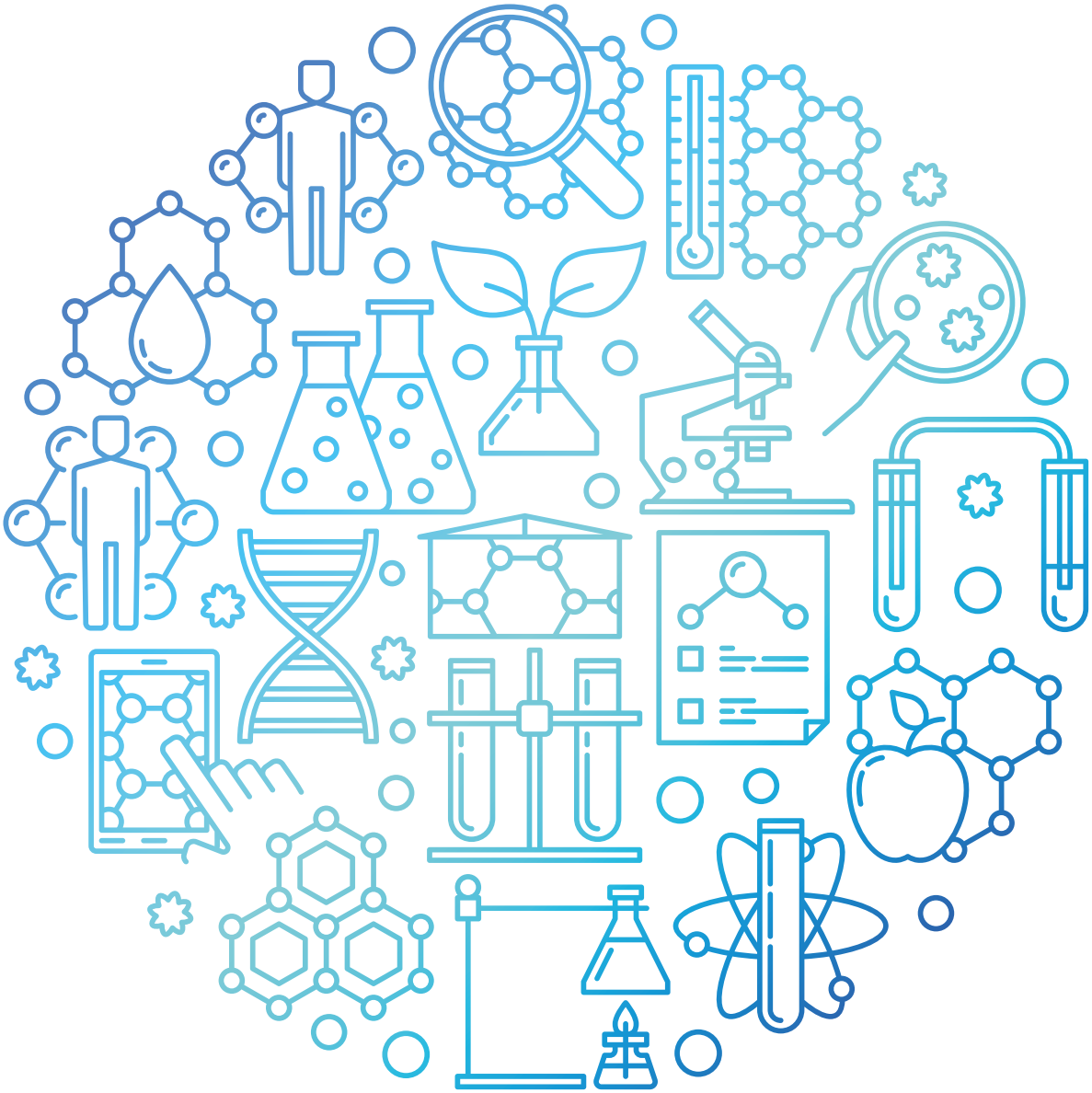


Is the new EU medical device legislation worth the wait?

Introduction

Divergence in the interpretation and application of EU rules, advances in technology and a need to respond to incidents such as the PIP breast implant scandal, has prompted the European Commission to introduce new rules for the regulation of medical devices. Regulation (EU) 2017/745 on medical devices (MDR) and Regulation (EU) 2017/746 on in-vitro diagnostics (IVDR), introduced on 26 May 2017, supersede three earlier Medical Device Directives (MDD) dating back to the 1990s. MDR will be fully applicable from 26 May 2020 while IVDR will be fully applicable from 26 May 2022

The new Regulations require:

- Re-certification of existing products and compliance with the General Safety and Performance Requirements;
- Updates to technical documentation, clinical data and labelling;
- Implementation of Unique Device Identification (UDI) to track devices;
- Classification of IVDs, which now require notified body review.

There is a staggered transitional period with some aspects, such as the notified body requirements, already legally binding since 26 November 2017 while others are not fully applicable until 2022.

Like the new EU Clinical Trials legislation, MDR and IVDR take the form of Regulations which means they are directly applicable and do not need to be transposed into national law. This should minimise differences of interpretation and improve consistency in the medical device industry across the EU.

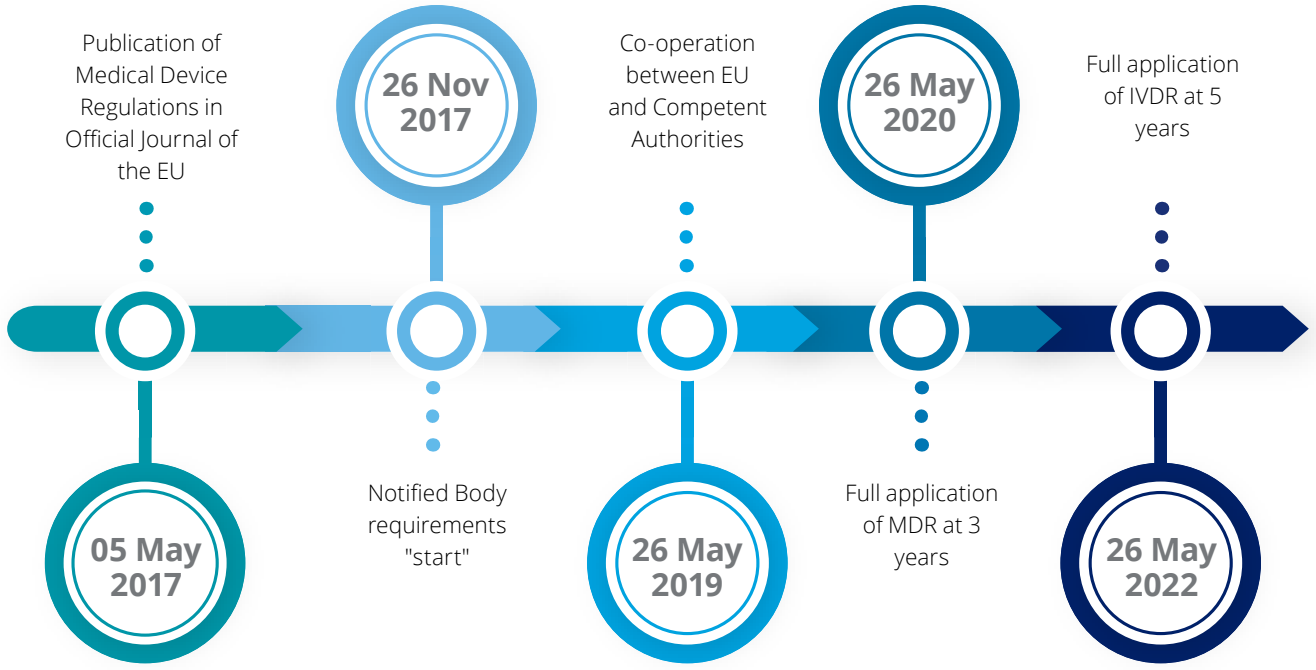


Figure 1. Timeline of implementation of MDR and IVDR

Bigger, wider, better?

So what are the main implications of the new Regulations? This article examines the impact on manufacturers, and to a lesser extent on notified bodies (Figure 2).

In addition to widening the scope of the legislation to include a broader range of products, the new Regulations impact all economic operators in the supply chain, including manufacturers, importers, distributers and authorised representatives.

Figure 2. Main implications of MDR and IVDR for manufacturers and Notified Bodies

Risk classification of devices and scope of the Regulations

Under the new Regulations, there are still four classes of medical device (Class I, IIa, IIb, III). However, the MDR reclassifies certain devices and brings additional devices within its scope including devices for cleaning, sterilising or disinfecting other medical devices, reprocessed single-use medical devices and certain devices with no intended medical purpose that are usually found in the beauty industry such as dermal fillers (MDR Chapter 1 and Annex XVI).

The IVDR introduces a rules-based system to classify IVDs into four different classes from class A (low risk) to class D (high risk). Existing IVDs already in accordance with the IVDR will be subject to a conformity assessment while new IVDs will be required to undergo assessment and certification by a notified body (appropriately designated for IVDs) prior to being placed on the market.

The new classification system and the broadening of the scope of the IVDR means that approximately 90% of IVDs will be subject to review by a notified body for the conformity assessment process, including genetic tests that provide information on predisposition to a medical condition or disease and tests that provide information to predict treatment response or reactions (companion diagnostics). This is a significant change, as most IVDs are currently self-declared without assessment by a notified body.

Clinical investigations

Perhaps the most significant change from the MDD to the MDR is the greater emphasis on clinical evaluation. There is an increased responsibility on manufacturers to document the effectiveness, safety and quality of their own devices. Clinical Investigations (CIs) are studies carried out on human subjects to verify the safety and/or performance of a specific medical device. The purpose is to verify the performance claimed by the manufacturer under normal conditions, determine any undesirable side effects and assess whether these constitute a risk when weighed against the expected benefits.

The requirements for CIs are significantly enhanced in the MDR with many specific provisions to ensure that patients enrolled in clinical studies are appropriately protected (Figure 3). To improve transparency, CI reports, summarising study results, will be made available to the public via a centralised European database (Eudamed) which those who manufacture and supply medical devices, as well as Notified Bodies, health institutions and Competent Authorities, will be able to access.

The new rules describe how CIs will be designed, notified and/or authorised, conducted, recorded and reported.

If this data is not gathered within the transition period, products may need to be withdrawn.

Similar to the streamlining of an application to conduct a study in the new Clinical Trials legislation, the MDR introduces a voluntary coordinated procedure where, for multi-site investigations, the sponsor submits a single application, which is transmitted via an electronic system to all Member States in which the CI is to be conducted. The coordinated procedure means that one member state is responsible for coordinating the assessment of the CI application.

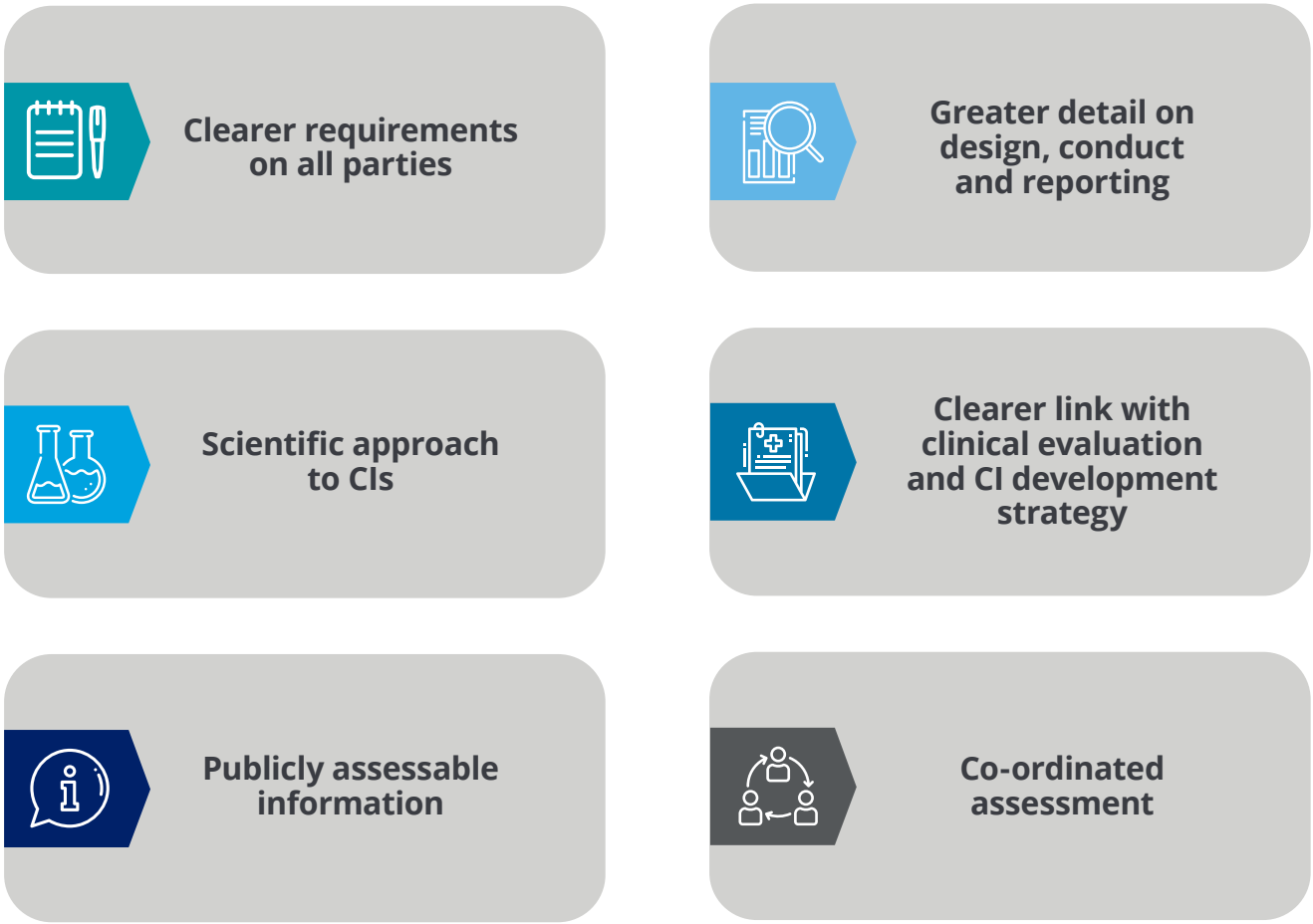


Figure 3. Key changes in the Clinical Investigation process in the MDR

Vigilance and post-market surveillance

The Regulations set out specific requirements for manufacturers and clarify the distinction between vigilance (reactive) and post-market surveillance (proactive).

Vigilance includes identifying and reporting serious incidents to the relevant Competent Authority (the HPRA in Ireland) and conducting field safety corrective actions (FSCA). As a rule, the time period for reporting will take account of the severity of the serious incident (Figure 4). In Ireland, it is important to note that the timeframe for reporting serious incidents is shorter than that specified in the European Commission guidelines.

If, after becoming aware of a potentially reportable incident, a manufacturer is uncertain about whether the incident is reportable, the manufacturer should submit a report within the relevant timeframe. Medical device users are also encouraged to report incidents. Suspected incidents or complaints may also be reported to the importer or the distributor of the device. This information will be shared with the manufacturer of the device.

Post-market surveillance involves monitoring the available information to periodically reconfirm that the benefits of the device continue to outweigh its risk. Manufacturers are required to compile safety reports, including post-market surveillance plans, post-market reports and Periodic Safety Update Reports in a manner analogous to the well-established process for pharmaceuticals.

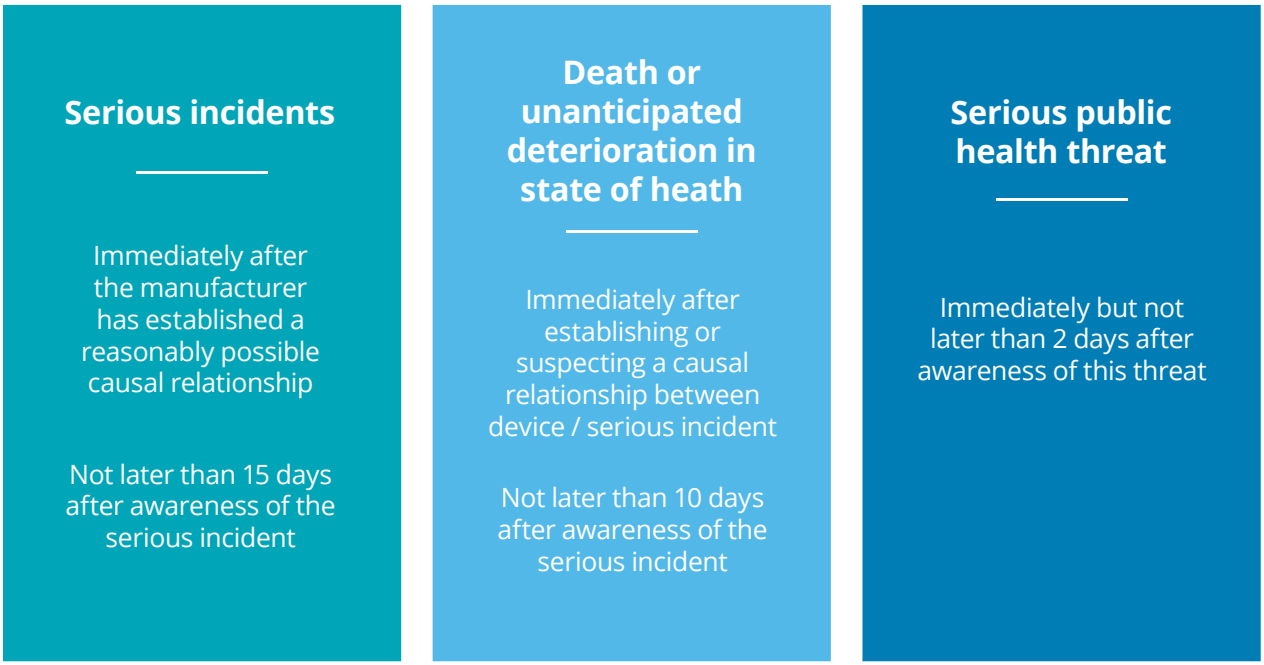
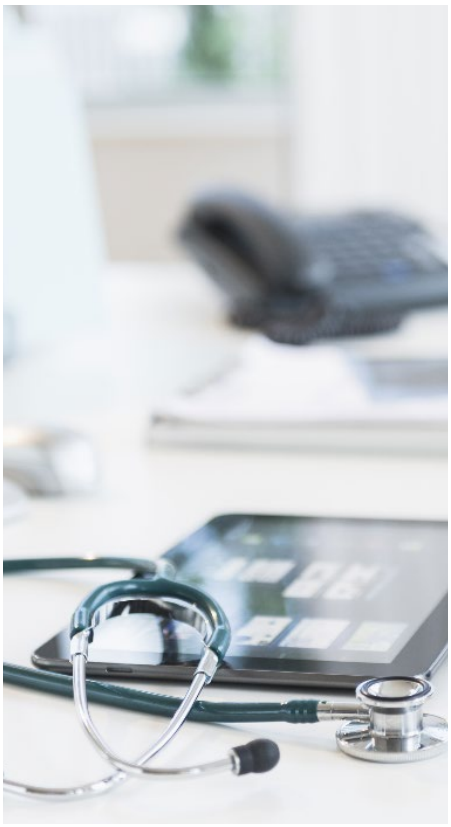


Figure 4. Time frames for reporting serious incidents



Person Responsible for Regulatory Compliance

The role of the Qualified Person is well established in the pharma sector. Now, for the first time, the new Regulations will require manufacturers to appoint a person with responsibility for the regulatory compliance of medical devices (PRRC). Article 15 of MDR 2017/745 requires that manufacturers shall have available within their organisation at least one PRRC who possesses either:

(a) a formal qualification such as a degree in law, medicine, pharmacy, engineering or other relevant scientific discipline and at least one year of professional experience in regulatory affairs or in quality management systems relating to medical devices; or

(b) four years of professional experience in regulatory affairs or in quality management systems relating to medical devices.

The five main responsibilities of the PRRC are to ensure that:

1. The device conforms to the manufacturer's quality system prior to release;
2. The technical documentation and EU declaration of conformity are properly maintained;
3. The post-market surveillance obligations are complied with;
4. The reporting obligations are fulfilled for serious incidents, field safety corrective actions and trend reporting;
5. The statement referred to in Section 4.1 of Chapter II of Annex XV is issued in the case of investigation devices.

A provision within MDR allows small enterprises to outsource the PRRC role rather than having that person within their organisation. However, if outsourced, an agreement must be in place between both parties and the contract PRRC must be listed as a critical supplier on the manufacturer's quality system.

Authorised Representative required for manufacturers based outside Ireland

Previously, under the MDD, manufacturers based outside of Europe required an Authorised Representative within Europe to act on their behalf. MDR expands the role of Authorised Representative (Articles 11 and 12 of Regulation (EU) 2017/745).

The authorised representative must

- verify the declaration of conformity, conformity assessment, technical documentation, registration requirements and manufacturer obligations;
- keep available a copy of the declaration of conformity, technical documentation and certificates;
- establish systems for provision of information to Competent Authorities and manufacturers, corrective and preventive action (CAPA) plans, registration, complaint handling, establishment, maintenance, termination of mandate, person responsible for regulatory compliance.

In addition, the Regulation stipulates that the authorised representative is legally liable for defective devices in the event that a manufacturer established outside the Union has not complied with its general obligations. Authorised representatives are required to have permanently and continuously at their disposal at least one person responsible for regulatory compliance (PRCC). The role of the Authorised Representative is very similar to that of the European Union Qualified Person for Pharmacovigilance (EU QPPV) which pharmaceutical companies must have in place if they market a medicinal product in the European Union.

Traceability/ UDI

A completely new feature of the Regulation is the unique device identification (UDI) system (MDR Article 27 and IVDR Article 24) which will apply to all devices placed on the EU market. The UDI will be a barcode, a QR code or any other machine-readable code. The aim is to enhance the identification and traceability of devices and the effectiveness of post-marketing safety-related activities. Economic operators (defined as manufacturers, importers and distributors) will need to keep records to identify any health institution or healthcare professional to which they have directly supplied a device. For Class III implantable devices, health institutions are required to retain records of the UDIs of devices they have supplied or been supplied with.

Economic Operators under the MDR

The Regulation clarifies the respective obligations of manufacturers, Authorised Representatives, importers and distributors [1].

Manufacturers will have a number of additional obligations, including:

- Having at least one person responsible for regulatory compliance;
- Ensuring that quality management systems meet the more stringent requirements;
- Applying conformity assessment procedures to place a product in the market

Authorised representatives will have a number of additional obligations, including:

- Identifying responsible person/s for regulatory compliance;
- Where the manufacturer is not established in a Member State and has not complied with its obligations, the authorised representative shall be legally liable for defective devices on the same basis as, and jointly and severally with, the manufacturer, and will need to ensure that sufficient financial coverage is in place.

Importers will have a number of additional obligations, including verifying that:

- The device has been CE marked;
- The device has been labelled correctly and has a UDI;
- The device is registered in the electronic system (Eudamed).

Distributors will have a number of additional obligations, including verifying that:

- The device has been CE marked;
- The device is accompanied relevant information to be supplied by the manufacturer;
- The importer has complied with their general obligations;
- A UDI has been assigned to the device.

Notified Bodies and the re-quirement for re-approval

Notified bodies around Europe, including the National Standards Authority of Ireland (NSAI), need to be re-approved by European authorities to show that they have the capacity and knowledge for the new regulation. Recent announcements from Lloyd's Register Quality Assurance (the LRQA) [2] and QS Zurich [3] that they will no longer offer notified body services and that they will not seek to become a notified body under the new medical device regulations point to a possible bandwidth difficulty for manufacturers and indeed, regulators.

Both Ireland and Germany are facing challenges in this regard and have already voiced concerns to the European Council over the lack of capacity for device regulation [4]. While the NSAI's certification is pending, with September 2019 likely to be the earliest date, the prospect of bottlenecks in the system is worrying for both manufacturers and patients. The list of notified bodies can be found on the NANDO database [5]. Currently there are four approved notified bodies designated under MDR.

Conclusion

The MDR/IVDR provides a harmonised regulatory framework to ensure the safety and performance of medical devices (including software and combination products), before and after they are placed on the market, putting a stronger onus on manufacturers to demonstrate that their devices meet the requirements by performing conformity assessments. The main impacts are greater transparency, extended scope, increased oversight of economic operators, heightened traceability throughout the supply chain via the Unique Device Identification (UDI) system and tougher requirements affecting numerous functions and activities across the entire lifecycle of devices, from development to clinical investigations, conformity assessment and post-market surveillance.

This will undoubtedly lead to a significant increase in workload for manufacturers and distributors. In practice, however, the shortage of notified bodies will inevitably cause bottlenecks for manufacturers, leading to delays and negative effects on patients. The success of the MDR will be impacted if these short-term capacity issues are not addressed.

The impact of Brexit cannot be ignored either: in addition to the relocation from London to Amsterdam, the EMA also faces a substantial workload stemming from the new legislation for which no additional resources have been made available [6]. Preparatory work on this legislation was tentatively scheduled for June 2019, but any work undertaken will be subject to availability of both human and financial resources. For example, Eudamed is currently being overhauled for the new regulations to increase capabilities and allow wider access. The implementing act to define detailed arrangements necessary for the setting up and maintenance of Eudamed is being drafted with an expected completion date of Q4 2019.

There is little in the new regulations about cybersecurity, perhaps because when they were drafted, cybersecurity was not perceived to be as serious a threat as it is today. It is likely that MDR will not be fit for purpose as systems evolve and the threat level changes [7]. Future regulations will need to have a greater focus on cyber safety and resilience.

Aside from this deficit, the short-term glitches in the new regulations should be capable of being resolved. While the immediate impact on manufacturers and notified bodies is yet more regulation with an increased workload, the goal of a safer, more robust and transparent medical device industry should be achieved.

[1] https://www.gov.uk/guidance/medical-devices-eu-regulations-for-mdr-and-ivdr

[2] https://www.lr.org/en/latest-news/lloyds-register-withdraws-mdd-and-ivdd-services

[3] https://www.quality-service.ch/en/?s=medical+device

[4] https://fora.ie/ireland-medical-device-regulation-4680897-Jun2019

[5] https://ec.europa.eu/growth/sectors/medical-devices

[6] https://www.ema.europa.eu/en/about-us/united-kingdoms-withdrawal-european-union-brexit

[7] https://www.raeng.org.uk/publications/reports/cyber-safety-and-resilience

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